2-(2′-chlorophenyl)quinolinium iodide in 50 ml. of hot 50% ethyl alcohol was added to a solution of 3.4 g. (0.01 mole) of silver *d*-camphorsulfonate dissolved in 20 ml. of 50% ethyl alcohol. The hot solution was filtered to remove the silver iodide and the filtrate was evaporated to dryness. The residue was dissolved in 50 ml. of chloroform, 200 ml. of absolute ether was added, and the solution was allowed to stand overnight in a refrigerator. The white solid (2.9 g.) melted at 188–190°. After recrystallization from absolute ether-chloroform and from acetone, the white granular solid melted at 190–191°.

Anal. Calcd. for $C_{27}H_{30}ClNO_4S$: C, 64.84; H, 6.05; S, 6.41; Cl, 7.09. Found: C, 64.39; H, 5.95; S, 6.37; Cl, 7.08.

All of the fractions in recrystallization of this substance gave the same optically inactive iodide when the aqueous solution of the *d*-camphorsulfonate salt was treated with potassium iodide. Also prepared by the same method were the *N*,3-dimethyl-2-(2′-chlorophenyl)quinolium *d*-α-bromo-π-camphorsulfonate, $[\alpha]_D^{28} = +47.3°$, and *N*,3-dimethyl-2-[2′-bromophenyl]quinolinium *d*-α-bromo-π-camphorsulfonate, $[\alpha]_D^{28} = +45.7°$, but it could not be demonstrated that either of these yielded diastereomers and no optical activity was demonstrated when they were reconverted to the iodides.

Ethyl o-bromobenzoylacetate (b.p. 116° at 0.4 mm.) was prepared from *o*-bromobenzoyl chloride and ethyl acetoacetate in a 41% yield using the method described for ethyl *p*-bromobenzoylacetate.[29] The 2-(*o*-bromophenyl)quinolines prepared from it are summarized at the bottom of Table III.

BLOOMINGTON, IND.

(29) C. E. Kaslow and S. J. Nix, *Proc. Indiana Acad. Science*, **61**, 121 (1952).

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

9-Vinylacridine: Preparation and Some Reactions of It and Related Substances of Possible Application in the Synthesis of Acridine Amino Alcohols

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Dehydrobromination of 9-α-bromoethylacridine gives 9-vinylacridine (III). The structure is confirmed by reduction of 9-ethylacridane. 9-α-Bromoethylacridine and 9-β-bromoethylacridine as well as III react with piperidine to give 9-β-piperidinoethylacridine.

Some time ago we reported[1] the preparation of acridine amino alcohols of type I. We also wished to prepare II and IIa, but the effort failed because we were unable to prepare the 9-metalated acridine derivatives necessary to react with the appropriate amino aldehydes.[2] The reverse procedure (in which an amino organometallic compound reacts with acridine-9-aldehyde [V]) cannot be applied here as one- and two- carbon amino organometallic compounds cannot be prepared.[3]

There are other approaches to this synthetic problem, however, and it is the purpose of this paper to present a partial investigation of one of them, namely, the route employing 9-vinylacridine (III). The results presented here are incomplete. We have, however, discontinued this work some time ago, and, as there is no likelihood of its being resumed, we would like to present the results at this time.

In 1936, O. Eisleb reported[4] a number of acridine derivatives which might lead to the preparation of II. Acridine-9-carboxyaldehyde (V) was condensed with nitromethane to yield XIV. The latter could not be reduced to the desired amino alcohol. He also prepared 9-acetylacridine (XV), which was subsequently converted to both XVI and XVII. He was unable to convert either of these to the desired amino alcohol.

In 1940, Braz and Gortinskaya[5] reported the conversion of acridine-9-carboxylic acid to XVI *via* the diazo ketone. XVI was mentioned as an intermediate for the synthesis of possible antimalarial pharmaceuticals, but as none of its reactions were described, it is reasonable to assume that these workers encountered the same difficulty as did Eisleb. As Eisleb did not characterize XVI, it is not possible to compare his substance with that of the Russian scientists.

Subsequently, Braz and Kore[6] studied the reaction of XVI with piperidine and with diethyl-

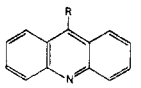
(1) T. D. Perrine and L. J. Sargent, *J. Org. Chem.*, **14**, 533 (1949).

(2) T. D. Perrine, *J. Org. Chem.*, **18**, 1356 (1953).

(3) Wittig and Wetterling (*Annalen*, **557**, 193–201 (1947)) report that ylides such as $(CH_3)_3N^+$-CH_2: behave like organometallic compounds and add to carbonyl compounds. We have not investigated the application of ylides to this problem. The writer has also been informed (personal communication from Dr. E. M. Fry of this laboratory) that diethylaminomethyl methyl ether reacts with lithium metal to yield 1,2-bisdiethylaminoethane. This is a coupling product of the expected diethylaminomethyllithium, reminiscent of that encountered in the reaction of lithium with benzyl halides. Thus the dialkylaminomethyl lithium compound probably may have a transitory existence and might be trapped.

(4) O. Eisleb, *Medizin und Chemie*, Band III, Bayer, Leverkusen a.Rh., 1936, p. 41.

(5) G I. Braz and T. V. Gortinskaya, *J. Gen. Chem. (USSR)*, **10**, 1751 (1940); *Chem. Abstr.*, **35**, 4025[8].



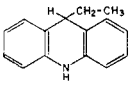
I, R = -CH(OH)-CH$_2$-CH$_2$-CH$_2$-NBu$_2$ II, R = -CH(OH)-CH$_2$-CH$_2$-NBu$_2$ IIa, R = -CH(OH)-CH$_2$-NBu$_2$

III, R = -CH=CH$_2$ IV, R = -CH$_3$ V, R = -CHO VI, R = -CH(OH)-CH$_3$

VII, R = -CH$_2$-CH$_2$OH VIII, R = -CH(Br)-CH$_3$ IX, R = -CH$_2$-CH$_2$X X, R = -CH(Br)-CH$_2$Br

XI, R = -CH(CH$_3$)-N(CH$_3$)-CH$_2$CH$_2$OH XII, R = -CH$_2$-CH$_2$NC$_5$H$_{10}$ XIII, R = -CH$_2$-CH$_2$-N(CH$_3$)-CH$_2$-CH$_2$OH

XIV, R = -CH(OH)-CH$_2$NO$_2$ XV, R = -C(=O)-CH$_3$ XVI, R = -C(=O)-CH$_2$Br XVII, R = -C(=O)-CH$_2$N=O

XVIII 

amine. No amino ketone was isolated, but they were able to recover acridone and XV, along with a large amount of amine hydrobromide. Speculations upon possible mechanisms for these reactions leads one to the conclusion that the presence of the 9-α-keto group is perhaps the feature of XVI, which is responsible for these untoward results. Unfortunately, the facile reduction of acridine itself discourages one from attempting to transform XVI into the corresponding carbinol, as has been done[7] with other α-halo ketones.

One very attractive synthesis of amino alcohols consists of the addition of secondary amines to epoxides. As the latter compounds may be prepared by the epoxidation of vinyl compounds, we decided to investigate the preparation and reactions of 9-vinylacridine (III). Perhaps the most logical approaches to III involve the dehydration of 9-α- (and β)-ethanols (VI and VII), and dehydrohalogenation of the derived 9-α- and β-haloethylacridines (VIII and IX). The first and third of these materials appeared to be the most attractive. All four were prepared by the methods described by Eisleb.

When VIII was treated rather gently with *t*-butanolic potassium hydroxide, we obtained pale yellow parallelograms of 9-vinylacridine (III) which melted at 85–87°. Hydrogenation of III yielded a tetrahydroderivative identical with the 9-ethylacridane (XVIII) obtained by an entirely unrelated sequence of reactions. Moreover, an addition reaction with piperidine, which will be discussed later in this paper, lends strong confirmatory evidence for the proposed structure. A quinuclidine-like rather than a vinyl configuration seems unlikely.

9-Vinylacridine resists ozonization, adds bromine to give the dibromide (X), and appears to add the elements of hydrogen chloride when treated with hypochlorous and hydrochloric acid. As would be expected of a compound of this structure, III behaves as an active vinyl monomer, and polymerizes readily with the production of resinous material, either on standing or when the free base is regenerated from its salts. An acetone solution of the perchlorate similarly undergoes polymerization. While considerable purification may be effected by sublimation and crystallization from petroleum ether, it is difficult to obtain III in a state of analytical purity. However, a sample of the base which had been treated with *t*-butyl hypochlorite followed by dibutylamine (in an abortive attempt to prepare the chlorhydrin and the amino alcohol), yielded III analytically pure, melting at 82–85°. Of the salts, the perchlorate is a suitable derivative, melting at 221–222° dec., while with picric acid one obtains (presumably) the picrate, which decomposes at 188°.

Of the remaining three methods proposed above for the synthesis of III, the dehydration of VII was not investigated at all, and the dehydrohalogenation of IX (x = chlorine) only in one experiment. The dehydration of VI led to a material of undetermined composition which showed a different melting point from that of III, although its analyses and salts suggest a similar or identical composition.

As alluded to above, 9-vinylacridine with piperidine yielded an adduct which subsequently proved to be XII, identical with the Mannich product obtained by Monti[8] from 9-methylacridine (IV), formaldehyde and piperidine hydrochloride. XII was also obtained by treatment of *either* VIII or IX[3] with piperidine. The reaction no doubt proceeds *via* III as an intermediate. Eisleb prepared a product which he formulated as XI by treating methylethanolamine with VIII. In the light of the present work, the true formulation of this product probably corresponds to XIII.

EXPERIMENTAL[9]

9-Methylacridine (IV) *and acridine-9-aldehyde* (V) were prepared as described previously.[1]

9-α-Hydroxyethylacridine (VI) was prepared by the action of methyllithium on V; m.p. 178–180°. Eisleb[4] reports m.p. 178–180° for this compound.

9-β-Hydroxyethylacridine (VII) was obtained by the action of formaldehyde on IV according to Eisleb.[4] When crystallized from benzene, it crystallized as white warts at temperatures above 40° and as yellow needles below this temperature. Both forms melt at 154° and are interconvertible. Eisleb gives the m.p. 154°.

9-α- (and β-) Bromoethylacridines (VIII and IX) were prepared by the method of Eisleb.[4] As might be expected, these compounds could not be obtained in a state of analytical purity. The β-bromoethylacridine hydrobromide ap-

(6) G. I. Braz and S. A. Kore, *J. Gen. Chem. (USSR)*, **23**, 909–913 (1953); *Chem. Abstr.*, **48**, 3979[d].

(7) P. G. Stevens, O. C. W. Allenby, and A. S. Dubois, *J. Am. Chem. Soc.*, **62**, 1424 (1940).

(8) L. Monti, *Gazz. Chim. Ital.*, **63**, 724 (1933); *Chem. Abstr.*, **28**, 2357[3].

(9) All melting points are corrected.

parently list a little hydrogen bromide when recrystallized from water.

Anal. Calcd. for $C_{15}H_{13}NBr_2$, m.w. 367.09; C, 49.07; H, 3.57. Found: C, 49.35, 49.60; H, 3.97, 3.90.

9-Vinylacridine (III). Warming 1 g. of VIII hydrobromide for 0.5 hr. on the steam bath with 25 ml. of a saturated solution of potassium hydroxide in *t*-butyl alcohol, and partitioning the cooled reaction mixture between water and ether gave III in the ether layer. The product was purified by sublimation and crystallization from petroleum ether (b.p. 30–60°), m.p. 85–87°, yield, 0.5 g. This material was not directly analyzed. However, material which was recovered from an attempted reaction with *t*-butyl hypochlorite followed by dibutylamine melted at 82–85°.

Anal. Calcd. for $C_{15}H_{11}N$, m.w. 205.25: C, 87.77; H, 5.40. Found: C, 87.53; H, 5.48.

The III perchlorate, quite insoluble in water or alcohol, may be crystallized from acetone by adding petroleum ether (b.p. 30–60°), m.p. 221–222° (rapid heating, darkens at 215°).

Anal. Calcd. for $C_{15}H_{12}NClO_4$, m.w. 305.72: C, 59.20; H, 3.96. Found: C, 59.07; H, 3.71.

Acetone solutions of this salt decompose on standing with the deposition of polymer but the base may be obtained quite pure by liberation from fresh solutions of the perchlorate.

Treatment of III with twice the theoretical amount of 1*M* bromine in acetic acid, followed by passing in hydrogen chloride, results in the immediate formation of a yellow crystalline precipitate of 9-α,β-dibromoethylacridine (X), m.p. 187–189°, (gassing, heated rapidly) which may be recrystallized from 75% acetone: 25% water, or from hydrochloric acid. The compound was vacuum dried 4 hr. at 76° prior to analysis.

Anal. Calcd. for $C_{15}H_{12}NBr_2Cl$, m.w. 401.55: C, 44.86; H, 3.01. Found: C, 45.10; H, 2.74.

If the drying were omitted the *sesquihydrate* was obtained.

Anal. Calcd. for $C_{15}H_{12}NBr_2Cl.1.5H_2O$: C, 42.03; H, 3.53. Found: C, 42.01; H, 3.74.

III promptly decolorizes solutions of potassium permanganate and bromine. It appears to resist ozonization, as a large amount of starting material may be recovered and aldehyde tests on the reaction mixture are negative. With picric acid, a *substance* is obtained which decomposes at 188–190° without melting. III appears to polymerize slowly when it is allowed to stand. A sample, m.p. 82–83°, after standing 4.5 days exposed to air melted at 83–86° with sintering at 81°. Treatment of III with water in the presence of *t*-butyl alcohol and base yields a material, m.p. 153–162°, which gives a strong melting point depression when mixed with VII.

After treatment of 1 mmole of III with 15 ml. of 0.14*N* monoperphthalic acid in ether, and the addition of 30 ml. of chloroform, the mixture was allowed to stand for 2 days; it yielded reddish brown crystals (from ether), m.p. 173–174°.

Anal. Calcd. for $C_{15}H_{13}ON$, m.w. 223.26: C, 80.69; H, 5.87. Found: C, 80.42, 80.56; H, 5.46, 5.49.

Treatment of the III from 1.0 g. of VIII hydrobromide with 5.0 ml. of 0.543*N* hypochlorous acid plus 2.0 ml. of hydrochloric acid for 45 min., yielded a complex mixture from which we isolated a base which was extracted from water by ether, m.p. 125° (from ether). This is perhaps a *chloroethylacridine.*

Anal. Calcd. for $C_{15}H_{12}NCl$, m.w. 241.72: C, 74.53; H, 5.00. Found: C, 74.64; H, 4.68.

Dehydration of VI was effected by heating with "naturcupfer C" copper bronze in a sublimation apparatus until an oil refluxed, then applying vacuum to sublime the product, which was purified as the *sulfate,* which darkens but does not melt by 270° (from ethanol or ethanol-ether).

Anal. Calcd. for $C_{15}H_{13}NSO_4$, m.w. 303.32: C, 59.39; H, 4.32. Found: C, 59.64; H, 4.37.

The *base* was obtained from the sulfate along with a certain amount of polymer, and was purified by sublimation and crystallized from petroleum ether (b.p. 30–60°); m.p. 108.2–109.4°. It was perhaps not analytically pure.[10]

Anal. Calcd. for $C_{15}H_{11}N$, m.w. 205.25: C, 87.77; H, 5.40. Found: C, 87.34, 87.21; H, 5.37, 5.11.

The material turns brown on standing. Treatment of the base with picric acid yields a substance which may be a *picrate hemihydrate,* m.p. 185–187° (from aqueous ethanol).

Anal. Calcd. for $C_{21}H_{14}N_4O_7 + 0.5H_2O$, m.w. 443.36: C, 56.89; H, 3.41. Found: C, 57.06; H, 3.51.

This base (from VI) is unsaturated to potassium permanganate. Attempted ozonization yielded a black tar which got hot on exposure to air. Considerable starting material, m.p. 108.3–109.1 was recovered, and aldehyde tests were negative. Attempted oxidation with chromic anhydride in glacial acetic acid led only to an extremely insoluble chromate salt, from which starting material could be recovered, m.p. 108°.

Preparation of 9-ethylacridane (XVIII). (*a*) *By hydrogenation of* III. A hydrogenation reaction of 1.0 g. of III (m.p. 87.5–88.5°) in 25 ml. of ethanol with 115 mg. of platinum oxide catalyst absorbed 275 ml. of hydrogen in 50 min. This is approximately the theoretical amount for two double bonds. The product, XVIII, was crystallized from petroleum ether (b.p. 30–60°) as beautiful white prisms, m.p. 112°.

Anal. Calcd. for $C_{15}H_{15}N$, m.w. 209.28: C, 86.08; H, 7.23. Found: C, 85.86; H, 7.24.

(*b*) *From diphenylamine and propionic anhydride.* Refluxing 50 g. of diphenylamine, 36 g. of propionic anhydride, and 35 g. of fused zinc chloride for 4 hr. led to 9-ethylacridine, m.p. 106–109°. Hydrogenation of the latter with platinum oxide catalyst in ethanol produced XVIII, m.p. 110–111.5°, undepressed upon admixture of material from (*a*).

Hydrogenation of VII (0.4 g.) with 40 mg. of platinum oxide catalyst in ethanol solution yielded a mixture of yellow prisms, m.p. 160–164°, and white prisms, m.p. 132.5–134°. The latter had the correct analysis for *9-β-hydroxyethylacridane.*

Anal. Calcd. for $C_{15}H_{15}ON$, m.w. 225.28: C, 79.97; H, 6.71. Found: C, 79.80; H, 6.81.

9-β-Chloroethylacridine, m.p. 112° was obtained when 1.4 g. of VII was let stand with a mixture of 0.5 ml. of thionyl chloride and 20 ml. of chloroform, then refluxed 1 hr., and the base liberated. As the base is heated, it fuses, then resolidifies to a yellow solid which melts at 228°.

Anal. Calcd. for $C_{15}H_{12}NCl$, m.w. 241.72: C, 74.55; H, 5.00. Found: C, 75.22; H, 5.05.

The base decomposed on standing. Treatment of the base with *t*-butanolic potassium hydroxide, according to the directions given for the preparation of III, yielded a substance, m.p. 75–80°, which is probably crude III.

9-β-Piperidinoethylacridine (XII). (*a*) *By addition of piperidine to* III. Freshly prepared III was heated overnight on the steam bath with excess piperidine. The excess piperidine was removed, leaving a brown oil which crystallized very readily upon adding acetone to pale yellow crystals, m.p. 134–136°. Repeated crystallization from acetone raised the m.p. to 137–138°.

Anal. Calcd. for $C_{20}H_{22}N$, m.w. 290.40: C, 82.71; H, 7.64. Found: C, 82.37, 82.36; H, 7.66, 7.66.

(*b*) *From* IV, *formaldehyde and piperidine.* Piperidinemethylol was prepared from 9.9 ml. of piperidine and 8.4 ml. of 36% formaldehyde, and diluted to a volume of 30 ml. with methanol. Three milliliters of this solution (0.01 mole) was added dropwise to a refluxing solution of 1.9 g. of IV in methanol. After a further 15 min. of refluxing the mixture was concentrated to dryness, washed with water, and the yellow XI crystallized from acetone, m.p. 135–136°. Monti[8] did not report the melting point of this material, but Eisleb[4] gives the value 137.5°. The hydrochloride melted at 171–173°. Monti reported the value as 169°.

(10) Acridine melts at 110° and the calculated analytical values are C, 87.12; H, 5.06.

(*c*) *From 9-α-bromoethylacridine* (VIII). Warming VIII hydrobromide on the steam bath with excess piperidine and washing the reaction mixture yielded the insoluble XI, m.p. 134–135°.

(*d*) *From 9-β-chloroethylacridine.* Following the procedure used by Eisleb with IX, we obtained pale yellow crystals of XI from acetone, m.p. 133°.

(*e*) *From 9-β-bromoethylacridine* (IX). Eisleb's procedure was repeated. The resultant XI melted at 135–136°.

By repeated crystallization, all of these XI specimens can be brought to melting point 135–137° and upon admixture with material from (*a*) no melting point depression is observed. With picric acid we obtained a material which sintered at 180° and melted at 218–220°. Monti reported the dipicrate to melt at 138–140°.

Acknowledgment. Microanalyses were performed by Betty Mount and Charles Kinser.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, UNIVERSITY OF CAIRO]

Thermochromism of Dixanthylenes. Reactions with Substituted Xanthones. III[1a]

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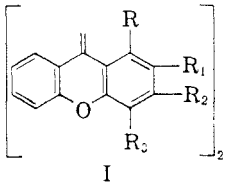
Substitution in dixanthylene (Ie) in position 1 and 1′, which hinders the planarity of the whole molecule, is detrimental to the development of thermochromic properties (Table I). Fission of the central ethylene linkage in dixanthylenes is brought about by the action of thionyl chloride followed by water to give the xanthone derivatives (Va–d) and by the action of sulfur at 270° to yield the corresponding xanthione derivatives (VI, Table III). The new xanthone derivative Vc, needed in this investigation has been synthesized. 1-Chloroxanthone (Va) condenses with aromatic thiols in the presence of potassium hydroxide to yield the corresponding arylmercapto derivatives (VIII, Table IV) which are oxidized readily to the corresponding sulfone derivatives (IX, Table IV). Photochemical dehydrogenation of 2-methylxanthene is effected by the action of Vb and/or Vg–h. 9-Phenyl-4-chloroxanthene (Xb) undergoes photochemical oxidation in sunlight in the presence of oxygen, yielding 4-chloro-9-phenylxanthyl peroxide (XIb). Reduction of substituted xanthones with lithium aluminum hydride and with metallic sodium and alcohol led to the formation of the reduction products, listed in Table V.

In continuation of the study of the constitutional changes in thermochromic substances,[1] we now have extended our previous investigations[1(a)] to show how substitution affects the thermochromic properties of dixanthylene (Ie) a strongly thermochromic substance. The crystals are colorless at liquid air temperature, turn blue-greenish on heating and the melt is deep blue-green. The results are shown in Table I. The substances were tested in boiling diphenyl ether or anisole solutions.

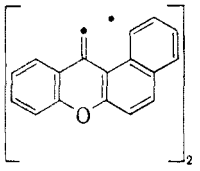
TABLE I

THERMOCHROMIC PROPERTIES

	R	R_1	R_2	R_3	
(a)	Cl	H	H	H	Very weakly thermochromic
(b)	CH_3	H	H	CH_3	Not thermochromic[1(a)]
(c)	CH_3	H	CH_3	H	Not thermochromic[1(a)]
(d)	Cl	H	H	CH_3	Not thermochromic[1(b)]
(e)	H	H	H	H	Strongly thermochromic[1(c)]
(f)	H	Br	H	H	Strongly thermochromic[1(a)]
(g)	H	Cl	H	H	Strongly thermochromic[1(b)]
(h)	H	CH_3	H	H	Strongly thermochromic
(i)	H	C_6H_5	H	H	Strongly thermochromic
(j)	H	H	H	Br	Strongly thermochromic[1(a)]
(k)	H	H	H	Cl	Strongly thermochromic[1(b)]
(l)	H	H	H	CH_3	Strongly thermochromic
(m)	H	CH_3	CH_3	H	Strongly thermochromic[1(a)]
(n)	H	CH_3	H	CH_3	Strongly thermochromic[1(a)]

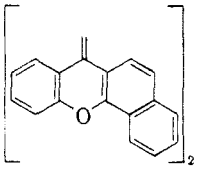


I



(Weakly thermochromic)

II



(Strongly thermochromic)

III

DISCUSSION

Recently, Schönberg, Mustafa, and Asker[1(d)] advanced a hypothesis that "in overcrowded molecules in which planarity is hindered, the degree of non-planarity changes with temperature. This is associated with the change of color, one reason being that resonance is related to planarity." Dixanthylenes, *e.g.*, Ie, a thermochromic compound, lose this property upon substitution at position 1 and 1′ (*cf.* Table I). The loss of the thermochromic properties is due to a constitutional change in I, overcrowding of the molecule to such a degree that planarity is hindered even at high

(1) (a) For part II *cf.* A. Mustafa, and M. E. D. Sobhy, *J. Am. Chem. Soc.*, **77**, 5124 (1955). (b) A. Schönberg, A. Mustafa, and M. E. D. Sobhy, *J. Am. Chem. Soc.*, **75**, 3377 (1953). (c) A. Schönberg and W. Asker, *J. Chem. Soc.*, 725 (1942). (d) A. Schönberg, A. Mustafa, and W. Asker, *J. Am. Chem. Soc.*, **76**, 4134 (1954).