sharply. Benzenesulfonyl chloride (1 ml.) was added to a solution of the solid in pyridine (5 ml.) and, after stirring overnight, the solution was poured into water (100 ml.). The resulting suspension was warmed on a steam bath, to hydrolyze excess benzenesulfonyl chloride, until a brown granular precipitate could be collected by filtration. Sublimation of this material at 120°/0.27 mm. gave a yellow solid (208 mg., 46%), m.p. 142–142.5°. Recrystallization from ligroin (b.p. 90–120°) did not change the m.p., but gave an analytical sample of yellow needles.

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 6.25; N, 5.44. Found: C, 70.35; H, 6.20; N, 5.61.

8-Chloro-4,5'-dimethylpsoralene (VId). A solution of sodium nitrite (140 mg., 2.0 mmoles) in water (*ca.* 3 ml.) was added slowly to a suspension of 8-amino-4,5'-dimethylpsoralene (400 mg., 1.75 mmoles) in conc. hydrochloric acid (10 ml.) that was cooled in an ice-salt bath to 0°. At no time during the addition did the temperature rise above 5°. After standing for 5 min., the clear solution was poured slowly into a boiling solution of cuprous chloride (396 mg.) in 6*M* hydrochloric acid (20 ml.). A gas was evolved and an orange precipitate was collected after allowing the solution to cool and diluting with an additional 60 ml. of water. After washing with 5% aq. sodium hydroxide, 5% hydrochloric acid, and water, the orange solid was recrystallized from 95% ethanol and then from benzene. Vacuum sublimation gave a colorless product (63 mg., 14.5%), m.p. 260.5–261°.

Anal. Calcd. for $C_{13}H_9ClO_3$: C, 62.79; H, 3.65; Cl, 14.26. Found: C, 62.49; H, 3.26; Cl, 14.42.

8-Cyano-4,5'-dimethylpsoralene (VIe). Diazotization of 10.80 g. (0.0471 mole) of 8-amino-4,5'-dimethylpsoralene in conc. hydrochloric acid (675 ml.) with sodium nitrite (3.27 g., 0.0474 mole) as described above gave a clear solution, which was neutralized with excess 15% aq. sodium carbonate, keeping the temperature below 5° and occasionally adding a drop of *n*-heptyl alcohol to eliminate foaming. The neutral solution was added slowly to an aq. cuprous cyanide[13] solution at 0–5° and the brown reaction mixture was stirred with ice bath cooling for 30 min., kept at room temperature for one hour, and quickly warmed to 60°. The next day, a brown solid (14.54 g.) was collected and 2.00 g. was twice sublimed at 250°/0.30 mm. to give a white solid (0.578 g., 37%), m.p. 287–289°. Recrystallization from glacial acetic acid gave a sample of m.p. 290.5–291.5°.

Anal. Calcd. for $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.86. Found: C, 70.33; H, 3.57; N, 5.95.

8-Bromo-4,5'-dimethylpsoralene (VIf). A suspension of 8-amino-4,5'-dimethylpsoralene (2.29 g., 0.0100 mole) in 48% hydrobromic acid (50 ml.) was diazotized with sodium nitrite (0.69 g., 0.0100 mole) and the clear solution was poured slowly into a boiling solution of cuprous bromide (2.0 g.) in 6% hydrobromic acid (100 ml.). After cooling to room temperature and diluting with water (200 ml.), a brown solid was collected and recrystallized twice from glacial acetic acid using Norit-A to obtain off-white needles (1.005 g., 34%), m.p. 261–261.5°.

Anal. Calcd. for $C_{13}H_9BrO_3$: C, 53.27; H, 3.09; Br, 27.26. Found: C, 53.26; H, 3.12; Br, 27.19.

4,5'-Dimethylpsoralene (VIg). Diazotization of 1.00 g. (4.37 mmoles) of 8-amino-4,5'-dimethylpsoralene in conc. hydrochloric acid (75 ml.) with sodium nitrite (301 mg., 4.36 mmoles) gave a clear solution, which was added slowly to a 30% aq. hypophosphorus acid solution containing powdered cupric sulfate (ca. 250 mg.) as a catalyst[14] at 0–5°. After refrigerating for several hours and standing overnight at room temperature, a light brown solid was collected, washed with 5% aq. sodium hydroxide, 5% hydrochloric acid, and sublimed at 150°/0.28 mm. Recrystallization from ethanol gave colorless, felted needles (367 mg., 39%), m.p. 165–165.5° (reported[3]: 161–162°).

Acknowledgment. This work was made possible by the interest and financial assistance of the Paul B. Elder Co., Bryan, Ohio, and the Upjohn Co., Kalamazoo, Mich. Microcombustion analyses and spectral analyses were carried out in the Physical and Analytical Chemistry Department of the Upjohn Co. and are gratefully acknowledged.

KALAMAZOO, MICH.

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[13] Prepared from cupric sulfate pentahydrate (15.4 g.) by the method of H. T. Clarke and R. R. Read, *Org. Syntheses*, Coll. Vol. I, 514 (1941).

[14] A. J. Nunn and K. Schofield, *J. Chem. Soc.*, 583 (1952).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY COLLEGE AT ALBANY[1]]

The Preparation and Properties of Some 1,2-Dihydrophthalazine Derivatives

RICHARD F. SMITH AND EDWARD D. OTREMBA

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The reduction of 2-methyl- and 2-ethylphthalazinium iodide with aqueous sodium borohydride yielded the corresponding 2-alkyl-1,2-dihydrophthalazines. Reduction of 2-benzylphthalazinium chloride was accompanied by debenzylation to give 1,2-dihydrophthalazine. Quaternization of 2-methyl-1,2-dihydrophthalazine resulted in the formation of 2,2-dimethyl-1,2-dihydrophthalazinium iodide (V) as evidenced by the facile conversion of the salt to α-*N*,*N*-dimethylamino-*o*-toluonitrile.

As part of a continuing investigation[2] of reduced diazaheterocycles, we now wish to report the results of our investigation of reduced phthalazines.

In 1895, Gabriel and Müller[3] reported that 2-methylphthalazinium iodide (I) could be converted to a mixture of 2-methyl-1,2-dihydrophthalazine (III) and 2-methyl-1(2*H*)-phthalazinone (IV) on treatment with one equivalent of aqueous potassium hydroxide. The volatile base (III) was separated by steam distillation in an inert atmosphere. Elderfield and Wythe[4] have suggested that the

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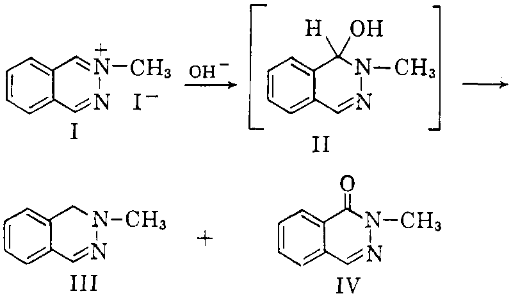
[1] Formerly: State University of New York, New York State College for Teachers.

[2] R. F. Smith, W. J. Rebel, and T. N. Beach, *J. Org. Chem.*, **24**, 205 (1959).

[3] S. Gabriel and F. Müller, *Ber.*, **28**, 1830 (1895).

[4] R. C. Elderfield and S. L. Wythe in *Heterocyclic Compounds*, Vol. 6, R. C. Elderfield, ed., John Wiley and Sons, New York, 1957, p. 190.

reaction probably proceeds *via* disproportionation of the pseudobase II. Reactions of this type have also been reported[5] from the treatment of the isoquinolinium salts with strong alkali. The free base III is unstable and readily undergoes air oxidation to the phthalazinone (IV), which can also be prepared by oxidation of I with silver oxide. Gabriel and Müller also reported analogous reactions with 2-ethylphthalazinium iodide.



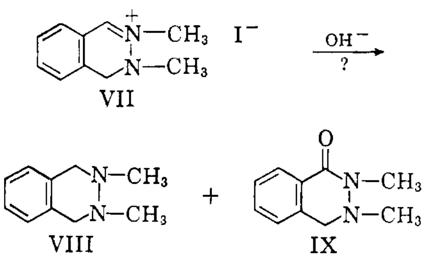
We have been successful in repeating the work of Gabriel and Müller and have now found that III can be obtained from I in 74% yield by reduction with aqueous sodium borohydride.

The free base III could be vacuum distilled but underwent rapid air oxidation to IV. The base readily formed a hydrochloride and a methiodide which proved to be identical with the derivatives of III prepared by the method of Gabriel and Müller. The structure of the methiodide is discussed below. The picrate of III decomposed on recrystallization to give high-melting material from which it was possible to isolate a small amount of 2-methylphthalazinium picrate.

In an analogous fashion, a 78% yield of 2-ethyl-1,2-dihydrophthalazine hydrochloride was obtained by reduction of 2-ethylphthalazinium iodide with aqueous sodium borohydride.

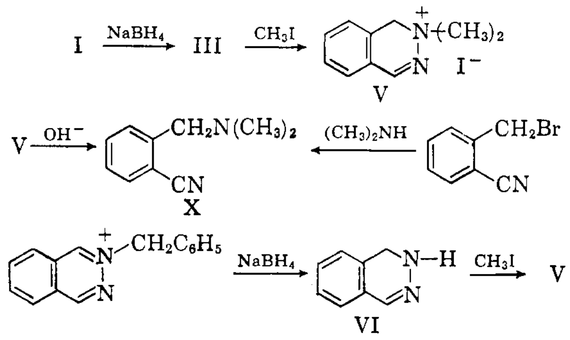
The product obtained by reduction of 2-benzylphthalazinium chloride with aqueous sodium borohydride failed to yield a crystalline picrate or hydrochloride. On refluxing the crude product with excess methyl iodide, a 31% yield of 2,2-dimethyl-1,2-dihydrophthalazinium iodide (V) was obtained, thus indicating that at least some debenzylation had accompanied reduction to give 1,2-dihydrophthalazine (VI). A lower melting methiodide was also formed but could not be identified.

Gabriel and Müller reported that the methiodide of III reacted with base and were able to isolate a picrate and hydrochloride (m.p. 159–161°) of the product. Due to insufficient amounts of material the structure of the product was not elucidated by the earlier workers. In a review of phthalazine chemistry, Elderfield and Wythe[4] have called attention to this reaction and suggested that perhaps quaternization gives 2,3-dimethyl-1,2-dihydrophthalazinium iodide (VII) and that subsequent treatment with base may yield, by analogy with the behavior of I, the products VIII and IX.

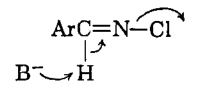


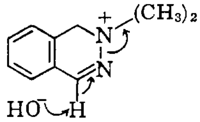
We have reinvestigated the above reaction and have determined that quaternization of III does not yield VII but the methiodide actually has structure V with quaternization occurring at the *N*-methyl position.

The structure of V was proved by the fact that on treatment with aqueous sodium hydroxide, a single basic product was obtained that proved to be α-*N*,*N*-dimethylamino-*o*-toluonitrile (X). The nitrile was also synthesized by alkylation of α-bromo-*o*-toluonitrile with dimethylamine.



The conversion of V to X resembles the base-catalyzed conversion of aromatic chloroimines to nitriles studied by Hauser[6] and co-workers with our intramolecular beta-elimination differing in the nature of the leaving group. This reaction has prompted us to undertake an investigation of the





synthesis of nitriles from quaternary hydrazones[7]

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[5] W. J. Gensler in *Heterocyclic Compounds*, Vol. 4, R. C. Elderfield, ed., John Wiley and Sons, New York, 1952, p. 474.

[6] C. R. Hauser, J. W. Le Maistre, and A. E. Rainsford, *J. Am. Chem. Soc.*, 57, 2674 (1935).

[7] P. A. S. Smith and E. E. Most, Jr., *J. Org. Chem.*, 22, 358 (1957), have reported that quaternary hydrazones of ketones fail to undergo Beckmann type rearrangements on heating but the base-catalyzed Neber rearrangement could be obtained with compounds having α-hydrogens.

of the type RCH=NN(R′)$_3$$^+X^-$. The results of these studies will be reported at a later date.

In the course of this work, appreciable discrepancies in melting points were noted between a number of the phthalazine derivatives reported in this study and the paper of Gabriel and Müller.[3] In all cases where discrepancies were noted, analytical results were found to support our structural assignments.

ADDED IN PROOF. A recent report[8] that hydrazones of the type RCH=NN(CH$_3$)$_2$ can be reduced to the corresponding hydrazine compounds by a large excess of methanolic sodium borohydride prompted us to attempt the reduction of the structurally analogous dihydro compound III under these conditions. It was found that III survived this treatment since the pure hydrochloride of III was recovered in 60% yield from the reaction mixture, and no other products could be isolated.

EXPERIMENTAL

Melting and boiling points are uncorrected. Analyses are by Mr. Kenneth Fleischer and his staff of the Sterling-Winthrop Research Institute. Infrared spectra were determined by Dr. Lawrence Daly of this laboratory and by Miss Katherine Martini of the Sterling-Winthrop Research Institute.

Phthalazine. The following procedure was found to be more convenient than the method of Gabriel and Müller[3] which is not well suited to the preparation of appreciable quantities of material. A procedure similar to the one described below has been reported recently by Mustafa[9] and co-workers, but the quantities of reactants given in their procedure are in error (insufficient hydrazine sulfate).

Forty grams (0.3 mole) of *o*-phthalaldehyde was suspended in 3 l. of water and stirred on the steam bath until the temperature had reached 80°. Forty-one grams (0.3 mole) of hydrazine sulfate was added in one portion with stirring followed by 1 l. of 1 *N* sodium hydroxide. The green suspension was evaporated *in vacuo* to 200 ml. and extracted with five 200-ml. portions of benzene, which was dried over magnesium sulfate. Evaporation of the solvent afforded 22 g. (56%) of phthalazine, m.p. 87–90°.

Further extraction of the aqueous solution with ethyl acetate resulted in the isolation of 0.9 g. of 1(2*H*)-phthalazinone, m.p. 183–184°. The compound was identified by analysis and mixed melting point with an authentic sample. The phthalaldehyde used in the above preparation was prepared 6 months earlier and was not repurified prior to use. Consequently, partial air oxidation of the phthalaldehyde to phthalaldehydic acid would account for the formation of this by-product.

Phthalazine quaternary salts: The picrates were obtained by warming the halides with a saturated ethanolic solution of picric acid (approximately 20 ml./g. of halide).

A. *2-Methylphthalazinium iodide* (I). This salt was obtained in 86% yield by the previously described method, m.p. 240–243° dec. The reported m.p. is 235–240°.

B. *2-Methylphthalazinium picrate.* This compound was obtained in 75% yield and was recrystallized for analysis from a large volume of ethanol as orange crystals, m.p. 199–200° dec.

Anal. Calcd. for $C_{15}H_{11}N_5O_7$: C, 48.26; H, 2.97; N, 18.76. Found: C, 48.60; H, 2.96; N, 18.80.

C. *2-Ethylphthalazinium iodide.* The procedure employed for the methiodide was used to give 95% of the product, m.p. 218–220° dec. The analytical sample was recrystallized from ethanol as yellow crystals, m.p. 225–228° dec. The reported[3] m.p. is 204–210°.

Anal. Calcd. for $C_{10}H_{11}N_2I$: C, 41.97; H, 3.88; I, 44.36. Found: C, 42.16; H, 3.91; I, 44.83.

D. *2-Ethylphthalazinium picrate.* This salt was obtained in 93% yield from the iodide. The analytical sample was recrystallized from a large volume of ethanol as yellow crystals, m.p. 167–169° dec.

Anal. Calcd. for $C_{16}H_{13}N_5O_7$: C, 49.61; H, 3.38; N, 18.08. Found: C, 49.69; H, 3.34; N, 17.98.

E. *2-Benzylphthalazinium chloride.* A solution consisting of 2 g. of phthalazine, 4 ml. of benzyl chloride, and 15 ml. of anhydrous methanol was refluxed for 3 hr. The cooled reaction mixture was diluted with a large volume of anhydrous ether. The resultant oil crystallized on standing overnight and was rapidly filtered, washed with ether, and dried in a vacuum desiccator. The yield was 3.5 g. (89%) of extremely hygroscopic white crystals, m.p. 171–175°. The compound was recrystallized with much difficulty from ethanol–ether, m.p. 175–178°. The reported[3] m.p. is 97–99°.

Anal. Calcd. for $C_{15}H_{13}N_2Cl$: N, 10.91. Found: N, 10.62.

A satisfactory carbon-hydrogen analysis could not be obtained. The analytical sample was found to melt at 130–135° after storage at room temperature for 4 months.

F. *2-Benzylphthalazinium picrate.* This derivative was obtained in quantitative yield from the chloride as yellow crystals, m.p. 182–184°. Recrystallization from methanol gave the analytical sample, m.p. 183–184°.

Anal. Calcd. for $C_{21}H_{15}N_5O_7$: C, 56.13; H, 3.36; N, 15.58. Found: C, 56.34; H, 3.82; N, 15.70.

Reduction of phthalazinium salts to 2-alkyl-1,2-dihydrophthalazines. A. *General procedure.* The powdered salts were added in small portions to a stirred 3% solution of a large excess (approximately a 3:1 salt to hydride weight ratio) of sodium borohydride in water. An exothermic reaction occurred, and the products separated as oils that were isolated by ether extraction. The ethereal solutions were dried over magnesium sulfate and the derivatives obtained by the appropriate treatment of the crude, undistilled bases.

B. *2-Methyl-1,2-dihydrophthalazine and derivatives.* The base could be distilled to yield 75% of product obtained as a pale yellow oil, b.p. 129–130° (17 mm.). However, a satisfactory analysis could not be obtained even when the compound was analyzed immediately following distillation. On standing, air oxidation rapidly occurred and crystals of 2-methyl-1(2*H*)-phthalazinone (IV) separated, m.p. 108–110°.

The *hydrochloride* was obtained in 75% yield by passing dry hydrogen chloride into the dried ether solution. The crude salt was obtained as a white solid, m.p. 132–135° dec. The compound is unstable and undergoes slow decomposition to a brown oil. The analytical sample was recrystallized from ethanol, m.p. 133–135° dec.

Anal. Calcd. for $C_9H_{11}N_2Cl$: C, 59.18; H, 6.07; Cl, 19.41. Found: C, 58.84; H, 6.11; Cl, 19.28.

The hydrochloride obtained by the base-catalyzed decomposition of 2-methylphthalazinium iodide had m.p. 134–136° (reported[3] m.p. 140–141°) and did not depress the m.p. of the above analytical sample.

The *picrate* was obtained as rust colored crystals, m.p. 95–98° dec. The reported[3] m.p. is 93–95°. On attempted recrystallization from ethanol, a very high-melting brown solid was formed from which a small amount of 2-methylphthalazinium picrate could be isolated by extraction with boiling ethanol, m.p. 199–200° dec. An authentic sample showed no depression of melting point on admixture with the above sample.

The *methiodide* (V) was prepared by refluxing the crude base (from the reduction of 12 g. of 2-methylphthalazinium iodide) with 12 ml. of methyl iodide in 50 ml. of ethanol for 3 hr. On cooling, 10.5 g. (83%) of product crystallized from

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(8) G. N. Walker, M. A. Moore, and B. N. Weaver, *J. Org. Chem.*, **26**, 2740 (1961).

(9) A. Mustafa, A. H. Harhash, and A. A. S. Saleh, *J. Am. Chem. Soc.*, **82**, 2738 (1960).

the reaction mixture as pale yellow crystals, m.p. 173–175°. The analytical sample was recrystallized from methanol as white crystals, m.p. 175–176°.

Anal. Calcd. for $C_{10}H_{13}N_2I$: C, 41.68; H, 4.55; I, 44.05. Found: C, 41.88; H, 4.59; I, 43.66.

The above analytical sample did not depress the melting point of a sample prepared by the quaternization of the base obtained by the method of Gabriel and Müller.[3] The infrared spectra of the two samples were also identical. The reported[3] melting point is 153–154°.

C. *2-Ethyl-1,2-dihydrophthalazine derivatives.* This compound could be most conveniently isolated in 78% yield as the *hydrochloride* by the method described above for the methyl analog. The crude salt was obtained as white crystals, m.p. 131–135° dec. The analytical sample was prepared by recrystallization from ethanol, m.p. 142–144° dec. with darkening above 130°. The salt is unstable and undergoes slow decomposition to a dark brown gum.

Anal. Calcd. for $C_{10}H_{13}N_2Cl$: C, 61.06; H, 6.66; N, 14.25. Found: C, 61.09; H, 6.45; N, 14.17.

The free base underwent extensive decomposition when refluxed for 6 hr. with excess methyl iodide in ethanol. A very small amount of quaternary salt was obtained by extraction of the resultant tar with ethyl acetate followed by dilution with ether. After several recrystallizations from ethanol, white crystals, m.p. 155–157° were obtained. By analogy with V, the compound has been assigned the structure *2-methyl-2-ethyl-1,2-dihydrophthalazinium iodide.*

Anal. Calcd. for $C_{11}H_{15}N_2I$: C, 43.72; H, 5.00; I, 42.00. Found: C, 43.89; H, 5.06; I, 42.19.

The *picrate* could not be obtained, but a very small amount of 2-ethylphthalazinium picrate, m.p. 167–169°, was obtained by extraction of the brown amorphous product with boiling ethanol. The compound was characterized by the identity of its infrared spectrum with that of an authentic sample.

D. *1,2-Dihydrophthalazine by reduction of 2-benzylphthalazinium chloride.* Reduction of the chloride by the general method described above resulted in the formation of an unstable oil. The hydrochloride was obtained as an oil that could not be crystallized. On treatment with ethanolic picric acid, a red solution was obtained that deposited an amorphous brown solid.

A solution consisting of the oil obtained by the reduction of 4.0 g. of the chloride, 7 ml. of methyl iodide, and 25 ml. of ethanol was refluxed for 3 hr. On cooling, 1.4 g. (31%) of 2,2-dimethyl-1,2-dihydrophthalazinium iodide crystallized, m.p. 174–176°. The identity of the product was established by analysis, a mixed melting point determination with an authentic sample and by its conversion to the hydrochloride of the aminonitrile (X). Dilution of the filtrate with ether yielded 1.4 g. of additional solid material, m.p. 138–142° which could not be identified. When a sample of this iodide was recrystallized from ethanol–ether, the melting point was raised to 140–142° dec. The compound melted with evolution of a potent lachrymator.

Anal. Found: C, 48.04; H, 6.05; N, 8.37.

A structure could not be assigned on the basis of this analysis.

α-N,N-Dimethylamino-o-toluonitrile (X) *from 2,2-dimethyl-1,2-dihydrophthalazinium iodide* (V). Treatment of 1 g. of V in 10 ml. of water with 10 ml. of 6 *N* sodium hydroxide resulted in the immediate formation of X. The oily base was separated by extraction with ether, dried, and converted to the following derivatives (yields based on V):

A. The *hydrochloride* was obtained in 80% yield by passing dry hydrogen chloride through the dried ethereal solution as white crystals, m.p. 225–227°. The analytical sample was recrystallized from ethanol, m.p. 226–227°. Gabriel and Müller[3] reported a m.p. of 159–161° for the salt obtained by the alkaline decomposition of their methiodide (no analysis given).

Anal. Calcd. for $C_{10}H_{13}N_2Cl$: C, 61.1; H, 6.7; N, 14.25. Found: C, 61.5; H, 6.5; N, 14.09.

The above salt had a strong nitrile band at 2220 cm.$^{-1}$ in the infrared, and the spectrum was identical with a sample prepared in the following manner: A reaction mixture consisting of 9.8 g. (0.05 mole) of α-bromo-*o*-toluonitrile,[10] 50 ml. of methanol, 4.1 g. (0.05 mole) of dimethylamine hydrochloride, and 5.3 g. (0.05 mole) of anhydrous sodium carbonate was stirred at room temperature for 2 days. The reaction mixture was evaporated to a small volume, acidified with dilute hydrochloric acid, and extracted with ether. The aqueous layer was made basic with sodium hydroxide and extracted with ether. On treatment of the dried ethereal solution with anhydrous hydrogen chloride, 2.5 g. (25%) of product, m.p. 220–224° was obtained. Recrystallization from ethanol gave the pure product, m.p. 225–227°.

B. The *picrate* was obtained in 88% yield as yellow crystals, m.p. 135–138°. The analytical sample was recrystallized from ethanol, m.p. 144–145°.

Anal. Calcd. for $C_{16}H_{15}N_5O_7$: C, 49.36; H, 3.88. Found: C, 49.20; H, 3.69.

C. The *methiodide* was obtained in 77% yield by refluxing the free base with 3 ml. of methyl iodide in 10 ml. of ethanol. The crude product was obtained by precipitation with ether as white crystals, m.p. 183–184°. The analytical sample was recrystallized from ethanol, m.p. 184–185°.

Anal. Calcd. for $C_{11}H_{15}N_2I$: C, 43.72; H, 5.00; N, 9.27; I, 42.00. Found: C, 43.99; H, 5.17; N, 9.12; I, 41.92.

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ALBANY, N. Y.

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(10) R. C. Fuson, *J. Am. Chem. Soc.*, **48**, 834 (1926).