colorless needles separated at once; yield, 4.0 g. (93%). Sublimation *in vacuo* gave faintly yellow, sturdy crystals, m.p. 189–190°. A mixture melting point determination with the material prepared by method A showed no depression, and infrared spectra were identical.

Treatment of the Complex (IV) with Acetic Anhydride.—A mixture of 1.1 g. of IV, 8 ml. of acetic anhydride, and 10 ml. of pyridine was heated on a steam bath for 40 min. and then evaporated to dryness under reduced pressure. Treatment of the crystalline residue with about 60 ml. of pentane and filtration gave a solid which was recrystallized from carbon tetrachloride to yield 0.46 g. (60%) of long needles, m.p. 115–120°. Sublimation raised the melting point to 118–120°. Diacetylhydroquinone is reported to melt at 123°.[10]

The infrared spectrum of the sublimed material [Nujol mull, principal bands at 5.49 (w), 5.67 (s), 5.80 (sh), and 6.66 μ] was identical with the spectrum of an authentic sample of hydroquinone diacetate.

The pentane filtrate was concentrated to a small volume, cooled, and filtered to give a solid (m.p. 91–104°) which was sublimed *in vacuo* to give 0.45 g. (70%) of 2,3-dimethylquinoxaline, m.p. 103–104° (lit.,[11] m.p. 106°). Its infrared spectrum was identical with the spectrum of an authentic sample of 2,3-dimethylquinoxaline.

Treatment of the Complex (IV) with Potassium Permanganate.—To a stirred mixture of the complex in aqueous acetone was added solid potassium permanganate until the purple color just persisted. The manganese dioxide was removed by filtration and rinsed with water followed by acetone, and the filtrate was extracted twice with ether. The ether extracts were dried over anhydrous sodium sulfate and evaporated to a small volume, whereupon long colorless needles, m.p. 103–104°, separated. A mixture melting point determination with authentic 2,3-dimethylquinoxaline showed no depression, and infrared spectra were identical.

Decomposition of the Complex (IV) with Base.—A mixture of 0.30 g. of IV in 20 ml. of 10% aqueous potassium hydroxide was extracted three times with chloroform, the chloroform extracts dried over anhydrous sodium sulfate and evaporated to give 0.23 g. of a colorless residue, m.p. 98–104°. Vacuum sublimation gave pure 2,3-dimethylquinoxaline, m.p. 103–105°, identical with an authentic sample. The aqueous basic layer was acidified with 2 *N* sulfuric acid and extracted three times with ether. The combined extracts were dried and evaporated to give 0.08 g. of a solid, m.p. 145–165°. Sublimation followed by crystallization from a mixture of carbon tetrachloride and ethanol gave hydroquinone, m.p. 171–172° (lit.[10] m.p. 169°). A mixture melting point determination with an authentic sample showed no depression, and infrared spectra were identical.

2-Methylquinoxaline–Hydroquinone Complex.—Mixing ethereal solutions of one equivalent of hydroquinone and two equivalents of 2-methylquinoxaline resulted in the separation of a pale yellow solid which was collected by filtration and recrystallized three times from ethanol. The complex melted at 137–138°.

Anal. Calcd. for $C_{24}H_{22}N_4O_2$: C, 72.34; H, 5.57; N, 14.06. Found: C, 72.07; H, 5.67; N, 13.91.

Two recrystallizations from chloroform yielded hydroquinone, m.p. 170–171°.

Resorcinol–2,3-Dimethylquinoxaline Complex.—An ethereal solution of 2.2 g. (20 mmoles) of resorcinol was added to an ethereal solution of 1.58 g. (10 mmoles) of 2,3-dimethylquinoxaline, and the precipitate which separated was collected by filtration; yield, 2.6 g., (95%), m.p. 179–182°. After three recrystallizations from benzene it melted at 180–182°.

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.78; H, 6.12; N, 10.63.

The material could be sublimed unchanged, but after recrystallization from ethanol it melted at 165–180°.

Catechol–2,3-Dimethylquinoxaline Complex.—Mixing ethereal solutions of equivalent amounts of catechol and 2,3-dimethylquinoxaline resulted in the immediate separation of long needles which, upon recrystallization from benzene, melted at 148–150°.

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.81; H, 6.02; N, 10.36.

(10) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley and Sons, Inc., New York, 1956, p. 326.

(11) Ref. 2b, p. 277.

Tris(thiocyclopropanone)

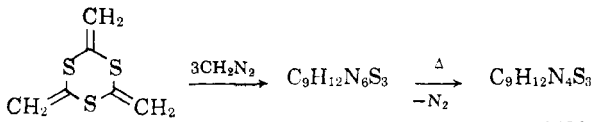
CHARLES C. PRICE AND JACQUELINE S. VITTIMBERGA[1]

Department of Chemistry, University of Pennsylvania, Philadelphia 4, Pennsylvania

Received May 31, 1962

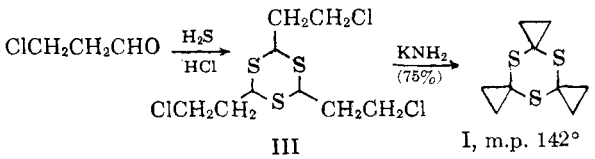
It seemed of some interest to us to prepare 2,4,6-tris(chloromethyl)-*s*-trithiane, an analog of sulfur mustard, bis(2-chloroethyl) sulfide, to investigate the possible properties of it and related compounds as potential biological alkylating agents. While our work was in progress, a number of these compounds were reported by Matlack, Chien, and Breslow.[2] We wish to report here principally on the successful synthesis of tris(thiocyclopropanone).

The first efforts in this direction involved the treatment of tris(methylene)-*s*-trithiane[2] with diazomethane.



II

In view of the reluctance of these products to eliminate nitrogen, the cyclization of tris(2-chloroethyl)-*s*-trithiane[2] by potassium amide in liquid ammonia was investigated and proved successful.



III I, m.p. 142°

Matlack, Chien, and Breslow[2] had reported that treatment of III with potassium *t*-butoxide in *t*-butyl alcohol gave a liquid identified by them as the ethylidene isomer of I. The structure of I was proven most conclusively by the n.m.r. spectrum

(1) Supported in part by U.S.P.H.S. Grant No. CY-2189. Abstracted in part from the doctoral dissertation of Jacqueline S. Vittimberga, June, 1961.

(2) A. S. Matlack, J. C. W. Chien, and D. S. Breslow, *J. Org. Chem.*, **26**, 1455 (1961).

(3) Th. J. DeBaer and H. J. Backer, *Rec. trav. chim.*, **73**, 229 (1954).

which showed a single peak at 8.82 τ. The high value of τ and the single peak are fully explained by the cyclopropane rings in I. The infrared spectrum offers further support, showing no bands expected for either a methyl group or a double bond. The ultraviolet spectrum of I (λ_{max} 231 mμ; log ϵ 2.94) when compared to that of III (λ_{max} 238; log ϵ 3.10), shows no conjugation between the cyclopropane rings and the sulfur atoms, in contrast to the spectrum of II (λ_{max} 245, log ϵ 4.20; 265, log ϵ 4.14). The structure assigned to II[2] was confirmed by hydrogenation over palladium on barium sulfate to a mixture of *cis*- and *trans*-2,4,6-trimethyl-*s*-trithiane.

Experimental

β-2,4,6-Tris(chloromethyl)-*s*-trithiane, 700 mg., m.p. 165–166° (lit.[2] m.p. 161°), was converted to II by treatment with 1.6 g. of potassium hydroxide in 50 ml. of methanol for 3 hr. at room temperature. After addition of an equal volume of water, extraction with five portions of chloroform, drying, and evaporation left 367 mg. (85%) of II as an analytically-pure, pleasant-smelling liquid, m.p. −21 to −19°, n_D^{23} 1.6753, (lit.[2] b.p. 74° (0.25 mm, 62%). Hydrogenation at 4 atm. with 5% palladium on barium sulfate in methanol gave a mixture of α- and β-trimethyl-*s*-trithiane, m.p. 72–77°, with correct analysis and identical in infrared spectrum to an authentic sample of the isomer melting at 98.5–100°, λ_{max} 238, log ϵ 2.98.

Treatment of 2,4,6-Tris(methylene)-*s*-trithiane with Diazomethane.—An ethereal solution of diazomethane was prepared from N-methyl-N-nitroso-*p*-toluenesulfonamide according to the method of DeBaer and Backer.[3] This solution, containing excess diazomethane (approximately 1.1 g.), was added to 292 mg. (1.7 mmoles) of freshly prepared 2,4,6-tris(methylene)-*s*-trithiane. The solution was kept at 0° to 2° for 4 days. After standing at room temperature for an additional 2 hr., 342 mg. of long white needles was separated by filtration. This compound became "mobile" when heated to 90° and melted with the evolution of gas at 129–131°. When the sample was heated several minutes at this temperature, a dark red oil was formed. The yellow mother liquor was held at 0°–2° for 2 days longer. An additional 35.1 mg. of small white prisms crystallized out of solution. The mother liquor was evaporated under a stream of nitrogen in the hood yielding an orange-red-solid and a small amount of yellow oil. The solid was separated and on heating melted at 118.5° with the evolution of gas. The temperature was then raised gradually and at 126–128° a vigorous evolution of gas occurred, and the liquid turned dark red.

Recrystallization from a small amount of cold chloroform by adding cyclohexane yielded flat, white needles which became "mobile" at 108° and melted at 132–133°, with yellowing and the evolution of gas.

Anal. Calcd. for $C_9H_{12}N_6S_3$: C, 35.97; H, 4.03; N, 27.98; S, 32.01. Found: C, 35.71; H, 3.84; N, 28.11; S, 31.97.

Analysis indicated this to be a **trispyrazoline**, a view supported by the infrared and ultraviolet spectra. The infrared spectrum contains bands at 6.50 μ assignable to either C=N or N=N absorption, 6.93 and 7.02 μ assignable to C—H, and other strong bands at 7.85, 9.64, 11.37, and 11.73 μ. The ultraviolet absorption spectrum taken in dioxane showed λ_{max} 230 mμ, log ϵ 4.48 and λ_{max} 333 mμ, log ϵ 2.52.

Attempted Decomposition of the Tri-adduct of Diazomethane and 2,4,6-Tris(methylene)-*s*-trithiane to I.—Twenty-five milligrams (0.08 mmole) of the triadduct of diazomethane and 2,4,6-tris(methylene)-*s*-trithiane was refluxed in 10 ml. of benzene for 16 hr. The benzene was removed leaving a crystalline material in a yellow oil. The solid fraction was recrystallized from benzene–hexane solution yielding a small amount of while solid melting at 147.3°–148°, with evolution of gas.

The infrared spectrum of this material contains bands at 6.53 μ assignable to either C=N or N=N, 6.93 and 7.03 μ assignable to C—H, and 9.75 μ which is in the region of cyclopropane absorption. Because of insufficient amount of sample, only nitrogen analysis was done.

Anal. Calcd. for $C_9H_{12}N_4S_3$: N, 20.55. Found: N, 20.85.

Increasing the time of reflux resulted in extensive decomposition of the starting material. When the triadduct was heated to its melting point (131°) a crystalline solid was obtained which has an infrared spectrum very similar to that of the material obtained from the benzene reflux. Ultraviolet irradiation caused either complete decomposition or no reaction.[4]

Preparation of 2,4,6-Tris(2-chloroethyl)-*s*-trithiane.—β-Chloropropionaldehyde was prepared from acrolein and anhydrous hydrogen chloride according to a method described by Moureu and Chaux.[5] To 250 ml. of glacial acetic acid, anhydrous hydrogen chloride was added for 90 min. at room temperature. After cooling the solution in an ice bath, hydrogen sulfide was bubbled in for 30 min. Then a solution of 80 g. (0.86 mole) of β-chloropropionaldehyde in 50 ml. of glacial acetic acid was added over a period of 2 hr. The hydrogen sulfide flow was continued for a total of 22 hr. longer. The reaction mixture was allowed to come to room temperature slowly during which time a solid separated. This was collected by filtration, dissolved in chloroform, and dried over anhydrous magnesium sulfate. Addition of water to the filtrate produced two more crops of oily crystals. After several recrystallizations from ethanol and from hexane, approximately 25 g. of white crystalline fractions ranging in melting points from 95–107° to 112–130° was obtained. After several recrystallizations from absolute ethanol, a sample which began melting at 115° and melted at 119–121° was obtained.

Anal. Calcd. for $C_9H_{15}Cl_3S_3$: C, 33.18; H, 4.64; Cl, 32.65; S, 29.52. Found: C, 33.14; H, 4.82; Cl, 32.88; S, 29.47.

A series of recrystallizations from ethyl acetate–hexane solution yielded a sample of *cis*-2,4,6-tris(2-chloroethyl)-*s*-trithiane melting at 129.5–131.5° (lit.[2], 131.5°, but the lit. sample did not have satisfactory analysis).

Anal. Calcd. for $C_9H_{15}Cl_3S_3$: C, 33.18; H, 4.64; S, 29.52. Found: C, 33.39; H, 4.65; S, 29.57.

The infrared spectrum of this material contains absorption bands at 6.96 μ attributable to aliphatic C—H vibrations, 7.04 μ assignable to the C—H of a negatively substituted carbon, and 14.18 and 14.92 μ possibly due to C—S and C—Cl bonds respectively. An ultraviolet absorption spectrum taken in dioxane showed λ_{max} 238 mμ, log ϵ 3.10.

Tris(thiocyclopropanone).—One gram of clean potassium was added to *ca.* 100 ml. of liquid ammonia containing iron oxide catalyst and the mixture was stirred until the blue color disappeared. This required about 15 min. Then 2,4,6-tris(2-chloroethyl)-*s*-trithiane (500 mg; 1.53 mmoles) in 35 ml. of anhydrous ether was added rapidly. A rust color developed after the addition. The mixture was stirred for 2 hr., after which 100 ml. of ether was added to the reaction mixture as the liquid ammonia was allowed to evaporate gradually. The color at this point was yellowish-green. After the ammonia had all evaporated, water was added slowly with external cooling. The organic layer was separated and the water layer extracted five times with a total

(4) K. L. Rinehart, Jr., and T. V. Van Auken, *J. Am. Chem. Soc.*, **82**, 5251 (1960), report that pyrazolines can be converted to cyclopropanes by ultraviolet irradiation.

(5) C. Moureu and R. Chaux, "Organic Synthesis," Coll. Vol. I, John Wiley and Sons, Inc., New York, 1941, p. 166.

(6) We are grateful to Dr. D. Y. Curtin of the University of Illinois for the n.m.r. spectrum of this compound.

of 50 ml. of ether. The extracts and original ether layer were combined, washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent yielded 246 mg. (75%) of white plates. After two recrystallizations from methanol a sample was obtained which melted at 141–142°.

Anal. Calcd. for $C_9H_{12}S_3$: C, 49.95; H, 5.59; S, 44.45. Found: C, 50.02; H, 5.65; S, 44.36.

The infrared spectrum of this compound contains bands at 3.33 μ (C—H of a strained ring), 7.05 μ (C—H of a strained ring), 9.58 μ and 9.76 μ (cyclopropane ring absorption region). An ultraviolet spectrum taken in dioxane showed λ_{max} 231 mμ, log ϵ 2.94.

The 60-Mc. n.m.r. spectrum of I shows only one signal from the twelve protons on the cyclopropane rings at −71 c.p.s. relative to tetramethylsilane as the internal standard.[5]

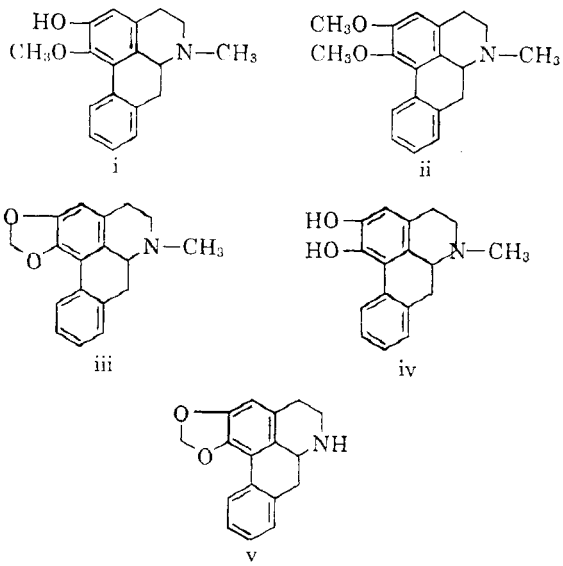
An Improved Synthesis of Noraporphines[1]

JERRY A. WEISBACH AND BRYCE DOUGLAS

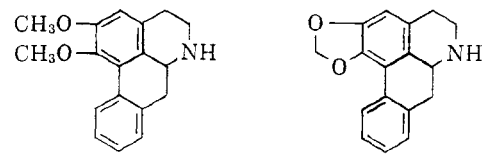
Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania

Received June 4, 1962

A great variety of aporphines and noraporphines have been isolated from natural sources.[3,4] The structures of a number of them were ascertained by degradation and verified by synthesis. However, the structures of subsequently isolated alkaloids have been determined more readily by using simple unambiguous conversions to one of the known compounds. In the noraporphine series this has been the usual procedure.[6–9] Thus there are only two of the natural noraporphines, anonaine[10,11] and laurotetanine,[12] which have been synthesized. A third, actinodaphne, was obtained as its O-methyl ether.[13]



During the course of a coordinated natural products isolation and pharmacological testing program, it became necessary to obtain a supply of nornuciferine I. As this molecule has not yet been found in nature,[13a] and since supplies of naturally occurring anonaine II were not available for transformation, a total synthesis was mandatory.



Application of the general procedure used by Barger and Weitnauer[10] in the preparation of anonaine II, modified at the reduction stage by the introduction of a current procedure, led to the preparation of a small amount of nornuciferine I, *via* III→IV→I. The unsatisfactory yield (3.3%) in the Pschorr cyclization is in contrast to the 22% of anonaine reported by the earlier workers. While the Pschorr reaction has never given good yields in the aporphine series,[14] it is not unreasonable to expect a yield of 10–20% in this series, if the final product is unsubstituted at position 4. Since this sequence did not seem promising as a source of the required amounts of nornuciferine, it was abandoned in favor of the following approach.

Reductive removal of masking O-benzyl groups is a well established procedure in aporphine chemistry since its introduction by Hey and Lobo.[13] However, a careful investigation of the aporphine literature revealed no precedent for the corresponding use and removal of N-benzyl groupings in this series. Since its application in this area gave promise of somewhat indirect, but more facile syntheses of all noraporphines as well as the needed supply of I, it was immediately applied. By utilizing the common intermediate III, and follow-

(1) A recent publication, M. Tomita, Y. Watanabe, and H. Furukawa [*J. Pharm. Soc. Japan*, **81**, 1644 (1961)] has designated *i* as nornuciferine. The use of the prefix *nor* to indicate an *O*-desmethyl relative of nuciferine[2] *ii* is contary to common usage in this family of compounds.[3,4] The only precedent for this nomenclature has been the naming[6] of the hydrolysis product of roemerine *iii* as norroemerine *iv*. This is a name which is more appropriately used to designate anonaine *v*. In this report we will use the prefix *nor* to indicate a des-N-methyl relationship and suggest that this policy be adhered to by future authors.

(2) H. R. Arthur and H. T. Cheung, *J. Chem. Soc.*, 2306 (1959).

(3) R. H. F. Manske, "The Alkaloids," Vol. IV, R. H. F. Manske and H. L. Holmes, ed., Academic Press, New York, 1954, p. 119.

(4) H. G. Boit, "Ergebnisse der Alkaloid Chemie bis 1960," Akademie Verlag, Berlin, 1961, p. 261.

(5) S. Yunusov, R. A. Konovalova, and A. P. Orekhov, *J. Gen. Chem. USSR.* **9**, 1868 (1939); *Bull. soc. chim. France.* 70 (1940).

(6) F. Faltis, G. Wagner, and E. Adler, *Ber.*, **77**, 686 (1944).

(7) J. Schmutz, *Helv. Chim. Acta* **42**, 335 (1959).

(8) T. Nakasato and S. Nomura, *Yakugaku Zasshi*, **79**, 1267 (1959).

(9) A. Rüegger, *Helv. Chim. Acta*, **42**, 754 (1959).

(10) G. Barger and G. Weitnauer, *ibid.*, **22**, 1036 (1939).

(11) L. Marion, L. Lemay, and R. Ayotte, *Can. J. Research*, **28B**, 21 (1950)

(12) I. Kikkawa. *J. Pharm. Soc. Japan*, **79**, 425 (1959).

(13) D. H. Hey and L. C. Lobo, *J. Chem. Soc.* 2246 (1954).

(13a) NOTE ADDED IN PROOF: The isolation of *l*-nornuciferine from the American Lotus, *Nelumbo lutea*, has recently been achieved. We wish to thank Professor M. Kupchan for informing us of this finding prior to publication.

(14) D. F. DeTar, *Org. Reactions*, 409 (1957).