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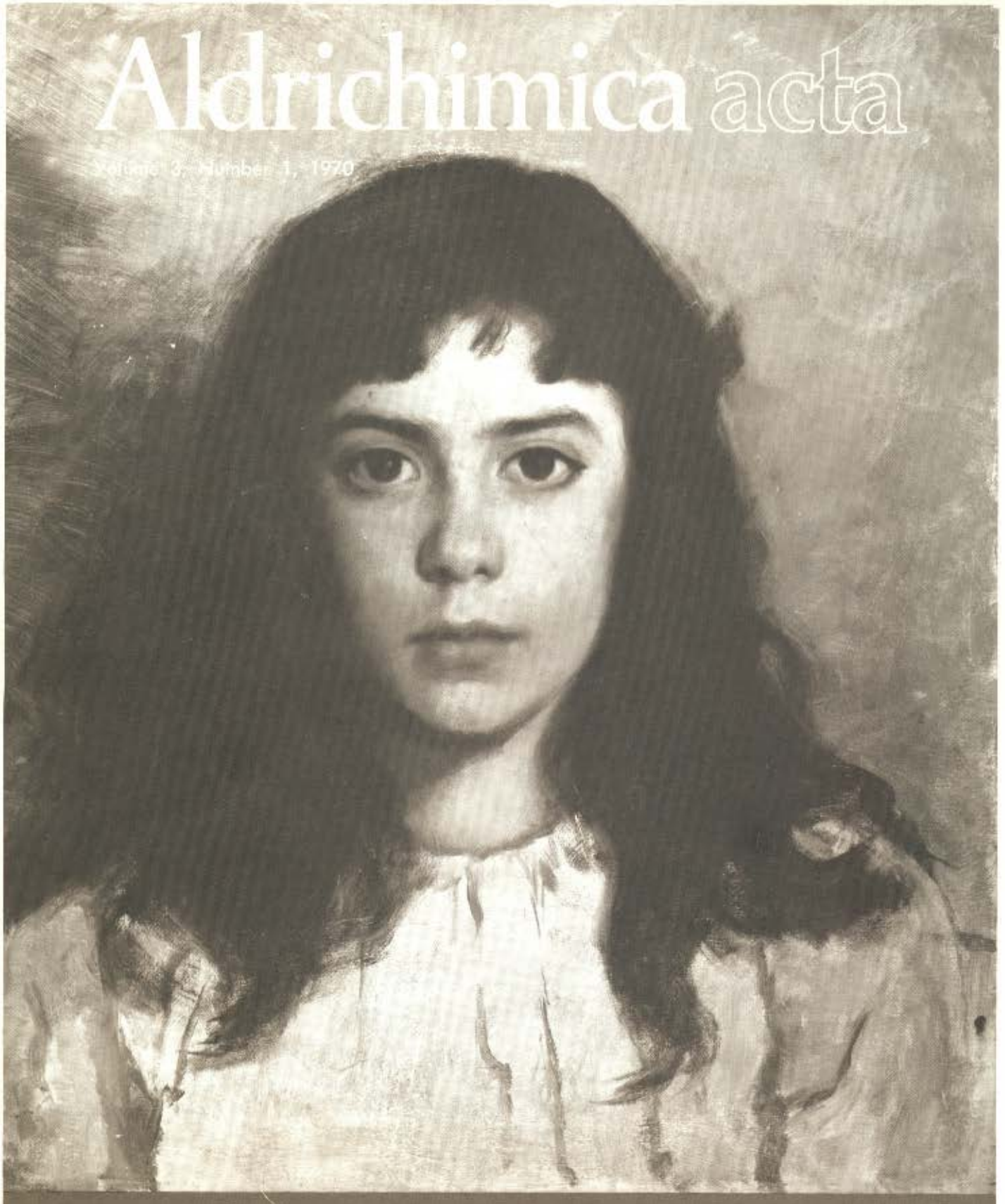
Volume 3, Number 1, 1970



Organothallium Chemistry-New Horizons in Synthesis

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ABOUT THE COVER

Our collector-chemist calls the painting of the intense little girl depicted on the cover his "Alfa-girl" because he bought it in a small Boston gallery after a day's discussion with our friends at Alfa. The gallery owner smiled at the suggestion that it looked like a sketch by John Singer Sargent, but the art-historian most knowledgeable about Sargent, Mr. David McKibbin at the Boston Athenaeum wrote: "Your head of a girl is stunning. . . . I have never been more sure of an unknown and I'd like to identify her." The canvas is on a Boston stretcher but, wrote Mr. McKibbin, "I know of no Boston subject and because the little girl is so attractive it seems unlikely had she lived here that it would not have been recorded or seen by any one who would have recorded it. Of course Sargent might have taken a prepared canvas with him to some place outside Boston such as Newport or Worcester, but I cannot think who this child might be. If you will tell me what you know of the canvas's provenance there may be a clue which I could interpret." Thereby hangs a tale of as yet uncompleted art-historical sleuthing: The gallery-owner told our chemist that he had bought the canvas from an antique store, "Recollections" in Brookline, Mass. The owner of that store well remembered the painting but the seller, a lady whose name he had forgotten, had moved to Florida; she had, he believed, once taken the sketch in payment of rent. The lady's sister still lived in Boston, and occasionally came to "Recollections"; next time she came in, he would ask her about her sister's name and address, and perhaps we shall discover our girl's identity yet.

The back of the canvas bears the name FRYE, perhaps the sitter's name, or that of a previous owner. We would appreciate hearing from any reader who knows the identity of this girl.

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Thallium Chemistry: A Study in International Cooperation

Alfred R. Bader

Dr. Alexander McKillop and Professor Edward C. Taylor

It is not often that a chemist has the chance to witness in intimate detail the development of an important new field of chemistry. What would have been our thoughts if we could have been with Professor Grignard when he first worked with magnesium compounds? At first, perhaps, some doubt that many chemists could ever get very excited about chemistry as way-out as that of magnesium organics, then amazement, and finally the realization that he is dealing with a series of reactions so versatile that the Grignard Reaction would soon become a household word among chemists. Thus were my thoughts when I first heard about thallium chemistry.

Some two years ago, friends at the Smith Kline & French Laboratories in Philadelphia invited me to visit with them to discuss with Professor E. C. Taylor how one might market a series of thallium-organics developed with SK&F grants at Princeton and the University of East Anglia. At first I was skeptical; all I knew about thallium compounds was that they are highly toxic, and the fact that β-dicarbonyl compounds gave stable thallium salts was interesting, but hardly earth-shaking. But I knew Professor Taylor and of his brilliant work in heterocyclics, and I thought it unlikely that he would get excited over a mere curiosity. And at the meeting I was soon convinced. The work on thallium organics began with the discovery by Dr. Alexander McKillop—a puckish Scotsman and enthusiastic chemist, then a post-doctorate fellow with Professor Taylor at Princeton—that thallous ethoxide reacted cleanly with β-dicarbonyl compounds to form stable, crystalline salts. With other students of Professor Taylor, the reactions of thallous ethoxide were explored, and when Dr. McKillop returned to Britain to teach at the University of East Anglia, it was decided to continue this international cooperation in the studies of the "Taylor-McKillop Reaction." How effective this has been is witnessed eloquently by the adjoining review article and the twenty papers by Professor Taylor and Dr. McKillop there cited.

How could Aldrich help best? Offering the various thallium salts of β-dicarbonyl compounds was one, albeit minor contribution. Much more important was the availability of the key intermediates: thallous ethoxide, thallic acetate, and thallic trifluoroacetate. Thallous ethoxide presented a particular problem: the Princeton preparative procedure involved thallium metal, refluxing ethanol and gaseous oxygen, had been used only to make 500 gram quantities of thallous ethoxide and could not be used safely to make larger quantities. Dr. Walter Tschannen, the head of our "kilo lab," spent some time with Professor Taylor's group at Princeton and then came home to perfect a pilot plant method safely to make twenty to thirty kilo lots of thallous ethoxide—a method that could be scaled up to make tons if needed. Thus thallous ethoxide is now freely available and reasonably priced. Even its toxicity appears to be less of a problem: an effective and inexpensive antidote for thallium poisoning, the simple pigment Prussian Blue, has just been described [H. Heydlauf, *European J. Pharm.*, **6**, 340 (1969)].

To exploit the commercial possibilities of thallium chemistry further, it was decided to set up a small company, Thallium Limited, specifically to make the products of thallium chemistry, allowing Aldrich to be this company's marketing arm. SK&F has filed patent applications on such key intermediates as thallic trifluoroacetate, and these patents might well become valuable; a small company specializing in thallium technology would be a flexible vehicle to make these inventions commercial realities. One of Dr. McKillop's students, Dr. Lionel Elsom, heads Thallium Limited which will soon be producing a good many compounds.

Princeton, Norwich, Philadelphia, Milwaukee—far apart, and yet working together closely and with a great deal of personal satisfaction to make thallium "one of the indispensable metals in synthetic organic chemical methodology."

Organothallium Chemistry-New Horizons in Synthesis

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Department of Chemistry, Princeton University,

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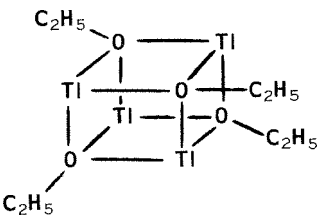
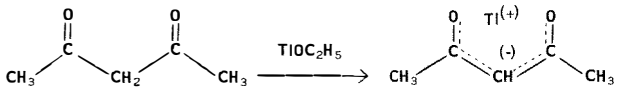
Anglia, Norwich, England

The last two decades have seen a tremendous upsurge of interest and activity in organometallic chemistry, with the result that there are now few metals the organochemistry of which has not been investigated in some detail. Prior to the initiation of our studies on organothallium chemistry in 1966, however, little was known of the organic chemistry of this group IIIB metal. This situation must be regarded as surprising, as not only is thallium abundant, inexpensive and readily available in a high state of purity, but sporadic reports during the past half century have clearly indicated that in certain reactions thallium derivatives are effective chemical intermediates. In this article we summarize the remarkable utility of thallium compounds in organic synthesis. We believe that the reactions discovered thus far presage a bright future for this versatile metal.

Our initial interest in thallium chemistry stemmed from curiosity about a statement made some years ago by Menzies and Wilkins[1] that the thallium(I) salt of ethyl acetonedicarboxylate was "readily soluble in cold ethyl or methyl iodide, thallous iodide being deposited on standing or heating". This startling statement about the apparent solubility of a β-dicarbonyl chelate in ethyl iodide (not a popular solvent for ionic compounds!) prompted the rash conclusion on our part that thallium(I) salts might be unusually covalent in character, thus raising exciting prospects of a wide spectrum of possible base-catalyzed reactions in homogeneous solution. A later report by Fear and Menzies[2] that reaction of the thallium(I) salt of ethyl acetoacetate with ethyl iodide resulted in apparent C-ethylation stimulated us to prepare some representative thallium(I) salts of β-dicarbonyl compounds and to investigate their physical and chemical properties.

We found that the most effective reagent for the formation of thallium(I) salts of β-dicarbonyl compounds was thallium(I) ethoxide. This remarkable compound is a covalent tetramer[3] which is soluble in most organic solvents (including heptane and benzene) and thus possesses considerable advantages over sodium ethoxide and other alkali metal alkoxides in that homogeneous base-catalyzed reactions can be carried out in non-polar solvents. Treatment of a benzene or petroleum ether solution of a β-dicarbonyl

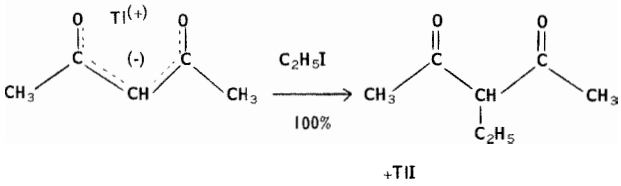




(eq. 1)

compound (e.g., acetylacetone, (eq. 1)) with 1 equivalent of thallium(I) ethoxide resulted in the instantaneous separation in quantitative yield of its thallium(I) salt.

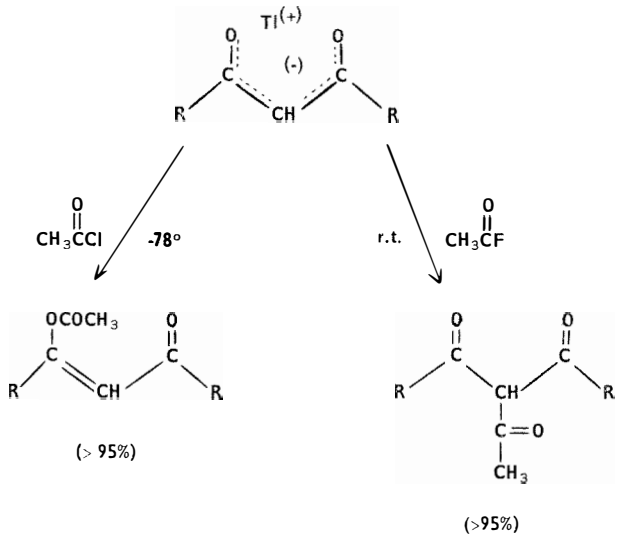
To our great surprise, and contrary to the previous report,[1] these salts were completely *insoluble* in cold ethyl iodide. Heating the suspension, however, resulted in the formation, *in quantitative yield,* of pure mono-C-ethylated product



(*eq. 2*)

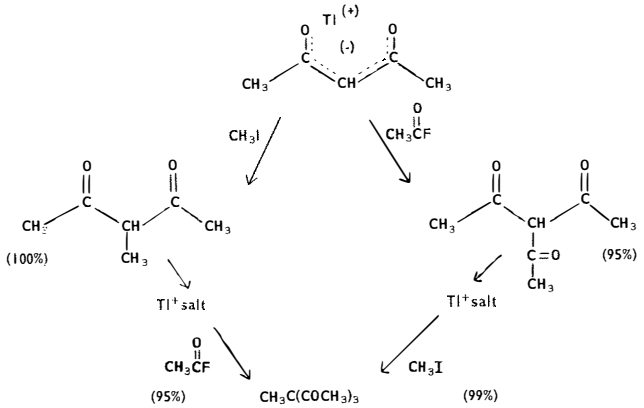
(eq. 2).[4] Ironically, the extreme insolubility of these thallium salts in alkyl iodides appears to be the key to the remarkable specificity of alkylation (and acylation) which we have observed upon treatment of these thallium(I) salts, in suspension, with alkylating and acylating agents.[4] It appears that reaction occurs at the crystal surface, literally "peeling away" the crystal until complete reaction has been achieved; retention of the geometry of the thallium(I) chelate in the transition state leads to regiospecificity rivalling that of an enzymatic reaction.

Not only are thallium(I) salts of β-dicarbonyl compounds alkylated regiospecifically, but they may also be acylated selectively on oxygen or on carbon, depending upon reaction conditions.[4] Thus, reaction with acid chlorides in ether suspension at $-78°$ leads to exclusive O-acylation, while treatment with acetyl fluoride in ether suspension at room temperature leads to exclusive C-acylation (eq. 3).



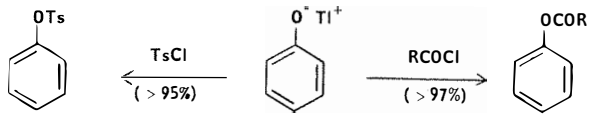
(*eq. 3*)

The remarkable effectiveness of this combination of regiospecific acylation and alkylation reactions is illustrated in eq. 4, which describes the synthesis of 1,1,1-triacetylethane.



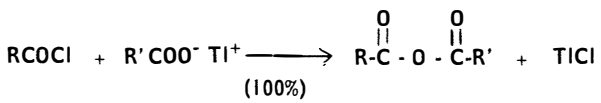
(*eq. 4*)

Thallium(I) ethoxide forms thallium(I) salts with a wide spectrum of acidic organic substrates, and the properties of the resulting thallium(I) salts resemble those of the above β-dicarbonyl salts: they are all highly crystalline, colorless, sharp-melting, light-insensitive and readily recrystallizable solids. They are also exceptionally useful intermediates in a wide diversity of synthetic reactions. Thus, treatment of an ether suspension of thallium(I) salts of phenols with an equimolar quantity of an acyl or aroyl halide at room temperature affords pure phenol esters in yields seldom lower than 97%. Phenol tosylates are prepared similarly (eq. 5).[5]



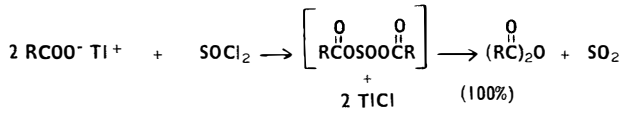
(*eq. 5*)

Treatment of thallium(I) carboxylates with a stoichiometric amount of an acyl or aroyl halide in ether suspension, followed by removal of thallium(I) chloride by filtration and evaporation of the ether, affords symmetrical or unsymmetrical carboxylic anhydrides (according to the choice of the acid chloride) in quantitative yield (eq. 6).[5]



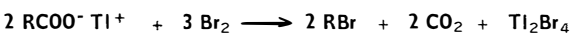
(*eq. 6*)

Symmetrical anhydrides are alternatively prepared by treatment of thallium(I) carboxylates with thionyl chloride in ether suspension at room temperature; the intermediate diacyl or diaroyl sulfites spontaneously lose sulfur dioxide (eq. 7).[5]



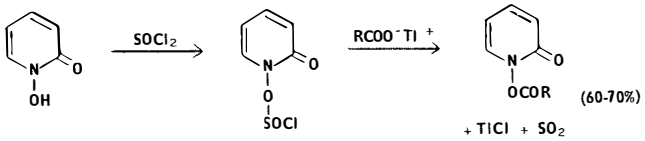
(eq. 7)

Thallium(I) carboxylates of *n*-alkanoic acids readily yield *n*-alkyl bromides upon treatment with bromine and carbon tetrachloride in a modification of the classical Hunsdiecker reaction (eq. 8).[6]



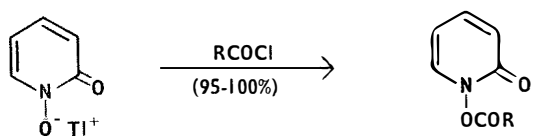
(eq. 8)

The utility of thallium(I) carboxylates in organic synthesis can be further illustrated by an improved preparation of Paquette's "active esters"[7] (eq. 9); this procedure



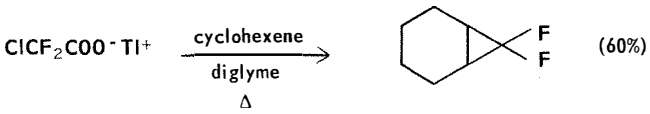
(eq. 9)

permits the direct conversion of an amino acid to a peptide without the necessity of intermediate formation of an acid chloride.[8] However, an even better route to these "active esters" involves treatment of the thallium(I) salt of 1-hydroxy-2(1*H*)-pyridone with acid chlorides; the reaction proceeds instantaneously at room temperature to give quantitative yields of products (eq. 10).[8]



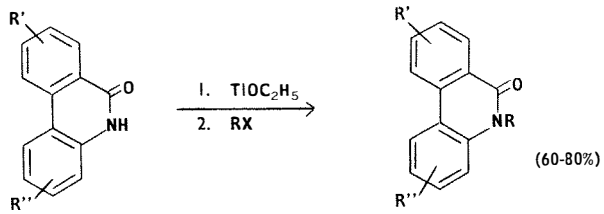
(eq. 10)

A common feature of all of the above metathetical reactions is the avidity of thallium for halide ion and the consequent separation of an insoluble thallium(I) halide from the organic reaction medium. As a result, facilitation of *intra*molecular halide abstraction by thallium(I) was to be anticipated. Thus, difluorocarbene is conveniently prepared by thermolysis of thallium(I) chlorodifluoroacetate (eq. 11).[9]



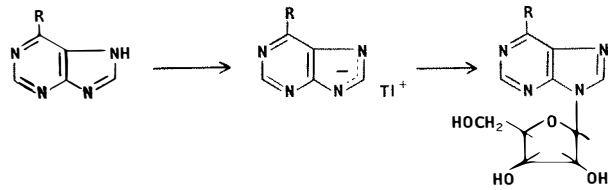
(eq. 11)

The physical properties of thallium(I) salts (solubility, crystallinity, stability) can also be used to advantage in the alkylation and acylation of a variety of heterocyclic compounds. For example, phenanthridones can be alkylated smoothly at room temperature via their thallium salts (eq. 12)[10]; previous procedures required formation of the



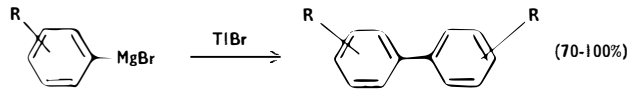
(eq. 12)

potassium salt by fusion with solid potassium hydroxide, followed by alkylation in a sealed tube at elevated temperatures.[11] A variety of purines readily form thallium(I) salts upon treatment in ethanol or DMF solution with thallium(I) ethoxide; in contrast to sodium or chloromercuri salts, these thallium(I) salts alkylate exclusively at position 9, and this reaction has been exploited for the preparation of nucleosides (eq. 13).[12]



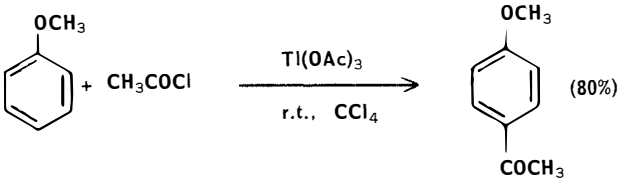
(eq. 13)

By-products of many of the above reactions are thallium(I) halides, and it is interesting to note that thallium(I) bromide is an extremely effective reagent for the synthesis of biaryls from aromatic Grignard reagents (eq. 14).[13]

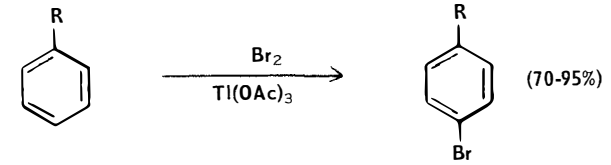


(eq. 14)

This superficially prosaic process has been shown to proceed via a complex series of redox reactions involving all three of the valence states of thallium (0, I and III). Facile interplay among these valence states is, in fact, a characteristic feature of much of thallium chemistry. It is somewhat surprising that the chemistry of thallium(III) has been generally neglected in view of the well-known position of its reduction potential between that of mercury (II) and lead (IV). Furthermore, thallium(III) compounds would be expected to be strong Lewis acids, and may be considered coordinatively unsaturated if the associated anion is considered as a monodentate ligand. We have found, for example, that thallium(III) acetate is an extremely effective Friedel-Crafts catalyst (eq. 15).[14] Furthermore, a combination of thallium(III) acetate and bromine has been found to effect exclusive *para* bromination; an ordered bromine-thallium(III) acetate-aromatic substrate complex appears to be involved in this highly specific electrophilic reaction (eq. 16).[15]

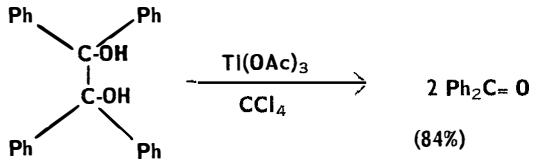


(eq. 15)



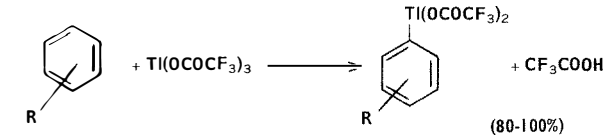
(eq. 16)

The mild, selective and non-radical oxidizing properties of thallium(III) acetate are illustrated by its utility in the cleavage of α-glycols (eq. 17).[16]

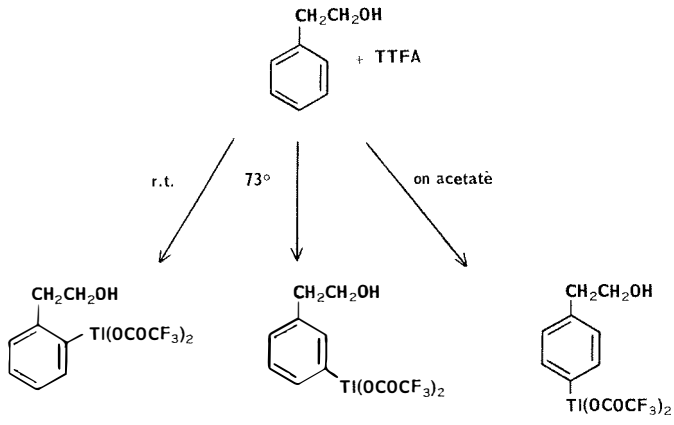


(eq. 17)

One of the most interesting and versatile thallium(III) reagents which we have discovered thus far is thallium(III) trifluoroacetate ($Tl(OCOCF_3)_3$,TTFA). Its extraordinary reactivity as an electrophilic metallating reagent is illustrated by its reaction with aromatic substrates, often at room temperature, to give arylthallium ditrifluoroacetates (eq. 18).[17] Kinetic investigations[18] have shown that thallation, like aromatic mercuration,[19] is one of the few examples of a freely reversible electrophilic substitution reaction. Thallation with TTFA of phenylethanol at room temperature (kinetic control) leads to *ortho* substitution, while thallation at 73° (thermodynamic control) gives predominant *meta* substitution. *Ortho* substitution, we believe, results from intramolecular delivery of the thallium electrophile from an intermediate Lewis acid-Lewis base complex between the TTFA and the side-chain hydroxyl group, and is thus subject to control by appropriate modification in the structure and size of the intermediate chelate. This is dramatically illustrated by the observation that thallation at room temperature (kinetic control) of the *acetate* of phenylethanol results in *para* substitution (eq. 19).[20]



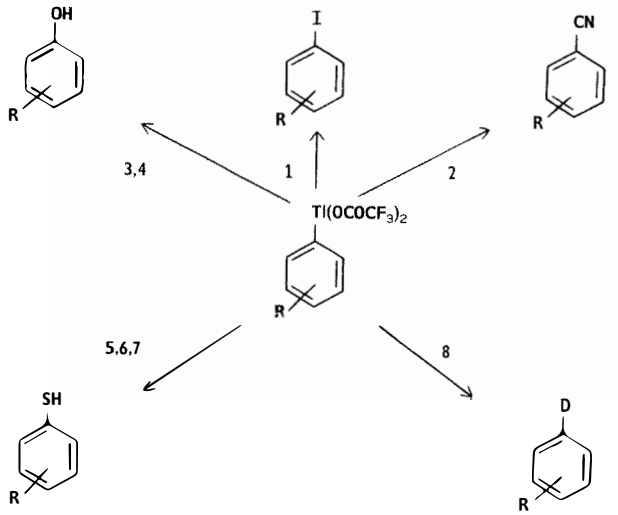
(eq. 18)



(eq. 19)

These arylthallium ditrifluoroacetates are versatile intermediates for the synthesis of a wide spectrum of substituted aromatic compounds. For example, treatment with aqueous potassium iodide at room temperature yields aromatic iodides.[21] Phenols are readily prepared by treatment with lead tetraacetate followed by triphenylphosphine.[22] It should be noted that it is not necessary to isolate the intermediate arylthallium ditrifluoroacetates in either of the above reactions; thallation can be carried out in trifluoroacetic acid solution and the appropriate reagents added directly to the reaction mixture.

Arylthallium ditrifluoroacetates may also be utilized as intermediates for the synthesis of aromatic nitriles[22] and thiophenols,[23] while reductive cleavage with lithium aluminum deuteride or aluminum amalgam in D_2O leads to specific deuteration of aromatic substrates.[24] These reactions are summarized in Scheme 1.

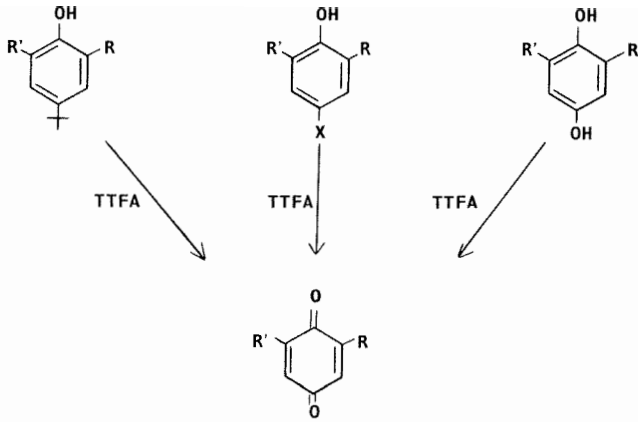


Reagents: 1. aq. KI 2. aq. KCN, $h\nu$ 3. $Pb(OAc)_4$ 4. PPh_3
5. $K^{+-}SCSN(CH_3)_2 \longrightarrow ArTl(SCSN(CH_3)_2)_2$
6. $h\nu$ in acetone gives mixture of ArSSAr and $ArSCSN(CH_3)_2$
7. [H] or H_3O^+ 8. $LiAlD_4$

SCHEME 1

It should be noted that control over the orientation of thallation, as illustrated above (eq. 19) with phenylethanol, has as its consequence control over isomer orientation in the above syntheses of iodides, phenols, nitriles, thiophenols, and deuterated aromatics.

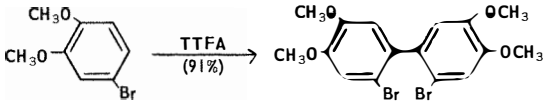
Just as lead tetratrifluoroacetate is a more powerful oxidizing agent then lead tetraacetate,[25] so TTFA is a more effective and versatile oxidizing agent than thallium(III) acetate. For example, we have found that a wide variety of *p*-*t*-butyl phenols are smoothly transformed into *p*-quinones upon treatment with TTFA in either TFA or carbon tetrachloride solution.[26] A variety of other *p*-substituted phenols are likewise converted to *p*-quinones upon treatment with TTFA. Hydroquinones can literally be titrated with TTFA and this reaction constitutes an extremely convenient procedure for their oxidation to *p*-quinones (eq. 20).[26]



R = R' = alkyl, halogen, etc.
X = halogen, OAc, NR_2, etc.

(eq. 20)

Finally, the reactivity and selectivity of TTFA as an oxidizing or metallating agent can apparently be extensively modified by the addition of appropriate co-reagents. For example, treatment of 4-bromoveratrole with TTFA and boron trifluoride etherate results in a smooth Scholl reaction (eq. 21)[27] in which oxidative coupling rather than



(eq. 21)

thallation has taken place.

It is widely recognized that organometallic chemistry offers some of the greatest challenges and promises some of the richest rewards in synthetic organic chemistry. We suggest that thallium may well be regarded in the future as one of the indispensable metals in synthetic organic chemical methodology.

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VOLUME 3, NUMBER 2, 1970

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ABOUT THE COVER

Our collector-chemist is rather opinionated about many Bible characters, and the one he likes the least among the "good guys" in the Old Testament is Joseph whom he considers a brilliant organizer, a fine servant, a bad brother and a worse son. Hence we were rather surprised when he purchased recently at a London auction this large (42 x 45 inches) painting of Joseph explaining the baker's dream. From 1748 to 1951 this had been in the collection of the Dukes of Bedford at Woburn Abbey, where it had been attributed to Rembrandt. Our collector is convinced that it is not by him but by someone around 1660 strongly influenced by Rembrandt. Sometime the artist will be identified: anyone who could depict in so masterly a manner the most difficult of all subjects—communication between men—deserves to be known.

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Synthesis of Benzocyclobutene and Derivatives

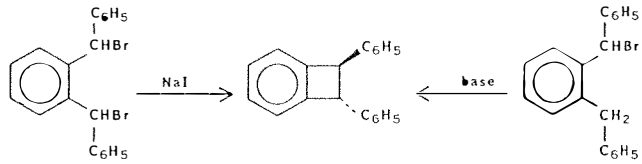
Irwin L. Klundt

Research Division, Aldrich Chemical Company, Inc.

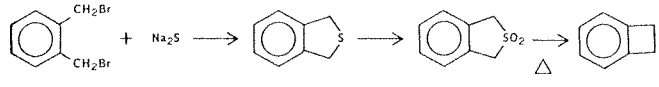
The benzocyclobutene ring system is a novel fused ring system that has attracted quite a number of investigators in the past decade. Although simple benzocyclobutenes are not available commercially, the ring system can be prepared by any one of the routes listed below. Aldrich offers a number of the intermediates necessary to prepare the ring system and in some cases the available starting material is only one step away from the final product.

The first synthesis of the benzocyclobutene ring system was reported sixty years ago by Finkelstein, a student of Johannes Thiele, in his doctoral thesis.[1] The field of benzocyclobutene chemistry then lay dormant until Cava repeated Finkelstein's synthesis in 1956.[2] Since then at least ten different synthetic methods have been reported. Finkelstein reacted $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene with sodium iodide in hot alcohol. A similar procedure has been used to prepare 1,2-diphenylbenzocyclobutene.[3]

(T 560-5 *)



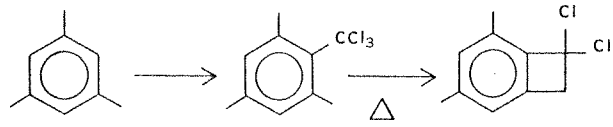
Two groups have investigated the pyrolysis of 1,3-dihydroisothianaphthene-2,2-dioxide.[4,5]



(D 4440-5 *)

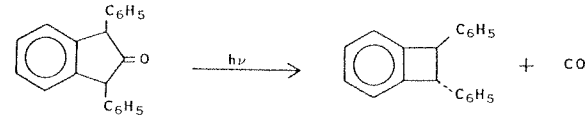
It has been shown that the temperature of the pyrolysis step can be lowered from 650–770° to 300–350° by irradiation with ultraviolet light.[6]

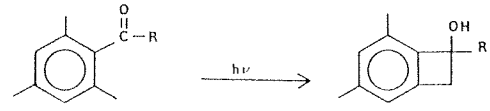
Hart[7] has reported a novel synthesis starting with hindered trichloromethyl-*o*-xylenes.



(M 720-0 *)

The photochemical expulsion of carbon monoxide from substituted 2-indanones has been reported to give benzocyclobutenes.[8] Photolysis of sterically hindered aromatic ketones produced a number of benzocyclobutenols.[9]

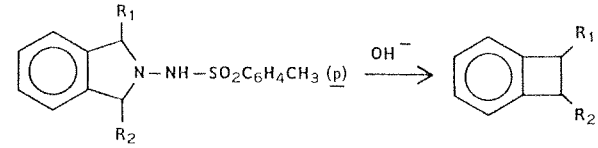




(R=CH3, T 7240-0 *)

R	% Yield
CH_3	70
C_2H_5	63
i-Pr	61
t-Bu	0

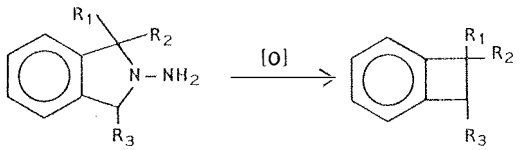
Treatment of the tosylamide of substituted N-aminodihydroisoindoles with base causes the elimination of nitrogen and the formation of substituted benzocyclobutenes.[10]



R	% Yield
$R_1=R_2=H$	16
$R_1=R_2=C_6H_5$	40

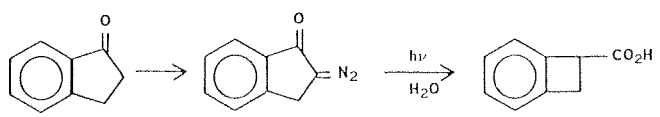
Cis and *trans*-1,2-diphenylbenzocyclobutene and 1,1,2-triphenylbenzocyclobutene have been prepared by oxidation of the corresponding 1-aminodihydroisoindole.[11]

° Aldrich Product Number



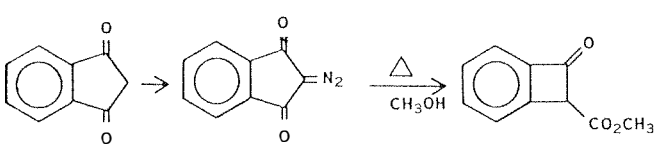
$R_1 = R_3 = C_6H_5$; $R_2 = H$
$R_1 = R_2 = R_3 = C_6H_5$

Several groups have employed the Wolff rearrangement of α-diazo-1-indanones to produce substituted benzocyclobutene carboxylic acids.[12] This method allows a great variety



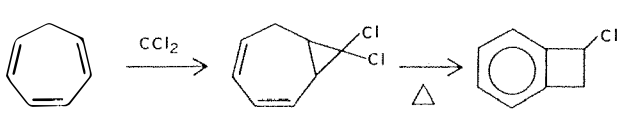
(I-230-4*)

of substituted benzocyclobutene carboxylic acids to be prepared but the scale of the reaction is limited by the size of the photolysis apparatus. An analogous method has also been used to prepare a β-ketoester.[13]

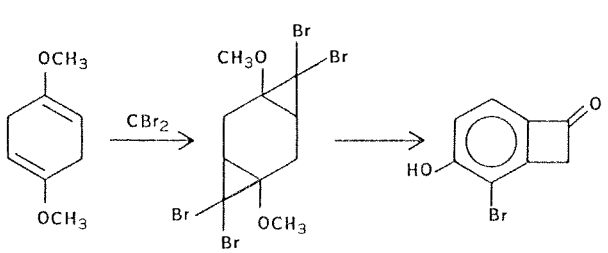


(I-200-2*)

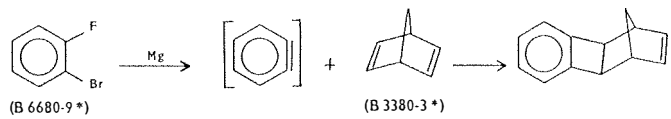
The reaction of carbenes with olefins and then conversion of the adduct to a benzocyclobutene has been reported by two groups.[14]



(C 9920-5*)

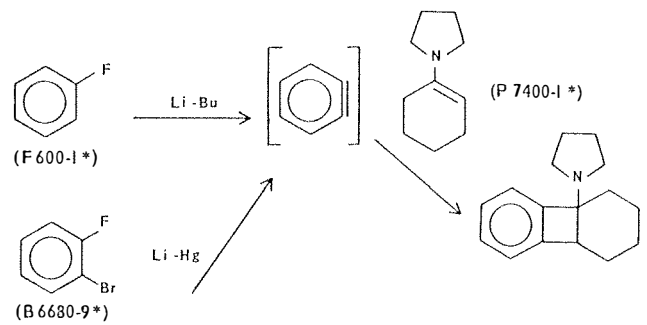


The reaction of benzyne with bicyclo[2.2.1]heptadiene produced the expected benzocyclobutene in 20% yield.[15] The



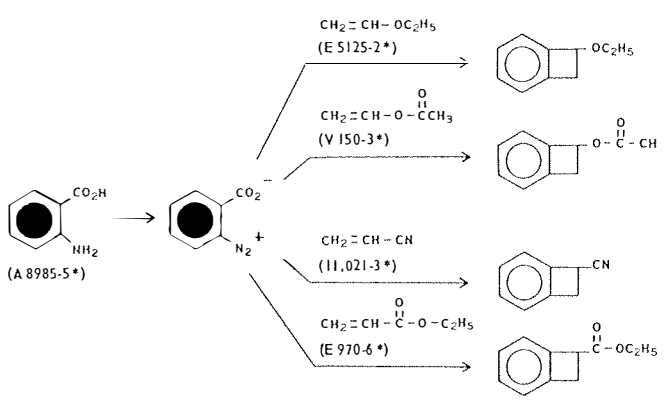
(B 6680-9*) (B 3380-3*)

reaction of benzyne with 1-pyrrolidinocyclohexene also gave a benzocyclobutene.[16] The nature of the product depended on the method of generation of benzyne.



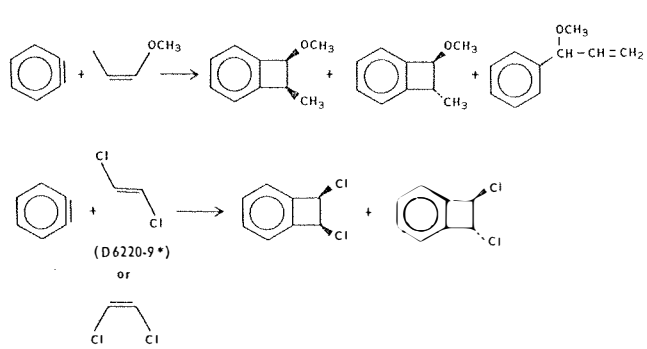
(B 6680-9*)

Several groups have reported the reaction of benzyne, generated from *o*-benzenediazonium carboxylate, with olefins to produce 1-substituted benzocyclobutenes.[17]



(A 8985-5*)

Several investigators have studied the stereochemistry of addition of benzyne to olefins to prepare 1,2-disubstituted benzocyclobutenes in hopes of determining if benzyne reacts as a diradical or a dipolar species.[18]

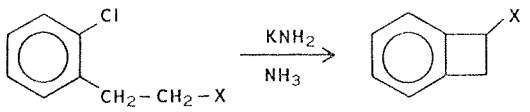


(D 6220-9*)
or

(D 6200-4*)

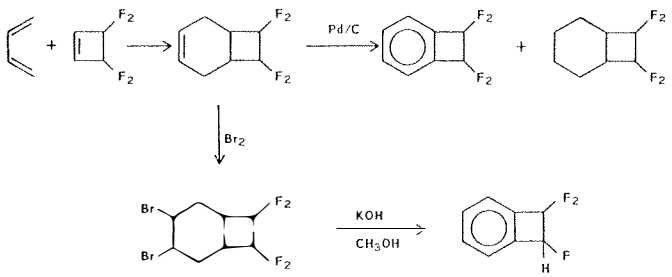
° Aldrich Product Number

Homocyclic ring closure *via* benzyne intermediates to prepare substituted benzocyclobutenes is a convenient method.[19] Various 1-substituted and ring substituted benzocyclobutenes have been prepared by this method.

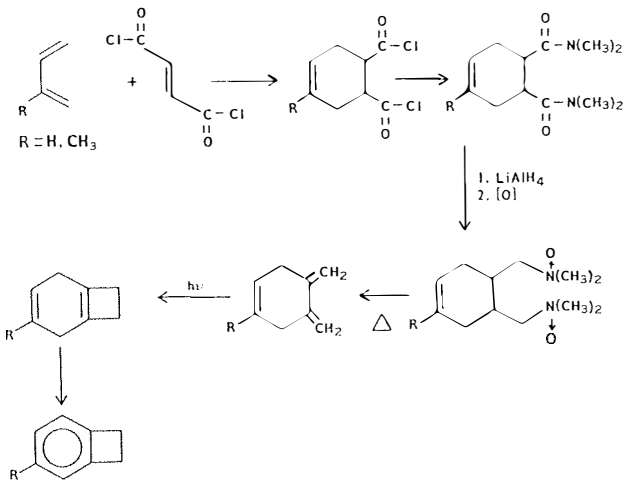


X	% Yield
$-CO_2C_2H_5$	10
$-CN$	61
$-SO_2C_6H_5$	47

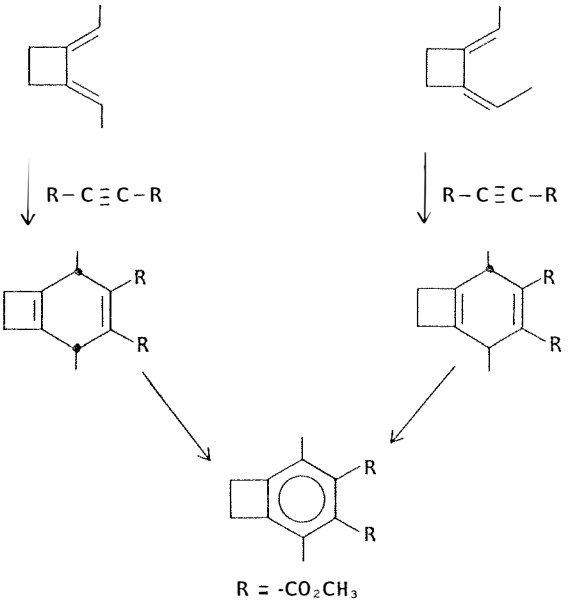
The dehydrogenation of a preformed bicylo[4.2.0]octane has been used to prepare the benzocyclobutene ring system.[20]



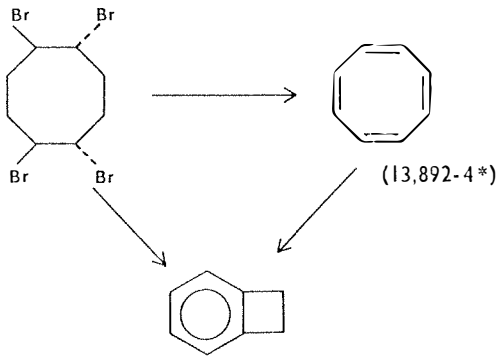
A Diels-Alder reaction to form a substituted cyclohexene ring, amine oxide pyrolysis and then a photochemical cyclization to give the desired bicyclic ring system has also been utilized.



The use of *cis* and *trans* 1,2 divinylcyclobutane in a Diel-Alder reaction with dimethyl acetylenedicarboxylate leads to the same benzocyclobutene derivative upon oxidation of the dihydro ring system.



Treatment of 1,2,5,6-tetrabromocyclo-octane or cyclo-octatetraene with a strong base produces benzocyclobutene.[21]



The availability of the benzocyclobutene ring system through the synthetic methods that have been summarized above will now enable reactions that have been studied on indan, tetralin and larger benzocycloalkanes to be investigated on the four membered ring analog.

A more detailed review of the methods of syntheses and chemistry of benzocyclobutene and its derivatives is in preparation.[22]

° Aldrich Product Number

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Steroidal Saponin Esters Elaborated by Poisonous Marine Echinoderms

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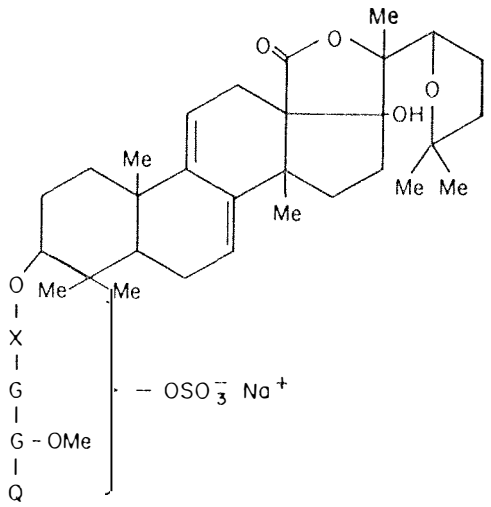
SUMMARY:

Certain members of the marine echinoderm family (e.g. sea cucumbers and starfish) elaborate potent toxins based on a steroid nucleus, a polysaccharide side chain, and a half-esterfied sulfuric acid residue that confers anionic character on the toxin. These agents are surfactants, and produce irreversible destruction of excitability in neuromuscular tissues with a potency dependent on retention of the anionic charge. The sugars in the side chain are principally of standard type (D-glucose, D-xylose, etc.), but also include residues of the terminally-reduced variety (D-quinovose, D-fucose) of monosaccharide. A striking example of toxin specificity in point of attack of excitable tissues by virtue of the polar nature of the collection of sugars on the side chain has been observed.

The past decade has witnessed an expansion of research interest in toxins elaborated by marine plants and animals, as part of a growing dedication to increase in man's understanding and use of sea resources. In particular, marine animal species yielding chemical principles of high biological activity and potential biomedical utility have received continuing attention in laboratories spread across the globe, but it is only of recent date that purified, chemically characterized components of the crude toxin mixtures synthesized by these animals for protective and offensive purposes have been employed in research. Particular success in purification, structure proof and subsequent biological study of toxin components has attended the efforts focussed on the steroidal saponin esters produced by members of the phylum Echinodermata, especially among the poisonous sea cucumbers and starfish, since these compounds are relatively stable substances stemming from their structures as half-esterified sulfuric acid salts. Accordingly, the present review will be devoted to a brief survey of known information on structure and bioactivity of these particular sulfate esters.

Lively interest in the toxic principle elaborated by the Bahamian sea cucumber *Actinopyga agassizi* Selenka followed initial studies[1] on isolation, properties and sugar components of the steroidal glycoside mixture known as Holothurin A. This steroid mixture contains several separable glycosides, each of which yields on acid hydrolysis four monosaccharides (xylose, glucose, 3-0-methylglucose and quinovose), a single molecule of sulfuric acid, and one of a mixture of closely related steroid aglycones. A provisional structure for a major component of Holothurin A, based on the structure deduced for the isolated genin 22,25-oxidoholothurinogenin,[2] contains the four sugars attached in glycosidic array at the 3-position, in the indicated sequence, and a sulfuric acid residue bound as a hemi-ester at some unknown sugar hydroxyl function. The resulting anion, containing structural components that render it compatible with both lipid and polysaccharide moieties in excitable biological membranes, possesses a wide variety of biological activities. Holothurin A is a powerful surfactant, acts as a potent agent in irreversible destruction of excitability in medullated nerve nodes,[3] in the



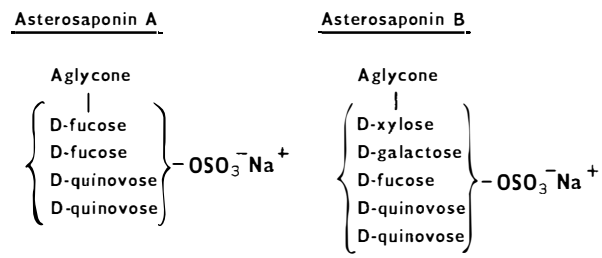
SUGAR	SYMBOL
D-GLUCOSE	G
D-XYLOSE	X
D-QUINOVOSE	Q
3-O-METHYLGLUCOSE	G-OMe

cholinergic neuromuscular junction[4] and in ganglion cells,[5] causes hemolysis of red blood cells,[6] and produces death in intact mammalian species (e.g. mice[4]) by a rapidly effective combination of central and peripheral actions. It is of great interest too that a considerable fraction of the biological potency of Holothurin A is linked to possession of a negative charge center, since removal of the sulfate group by selective hydrolysis causes a sharp diminution[4,5] in its ability to destroy membrane excitability. Further, the properties of the desulfated derivative are such that, despite its lowered intrinsic potency as a toxin on loss of formal negative charge, it is able to protect[4,5] against a considerable fraction of the irreversible actions effected by the anionic Holothurin A on neuromuscular and ganglionic tissues.

The biosynthesis of Holothurin A by poisonous sea cucumbers is not limited to western hemisphere species, since essentially the same mixture of steroidal saponin sulfate esters is elaborated by the echinoderms *H. vagabunda* and *H. lubrica* found in Asian Pacific waters.[7] The same set

of four side chain sugars, including the terminally-reduced monosaccharide D-quinovose, is found in the Asian product. But interestingly, the Asian species also elaborate a second steroidal saponin Holothurin B,[7] which still possesses high activity in blockade of neuromuscular tissues[3] but only contains two sugar residues in its glycosidic chain, D-xylose and D-quinovose.

Findings with regard to variation in the nature and number of sugar residues attached to the steroid nucleus of echinoderm toxins logically lead to general inquiry into the role of the sugars in promoting bioeffectiveness and specificity in action of these saponins. Both Holothurin A and B, for example, possess a mixture of normal sugars and a terminally-reduced sugar (D-quinovose) in their glycosidic chain complement, for reasons which remain obscure. However, some clues as to the functional utility of glycosidically bound normal vs. reduced sugars in directing *specificity* of biological attack in excitable mammalian tissues have emerged recently, starting with elegant work on isolation and characterization of the steroidal saponins from the Japanese starfish *Asterias amurensis* by Hashimoto and Yasumoto.[8,9] These investigators isolated two distinct saponin fractions from the starfish tissue, and purified them respectively to the state of crystalline mixtures designated as Asterosaponin A and Asterosaponin B. Each Asterosaponin fraction furnished the same mixture of aglycones on hydrolysis, and each possessed one sulfate residue per molecule bound as an hemi-ester, but they differed with respect to sugar content. In graphic summary, without commitment on the order of sugar attachments, Asterosaponin A was



found to contain only sugars of the terminally reduced type (fucose and quinovose), whereas Asterosaponin B was characterized by possession of a mixture of normal (xylose, galactose) and reduced (fucose, quinovose) sugars. Biologically, the net result of this difference in sugar distribution is striking.[3] Both substances are quite powerful in destruction of excitability of a cholinergic neuromuscular preparation (rat phrenic nerve-diaphragm), but with clear specificity as to the sector of the junctional tissue preferentially affected; Asterosaponin A is more potent in depression of responses elicited by stimulation of the nerve sector of the preparation than those produced by direct stimulation of muscle, while Asterosaponin B displays an inverted activity sequence. Apparently, the reduced surface polarity of the sugar chain in Asterosaponin A leads to preferential activity on the neural side of a neuromuscular junction, in contrast with behavior in which the mixed polarity of the sugar collection in Asterosaponin B adapts it for preferred action at the level of polar loci on the postsynaptic membrane and underlying muscle fibrils.

Findings such as those with the Asterosaponins point to a very general value of marine steroidal glycosides in probing the mechanisms of functionality in mammalian tissues. Rather subtle changes in the structure of polysaccharide tails, in structure of the steroid nucleus, and in the presence/absence or placement of an anionic charge center may effect profound changes in the mode or position of saponin attack on receptor populations in biological membranes. Control of these structural features, naturally and by alteration, therefore permits high selectivity in the design of molecular probes for basic study of action mechanisms.

Finally, investigational emphasis can also be reversed in the sense of the fascinating game of assessing why and how a given marine creature inserts the particular segments of interaction specificity that he does into his defensive and aggressive chemical weapons. Taking the two Asterosaponins and their depot starfish as a case in point, at least two unanswered questions are immediately apparent: (1) in the teleological processes leading ultimately to the biosynthesis of the saponins, was there deliberate biological intent of ensuring a high probability of paralysis of key junctions in a potential predator (or food item) by a multiplicity of positive blocking actions, guarding against failure of a single pointed attack; and (2) how does the starfish ensure his own internal protection against his stored saponin agents? Seeking solutions to such questions adds additional spice to the important task of using saponins of marine origin for probing the intricacies of excitable tissue function in man and related mammals.

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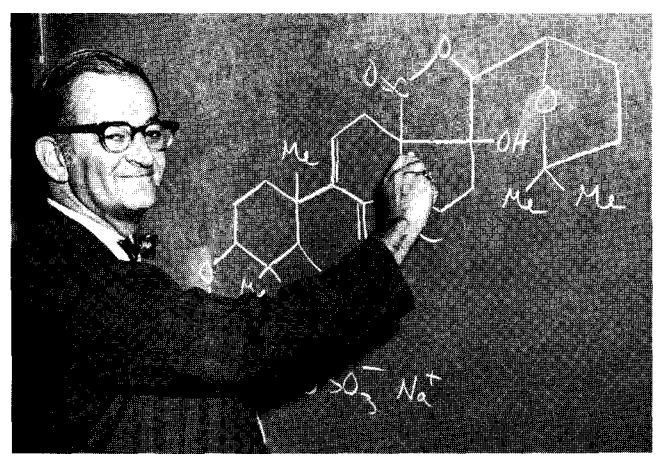

Dr. S. L. Friess

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Aldrichimica acta

Volume 3, Number 3, 1970

Special Liquid Crystal Edition

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ABOUT THE COVER

Our chemist who collects old paintings spent a couple of days worrying about the work reproduced on our cover. He had been visiting with our British associates, Ralph N. Emanuel Ltd. in London, at the time of last summer's biggest old master auction at Christie's, and at the preview two days before the auction had liked this work by Aert de Gelder best of all.

Aert de Gelder was one of Rembrandt's ablest and last students, who carried Rembrandt's tradition well into the 18th century. This painting hung very high at Christie's, and a heavy varnish made viewing even more difficult. Nonetheless, our collector was convinced that this was a genuine and fine Aert de Gelder, painted in the 1670's, a work quite unknown to him, and—as it turned out—unknown even to art historians.

That evening he got a rude shock when he was invited to the home of a friend, one of England's great connoisseurs of old paintings, who told him that this Aert de Gelder was the one painting in the sale that he would really like to buy. His concern was increased when next day a professor of art history at our chemist's Canadian alma mater urged him to buy just that painting for the school's collection—if three men each liked this the best, what chance had one against the scores of great dealers from all over the world? And yet the painting brought less than Christie's estimate and only a small fraction of one percent of the price of an unexciting Rembrandt in that sale. Whether this was due to the poor hanging, the dirty varnish or the fact that the painting was quite unknown and one of the first in the sale—who knows, and our chemist does not care.

To him it is much more than just a genre painting of a wineseller, the title in the auction-catalog. De Gelder liked biblical subjects, and perhaps this depicts Elisha with the widow of the prophet Obadiah (2. Kings *4*) whose jars he filled with oil to allow her to repay her husband's debts.

In any case, de Gelder depicted a warm human relationship—man and woman really care for each other; it is the kind of relationship that we strive for with our customers—individual service to individual human beings. If only we also could perform miracles!

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Liquid Crystals and Science

James L. Fergason, Associate Director, Liquid Crystal Institute, Kent State University

The natural beauty of liquid crystals is often reflected in colors which might dazzle the impressionist's mind. But to the scientist or the engineer they bring to mind endless applications which are possible today or, with improved materials, tomorrow.

Applications of liquid crystals have touched every field of science or engineering. For the basic scientist, they have provided some needed answers for biological systems and for the behavior of matter. They have been used to very accurately determine the structure of the molecules by their use as NMR solvents and to separate geometric isomers using gas liquid chromatography.

The first widely used liquid crystalline system was the cholesteric, which is formed from cholesterol esters. At the present time, it is the most sensitive temperature-measuring device, at room temperature, known to man. Along with the unusual temperature sensitivity, the material is capable of very high resolution in the order of 1,000 lines per inch as well as time constants as short as 10 milliseconds. This would indicate that on a square inch of material, the temperature could be measured 100 times per second at 1 million points. This rather astounding property has been used to build many different types of devices as well as the direct mapping of temperature.

The direct mapping of temperature finds its widest use in biology where we all know an abnormal temperature indicates a malfunction. Everything from infection to malignant growths generate thermal patterns which can be easily measured.

In the accompanying table (page 4) we have listed some cholesterol esters and some of their applications.

Just coming to the fore is the nematic phase which has found its greatest use in the solvation of other molecules. In an ordinary isotropic liquid, the direction of molecules dissolved is random. But in a liquid crystal, the molecules no longer have random directions but are aligned to some extent parallel to the direction of alignment of the liquid crystal. Although they are still free to move, they show a structure which was previously masked by thermal motion. This becomes important in several areas. By aligning a molecule which absorbs UV radiation in a liquid crystal which transmits the radiation, pleichroic absorption can be measured and many of the factors involved in electronic spectra can be further elucidated. In NMR this important property allows the direct interaction of protons in the molecule to be measured, and from these interactions which depend upon their direction with respect to the applied field and to their distance apart, bond angles and bond distances can be obtained. This same property is being used with nematic liquids to modulate light for display purposes. Thus, the property used by the physicist and chemist for measurements is also used by the engineer as a means of displaying information.

The ability of nematic liquids to change the polarization of light is well known. They act as crystals which are birefringent. However, because they are liquids, the direction of birefringence can be very readily controlled, either by an applied electric or magnetic field. In the field of engineering, the electric field effects are being used to generate new types of displays and to control the transmission of mirrors and windows.

The wide use of liquid crystals can only mean an expanding realm of applications. At the present time the nematic and cholesteric are the phases which have applications. Smectic phases, which are even more varied than the nematic, have not been used. This phase is still in the laboratory curiosity stage. However, many of its properties are tantalizing from the standpoint of their unusual optical properties. For instance, liquids which are biaxial, that is they have three independent indices of refraction, exist. Materials with as many as seven phases between isotropic liquid and crystalline solid exist.

In the accompanying figure, the number of possible phases with different properties, both optical and mechanical, are shown. Individual phases which are known have not been used for practical applications. They represent a huge storehouse of natural phenomena which will change our every day existence.

The application of liquid crystals depends on their dynamic changes with very low energies. Thus, they are able to change and control our perception of the environment in a dynamic sense and change our visual perception of our surroundings.

Technology has been concerned with providing more energy per person. With the increased pollution of our world, we need to consider further how do we do things with less energy. Liquid crystals do this. They use very small energies to change their optical properties. It is interesting that liquid crystals were originally considered by Lehmann as a possible source of power when he saw the relationship of biological systems to liquid crystal systems. However, the resulting applications have been a reduction of power.

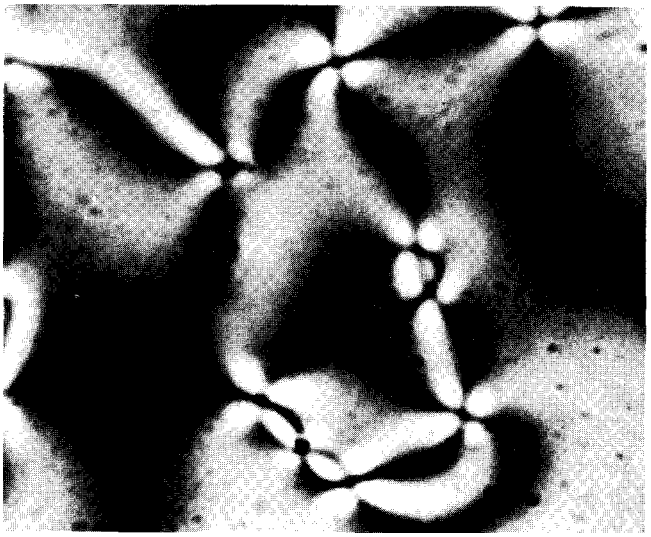
The study of liquid crystalline states represents a field which promises to be as rich as solid state physics. The revolution which was made by the oncoming of the transistor may be small compared to the revolution which is coming from the understanding of the liquid crystalline state.

James L. Fergason

Liquid Crystals and Modern Art

Alfred R. Bader

It seems to me that the most striking difference between modern artists and the old masters lies in the effort of the modern artist to create something radically new. Abstract expressionists, pop artists, op artists—whatever they are called—vie with each other to create works which are visually distinctively new. Beauty, character, lasting impression on the viewer are less important; what counts is that the "art" be new and hence different. And so you can see in



1. Nematic liquid: 4,4'-dioctyloxyazoxybenzene
50x Photomicrograph

our Milwaukee Art Center a blackboard by Edward Reinhardt—the "ultimate" in art: tasteless, odorless, formless, nothing, and another blackboard with a doodle by Cy Twombly, which as a Sunday School teacher I would give no second thought before erasing from the blackboard. My grandparents would have thought us crazy, and I suspect my grandchildren will also.

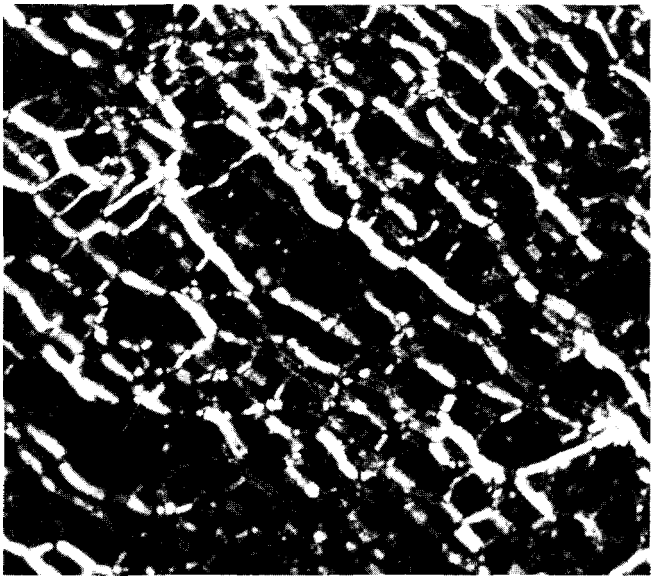
Basically this striving after the radically new is the result of the artists' traumatic experiences caused by the invention of photography. Most 19th century art was painstakingly realistic, and hence most vulnerable to the competition by the photograph. What sweet nothing could a Munich School painter depict that a photograph could not do better? Had the photograph been invented in the 17th century, the answer would have been different: no photograph can match Rembrandt's delineation of a man's character or Jakob Ruisdael's melancholy in landscapes.

What photography has done to modern artists is to separate the men from the boys. The men—artists like Andrew Wyeth and Edward Hopper—have taken up the challenge to compete with photography through mood in realism, and the ablest have been successful. The boys have taken refuge in gimmicks, and Madison Avenue has touted these as the latest in art. One of my favorite stories when I was a boy was of the artist who was introduced to a German court as one of the world's greatest portraitists. But there was one hitch: only people who had never lied would see the true beauty of these works. Naturally the prince and the princess had themselves painted and the entire court came to admire these wonderful works. Until a little boy said to his father: "Daddy—but there is nothing on the canvas." Thus it is with modern art.

Naturally artists have turned to chemistry and physics in their quest for the new. I am not thinking here of improved pigments, media or varnishes, but of the use of science to create new visual experiences. Light and sound are being used in art as they have long been used no less blatantly in advertisements on Coney Island. Optical illusions dazzle you from the walls of museums. Shapes of all kinds made from all sorts of plastics allegedly are new forms of art.

And so, naturally, liquid crystals appear in art. Liquid crystals are substances which, within definite temperature ranges, behave mechanically as liquids of varying viscosities yet exhibit many of the optical properties of crystals. It is quite a common phenomenon; it has been estimated that at least 5 of every thousand compounds are liquid crystals. Optically, liquid crystals scatter light in symmetrical patterns and reflect different colors depending on the angle from which it is viewed.

The first to observe the phenomenon of liquid crystals were the Austrian botanist, Friedrich Reinitzer, working with cholesteryl benzoate, and the German physicist, O. Lehmann, who coined the name "liquid crystal" (flüssige Kristalle), wrote the first book on the subject, and studied particularly the optical properties of liquid crystals. Around 1910, a group of students of Professor Vorländer at the University in Halle an der Saale studied the relationship between chemical structure and liquid crystallinity. Unfortunately several of these Ph.D. theses were not published, and of the most interesting of these, the thesis of M. E. Huth, 1909, is available from Aldrich. In the twenties and thirties some of the most eminent theoreticians, for instance



2. Cholesteric liquid: cholesteryl pelargonate
50x Photomicrograph
Aldrich No. C7880-1

3. *Smectic liquid: many Schiff's bases of terephthaldehyde look like this.*
50x Photomicrograph
Aldrich No. 12229-7

Bragg and de Broglie, studied liquid crystals, but as there then seemed to be no practical applications, the subject became one of interest only to writers of textbooks. In the late fifties however, J. L. Fergason, then at Westinghouse, G. H. Brown at Kent State University and a group of scientists in Russia under I. G. Chistyakov began intensive new studies of liquid crystals because of the hope—which has since materialized—of important practical applications. Just how much work is being done currently is evident from a compilation, available from Aldrich, of articles dealing with liquid crystals; this lists 353 papers published in 1965–69. The practical applications have ranged from optical thermometers to the detection of traces of chemical vapors and medical diagnosis, such as the detection of breast-cancer, and of course to the formation of new visual images in art. The compounds most commonly used in art have been the esters of cholesterol with which we can obtain a great many colors and, intriguingly, temperature sensitivities. A 1:1 mixture of cholesteryl pelargonate and cholesteryl oleyl carbonate, for instance gives a beautiful color play near body temperature. Add just a few percent of cholesteryl chloride, and you broaden the temperature range. Add more of the chloride and you get colors much less temperature sensitive but irridescent—with 20% chloride blue and with 30% red. Aldrich now offers some 38 cholesterol derivations with which an infinite variety of color-plays and temperature sensitivities can be obtained. For the novice, it is important to remember, that all of these cholesterol derivatives are colorless as solids and as liquids, and that they pass through the series of bright colors as they are cooled through their liquid crystal phase. Many pass in color from violet to blue to green to yellow to red to colorless; others change only from red to green; still others from red to green and back to red or from red to green to blue. In every instance, traces of impurities change the color, and this of course is the basis for the analysis of traces of solvents. An 80:20 mixture of cholesteryl pelargonate and cholesteryl chloride, for instance, is green at room temperature; a trace of chloroform changes this to red, a trace of petroleum ether to blue, and this change is reversible. The closest visual analogy that I can think of to describe the appearance of many liquid crystal mixtures is that of the black opal. Beautiful, yes—but is it really a work of art?

In this connection I can do no better than quote from letters of a very able Canadian artist, Jack Wise, whom we had sent some cholesteryl esters: "I wish I could report a great success with my experiments, but alas, body-lipid wouldn't respond to the wish for a permanent ordering. . . . As a total experience, it was invaluable to me that I again attempt to make a technological creation conform to my own aesthetic direction. I don't completely dismiss the possibilities of Liquid-Crystals in Art—but here again, man would become the servo-mechanism of a specialized substance, doing what *its* requirements dictated—function would follow form. I make no value judgment—but am, perhaps, too reactionary in my own aesthetic responses to new media. Certainly McLuhan is right about the "media" becoming the message, and I'm skeptical about a technological aesthetic replacing an iconographic one. I do see an entirely new color-television technology, walls which respond to mood—the whole gamut of environmental trips—still, of prime interest to me is the *form* of the imagery—the bones, as it were, and not the flesh. My chief difficulty was with the bleeding, mesomorphic *aliveness* of the crystals—like trying to fix a rigid pattern using a colony of ants—and I could see that an entirely new approach would have to be used in order to utilize the crystals to advantage; I just haven't the time to radically change my methodology—and the liquid crystals obviously require such a study in depth. . . . I hope you will keep in mind, though, that I have only

4. *Smectic droplet*
50x Photomicrograph

found that liquid-crystals could not be bent to my purpose. I have long been interested in the possibilities of putting "Science" to the service of "Art," and have, alas, too often found that the artist ends up servant of the technology. Of course there is a fine point of debate as to whether the simplest of pigments isn't "technology," the most rudimentary actions in producing them "scientific." I suspect that this debate has more to do with man's psychology than his logic, that the questions will never be answered since they are 'after the fact.'

"And yet, after all my protestations, there remains a tantalizing quality to your liquid-crystals—far more so to me than, say, holography or the more mechanical applications of light. . . . Would it not be interesting to apply some small icon of liquid-crystals to one of the cave-walls of Altamira?"

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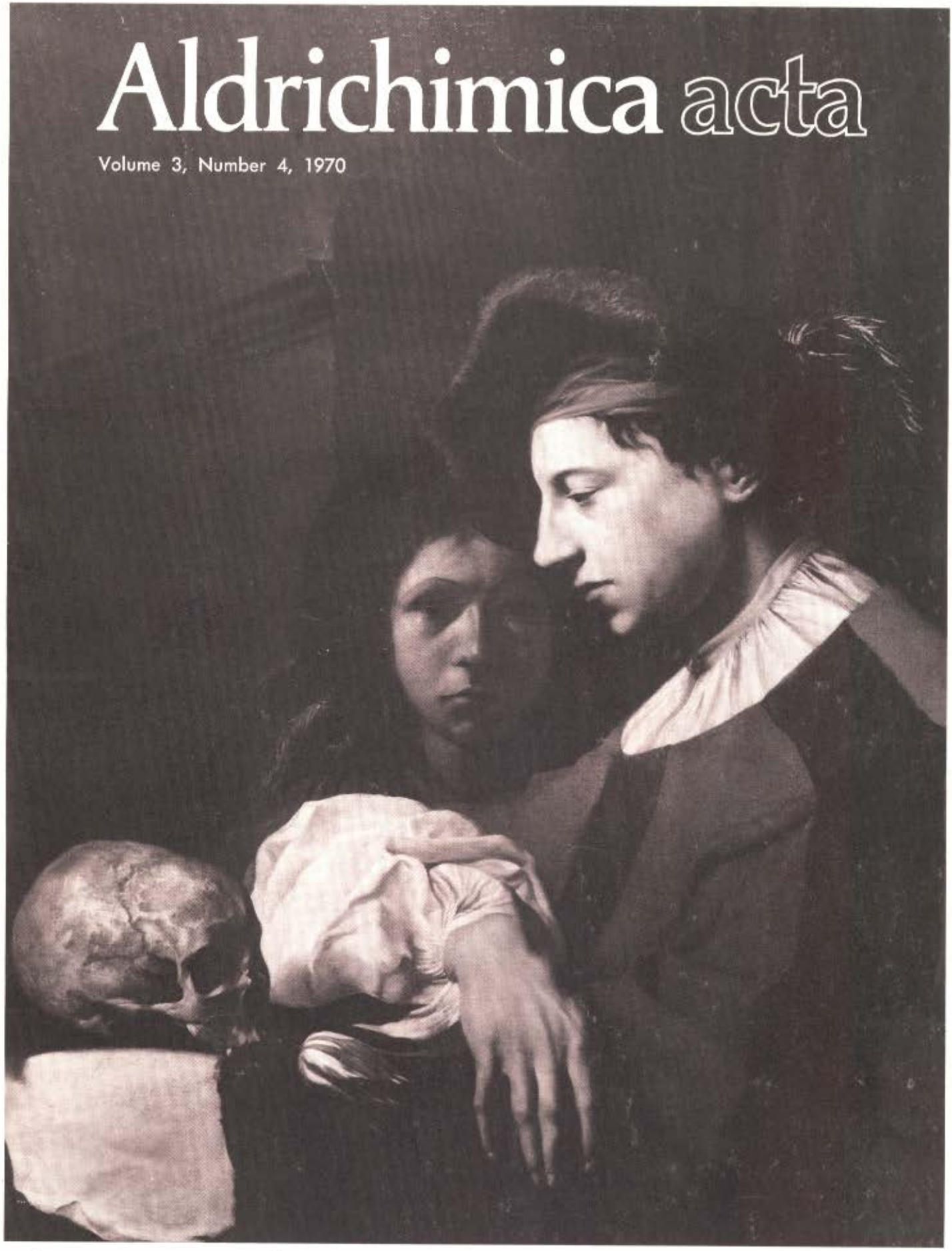

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ABOUT THE COVER

We once asked our chemist-collector what qualities he looked for first, when considering the acquisition of a painting. We had expected him to reply that the painting be by a famous artist and preferably 17th century Dutch, and we were surprised neither to be a prerequisite. Different, well-drawn and in good condition!

Whatever one might think of the painting (oil on canvas, 40 by 31 inches) here reproduced, it is certainly different. At one time it was thought to be Tuscan, though it is probably by a Haarlem artist of the middle of the 17th century—an artist who was certainly not in the mainstream of Dutch art.

Perhaps the melancholy expressions of the two boys suggest some personal tragedy in their lives, or we may see here simply an allegory on the vanities of life, on fleeting time. It has often seemed to us that of many foolish sayings "time is money" is the most mistaken. Time is life, the one commodity that money cannot buy, and this vanitas painting beautifully makes the point.

Time is life, and we at Aldrich are proud to know that we have saved scientists around the world millions of man-hours of work by providing chemicals which—without us—would have to have been made individually and laboriously.

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Batrachotoxin, a Novel Steroidal Alkaloid with Selective Effects on Biomembrane Permeability

John Daly, Chief, Section on Pharmacodynamics, National Institutes of Health, Bethesda, Maryland 20014
Bernhard Witkop, Chief, Laboratory of Chemistry, National Institutes of Health, Bethesda, Maryland 20014

During their evolution, amphibians developed an amazing variety of pharmacologically active compounds, which play a role in defending the frog, toad, newt or salamander, against predators. These defensive principles are remarkable for both their chemical and pharmacological diversity. They include biogenic amines, peptides, proteins, steroids, steroidal alkaloids and a variety of other compounds. Their pharmacological activities encompass cardio-, myo- and neuro-toxins, cholinomimetics, sympathomimetics, vasoconstrictors, hypotensive agents and hallucinogens. Among these compounds are some of the most powerful venoms known. A few examples are give in Fig. 1.

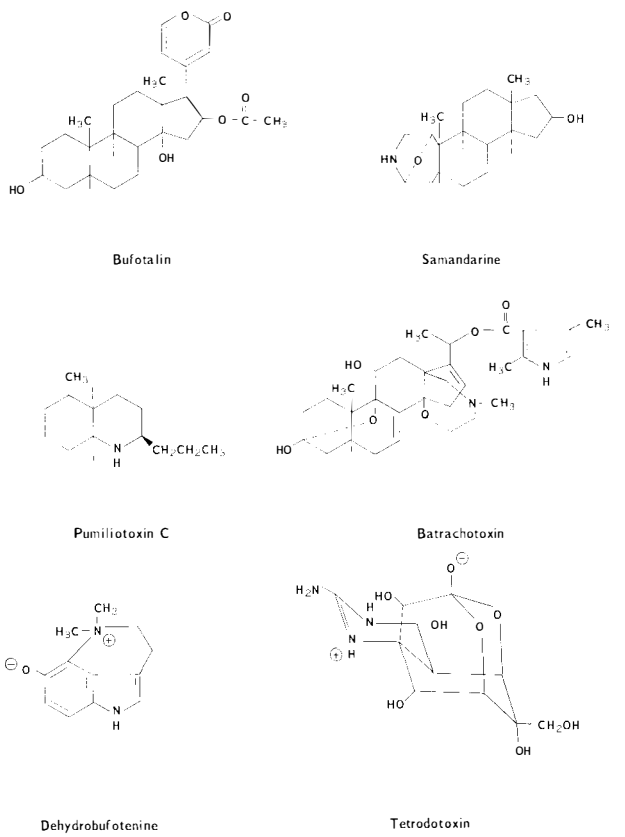

Fig. 1. Pharmacologically Active Substances Isolated from Various Amphibians

Among these venoms, perhaps the most interesting, from both the chemical and pharmacological standpoint, is the steroidal alkaloid, batrachotoxin, which is found in the skin of a small, brightly colored, Colombian frog of the genus *Phyllobates* (Fig. 2). The poisonous character of skin

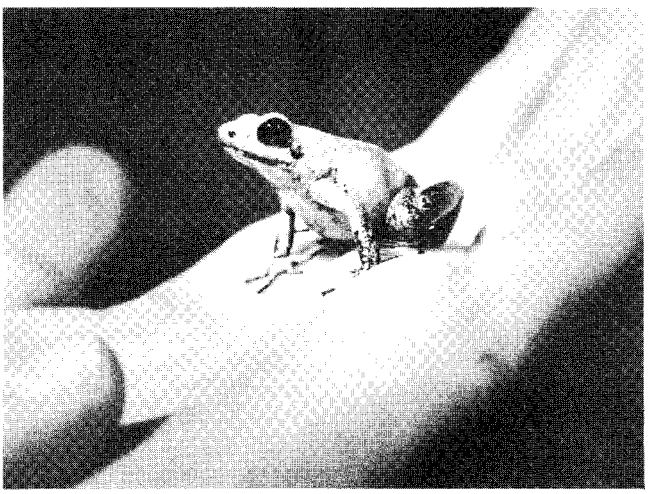

Fig. 2. The Colombian Poison Arrow Frog, *Phyllobates aurotaenia*

secretions of this frog was recognized long ago by the Indians of the Pacific rain forests in Colombia and they developed methods for obtaining the venom and using it on their blowdarts for hunting birds and small game. The use of blowguns and darts poisoned with the milky secretion from this small frog persists even to this day in the upper reaches of the Rio San Juan in the Choco jungle of western Colombia. The first scientific report on this venom appeared in 1871. Subsequently, the gross toxicological effects of the crude extracts have been published, but it remained for our own studies initiated in 1961 to demonstrate that the active ingredient from extracts of this frog was one of the most toxic substances known so far (Table I). Only certain bacterial toxins, such as the one from

Table I Toxic Substances with Their LD_{50} for Subcutaneous Administration in Mice

Substance	LD_{50} $\mu g/kg$
Batrachotoxin	2
Tetrodotoxin	8
Bufotalin	400
Curare	500
Strychnine	500
Sodium Cyanide	10,000

Botulinus, surpass it in toxicity. The structure and mechanism of action of such a potent venom were indeed of great interest.

Investigation of batrachotoxin was handicapped by the paucity of material and by its lability. The skin of an adult frog, approximately 3 cm in length, contains only 80 micrograms of toxic congeners consisting mainly of batrachotoxin, homobatrachotoxin, pseudobatrachotoxin and batrachotoxinin A. The frog which occurs in a rather inaccessible region of Colombia was difficult to obtain in large numbers, but in the course of four expeditions, approximately 7000 frogs were collected. Methods for the isolation and separation of the active principles were developed, which minimized losses resulting from their great lability.

Preliminary investigation indicated that these compounds were weak bases with a pk of approximately 7.5. High resolution mass spectrometry indicated that batrachotoxin and homobatrachotoxin were steroidal alkaloids with the empirical formula $C_{24}H_{33}NO_4$. The much less toxic batrachotoxinin A, on the basis of mass spectral data, was closely related in structure, but contained the additional elements of water in its molecular ion of $C_{24}H_{35}NO_5$. Since the compounds were weakly basic and since the mass spectra indicated only one nitrogen, it was quite surprising when, in the course of microchemical investigation, it was discovered that batrachotoxin and homobatrachotoxin gave a strong positive Ehrlich's test indicative of the presence of a pyrrole moiety. In view of the evidence, the conclusion was inevitable that the basic nitrogen in (homo)batrachotoxin was part of a potential pyrrole ring which converted to a pyrrole under the strongly acid conditions of the Ehrlich's reaction.

A crystalline derivative suitable for X-ray analysis was finally obtained in 1967, when Dr. Tokuyama succeeded in preparing a crystalline *p*-bromobenzoate derivative of batrachotoxinin A, the least toxic of the congeners. X-ray analysis of a tiny crystal of this derivative by the "symbolic addition procedure" of Jerome and Isabella Karle established its structure as the 20-α-*p*-bromobenzoate of batrachotoxinin A (Fig. 3).

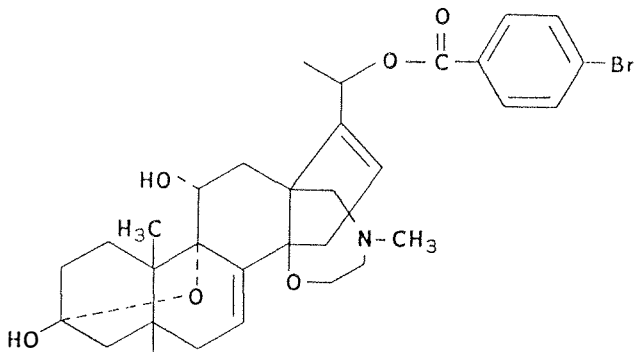

Fig. 3. Batrachotoxinin A 20α-*p*-bromobenzoate

With the structure of one of the bases now known, reexamination and reinterpretation of the physical and spectral properties of batrachotoxin and homobatrachotoxin led to the elucidation of the actual venom. Thus, when the mass and n.m.r. spectra of bactrachotoxinin A were compared with those of (homo) batrachotoxin, the presence of a common steroid moiety in all of these bases became apparent. Batrachotoxin and homobatrachotoxin, however, exhibited ultraviolet spectra with λmax at 234 and 264 mμ, indicative of a conjugated system, infrared absorption bands at 1690 cm^{-1}, typical of a carbonyl group or perhaps a vinyl ether, and, of course, the positive Ehrlich reaction due to a (potential) pyrrole system. In addition, the n.m.r. spectra showed that batrachotoxin contained two additional methyl groups and homobatrachotoxin, an additional methyl and ethyl group not present in the n.m.r. spectrum of batrachotoxinin A. It was impossible to rationalize structures for (homo)batrachotoxin in terms of solely a C_{24} steroid structure closely related to batrachotoxinin A. The inescapable conclusion was that the true molecular ion *had so far escaped detection* in the mass spectra of (homo)batrachotoxin and that these compounds contained the steroid system of batrachotoxinin A plus an additional moiety responsible for the ultraviolet chromophore, the carbonyl band, the pyrrole reactions and the additional methyl and ethyl groups. It was postulated that this moiety consisted of a dimethylpyrrole-carboxylate ester in the case of batrachotoxin and an ethylmethylpyrrole-carboxylate in the case of homobatrachotoxin. The mass spectra of batrachotoxin and homobatrachotoxin *did contain* additional low-mass nitrogen-containing fragments not present in the spectra of batrachotoxinin A. These fragments, for example, $C_8H_{11}NO_2$ in homobatrachotoxin and $C_7H_9NO_2$ in batrachotoxin, could well have arisen from an ethylmethylpyrrole-carboxylic ester or a dimethylpyrrole-carboxylic ester, respectively. It now remained to prove that batrachotoxin and homobatrachotoxin were, indeed, dialkylpyrrole-carboxylates of batrachotoxinin A.

The mass spectrum of batrachotoxin was reexamined and great attention was given to detecting the true molecular ion. As predicted for a dimethylpyrrole-carboxylate of batrachotoxinin A, a very weak molecular ion was found at m/e 538. Batrachotoxin was then hydrolyzed in base. A low yield of a compound identical with batrachotoxinin A was obtained.

The next task was to establish the position of esterification and nature of the dialkylpyrrole-carboxylate moiety. Comparison of the n.m.r. and mass spectra of (homo)-batrachotoxin and batrachotoxinin A and its 20α-*p*-bromobenzoate clearly established that the position of esterification in (homo)batrachotoxin was the 20α-hydroxyl group. Thus, the resonance peak for the 20β-hydrogen in batrachotoxin A appeared at 4.58 δ, while in (homo)batrachotoxin and the 20α-*p*-bromobenzoate of batrachotoxinin A, it is shifted downfield, approximately 1.3 ppm, a change compatible with esterification of the 20α-hydroxyl group.

The ring substitution pattern of the dialkylpyrrole-carboxylate moiety was now investigated. A comparison of ultraviolet spectra of ethylpyrrole carboxylates with those of (homo)batrachotoxin demonstrated the presence of a pyrrole-3-carboxylate in these alkaloids. The position of the two alkyl substituents was determined by n.m.r. spectroscopy using two different solvents and observing the shifts in position of methyl resonance in (homo)batrachotoxin and ethyl-dimethylpyrrole-3-carboxylates. **Batrachotoxin was shown to be batrachotoxinin A 20α-2,4-dimethylpyrrole-3-carboxylate and homobatrachotoxin to be batrachotoxinin A 20α-2-ethyl-4-methyl-pyrrole-3-carboxylate.**

This assignment of structure was confirmed by the partial synthesis of batrachotoxin, *viz*, by acylation of the allylic 20α-hydroxyl of batrachotoxin with the mixed anhydride prepared from 2,4-dimethylpyrrole-3-carboxylic acid and ethyl chloroformate (Fig. 4). The synthetic material was identical in all respects with natural batrachotoxin.

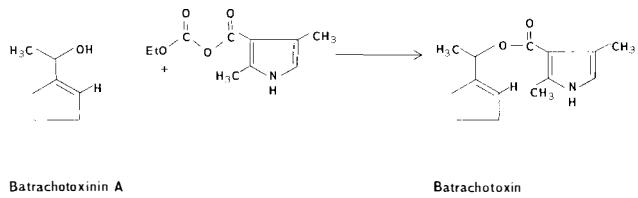

Fig. 4. Partial Synthesis of Batrachotoxin from Batrachotoxinin A

A variety of other synthetic analogs of batrachotoxin were prepared in a similar manner. The effect of different ester moieties on the toxicity of batrachotoxinin A is shown in Table II.

Table II Effect of the Ester Moiety on the Toxicity of Batrachotoxinin A Esters on Subcutaneous Administration in Mice

20-α-Ester Moiety	LD_{50} (μg/kg)
None (batrachotoxinin A)	1000
2,4-Dimethylpyrrole-3-carboxylate (batrachotoxin)	2
2-Ethyl-4-methylpyrrole-3-carboxylate (homobatrachotoxin)	3
2,5-Dimethylpyrrole-3-carboxylate	2.5
4,5-Dimethylpyrrole-3-carboxylate	260
2,4,5-Trimethylpyrrole-3-carboxylate	1
2,4-Dimethyl-5-ethylpyrrole-3-carboxylate	8
2,4-Dimethyl-5-acetylpyrrole-3-carboxylate	250
N,2,4,5-Tetramethylpyrrole-3-carboxylate	> 1000
Pyrrole-2-carboxylate	> 1000

The many unusual structural features in batrachotoxin, such as the 3α,-9α-hemiketal bridge, the 7-membered 14β,18β-heterocyclic ring, the Δ^{16} double bond, and the unique 20β-(2,4-dialkylpyrrole-3-carboxylate) pose many interesting biogenetic questions and, in addition, a major challenge to the synthetic organic chemist.

The pharmacology of batrachotoxin has proven no less interesting than its history and chemistry. When administered subcutaneously to mice, approximately 0.2 μg of batrachotoxin causes partial paralysis of the limbs. This state is soon interrupted by violent convulsions, dyspnea and death within a course of eight minutes. Cardiac effects and neuromuscular blockade both appear to play a role in the toxicology of the venom. The mechanism of action of batrachotoxin in eliciting neuromuscular blockade has now been the subject of elegant investigations by Dr. E. X. Albuquerque and his collaborators, who have used pharmacological, biochemical and ultrastructural techniques. Their results demonstrate that batrachotoxin is an extremely important tool for the study of events in nerve, synapse and muscle.

These events are summarized schematically in Fig. 5 and are currently thought to consist of: 1. Generation of an action potential in nerve; *i.e.*, depolarization of the nerve membrane with *passive* diffusion of sodium ions into the axon (increase in sodium permeability), followed by repolarization due to passive diffusion of potassium ions out of the axon (increase in potassium permeability). The membrane potential with excess sodium ions outside and excess potassium inside the cell is maintained by the action of the sodium pump ($Na\text{-}K^+$ activated ATPase) which transports sodium ions out of, and potassium ions into, the cytoplasm; 2. a calcium-dependent quantal release of acetylcholine as a result of depolarization of the membrane of the presynaptic terminal; 3. interaction of acetylcholine with receptors in the muscle endplate resulting in depolarization of the muscle membrane, generation of a muscle action potential and a concomitant liberation of calcium ions from the sarcoplasmic reticulum into muscle cytoplasm; 4. combination of calcium ions with troponin which thereby permits the interaction of actin and myosin, the basic process of muscle contracture; 5. sequestration of calcium ions, followed by inhibition of actinmyosin interaction by troponin and muscle relaxation.

This complex series of events has been elucidated in large measure through the use of compounds which specifically interact at one of these molecular steps. A few examples are given in Fig. 5.

Batrachotoxin blocks neuromuscular transmission and then evokes a powerful muscle contracture in isolated nerve-muscle preparations. The work of Dr. Albuquerque and collaborators has now demonstrated that batrachotoxin does not affect the action potential-generating system of either nerve or muscle and that the acetylcholine sensitivity

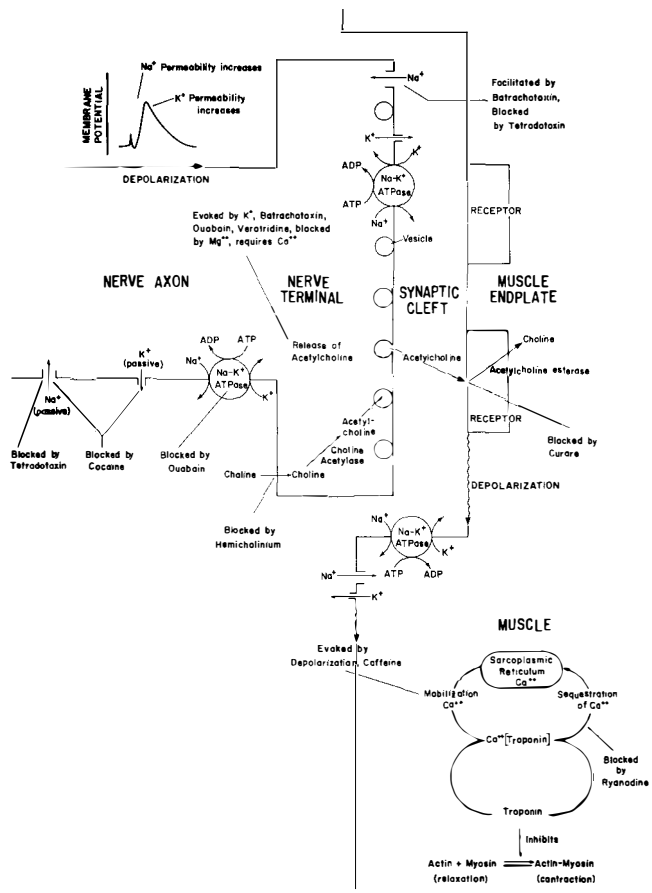

Fig. 5. A Schematic Diagram of Neuromuscular Transmission and Probable Interactions of Various Drugs with This System

of the muscle endplate is unaffected, suggestive of blockade of transmission in the presynaptic terminal. Batrachotoxin does not inhibit Na^+-K^+-ATPase as does ouabain. Instead, it appears to cause a specific increase in the permeability of excitable membranes, especially the presynaptic terminal, to sodium ions. This increase in sodium permeability results in depolarization of the presynaptic terminal and a concomitant calcium-dependent increase in acetylcholine release. The subsequent block in transmitter release appears due to complete depolarization of the nerve terminal. **The effects of batrachotoxin can be prevented by tetrodotoxin** which blocks *passive* diffusion of sodium ions through excitable membranes. The muscle contracture caused by batrachotoxin appears to be due to muscle depolarization elicited by an increase in sodium permeability in the muscle membranes. The extreme toxicity of batrachotoxin has been related to effects on cardiac conduction which result in extra systoles and ventricular fibrillation. These toxicological effects seem to have their molecular origin in the selective action of batrachotoxin on the permeability of the cardiac membrane to sodium. Such an agent with selective effects on membrane permeability should find wide application in studies of nerve, muscle and synapse. Indeed, studies on the interrelation of nervous activity, biogenic amines and cyclic AMP formation in brain slices (Shimizu *et al.*, 1970) have already made use of batrachotoxin, as a potent and selective depolarizing agent, and have confirmed the fact that tetrodotoxin is a specific antagonist.

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3. T. Tokuyama, J. Daly, B. Witkop, I. L. Karle and J. Karle, J. Amer. Chem. Soc., **90,** 1917 (1968).
4. T. Tokuyama, J. Daly and B. Witkop, J. Amer. Chem. Soc., **91,** 3931 (1969).

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2. S. O. Kayaalp, J. E. Warnick and E. X. Albuquerque, Pharmacologist **11,** 287 (1969).
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6. E. X. Albuquerque, J. E. Warnick, J. W. Daly, T. Tokuyama and B. Witkop, Science. In press.
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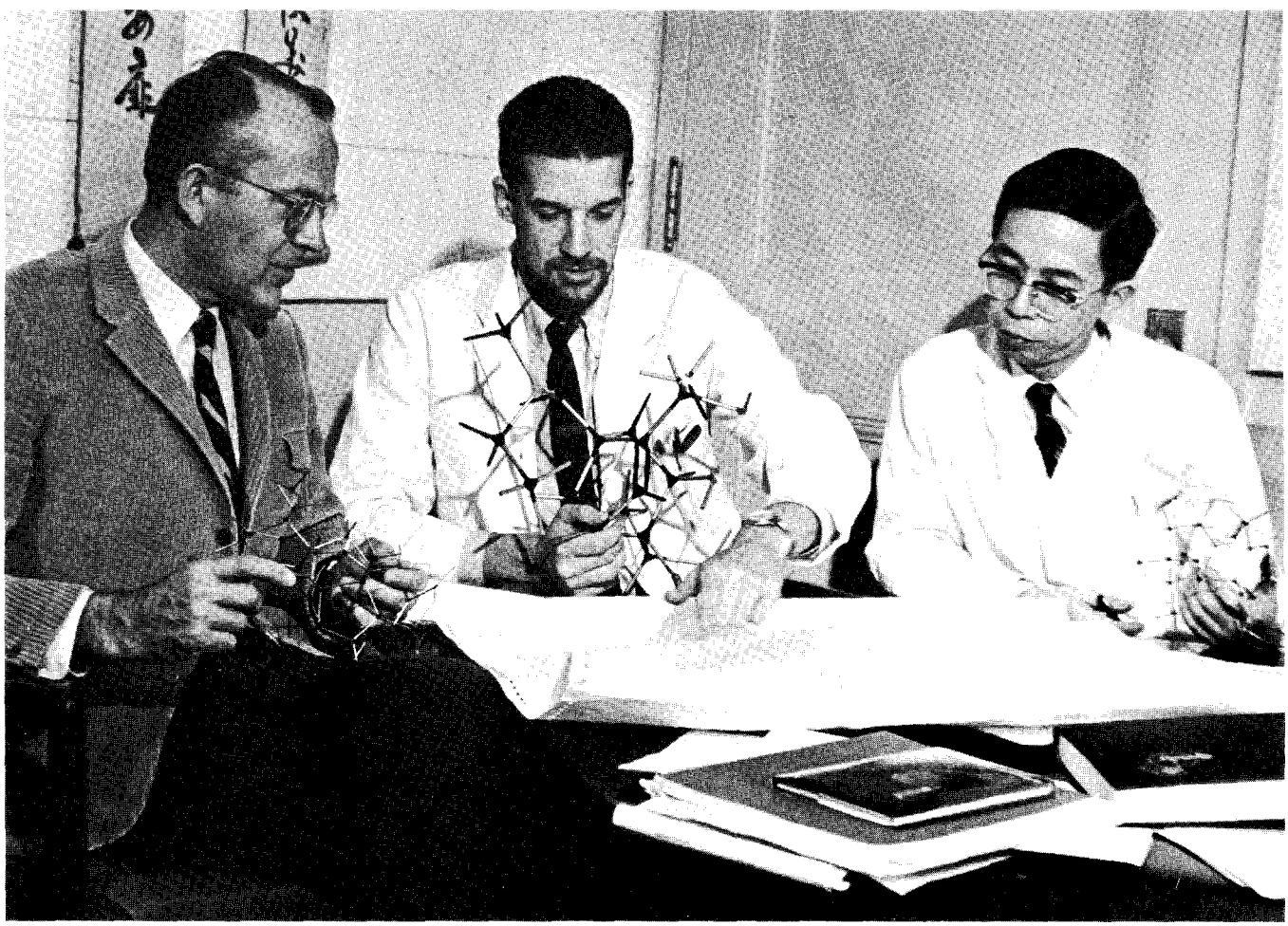
8. Narahashi, T., E. X. Albuquerque and T. Deguchi, Biophysical Society Abstracts 14th Annual Meeting, Baltimore, Maryland, 1970, p. 183 a.
9. J. E. Warnick and E. X. Albuquerque, Fed. Proc. **29,** 715 (1970).



Doctors Witkop, Daly and Tokuyama

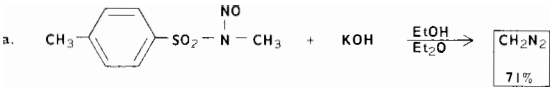
Preparation and Reactions of Diazomethane

Harvey B. Hopps, Research Division, Aldrich Chemical Company, Inc.

Diazomethane is one of the most versatile reagents available to the organic chemist. Not only does it serve as a methylene precursor but it also will produce some interesting heterocyclic systems. The aim of this review is to provide examples of some of its many applications from the synthetic point of view. Both well known examples and reactions described in the recent literature are presented. As diazomethane is both toxic and explosive, all work with it should be carried out behind a safety shield in an efficient hood. Further details of safety in the preparation and handling of diazomethane are included in the discussions of de Boer and Backer[1] and Moore and Reed.[2] Aldrich has always been interested in reagents used to prepare diazomethane. Our first precursor offered for sale in 1951 was N-methyl-N′-nitro-N-nitrosoguanidine (MNNG), one of the reagents listed below.

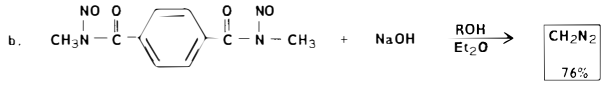
PREPARATION OF DIAZOMETHANE

The reaction of Diazald® (N-methyl-N-nitroso-p-toluenesulfonamide) with base, first discovered by de Boer and Backer,[1,3] is also described on page 732 of the Aldrich Catalog 15[4] (this catalog has the brewer on the cover).

a. 

(D 2800-0*)

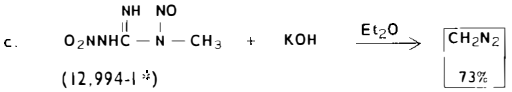
A second useful reagent is N,N′-dimethyl-N,N′-dinitrosoterephthalamide [bis-(N-methyl-N-nitroso)terephthalimide] described by Moore and Reed.[2]
This reagent was first developed by the E. I. du Pont de Nemours and Company under the trade name EXR-101.

b. 

(D 15,558-6*)

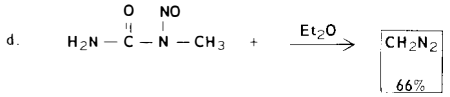
McKay[5] has described the generation of diazomethane from N-methyl-N′-nitro-N-nitrosoguanidine (MNNG). MNNG produces diazomethane with aqueous base and is thus easier to use than Diazald®, which requires alcoholic base.

A drawback is that many people become allergic to MNNG and it has been shown to be a potent mutagenic agent[6] so it should be handled with great care.

c. 

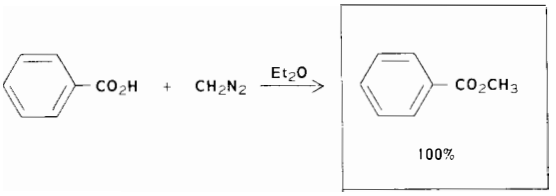
(12,994-1*)

Finally, the use of methylnitrosourea is shown.[7] This reagent was for many years the ragent of choice,[8] but it must be stored in the refrigerator as it decomposes at room temperature.

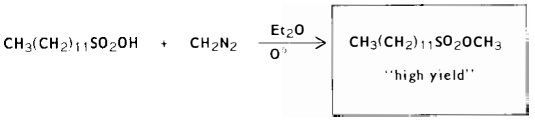
d. 

REACTIONS OF DIAZOMETHANE

(1) *Methyl Esters from Carboxylic Acids*[7]



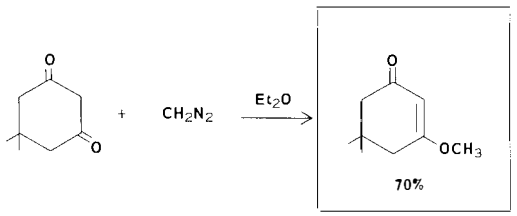
(2) *Methyl Sulfonates from Sulfonic Acids*[9]



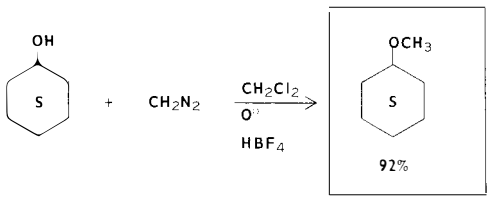
° Aldrich Catalog numbers

° Aldrich Catalog numbers

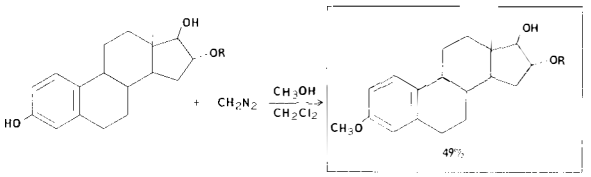
(3) *Enol Ethers from Carbonyl Compounds*[10]



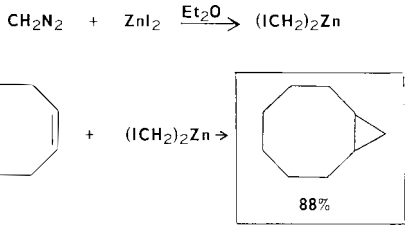
(4) *Methyl Ethers from Alcohols*[11]



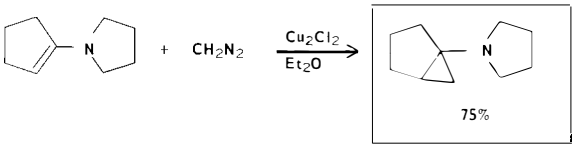
(5) *Methyl Aryl Ethers from Phenols*[12]



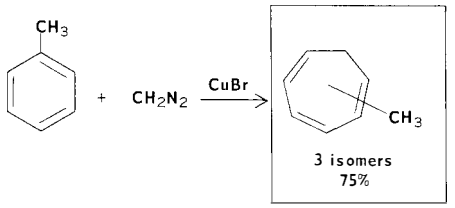
(6) *Cyclopropanes from Olefins*[13]



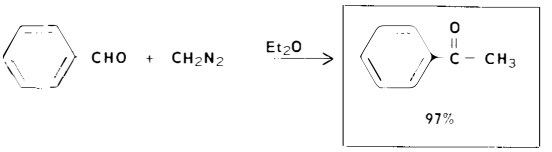
(7) *Cyclopropane Formation from Enamines*[14]



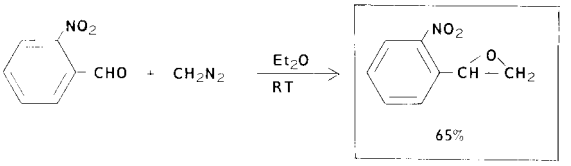
(8) *Cycloheptatrienes from Substituted Benzenes*[15]



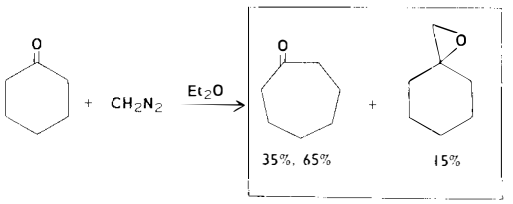
(9) *Ketones from Aldehydes*[16]



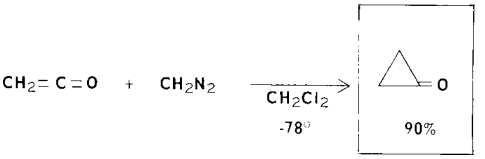
Epoxide formation is a side reaction which in certain cases will represent the major product. The presence or absence of alcohol and nature of substituent groups are thought to influence the reaction as is seen below:[17]



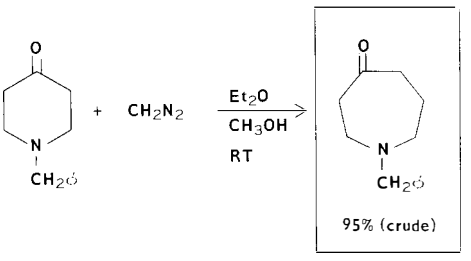
(10) *Ring Expansion of Ketones*[18]



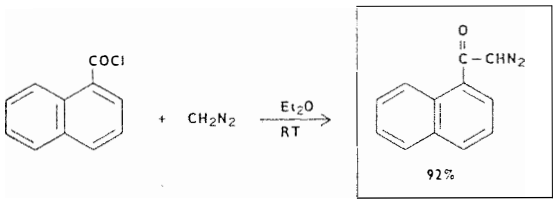
Cyclopropanone Formation[19]



Heterocyclic Ketone Ring Expansion[20]



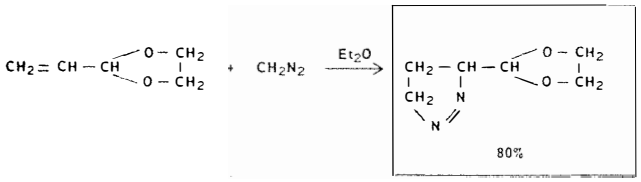
(11) *Diazoketone Formation from Carboxylic Acid Halide*[21]



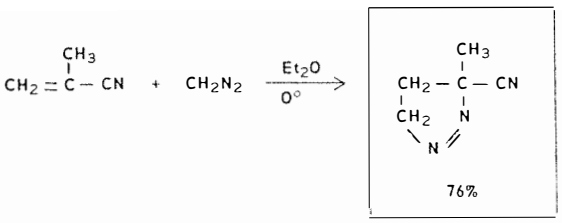
Diazoketones can be converted into acids[21] (Arndt-Eistert Reaction) or α-chloroketones.[22]

(12) *Pyrazoline Formation*

a. Simple Olefins[23]

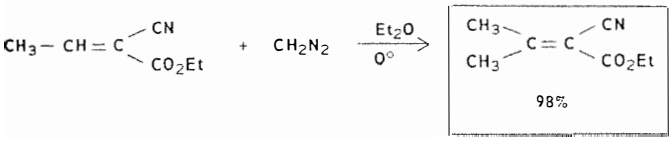


b. Activated Olefins[24]



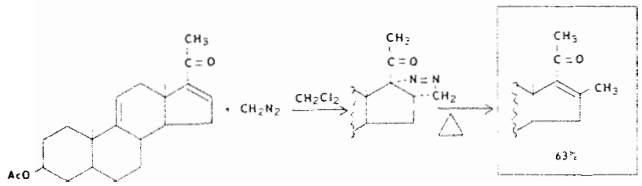
These pyrazolines produce cyclopropanes upon pyrolysis. The following olefin produced no pyrazoline.[25]

c.

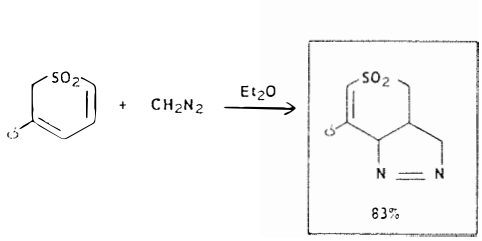


Another divergence is the pyrazoline decomposing to produce a methyl olefin rather than a cyclopropane.[26]

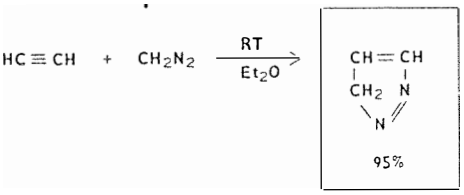
d.



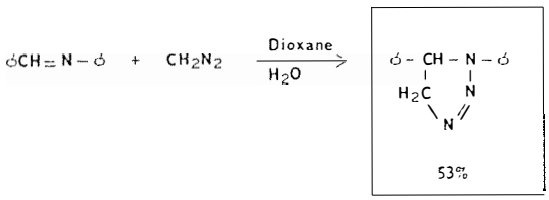
Finally, an example of pyrazoline formation accompanied by rearrangement has been reported.[27]



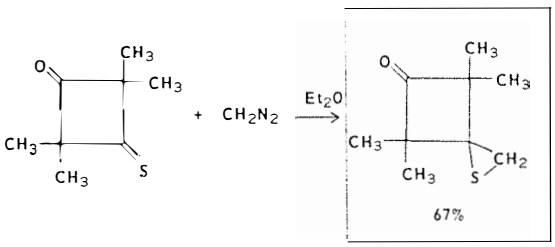
(13) *Pyrazoles from Acetylenes*[28]



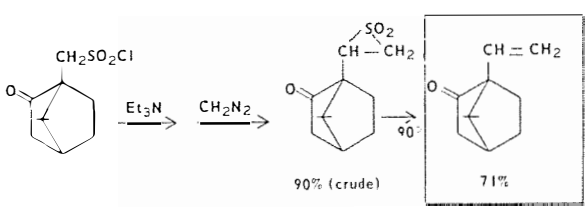
(14) *Triazolines from Schiff's Bases*[29]



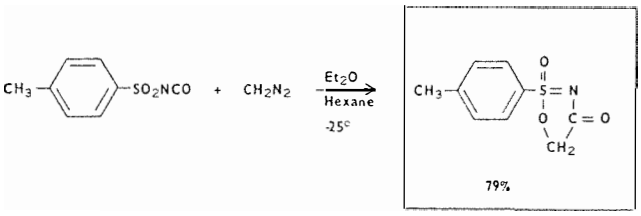
(15) *Thiirane Ring Formation*[30]



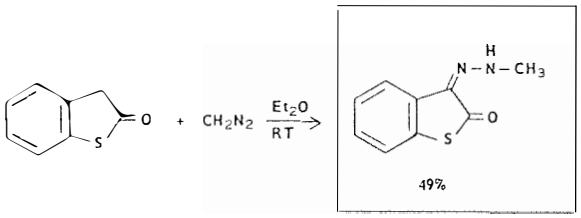
(16) *Olefin Formation*[31]



(17) *Reaction with Sulfonylisocyanates*[32]



(18) *Methylhydrazine Formation*[33]



In conclusion the relative reactivity of functional groups toward diazomethane has been studied by Kosak[34] who found the order

$$-CO_2H > -COBr > -COCl > -OH > -COCH_3$$

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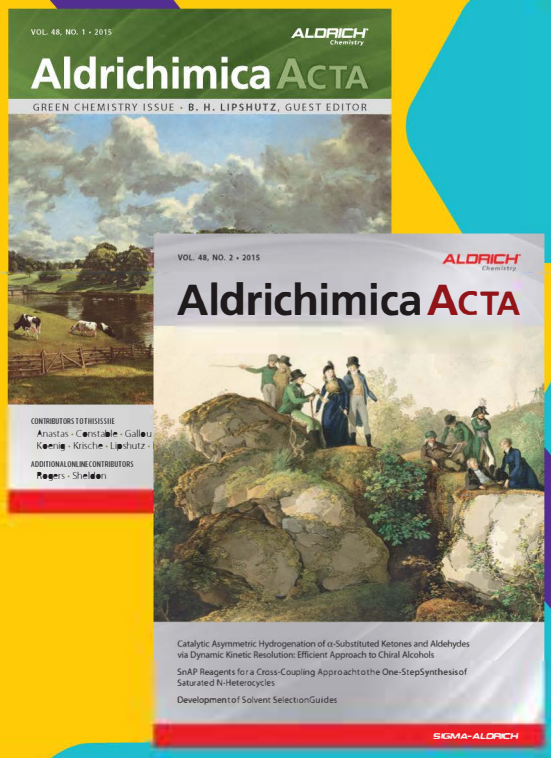

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