

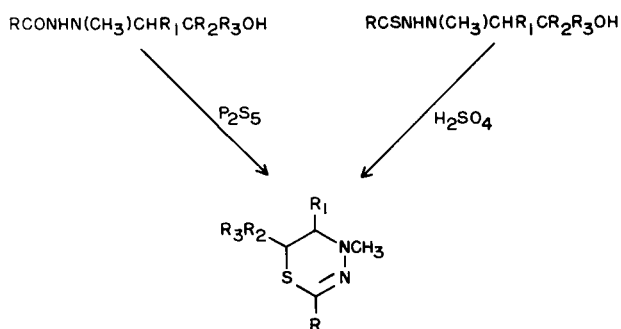
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5,6-Dihydro-4H-1,3,4-Thiadiazines. II. Synthesis and Use of 1-(1-Methylhydrazino)-2-propanethiol for the Preparation of Various Thiadiazines and a 2-Thiazolidinethione

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This paper reports the synthesis of 1-(1-methylhydrazino)-2-propanethiol and the results of a study of its reactions with benzaldehyde, benzonitrile, benzoyl chloride, triethyl orthoformate, succinonitrile, cyanogen bromide, and cyclopropylcyanide to give a thiadiazine directly or a product which can be converted to a thiadiazine. It also reports the condensation of 1-(1-methylhydrazino)-2-propanethiol with carbon disulfide to yield a 2-thiazolidinethione.

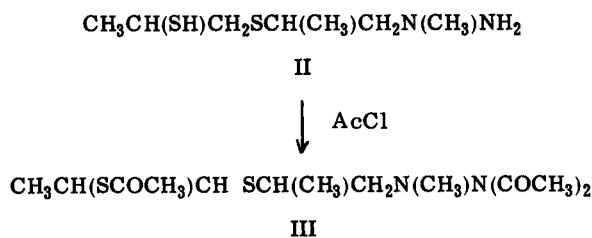
In the previous paper of this series (1), the synthesis of the 5,6-dihydro-4H-1,3,4-thiadiazine heterocycle by treatment of a 2-(β -hydroxyalkyl)-carboxylic acid hydrazide with phosphorus pentasulfide and by sulfuric acid cyclodehydration of a 2-(β -hydroxyalkyl)thiocarboxylic acid hydrazide was reported. The scope of the phosphorus pentasulfide reaction was investigated, *cis* and *trans* isomers were prepared, and the mechanisms of these reactions were discussed. Because certain members of the previously reported series of thiadiazines possessed biological activity (2) and because of the novelty of the 5,6-dihydro-4H-1,3,4-thiadiazine system (1), synthesis in this area was continued.



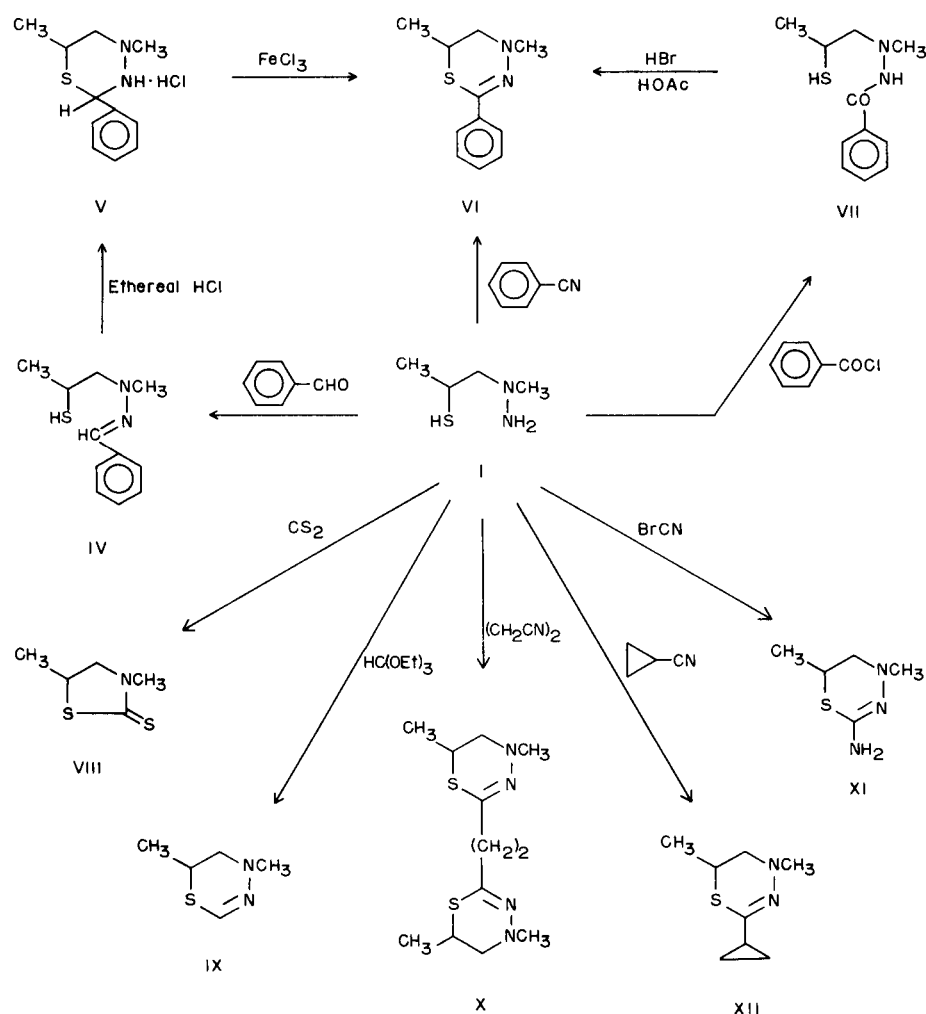
This paper reports the synthesis of 1-(1-methylhydrazino)-2-propanethiol (I) and its reaction with different reagents to give either a 5,6-dihydro-4H-1,3,4-thiadiazine directly or a precursor which can be converted to a 5,6-dihydro-4H-1,3,4-thiadiazine. Also reported is the condensation of I with carbon disulfide to give 3,5-dimethyl-2-thiazolidinethione (VII).

1-(1-Methylhydrazino)-2-propanethiol (I) was prepared by slow addition of propylene sulfide to rapidly stirred, refluxing methylhydrazine either in the absence of benzene or with benzene (200 ml.) present. When benzene was omitted the hydrazinothiol (I) was obtained in only 36% yield and when benzene was present it was obtained in 84% yield. The significant improvement in the yield of I produced by the addition of benzene to the reaction mixture correlates with the results reported by Braz (3) on the use of benzene to retard polymer formation in opening of thioepoxides with amines.

In both experiments (with or without benzene) a higher boiling (150° at 15 mm.) colorless liquid was obtained. This material was assigned the structure 1-(1-methylhydrazinoisopropylthio)-2-propanethiol (II) on the basis of elemental analyses and nmr and infrared spectral data obtained on analysis of II and its triacetyl derivative III.



The infrared spectrum of the hydrazinothiothiol (II) showed NH₂ (3.03 μ) and SH (4.01 μ) and the nmr showed three exchangeable protons (NH₂ and SH) by loss of integral when D₂O was added, two methyls of type CH₃CH< dissimilar to the extent that they are shifted 6 cps apart (76 and 82 cps with J's = 6 cps), and an NCH₃ singlet at 147 cps. The hydrazinothiothiol (II) yielded, upon treatment with acetyl



chloride in pyridine-benzene, a triacetyl derivative (III) whose infrared spectrum showed an absence of NH₂ and SH and the presence of CH₃COS-R and (CH₃CO)₂N-N< type carbonyls (strong bands at 5.85 and 5.92 μ). The nmr of the triacetyl derivative (III) showed that the acetyl methyls lie as two single peaks at 138 (one acetyl) and 145 cps (two acetyls). This correlates well with the infrared analysis and indicates acetylation of the SH with one acetyl and the NH₂ with two acetyls.

Hydrazinothiol I was allowed to react with benzaldehyde in refluxing ethanol in the presence of a few drops of pyridine to give the (2-mercapto-1,3,4-dimethyl-5,6-dihydro-1,3,4-thiadiazine) methylhydrazone of benzaldehyde (IV). That structure IV was the open-chain hydrazone and not the tetrahydrothiadiazine ring tautomer was substantiated by the results of infrared and ultraviolet analyses. The infrared spectrum in carbon tetrachloride showed the absence of NH stretch and the presence of a weak SH absorption at 3.91 μ and -C=N-N as two strong, sharp peaks at 6.26 and 6.40 μ. The ultraviolet analysis further substantiated the presence of the hydrazone chromophore by showing a λ max

(heptane) at 297 mμ with ε = 12,500. The λ max in MeOH was at 298 mμ with ε = 2,900.

Treatment of an isopropyl alcohol solution of the (2-mercapto-1,3,4-dimethyl-5,6-dihydro-1,3,4-thiadiazine) methylhydrazone of benzaldehyde (IV) with ethereal hydrogen chloride gave tetrahydro-4,6-dimethyl-2-phenyl-1,3,4-thiadiazine hydrochloride (V). That V is the hydrochloride of the ring tautomer instead of the open-chain tautomer was substantiated by the results of infrared and ultraviolet analyses. The infrared spectrum showed a fairly strong, sharp band at 3.16 μ. This wavelength is too low, and the band too intense, to result from C-H stretching, it almost certainly is N-H stretch. The presence or absence of SH cannot be determined due to interference caused by NH⁺ absorption from 3.7-4.8 μ. The two strong, sharp bands at 6.26 and 6.40 μ present in the spectrum of hydrazone IV were absent. The ultraviolet analysis further demonstrated the absence of the benzaldehyde hydrazone chromophore as evidenced by a lack of significant absorption in the 220-400 mμ region; λ max (MeOH) 306 mμ (ε = 372).

Additional ultraviolet studies indicated that ring-

chain tautomerism occurred in methanol solution and that at equilibrium the open-chain hydrazone tautomer predominated. This was evidenced by the fact that allowing the methanol solution of tetrahydrothiadiazine hydrochloride V that had exhibited insignificant absorption to stand at ambient temperature resulted in an increase in absorption with time until an equilibrium point was reached after 72 hours where the methanol solution exhibited λ max's at 233 and 306 m μ with ϵ 's of 11,000 and 5,200, respectively. Ultraviolet analysis of an equilibrated (72 hours) methanolic solution of the open-chain tautomer IV which had been treated with an equivalent of methanolic hydrogen chloride gave λ max's at 231 and 306 m μ with ϵ 's of 10,500 and 5,000, respectively. Thus in the liquid form (free-base IV) and in methanol solution at equilibrium the open-chain tautomer predominates and in the solid state (hydrochloride V) the ring tautomer predominates.

Oxidation of tetrahydrothiadiazine hydrochloride (V) with ferric chloride in aqueous solution gave 4,6-dimethyl-2-phenyl-5,6-dihydro-4*H*-1,3,4-thiadiazine (VI) in nearly quantitative yield. To determine whether or not this oxidation could be accomplished by oxygen, a stream of oxygen was bubbled through a methanolic solution of tetrahydrothiadiazine hydrochloride (V) for four hours. At the end of this time the methanolic solution was evaporated *in vacuo* and the tetrahydrothiadiazine hydrochloride (V) was recovered essentially unchanged.

4,6-Dimethyl-2-phenyl-5,6-dihydro-4*H*-1,3,4-thiadiazine (VI) was prepared directly in 15% yield by condensation of hydrazinothiol (I) with benzonitrile in refluxing ethanol.

Treatment of 1-(1-methylhydrazino)-2-propanethiol (I) with benzoyl chloride yielded 2-(2-mercapto-propyl)-2-methyl benzoic acid hydrazide (VII). Cyclodehydration of mercaptohydrazide VII with gaseous hydrogen bromide in glacial acetic acid gave 85% yield of thiadiazine VI. Cyclodehydration of VII with polyphosphoric acid gave only 38% yield of thiadiazine VI and attempted cyclodehydration of VII with concentrated sulfuric acid produced no VI but instead gave an 81% yield of benzoic acid. These results are similar to the results obtained in experiments carried out on acid-catalyzed cyclodehydrations of 2-(β -hydroxyalkyl)carboxylic acid hydrazides (4). Also, it is interesting to note that polyphosphoric acid cyclodehydration of *erythro*-(-)-2-methyl-2-(α -methyl- β -hydroxy- β -phenethyl)-*p*-chlorothiobenzoic acid hydrazide yielded *trans*-4,5-dimethyl-2-(*p*-chlorophenyl)-6-phenyl-5,6-dihydro-4*H*-1,3,4-thiadiazine and *cis*-4,5-dimethyl-2-(*p*-chlorophenyl)-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (1).

Condensation of 1-(1-methylhydrazino)-2-propanethiol (I) with carbon disulfide effected by heating at 150° in a sealed container for 2.5 hours gave a 54% yield of 3,5-dimethyl-2-thiazolidinethione (VIII) instead of the expected 3,4,5,6-tetrahydro-4,6-di-

methyl-2*H*-1,3,4-thiadiazin-2-thione. The proposed structure of thiazolidinethione VIII was assigned based on the results of elemental, nmr, and infrared analysis and molecular weight determination. The infrared spectrum demonstrated the absence of NH or SH and exhibited a very strong band at 6.67 μ (C=S). The nmr spectrum showed a doublet at 88 cps. (4-CH₃), a singlet at 196 cps. (NCH₃), and a multiplet at 212-262 cps. (3 protons). Further attempts to prepare the desired 3,4,5,6-tetrahydro-4,6-dimethyl-2*H*-1,3,4-thiadiazine-2-one by allowing hydrazinothiol I to react either with carbon disulfide in refluxing ethanol or with thiophosgene in toluene-pyridine were unsuccessful and only tarry intractable mixtures were obtained.

The sulfuric acid-catalyzed condensation of triethyl orthoformate and 1-(1-methylhydrazino)-2-propanethiol (I) gave a 68% yield of 4,6-dimethyl-5,6-dihydro-4*H*-1,3,4-thiadiazine (IX). The infrared spectrum of thiadiazine IX showed a shift of the -SC=N- band to 6.40 μ . The nmr spectrum showed the usual resonance pattern for the 4,6-dimethyl-5,6-dihydro-substituted thiadiazine system and the proton at the 2-position as a singlet at 427 cps.

Condensation of 1-(1-methylhydrazino)-2-propanethiol (I) with succinonitrile in refluxing ethanol in the presence of a catalytic amount of sodium ethoxide gave a 10% yield of 2,2'-ethylenebis(5,6-dihydro-4,6-dimethyl-4*H*-1,3,4-thiadiazine) (X). The -SC=N- band appeared at 6.31 μ and the ethylene bridge protons in the nmr occurred as a singlet at 154 cps. Also, the nmr indicated the molecule is symmetrical about a plane drawn diagonally across the ethylene bridge as evidenced by the fact that analogous protons in the two thiadiazine rings exhibited identical chemical shifts and couplings.

1-(1-Methylhydrazino)-2-propanethiol (I) reacted with cyanogen bromide to give a 26% yield of 2-amino-5,6-dihydro-4,6-dimethyl-4*H*-1,3,4-thiadiazine (XI). The infrared showed four fairly sharp, medium intensity bands at 2.89, 2.97, 3.03, 3.16 μ for the NH₂ and a very strong band at 6.15 μ with a medium strong shoulder at 6.30 μ for -S(NH₂)C=N. The increased intensity of this band correlates with the addition of a second electrophilic polar group to the carbon atom. Nmr showed the NH₂ as a broad singlet at 244 cps.

1-(1-Methylhydrazino)-2-propanethiol (I) was allowed to react with cyclopropyl cyanide in refluxing ethanol to give a 45% yield of 2-cyclopropyl-5,6-dihydro-4,6-dimethyl-4*H*-1,3,4-thiadiazine (XII). Nmr showed the four secondary cyclopropyl protons as a complex multiplet centered at 45 cps and the one tertiary proton as a complex multiplet centered at 93 cps.

Synthesis and biological evaluation of thiadiazine derivatives in our laboratories will be continued. A study of a series of basically substituted thiadiazines similar to the previously reported pyridyl oxadiazines (6) is in progress.

EXPERIMENTAL

The melting points were obtained in a capillary tube with the Thomas-Hoover Uni-Melt and are corrected. The elemental analyses were done by Midwest Microlabs., Inc., Indianapolis, Indiana. The nmr spectra were obtained at 60Mc., with a Varian A-60 spectrophotometer, for 10% deuteriochloroform solutions containing TMS as an internal standard. Infrared spectra were obtained with a Perkin-Elmer 337 grating spectrophotometer. The glc. analyses were obtained on an Aerograph autoprep A-700. Ultraviolet spectral tracings were obtained with a Bausch and Lomb Spectronic 505 and the maxima were measured with a Beckman DU.

1-(1-Methylhydrazino)-2-propanethiol (I).

Method A.

Propylene sulfide (74 g., 1 mole) was added, dropwise, over a period of 30 minutes to stirred, refluxing methylhydrazine (345 g., 7.5 moles). After the addition was completed, the mixture was stirred and heated at reflux temperature for 22 hours. The excess methylhydrazine was recovered by distillation and the remaining of the reaction mixture was distilled *in vacuo* to give 43 g. (36%) of colorless liquid, b.p. 68-72° (20 mm); analytical sample boiled 70-71° (19 mm); λ max (film) 3.01 (NH₂), 3.95 (SH), and 6.90 and 12.2 μ (s); nmr, 77 cps (CH₃ doublet, J = 7 cps), 149 cps (NCH₃, singlet), 182-205 cps (multiplet, 1 proton), and 137-165 (multiplet, 4 protons); glc (105°, 5', 4% SE 30/Chromosorb W/AW, He 300 ml./min.) t = 1.6 minutes.

Anal. Calcd. for C₄H₁₂N₂S: C, 39.96; H, 10.06; N, 23.30. Found: C, 40.21; H, 9.95; N, 23.66.

After collecting I which boiled at 68-72° (20 mm), the distillation was continued to give 8.5 g. (9%) of II, b.p. 146-149° (15 mm); λ max (film) 3.03 (NH₂), 4.01 (SH), 6.90 and 12.2 μ (s); nmr showed 3 exchangeable protons (NH₂ and SH) by loss of integral when deuterium oxide was added, nmr, 76 (CH₃ doublet, J = 6 cps), 82 (CH₃ doublet, J = 6 cps), 140-155 (multiplet, 5 protons, 3 of these are NCH₃), 147 (NCH₃, singlet), and 157-195 cps (multiplet, 6 protons); glc (105°, 5', 4% SE 30/Chromosorb W/AW, He 300 ml./min.) t = 6.0 minutes.

Anal. Calcd. for C₇H₁₄N₂S₂: C, 43.26; H, 9.34; N, 14.41; S, 32.99. Found: C, 43.13; H, 9.46; N, 14.26; S, 33.24.

Method B.

To a stirred, heated mixture of 200 g. (4.4 moles) of methylhydrazine and 300 ml. of benzene was added, dropwise, over a period of 1.3 hours, 107 g. (1.4 moles) of propylene sulfide. The mixture was stirred and heated at reflux temperature for 2 hours, stirred overnight, and distilled *in vacuo* to yield 146 g. (84%) of I (b.p. 76-81° at 20 mm) and 7.4 g. (4%) of II (b.p. 159-162° at 22 mm).

1-[1-(2, 2-Diacetyl-1-methylhydrazino)isopropylthio]isopropyl Thioacetate (III).

To a stirred, ice-bath cooled mixture of 10 g. (0.05 mole) of II, 30 ml. of pyridine, and 30 ml. of benzene was added, dropwise, over a period of 20 minutes, 12 g. (0.16 mole) of acetyl chloride. The mixture was allowed to remain at 0° for 1.5 days, was heated on a steam-bath for 1 hour, cooled, poured onto crushed ice, and extracted with chloroform. The washed (water) and dried (magnesium sulfate) chloroform solution was distilled *in vacuo* to give 9.2 g. (59%) of light yellow-colored oil, b.p. 156-159° (0.1 mm); infrared showed absence of NH and SH and λ max (CCl₄) 5.85 (s) (C=O), 5.92 (s) (C=O), 7.35 (ms), and 8.13 μ (s); nmr, 76 (methyl doublet, J = 6 cps), 138 (CH₃COS, singlet), 145 (CH₃CO)₂N, singlet), and 170 cps (CH₃N, singlet).

Anal. Calcd. for C₁₃H₂₄N₂O₃S₂: C, 48.72; H, 7.55; N, 8.74; S, 20.01. Found: C, 48.81; H, 7.72; N, 9.05; S, 19.72.

(2-Mercaptopropyl)methylhydrazone of Benzaldehyde (IV).

A mixture of 10 g. (83 mmoles) of I, 8.8 g. (83 mmoles) of benzaldehyde, 50 ml. of absolute ethanol, and 2 drops of pyridine was heated on a steam-bath for 1 hour and then distilled *in vacuo* to give 12 g. (69%) of faintly yellow-colored oil, b.p. 128-131° (0.5 mm); infrared showed absence of NH stretch and λ max (carbon tetrachloride) 3.91 (w) (SH), 6.26 (s), and 6.40 μ (s) (C=NN); ultraviolet λ max (heptane) 297 m μ (ϵ , 12,500), λ max (MeOH) 298 m μ (ϵ , 2,900), and λ max (MeOH + 1 equiv. methanolic HCl) 231 (ϵ , 10,500) and 306 m μ (ϵ , 5,000).

Anal. Calcd. for C₁₁H₁₆N₂S: C, 63.42; H, 7.74; N, 13.45. Found: C, 63.83; H, 8.02; N, 13.38.

Tetrahydro-4,6-dimethyl-2-phenyl-1,3,4-thiadiazine Hydrochloride (V).

A solution of 12 g. of the (2-mercaptopropyl)methylhydrazone of benzaldehyde (IV) in a minimum of isopropyl alcohol was treated with ethereal hydrogen chloride, enough ether was added to cause the so-

lution to become slightly turbid, and it was placed in a refrigerator for 18 hours. The hydrochloride was removed by suction filtration and recrystallized from isopropyl alcohol-ether to give 9.4 g. (75%) of white solid, m.p. 187-189°; λ max (nujol) 3.16 (ms) (NH), 3.87 (m) (N⁺), 6.56 (w), and 6.85 μ (s); ultraviolet λ max (MeOH) 306 m μ freshly prepared ϵ 372, 1 hr., ϵ 504, 4 hr., ϵ 3040, 72 hr., ϵ 5200 and λ max 233 ϵ 11,000.

Anal. Calcd. for C₁₁H₁₆N₂S·HCl: C, 53.97; H, 7.00; Cl, 14.48; N, 11.44. Found: C, 54.21; H, 7.03; Cl, 14.57; N, 11.39.

Condensation of I with Benzonitrile to give 5,6-Dihydro-4,6-dimethyl-2-phenyl-4H-1,3,4-thiadiazine (VI).

A mixture of 20 g. (0.17 mole) of I, 17 g. (0.17 mole) of benzonitrile, and 200 ml. of ethanol was heated at reflux temperature for 18 hours and then distilled *in vacuo* to give 5.1 g. (15%) of light yellow-colored oil, b.p. 116-119° (0.5 mm); infrared showed absence of NH, SH, and C≡N, and λ max (film) 6.01 (m) (C=N), 9.81 (s), 10.5 (s), and 13.1 μ (s); nmr, 76 (CH₃ doublet, J = 6 cps), 140 (quartet, 1 proton), 175 (NCH₃, singlet), 180 (quartet, 1 proton), 214 (multiplet, 1 proton), 437 (multiplet, 3 protons), and 462 cps (multiplet, 2 protons); glc (190°, 5', 4% SE 30/Chromosorb W/AW, He 250 ml./min.) t = 99 seconds.

Anal. Calcd. for C₁₁H₁₄N₂S: C, 64.03; H, 6.84; N, 13.58; S, 15.54. Found: C, 63.91; H, 6.75; N, 13.78; S, 15.82.

Ferric Chloride Oxidation of V to VI.

To a stirred solution of 2.4 g. (9.6 mmoles) of V in 250 ml. of water, heated to the reflux temperature, was added, dropwise, over a period of 30 minutes a solution of 7.8 g. (29 mmoles) of ferric chloride hexahydrate in 350 ml. of water. After the addition was completed, the mixture was stirred and heated at reflux temperature for 40 minutes, cooled in an ice-bath, basified to pH 10 with cold sodium hydroxide solution, and extracted thoroughly with methylene chloride. The washed (water) and dried (magnesium sulfate) methylene chloride solution was evaporated *in vacuo* to give 2.1 g. (100%) of yellow-colored oil that infrared and n.m.r. analyses indicated to be VI. Glc indicated ~95% purity and 50:50 admixture with authentic VI (VI indicated from condensation of I with benzonitrile) showed one major peak at t = 175 seconds (165°, 5', 4% SE 30/Chromosorb W/AW, He 200 ml./min.).

2-(2-Mercaptopropyl)-2-methyl Benzoic Acid Hydrazide (VII).

To a stirred mixture of 25 g. (0.21 mole) of I, 50 ml. of triethylamine, and 100 ml. of methylene chloride was added, dropwise, over a period of 30 minutes, a solution of 32 g. (0.23 mole) of benzoyl chloride in 25 ml. of methylene chloride. The mixture was stirred and heated at reflux temperature for 2 hours, allowed to come to ambient temperature, poured onto crushed ice, and the two phases were separated. The methylene chloride phase was diluted with 200 ml. of chloroform, washed with water, dried over magnesium sulfate, and concentrated *in vacuo*. The residual white solid (14 g., m.p. 124-154°) was recrystallized three times from methanol-ether (1:6) to give 8.2 g. (18%) white crystalline material, m.p. 148-150°; λ max. (nujol) 3.05 (NH), 3.95 (SH), and 6.05 μ (C=O).

Anal. Calcd. for C₁₁H₁₆N₂SO: C, 58.90; H, 7.19; N, 12.50; S, 14.29. Found: C, 58.76; H, 7.19; N, 12.48; S, 14.54.

Hydrogen Bromide-Acetic Acid Cyclodehydration of VII to VI.

A solution of 0.90 g. (4.0 mmoles) of VII in 50 ml. of glacial acetic acid was saturated with gaseous hydrogen bromide and then the solution was allowed to stand at ambient temperature for 5 days (5). The solution was concentrated *in vacuo*, and the residue was cooled, dissolved in methanol, treated with activated charcoal, and filtered. The filtrate was poured into a mixture of ice and sodium hydroxide solution. The basic mixture was extracted with methylene chloride. The methylene chloride extracts were dried over magnesium sulfate and evaporated to dryness *in vacuo*. The residual tan oil (830 mg.) was chromatographed on 20 g. (13 cm. length column) of alumina (Merck No. 71695) using benzene as eluant. There was obtained 700 mg. (85%) of pure liquid VI (i.r., n.m.r., glc compared with authentic VI).

Polyphosphoric Acid Cyclodehydration of VII to VI.

A thoroughly triturated mixture of 0.90 g. (4 mmoles) of VII and 38 g. of polyphosphoric acid (Matheson Coleman Bell No. 8096) was heated on a steam-bath for 3 hours. The cooled mixture was diluted with an ice-water mixture, basified with a cold sodium hydroxide solution, and extracted with chloroform. Evaporation of the dried (magnesium sulfate) chloroform solution gave 0.62 g. of tan oil which an infrared spectrum indicated was a mixture of VI and VII. Chrom-

atography on 15 g. (10 cm. length) of alumina (Merck No. 71695) gave 0.32 g. (38%) pure VI.

Attempted Concentrated Sulfuric Acid Cyclodehydration of VII to VI.

Compound VII (0.75 g., 3.3 mmoles) was added, portionwise, to 10 ml. of concentrated sulfuric acid and the mixture was stirred at ambient temperature for 1.5 hours. The mixture was poured onto crushed ice and extracted with methylene chloride. Evaporation of the dried (magnesium sulfate) methylene chloride extract gave 0.30 g. (81%) of benzoic acid, white needles, m.p. 121-122°. Also, infrared spectrum indicated material was benzoic acid.

3,5-Dimethyl-2-thiazolidinethione (VIII).

To 120 g. (1.0 mole) of I that was being stirred and cooled in an ice-bath was added, dropwise, 121 ml. (2.0 moles) of carbon disulfide. The addition of the first mole of carbon disulfide produced an exothermic reaction. After the addition was completed, the mixture of gummy material and liquid was transferred to a one liter capacity, stainless steel, Parr bomb and heated at 100-150° for 2.5 hours (maximum pressure attained was 500 p.s.i.). The mixture was allowed to cool, dissolved in one liter of chloroform, washed with five 400-ml. portions of water, dried over magnesium sulfate, and distilled *in vacuo* to give 121 g. of red-colored liquid, b.p. 150-170°. The material was redistilled *in vacuo* to give 80 g. (54%) of a straw-colored liquid, b.p. 133-140° (0.4 mm.); λ max. (carbon tetrachloride) 6.66 (vs), 7.71 (vs), 9.83 (s), and 11.1 μ (ms); nmr, 88 (4-CH₃ doublet), 196 (NCH₃, singlet), 212-262 cps. (multiplet, 3 protons); mol. wt. determination 155 (methyl ethyl ketone solvent-ebullimetric method).

Anal. Calcd. for C₆H₈NS: C, 40.81; H, 6.16; N, 9.52; S, 43.51. Found: C, 40.43; H, 6.25; N, 9.84; S, 43.39.

5,6-Dihydro-4,6-dimethyl-4H-1,3,4-thiadiazine (IX).

A mixture of 15 g. (0.12 mole) of I, 27 g. (0.18 mole) of triethyl orthoformate, and 0.5 g. of concentrated sulfuric acid was heated in an oil-bath at 125° for 30 minutes (collected ~30 ml. of distillate). The oil-bath temperature was elevated to 185° and the mixture was kept at this temperature for 30 minutes (collected ~10 ml. of distillate). One gram of anhydrous sodium acetate was added to the reaction mixture and then it was distilled *in vacuo* to give 11 g. (68%) of pale-green liquid, b.p. 90-95° (13 mm.). Redistillation gave 10 g. (62%) of colorless liquid, b.p. 115° (75 mm.); i.r. showed absence of NH and SH, and S-C=N at 6.4 μ ; nmr, 78 (doublet, J = 7 cps., 6-CH₃), 144 (quartet, 1 proton), 169 (NCH₃, singlet), 183 (quartet, 1 proton), 215 (multiplet, 1 proton), and 427 cps. (singlet, HCS=N); glc (105°, 5', 4% SE 30/Chromsorb W/AW, He 200 ml./min.) t = 76 seconds.

Anal. Calcd. for C₈H₁₀N₂S: C, 46.12; H, 7.74; N, 21.52. Found: C, 46.05; H, 8.09; N, 21.50.

2,2'-Ethylenebis-5,6-dihydro-4,6-dimethyl-4H-1,3,4-thiadiazine (X).

A mixture of 60 g. (0.5 mole) of I, 20 g. (0.25 mole) of succinonitrile, 1.0 g. of sodium, and 300 ml. of absolute ethanol was heated at reflux temperature for 22 hours. The mixture was concentrated *in vacuo* and the residual oil was mixed with ice-water. The mixture was extracted with chloroform. The dried (magnesium sulfate) chloroform extract was evaporated *in vacuo* to give 61 g. of red-colored oil. The 61 g. of oil was chromatographed on 600 g. (5 x 34 cm. column) of alumina (Baker No. 0537) using 1,500 ml. of hexane-benzene (50:50) as eluant. This yielded 19 g. of oil which an infrared spectrum (λ max. (film) 2.9, 3.0, 6.15 μ and no fingerprint except

13.25 μ) indicated was not X. Continued elution with 2,000 ml. of hexane-benzene (25:75) yielded 9.3 g. of semicrystalline material which after two recrystallizations from ethyl acetate-hexane gave 7.0 g. (10%) of colorless, rectangular needles, m.p. 90-92°; infrared showed absence of NH and SH and λ max (nujol) 6.31 μ (SC=N); nmr, 77 (doublet, J = 7 cps, 2 methyls), 136 (quartet, 2 protons, one on each ring in 5-position), 154 (ethylene singlet), 170 (singlet, two NCH₃), 180 (quartet, 2 protons, one on each ring in 5-position), 215 cps (multiplet, 2 protons, one on each ring in 6-position).

Anal. Calcd. for C₁₂H₂₂N₄S₂: C, 50.31; H, 7.74; N, 19.56; S, 22.38. Found: C, 50.53; H, 7.64; N, 19.70; S, 22.46.

2-Amino-5,6-dihydro-4,6-dimethyl-4H-1,3,4-thiadiazine (XI).

To a stirred mixture of 22 g. (0.20 mole) of cyanogen bromide and 200 ml. of water was added, dropwise, over a period of 1 hour, a solution of 24 g. (0.20 mole) of I in 50 ml. of water. After the addition was completed, the mixture was heated at reflux temperature for 1 hour, decolorized with activated charcoal, cooled, basified with cold sodium hydroxide solution, and extracted with chloroform. Evaporation of the dried (magnesium sulfate) chloroform extract gave 20 g. of yellow oil, λ max (film) 2.91, 3.05, 3.10, 6.24, 6.91, and 13.25 μ . Distillation of this oil *in vacuo* yielded 7.7 g. (26%) of slightly yellow-colored liquid, b.p. 78-80° (0.1 mm) analytical sample boiled at 79° (0.1 mm); λ max (carbon tetrachloride) 2.89, 2.97, 3.03, 3.16, (NH₂), 6.15, 6.30 (C=N), 6.92, 7.81, and 10.1 μ ; nmr. (carbon tetrachloride), 78 (CH₃ doublet, J = 7 cps), 152 (quintet, 1 H), 155 (NCH₃, singlet), 171 (quartet, 1 H), 210 (multiplet, 1 H), and 244 cps (broad signal, NH₂); glc (175°, 5', 4% SE 30/Chromsorb W/AW, He 250 ml./min.) t = 360 seconds.

Anal. Calcd. for C₈H₁₁N₃S: C, 41.35; H, 7.63; N, 28.94. Found: C, 40.97; H, 7.88; N, 28.64.

2-Cyclopropyl-5,6-dihydro-4,6-dimethyl-4H-1,3,4-thiadiazine (XII).

A mixture of 23 g. (0.19 mole) of I, 13 g. (0.19 mole) of cyclopropyl cyanide, and 100 ml. of ethanol was heated at the reflux temperature for 30 hours and then distilled *in vacuo* to give 15 g. (45%) of straw-colored oil, b.p. 105-113° (14 mm); nmr, 45 (4-cyclopropyl protons), 77 (CH₃ doublet, J = 7 cps), 93 (1-cyclopropyl proton), 134 (quartet, 1 proton), 167 (NCH₃), 183 (quartet, 1 proton), and 211 cps (multiplet, 1 proton); glc (135°, 5', 4% SE 30/Chromsorb W/AW, He 250 ml./min.) t = 99 seconds.

Anal. Calcd. for C₉H₁₄N₂S: C, 56.43; H, 8.29; N, 16.45. Found: C, 56.20; H, 8.54; N, 16.36.

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Synthesis of Certain Tricyclic Quinoline Derivatives as Potential Antiamebal Agents (I)

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Synthesis of the fused tricyclic systems, 1,2,3,3a,4,5-hexahydropyrrolo[1,2a]quinoline (I) and 2,3,4,4a,5,6-hexahydro 1*H*-benzo[*c*]quinolizine (II), each bearing an ethoxyl substituent on the benzene ring, has been achieved. The compounds combine certain structural features of the alkaloid emetine and of 8-quinolinols.

As a part of a continuing study of fused tricyclic systems based on the quinoline nucleus and possessing certain structural features present in emetine and in 8-quinolinols, 9-ethoxy-1,2,3,3a,4,5-hexahydropyrrolo[1,2a]quinoline (I) and 10-ethoxy-2,3,4,4a,5,6-hexahydro 1*H*-benzo[*c*]quinolizine (II) were required. The starting material for both I and II, 8-ethoxyquinaldine (III), was reported by Vaidya and Cannon (2) to have a melting point of 52-53°. However, the material obtained in the present study by the method of Vaidya and Cannon, upon recrystallization from ether, showed a melting point of 76-78°. Preparation of I was attempted utilizing a method applied by Prelog and Metzler (3) in the pyridine system. Reduction of IV to V was attempted using tin and hydrochloric acid (4); sodium and ethanol (5); and hydrogen in the presence of platinum oxide (6). Best results were obtained using the catalytic method of reduction. Compound V was extremely unstable in air, turning black within a short time. It could be stored for some weeks in light-proof, air tight containers. When V was treated with hydrobromic acid according to the procedure of Prelog and Metzler (3), VI was not obtained; rather, V was dehydrated and the ether cleaved to a product which on the basis of spectral and elemental analytical data is concluded to be 8-hydroxy-2-allyl-1,2,3,4-tetrahydroquinoline hydrobromide (VII). Löffler and Flügel (7) isolated an analogous dehydration product in the piperidine series as a side product in the treatment of 2-(3-hydroxypropyl)-piperidine with concentrated sulfuric acid. Successful cyclodehydration of V to I was attained by use of a mixture of concentrated sulfuric and glacial acetic acids (7) or of phosphorus pentoxide in dry xylene. The latter reagent provided a more satisfactory reaction.

Attempts were made to prepare II by a method analogous to that leading to I. When the lithium derivative of 8-ethoxyquinaldine (III) was treated with trimethylene oxide, the starting heterocycle was recovered unchanged. The lithium derivative of III

was treated with 1-bromo-3-chloropropane to form 10-ethoxy-1,2,3,4-tetrahydrobenzo[*c*]quinolizinium bromide (VIII) in one step. VIII was reduced catalytically to II.

EXPERIMENTAL (8)

8-Ethoxy-2-(3-hydroxypropyl)quinoline (IV).

8-Ethoxyquinaldine (III) (2) (18.7 g., 0.1 mole) dissolved in a minimum amount of anhydrous ether (260 ml.) was added dropwise with stirring over 0.5 hour to a solution of *n*-butyl lithium (67 ml. of 1.65 *M*) in hexane (Foot Mineral Co.), while bubbling nitrogen through the mixture. The resulting dark red solution was cooled in an ice-salt mixture, and a solution of 11 g. (0.25 mole) of ethylene oxide in 100 ml. of anhydrous ether was added dropwise with stirring under a stream of nitrogen. Approximately half of the ether was removed on a steam bath; 75 ml. of benzene was added to the residue and the remainder of the ether was removed. The resulting mixture was refluxed 2 hours, then it was cooled, treated with ice, and was extracted repeatedly with ether. The combined ethereal extracts were reduced in volume on a steam bath, washed with water, and were dried over anhydrous sodium sulfate. The ether was removed, and the dark syrupy residue was distilled at 140-160° (0.5 mm.); a heavy orange syrup resulted, which on cooling and agitating deposited white solid material. This solid material was collected on a filter, washed with ether, and recrystallized from 2-propanol. The resulting white acicular crystals showed m.p. 92-93°. Yield, 10.9 g. (47%). An infrared spectrum (Nujol) showed peaks at 2.95 μ (OH); 9.5 μ (C-O stretching of an alcohol); and at 8.0 and 9.7 μ (C-O-C stretching of an ether).

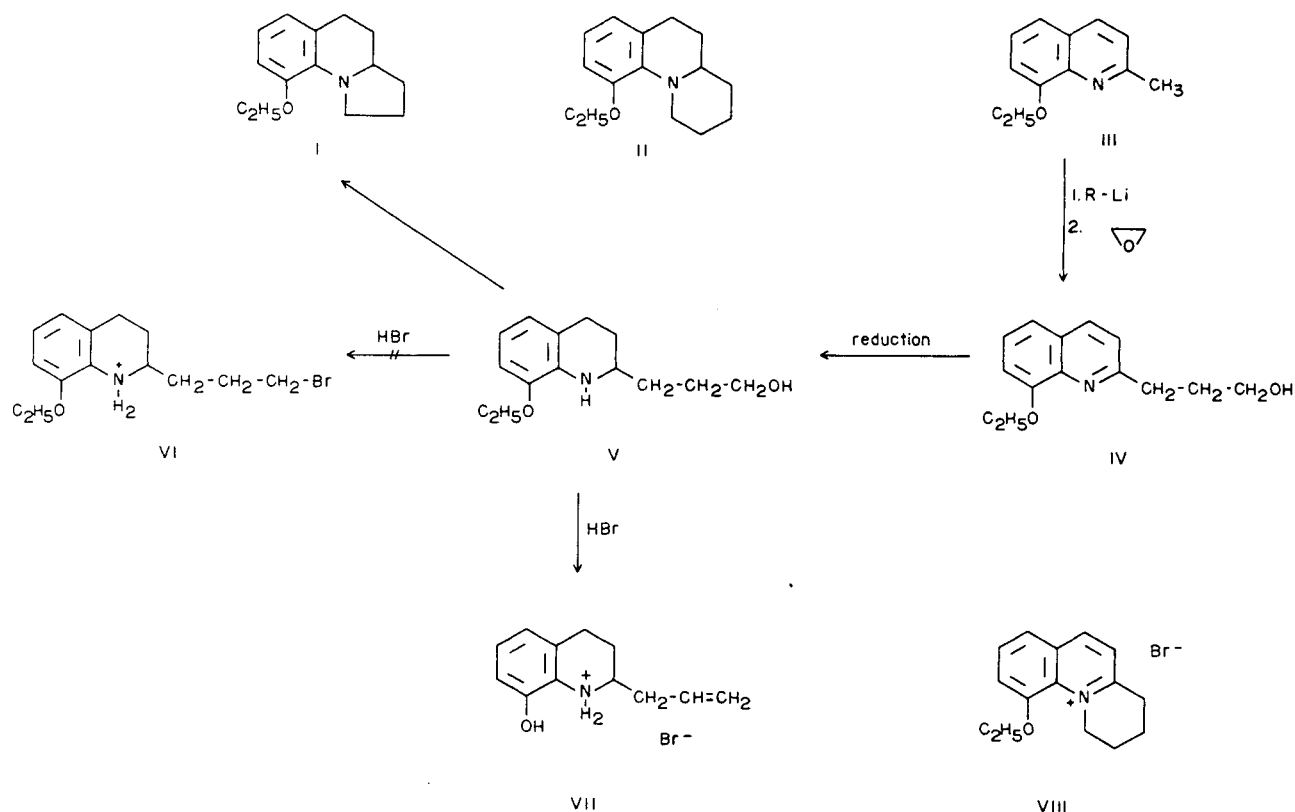
Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.75; H, 7.41; N, 6.06. Found: C, 72.24; H, 7.14; N, 5.97.

A picrate salt crystallized from ethanol as yellow needles, m.p. 135.5-136.5°.

Anal. Calcd. for $C_{20}H_{20}N_4O_6$: C, 52.18; H, 4.38; N, 12.17. Found: C, 52.19; H, 4.79; N, 11.98.

8-Ethoxy-2-(3-hydroxypropyl)-1,2,3,4-tetrahydroquinoline (V).

Compound IV (11.5 g., 0.05 mole) in 200 ml. of anhydrous, acetone-free methanol was reduced in a Parr model 3910 hydrogenation apparatus in the presence of 0.2 g. of platinum oxide, at room temperature and a maximum pressure of 40 p.s.i.g. Approximately 4 hours was required for the calculated amount of hydrogen to be absorbed. The catalyst was removed on a filter and the filtrate was concentrated on a steam bath under a stream of nitrogen. The residue of thick, yellowish liquid was distilled, yielding 11.35 g. (96%)



of a viscous white liquid, b.p. 180° (0.5 mm.); n_D^{24} 1.5546, d_4^{25} 1.247. An infrared spectrum (carbon tetrachloride) showed a peak at 2.95μ (N-H stretching broadened by associated O-H stretching). A picrate salt of V recrystallized from ethanol, m.p. $167-168.5^{\circ}$.

Anal. Calcd. for $C_{20}H_{24}N_2O_3$: C, 51.70; H, 5.22; N, 12.07. Found: C, 52.07; H, 5.13; N, 11.89.

8-Hydroxy-2-allyl-1,2,3,4-tetrahydroquinoline Hydrobromide (VII).

Compound V (2.0 g., 0.0085 mole) was neutralized with dilute hydrobromic acid and the resulting mixture was evaporated to dryness. The crude hydrobromide salt was sealed in an ampul containing 15 ml. of 68% hydrobromic acid and the ampul was maintained at 120° for 5 hours. The contents of the ampul were transferred to a flask from which the volatile components were removed under reduced pressure. The dark brown, viscous residue was mixed with 5 ml. of acetone and was kept in a refrigerator overnight. A brown solid separated which was collected on a filter and was recrystallized from acetone, m.p. $272-277^{\circ}$. Subsequent crystallization from absolute ethanol gave m.p. $283-286^{\circ}$ (decomp.). Yield, 0.50 g. (22%). The infrared spectrum (potassium bromide) showed peaks at 2.90μ (free phenolic OH); 3.20μ (phenolic O-H stretching); 3.85μ (secondary amine salt); 6.10μ (C=C stretching); 7.35 and 7.53μ (O-H deformation); and 11.0μ (CH_2 wagging for terminal vinyl group). The material gave a deep red-orange color with ferric chloride test solution.

Anal. Calcd. for $C_{12}H_{16}BrNO$: C, 53.36; H, 5.97; Br, 29.56; N, 5.16. Found: C, 53.49; H, 6.26; Br, 28.79; N, 4.97.

9-Ethoxy-1,2,3,4,5-hexahydropyrrolo[1,2a]quinoline (I).

Method A.

Compound V (10.0 g., 0.0425 mole) was refluxed for 3.5 hours with a mixture of 6 ml. of glacial acetic acid and 13 ml. of concentrated sulfuric acid. The resulting solution was permitted to cool, was made alkaline with sodium hydroxide, diluted to 100 ml. with water, and was extracted repeatedly with ether. The ether was removed from the combined extracts on a steam bath and the remaining dark, semisolid material was distilled, b.p. 120° (0.75 mm.). Yield, 7.20 g. (78%) of a yellowish liquid. The infrared spectrum was identical with that of the product of Method B.

Method B.

A mixture of 10.0 g. (0.0425 mole) of V, 20.0 g. of phosphorus pentoxide, and 140 ml. of sodium-dried xylene was raised to 135° over 3 hours, and the mixture was refluxed for 20 hours. After cooling, the xylene layer was decanted and the solvent was removed under reduced pressure. The residue and the residue from the reaction flask were made strongly alkaline with concentrated sodium hydroxide solution and were extracted repeatedly with ether. The combined ether extracts were concentrated on a steam bath, and the remaining dark blue liquid was distilled, yielding 7.85 g. (85%) of a lemon-yellow, mobile liquid, b.p. 130° (0.55 mm.); n_D^{22} 1.5655, d_4^{22} 1.093. The infrared spectrum (carbon tetrachloride) showed no absorption between 2.5 and 3.2μ (N-H, O-H). The nmr spectrum (neat) demonstrated a triplet centered at 1.22δ (3 protons); a multiplet centered at 1.69δ (6 protons); a multiplet centered at 2.59δ (2 protons); a multiplet centered at 3.17δ (2 protons); a quartet centered at 3.72δ (2 protons); a very broad multiplet lying between 3.5 and 4.0δ (1 proton); and a singlet centered at 6.50δ (3 protons). A picrate salt of I recrystallized from ethanol, m.p. $180-182^{\circ}$.

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 53.81; H, 4.93; N, 12.55. Found: C, 53.87; H, 4.71; N, 12.54.

A hydrobromide salt of I recrystallized from acetone, m.p. $182-183^{\circ}$.

Anal. Calcd. for $C_{14}H_{20}BrNO$: C, 56.36; H, 6.76; Br, 26.77; N, 4.70. Found: C, 56.73; H, 6.72; Br, 24.98; N, 4.62.

A picrolonate (3) salt of I recrystallized from ethanol, m.p. $165-166^{\circ}$.

Anal. Calcd. for $C_{24}H_{27}N_3O_6$: C, 59.85; H, 5.65; N, 14.54. Found: C, 59.42; H, 5.73; N, 14.52.

10-Ethoxy-1,2,3,4-tetrahydrobenzo[c]quinolinium Bromide (VIII).

To an efficiently stirred and cooled solution of 18.7 g. (0.1 mole) of 8-ethoxyquinoline (III) (2) in 250 ml. of anhydrous ether was added 0.1 mole of *n*-butyl lithium in hexane. Stirring was continued for 0.5 hours, then 15.8 g. (0.1 mole) of freshly distilled 1-bromo-3-chloropropane (Aldrich Chemical Co.) in 100 ml. of anhydrous ether was added in a slow stream. Sodium-dried benzene (200 ml.) was added, and the mixture was refluxed 8 hours. The solvents were removed under reduced pressure; 50 ml. of water was added to the residue and the resulting mixture was extracted repeatedly with ether. The combined ether extracts were evaporated under reduced pressure; the resulting black oil was taken up in 50 ml. of benzene and this solution was heated in a pressure bottle at 79° for 100 hours. The

contents of the bottle, on cooling, deposited a black solid which was collected on a filter and was recrystallized several times from 2-propanol (charcoal). Yield, 4.33 g. (14%) of white crystals, m.p. 211-212° (decomp.). A nmr spectrum (deuterium oxide) demonstrated a triplet centered at 1.00 δ (3 protons); a multiplet centered at 1.48 δ (4 protons); a multiplet centered at 2.92 δ (2 protons); a quartet centered at 3.66 δ (2 protons); a multiplet centered at 4.47 δ (2 protons); a multiplet centered at 7.00 δ (3 protons); a doublet centered at 7.15 δ (1 proton); and a doublet centered at 7.95 δ (1 proton).

Anal. Calcd. for $C_{15}H_{18}BrNO$: C, 58.46; H, 5.88; Br, 25.93; N, 4.55. Found: C, 58.67; H, 5.86; Br, 25.64; N, 4.67.

10-Ethoxy-2,3,4,4a,5,6-hexahydro-1H-benzo[c]quinolizine Hydrobromide (II).

A modification of the method of Bradsher and Desai (9) was employed. VIII (1.30 g., 0.0042 mole) in 100 ml. of anhydrous methanol was hydrogenated in the presence of 0.1 g. of platinum oxide at an initial pressure of 40 p. s. i. g. When absorption of hydrogen ceased (approximately 2 hours), the solution was filtered and the filtrate was concentrated under reduced pressure. The viscous brown residue was taken up in a minimum amount of methanol and crystallization was induced by dropwise addition of ether. The resulting crystalline material was recrystallized repeatedly from 2-propanol (charcoal) to yield 0.884 g. (67%) of a white, microcrystalline solid, m.p. 214-215°. An infrared spectrum (potassium bromide) showed a broad peak at 4.05 μ ($N-H^+$ stretching). A nmr spectrum (deuterium oxide) demonstrated a triplet centered at 0.93 δ (3 protons); a broad multiplet centered at 1.50 δ (8 protons); a multiplet centered at 2.45 δ (2 protons); a multiplet centered at 3.10 δ (2 protons); a quartet centered at 3.70 δ (2 protons); a broad multiplet lying between 3.5

and 4.0 δ (1 proton); and a multiplet centered at 6.62 δ (3 protons).

Anal. Calcd. for $C_{15}H_{22}BrNO$: C, 57.69; H, 7.10; N, 4.49. Found: C, 57.88; H, 7.20; N, 4.27.

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