After fifteen minutes the drowned mixture was filtered and the solid was purified by solution in aqueous sodium hydroxide and reprecipitation of the **3,3'-dinitro-1,1'-ethylenebisurea (VI)** as colorless needles; yield, 0.67 g.; m. p. 197–198° dec. The compound is practically insoluble in the common organic solvents.

Anal. Calcd. for $C_4H_8N_6O_6$: C, 20.3; H, 3.4. Found: C, 19.7; H, 3.4.

The dinitrate salt of ethylenebisurea was obtained by adding 200 cc. of nitric acid (d. 1.42) to a solution of 60 g. of ethylenebisurea in 200 cc. of water and cooling; weight, 94.4 g. (92%); m. p. 150–151°. Addition of 13.6 g. of the dinitrate salt with stirring to 43.2 cc. of concentrated sulfuric acid at −5° and drowning after thirty minutes gave 5 g. of dinitro compound with m. p. 180–182°; after solution in alkali, the product melted at 190–192°. A mixture of 1.36 g. of the dinitrate salt and 5 cc. of acetic anhydride, which was warmed on a steam-bath for fifteen minutes, gave 0.56 g. (m. p. 183–185°) of the dinitro compound; after treatment with alkali, the product (0.4 g.) had m. p. 196–197°.

Reactions of 3,3'-Dinitro-1,1'-ethylenebisurea.—A solution of 2 g. of the dinitro compound in 60 cc. of concentrated aqueous ammonia was refluxed for one hour. Evaporation of the solution and recrystallization of the residue from aqueous alcohol gave ethylenebisurea; m. p. 191–192° alone and when mixed with an authentic specimen.

When a mixture of 2.36 g. of the dinitro compound, 3 g. of aniline and 30 cc. of water was refluxed for one hour 1.5 g. of 3,3'-diphenyl-1,1'-ethylenebisurea precipitated; after recrystallization it melted at 246–246.5° alone and when mixed with a sample prepared from anhydrous ethylenediamine and phenyl isocyanate.[11]

Methylolation of EDNA with Formaldehyde.—In an attempt to prepare an explosive polymer 10 g. of powdered EDNA, 8 g. of polyoxymethylene and 1 g. of potassium carbonate in 100 cc. of 95% ethanol was refluxed for one hour. The filtered solution was concentrated to a small volume, and the residue, which crystallized on scratching, was filtered and washed with alcohol; weight, 10.1 g.; m. p. 110–125°. When recrystallized from water containing formalin it formed colorless diamond-shaped crystals, m. p. 124–126°. The same compound was formed by recrystallization of EDNA from water containing formalin. When heated alone the compound is decomposed to EDNA. It was shown later by Dr. G. F Wright that the compound is the monomethylol derivative, $NO_2NHCH_2CH_2N(NO_2)$-CH_2OH.

Summary

The preparation and nitration of 2-imidazolidone, ethylenebisurethan, ethylenebisacetamide and cyclic ethyleneoxamide to dinitro derivatives and the hydrolysis of the dinitro derivatives to the high explosive ethylenedinitramine (EDNA) are described.

Ethylenebisurea, which was prepared from ethylenediamine and urea, is nitrated at the terminal amino groups.

In two instances a mixture of acetic anhydride and 98% nitric acid was able to nitrate compounds which remained unchanged in 98% nitric acid alone or mixed with concentrated sulfuric acid.

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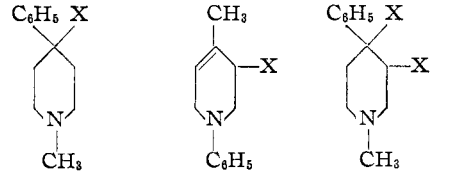
[Contribution from the Laboratory of Organic Chemistry of the University of Wisconsin]

Piperidine Derivatives. XXIII. Certain Halogenated 1-Methyl-4-Phenylpiperidines and Related Compounds

By S. M. McElvain and John C. Safranski, Jr.

This paper reports the preparation and properties of some halogeno and hydroxy derivatives of 1-methyl-4-phenyl-piperidine and tetrahydropyridine (II–VIII), which were obtained from 1-methyl-4-phenyl-4-hydroxypiperidine (I). The action of thionyl chloride on the hydrochloride of I produced an inseparable mixture of the hydrochlorides of 1-methyl-4-phenyl-4-chloropiperidine (II) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (IV). The chlorine content of this mixture indicated that it contained approximately 70% of II; its composition was further shown by the fact that an aqueous potassium hydroxide solution or ethylmagnesium bromide in ether converted it to the tetrahydropyridine IV. In contrast to these complete dehydrohalogenations, the 4-chloro component of this mixture was dehydrohalogenated only to the extent of 25% when an ether solution of the mixture was refluxed for two hours.



I, X is OH
II, X is Cl
III, X is Br

IV, X is H
V, X is OH
VI, X is Br

VII, X is Br
VIII, X is OH

A salt of the tetrahydropyridine IV was obtained when the carbinol I was heated with concentrated hydrochloric or hydrobromic acid. The hydrobromide of IV added hydrogen bromide in glacial acetic acid solution to form the hydrobromide of III. Although the latter compound was obtained in 95% purity from this reaction, all attempts to purify it further by recrystallization caused extensive dehydrobromination.

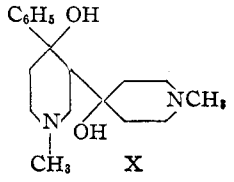
From the addition of bromine to the hydrobromide of IV the two racemic forms of 1-methyl-3,4-dibromo-4-phenylpiperidine (VII) hydrobromide were isolated. Analysis of this salt by the Volhard procedure (an acid solution) gave values indicating that two of the bromines had been titrated, while the analysis by the Mohr procedure (basic solution) gave values corresponding to the titration of all three of the bromines present in this salt. After these results in the Mohr titration, it was not surprising to find that an aqueous solution of sodium cyanide or potas-

sium hydroxide converted VII to the carbinol V, which was also obtained by the action of aqueous alkali on VI. That the course of the reaction of VII first involved its dehydrobromination to VI was shown by the rapid solution (within twenty minutes) of the water-insoluble dibromo derivative VII when it was stirred with water. Evaporation of this solution left a quantitative yield of the hydrobromide of 1-methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine (VI). This same salt was obtained when an aqueous solution of the hydrobromide of VII was evaporated to dryness. A Volhard titration of the hydrobromide of VI gave only the ionic bromine, but the Mohr titration showed both of the bromines present in this salt. Inasmuch as allyl bromide shows no appreciable reaction under the conditions of the Mohr titration, it appears that the high reactivity of the 3-bromo substituent of VI and VII in this analytical procedure is due to its rapid transformation into the ionic halogen of the cyclic ethylene-imonium structure IX in the basic medium in which this titration is carried out. If the intermediate IX is produced from VI in alkaline medium, there was a question as to whether V represents the correct structure of the product obtained from the action of bases on the dibromo compound VII. Reitsema[1] found that 1-methyl-3-chloropiperidine undergoes a rearrangement, when caused to react with benzylamine, to yield 1-methyl-2-benzylmethylaminopyrrolidine. The formation of this product was rationalized on the basis of the formation of an intermediate cyclic ethylene-imonium structure similar to IX. Fuson and Zirkle[2] have used an analogous cyclic intermediate to explain the conversion of 1-ethyl-2-chloromethylpyrrolidine hydrochloride to 1-ethyl-3-chloropiperidine in presence of base. It is obvious that the cleavage of the ethylene-imine ring of IX could yield either a pyrrolidine or a piperidine derivative.

IX

The structure V was shown to be correct by the following reactions. After an aqueous solution of the hydrobromide of VI was refluxed for thirty-four hours, all of the halogen was ionic (Volhard titration). Evaporation of this solution left the hydrobromide of VIII; apparently the hydrobromide of V was first formed and the hydrobromic acid thus produced caused the hydration of the double bond of V. When an aqueous solution of the hydrobromide of VI was treated with an excess of silver nitrate, the precipitated silver bromide filtered off and the solution made basic, both V and VIII were obtained. Finally, refluxing an aqueous solution of V with two equivalents of hydrobromic acid for eleven hours followed by evaporation yielded the hydrobromide of VIII. These conversions of the hydrobromide salts of V and VI to the same dihydroxy compound (VIII), together with the previously mentioned conversion of VII to VI, establish the structure of V.

Although the preparation of 1-methyl-4-phenyl-4-hydroxypiperidine (I) was reported[3] subsequent to the initiation of the work described above, it would seem of interest to record certain observations on the preparation of this compound in this Laboratory. The reaction of 1-methyl-4-piperidone with a solution of phenylmagnesium bromide gave I in variable yields; the maximum yield of 57% was obtained with a freshly prepared Grignard solution. When a three-week-old solution of the Grignard reagent was used, the yield of I dropped to 35%; accompanying this product were a 17% yield of 1-methyl-4-piperidinol and a 14% yield of 1-methyl-3-(1'-methyl-4'-hydroxy-4'-piperidyl)-4-hydroxy-4-phenylpiperidine (X). The latter product doubtless was formed by the aldolization of the piperidone followed by reaction of the resulting hydroxyketone with the Grignard reagent. An analogous hydroxyketone, 1-butyl-3-(1'-butyl-3'-hydroxy-4'-piperidyl)-4-piperidone has been reported[4] as the sole product from the reaction of 1-butyl-4-piperidone with cyclohexylmagnesium bromide.



X

The most satisfactory procedure found for the preparation of the carbinol I was by the reaction of 1-methyl-4-piperidone with phenyllithium. The yield of I was 76% and that of X only 8%; none of the reduction product, 1-methyl-4-piperidinol, was formed in this reaction.

Experimental

1-Methyl-4-hydroxy-4-phenylpiperidine (I) and 1-Methyl-3-(1'-methyl-4'-hydroxy-4'-piperidyl)-4-phenylpiperidine (X). (a) From Phenylmagnesium Bromide.—A solution of 125 ml. of three-week-old standardized phenylmagnesium bromide (0.20 mole) was placed under an atmosphere of nitrogen in a 500-ml. three-necked round-bottom flask equipped with a Hershberg mercury-sealed stirrer, total take-off reflux condenser and dropping funnel. The flask was heated on a steam-bath and 40 ml. of ether removed by distillation and replaced by 150 ml. of anhydrous benzene. To the resulting solution 17.68 g. (0.156 mole) of 1-methyl-4-piperidone[5] in 150 ml. of dry benzene was added over a period of one hour. The solution was stirred for two additional hours and then hydrolyzed with 40 ml. of 20% hydrochloric acid. The two layers were separated; the water layer was made basic with solid potassium hydroxide and extracted with eight 100-ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate and distilled to yield 2.5 g. (14%) of unchanged 1-methyl-4-piperidone (XVII), b. p. 45–48° (6.0 mm.), 3.0 g. (17%) of 1-methyl-4-piperidinol,[6] b. p. 80–85° (6.0 mm.); 1.0 g. of biphenyl, b. p. 85–95° (6.0 mm.); 10.5 g. (35%) of 1-methyl-4-

(1) Reitsema, THIS JOURNAL, **71**, 2041 (1949).
(2) Fuson and Zirkle, *ibid.*, **70**, 2760 (1948).
(3) Jensen and Lundquist, *Dansk Tids. Farm.*, **17**, 173 (1942); *C. A.*, **40**, 4086 (1946).
(4) Ziering, Berger, Heineman and Lee, *J. Org. Chem.*, **12**, 894 (1947).
(5) McElvain and Rorig, THIS JOURNAL, **70**, 1820 (1948).
(6) McElvain and Rorig, *ibid.*, **70**, 1826 (1948).

hydroxy-4-phenylpiperidine[6] (I), b. p. 128–130° (0.9 mm.), m. p. 114–115° (after recrystallization from acetone), and 3.4 g. (14%) of 1-methyl-3-(1′-methyl-4′-hydroxy-4′-piperidyl)-4-hydroxy-4-phenylpiperidine (X), b. p. 195–205° (0.9 mm.), m. p. 185–186.5° after recrystallization from acetone.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$ (X): C, 71.02; H, 9.27. Found: C, 70.48; H, 9.66.

When the same reaction is run with freshly prepared Grignard solution and 10.0 g. of the piperidone a 57% yield of I was obtained.

(b) **From Phenyllithium.**—Under an atmosphere of nitrogen in a 500-ml. three-necked round-bottom flask equipped with a Hershberg mercury-sealed stirrer, reflux condenser and dropping funnel, were placed 3.0 g. (0.43 atom) of lithium wire and 200 ml. of anhydrous ether. The stirrer was started and 2 ml. of bromobenzene was added while the flask was heated on a steam-bath until the reaction began. At this point the heating was discontinued and the remainder of a total of 33.0 g. (0.21 mole) of bromobenzene was added over a period of thirty minutes. The separatory funnel was washed with 20 ml. of dry ether and the reaction stirred at room temperature for three hours, after which time a few small pieces of lithium wire remained. The flask and its contents were immersed in an ice-bath and cooled to and maintained at 0–5° during the addition of 17.0 g. (0.15 mole) of 1-methyl-4-piperidone. After the reaction mixture was stirred for two additional hours at room temperature, it was hydrolyzed by the slow addition of 40 ml. of water, during which time the flask and its contents were kept cool in an ice-bath. The ether and water layers were separated and the latter extracted with eight 50-ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate and the ether removed by distillation. The residue when distilled yielded 21.7 g. (76%) of 1-methyl-4-hydroxy-4-phenylpiperidine (I), b. p. 123–128° (0.5 mm.), m. p. 114–115° (after recrystallization from acetone) and 1.7 g. (8%) of 1-methyl-3-(1′-methyl-4′-hydroxy-4′-piperidyl)-4-hydroxy-4-phenylpiperidine (X), b. p. 190–200° (0.45 mm.), m. p. 185–186.5° after recrystallization from acetone.

Reaction of the Hydrochloride of I with Thionyl Chloride. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (IV) Hydrochloride.—A solution of 11.3 (0.05 mole) of 1-methyl-4-hydroxy-4-phenylpiperidine hydrochloride (I) in 175 ml. of chloroform was cooled to 0° and 11.8 g. (0.10 mole) of thionyl chloride in 15 ml. of chloroform added over a period of twenty minutes. The resulting solution was held at 0° for two additional hours and then kept at room temperature for one hour. The chloroform and excess thionyl chloride were removed under diminished pressure at room temperature. The residue was treated with acetone, which caused the crystallization of 11.5 g. of a mixture of the hydrochlorides of II and IV, m. p. 238–245°. Efforts to separate these salts from each other by recrystallization from ethanol and ethanol–acetone were unsuccessful. Halogen analysis of this mixture of salts indicated that it was composed of 70% of the hydrochloride of II and 30% of the hydrochloride of IV.

A solution of 0.25 g. of this salt mixture in 5 ml. of water was made alkaline with potassium hydroxide and then extracted with four 10-ml. portions of ether. The combined ether extracts were dried over Drierite and hydrogen chloride added to precipitate 0.17 g. (77%) of **1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (IV) hydrochloride,** m. p. 248–250°. This salt has been reported[4] to melt at 241–243° (cor.).

Anal. Calcd. for $C_{12}H_{16}ClN$: C, 68.72; H, 7.69; Cl, 16.9. Found: C, 68.40; H, 7.61; Cl, 16.8.

IV was also obtained from the action of ethylmagnesium bromide on the mixture of II and IV. In a 250-ml. three-necked round-bottom flask equipped with a Hershberg mercury-sealed stirrer, reflux condenser, and dropping funnel, 0.034 mole of ethylmagnesium bromide in 100 ml. of ether was placed under nitrogen. Over a period of one hour, 3.5 g. (0.023 mole) of the mixture of the hydrochlorides II and IV was added in small increments to the Grignard solution. Stirring was continued for two additional hours. The ether then was removed by siphoning with the aid of a positive pressure of nitrogen; the residual solid gum was washed with two 50-ml. portions of ether. Titrations of an aliquot of the ether extracts showed 0.005 mole of Grignard reagent unreacted. The ether extracts were treated with 30 ml. of water to decompose the excess Grignard reagent and magnesium bromide dietherate; the ether layer was separated from the water and dried over Drierite. Addition of hydrogen chloride precipitated 0.35 g. of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride. The water layer was made basic and extracted with ether; after drying the ether extracts over Drierite, addition of hydrogen chloride precipitated an additional 0.40 g. of the hydrochloride of IV. The solid gum from which the ether had been decanted was treated with 20 ml. of water; this aqueous solution was extracted with ether and the extract dried over Drierite; 1.8 g. of the hydrochloride of I precipitated upon addition of hydrogen chloride. Total yield of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride was 2.55 g. (88%).

The most convenient procedure for the preparation of IV starts with the carbinol I. In a 50-ml. Claisen flask 10.4 g. (0.05 mole) of I was dissolved in 30 ml. of concentrated hydrochloric acid. This solution was heated on a steam-bath for four hours and then evaporated to dryness on a steam-bath under reduced pressure. The solid residue was recrystallized from commercial absolute ethanol to yield 11 g. (80%) of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride, m. p. 248–250°.

The hydrobromide, m. p. 216–218°, was prepared in a similar manner using 48% hydrobromic acid instead of hydrochloric acid with the carbinol I.

Anal. Calcd. for $C_{12}H_{16}BrN$; Br, 31.4. Found: Br, 31.2.

1-Methyl-4-bromo-4-phenylpiperidine (III) Hydrobromide.—A solution of 5.8 g. (0.023 mole) of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrobromide in 100 ml. of glacial acetic acid contained in a 250-ml. Erlenmeyer flask was immersed in a beaker of water at 15° and 15 equivalents of anhydrous hydrogen bromide passed in over a period of two hours. This solution was allowed to stand overnight at room temperature and then the acetic acid was removed under reduced pressure at a maximum distillation temperature of 45°. The residue was treated with anhydrous acetone to precipitate 7.0 g. (94%) of 1-methyl-4-bromo-4-phenylpiperidine (III) hydrobromide, m. p. 217–219° (dec.). Halogen analysis (calcd. Br, 47.7; found Br, 45.5) showed that this material was 95% pure. Recrystallization from chloroform–ether resulted in a product in which the halogen content was lowered; these solutions also fumed in moist air indicating dehydrohalogenation was taking place.

1-Methyl-3,4-dibromo-4-phenylpiperidine (VII) Hydrobromide.—To a solution of 18.0 g. (0.071 mole) of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (IV) hydrobromide in 1100 ml. of glacial acetic acid contained in a three-liter flask equipped with a glass stirrer and dropping funnel, was added, over a period of one hour, 11.5 g. (0.072 mole) of bromine in 110 ml. of glacial acetic acid. After stirring for two additional hours, the glacial acetic acid was removed under reduced pressure at about 45°. Anhydrous acetone was added to the solid residue and 28.5 g. (96%) of 1-methyl-3,4-dibromo-4-phenylpiperidine (VII) hydrobromide, m. p. 126–129° (dec.), was precipitated. After recrystallization from absolute ethanol, a white solid, m. p. 131–132° (dec.), was obtained.

Anal. Calcd. for $C_{12}H_{16}Br_3N$: Br (2), 38.6; Br (3) 57.9. Found: Br (Volhard), 39.1; (Mohr), 57.2.

In some runs an oil was obtained after evaporation of the acetic acid; solution and crystallization of this material from acetone yielded a higher melting, 189–191° (dec.), isomeric hydrobromide. A sample of the lower melting (131–132°) form isomerized to this higher melting form on standing at room temperature.

1-Methyl-3,4-dibromo-4-phenylpiperidine (VII).—A solution of 1.0 g. (0.0024 mole) of 1-methyl-3,4-dibromo-4-phenylpiperidine hydrobromide in 5 ml. of water was treated with 0.14 g. (0.0024 mole) of potassium hydroxide in 3 ml. of water. The precipitate was removed by filtration as rapidly as possible to yield 0.53 g. (68%) of VII, m. p. 85–90° (dec.). It was not found desirable to run this reaction in large quantities as rapid filtration of the free base is necessary to prevent losses due to dehydrohalogenation. Because of the reactive halogen in this compound, attempts to further purify it by recrystallization were unsuccessful.

Anal. Calcd. for $C_{12}H_{15}Br_2N$: Br (1), 24.0; Br (2), 48.0. Found: Br (Volhard), 24.5; (Mohr), 48.4.

1-Methyl-3-hydroxy-4-phenyl-1,2,3,6-tetrahydropyridine (V). (a) **From the Reaction of VII with Aqueous Sodium Cyanide.**—A solution of 10 g. (0.024 mole) of hydrobromide of VII in 300 ml. of water in a 500-ml. flask equipped with a Hershberg stirrer and dropping funnel was treated with 1.35 g. (0.025 mole) of potassium hydroxide in 10 ml. of water; then a solution of 2.5 g. (0.051 mole) of sodium cyanide in 25 ml. of water was added over a period of one hour. Stirring was continued for six hours and then the solution was separated from a trace of thick oil by filtration. The basic filtrate was extracted with ten 100-ml. portions of ether and dried over anhydrous sodium sulfate. The ether was removed by distillation on a steam-bath and the residue fractionated to yield 2.0 g. (44%) of 1-methyl-3-hydroxy-4-phenyl-1,2,3,6-tetrahydropyridine (V), b. p. 105–115° (2.0 mm.). Cooling in Dry Ice–acetone caused crystallization to a light yellow solid, m. p. 37–43°. Recrystallization from petroleum ether (b. p. 90–100°) at −70° yielded a solid, m. p. 45–47°.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.14; H, 7.99. Found: C, 75.99; H, 7.85.

The methiodide was prepared in ether and recrystallized from ethanol to yield a white solid, m. p. 167–168°.

Anal. Calcd. for $C_{13}H_{18}NOI$: C, 47.10; H, 5.47. Found: C, 47.33; H, 5.42.

The picrate was prepared by adding a saturated ethanolic solution of picric acid to an ethanolic solution of the free base. Recrystallization from ethanol yielded bright yellow needles, m. p. 156–157°.

Anal. Calcd. for $C_{18}H_{18}N_4O_8$: C, 51.67; H, 4.34. Found: C, 51.41; H, 4.31.

(b) **From the Reaction of VI with Aqueous Potassium Hydroxide.**—In a 100-ml. three-necked flask equipped with a reflux condenser, Hershberg stirrer and dropping funnel was placed a solution of 10.0 g. (0.03 mole) of the hydrobromide of VI in 50 ml. of water and to it was added a solution of 3.4 g. (0.06 mole) potassium hydroxide in 10 ml. of water. The resulting basic solution was refluxed for two hours, allowed to cool, and then extracted with eight 50-ml. portions of ether. After drying over Drierite, the combined ether extracts were distilled to yield 3.8 g. (67%) of V, b. p. 99–103° (1.0 mm.). This oil did not crystallize on cooling alone or in petroleum ether solution; however, the methiodide and picrate salts were identical to those obtained from the product resulting from the action of aqueous sodium cyanide on VII.

1-Methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine (VI) Hydrobromide.—(a) In a 500-ml. Claisen flask was placed a solution of 56.8 g. of 1-methyl-3,4-dibromo-4-phenylpiperidine VII hydrobromide in 300 ml. of water. The water was removed under reduced pressure. After drying under reduced pressure a quantitative yield (44.8 g.) of the hydrobromide of VI, m. p. 162–165° (dec.), was obtained. Recrystallization from glacial acetic acid yielded a white solid, m. p. 182–183° (dec.).

Anal. Calcd. for $C_{12}H_{15}Br_2N$: Br (1), 24.0: Br (2), 48.0. Found: Br (Volhard), 23.9; (Mohr), 48.2.

(b) A suspension of 1 g. of 1-methyl-3,4-dibromo-4-phenylpiperidine (VII) in 30 ml. of water was stirred for twenty minutes, during which time the solution became homogeneous. The water was removed under reduced pressure to leave a 0.90 g. (90%) of the hydrobromide of VI, m. p. 162–168° (dec.); recrystallization from glacial acetic acid yielded a product m. p. 182–183° (dec.).

1-Methyl-3,4-dihydroxy-4-phenylpiperidine (VIII).—(a) A solution of 8.3 g. of 1-methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine (VI) hydrobromide in 250 ml. of water was heated for thirty-five hours at 100°. At this point the hydrolysis was complete as indicated by the fact that a Volhard titration of an aliquot showed all the halogen of the original compound to be in the ionic form. The water was removed under reduced pressure to yield a gummy residue, which was divided into two approximately equal portions. The one was dried for eight hours at 0.2 mm. and then treated with 10 ml. of anhydrous acetone to yield 2.0 g. (28%) of the hydrobromide of VIII, m. p. 176–179°. After two recrystallizations from absolute ethanol, this salt melted at 215–216°.

Anal. Calcd. for $C_{12}H_{18}BrNO_2$: Br, 27.7. Found: Br, 27.3.

The other portion of the gummy residue was made basic with potassium hydroxide and extracted with eight 50-ml. portions of ether and a similar amount of chloroform. The extracts were combined and evaporated to dryness and the residue dried for two hours at 0.2 mm. The resultant solid material was recrystallized from benzene to yield 1.2 g. (23%) of crude product, m. p. 125–154°. On recrystallization from petroleum ether (b. p. 90–100°), fine white needles of 1-methyl-3,4-dihydroxy-4-phenylpiperidine (VIII), m. p. 159–160°, were obtained.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27. Found: C, 69.59; H, 8.09.

(b) A solution of 0.3 g. of 1-methyl-3-hydroxy-4-phenyl-1,2,3,6-tetrahydropyridine (V) and 0.29 g. of 48% hydrobromic acid in 8 ml. of water was heated at 100° for eleven hours. The water was removed under reduced pressure on a steam-bath and the solid residue dried at 0.2 mm. for six hours. It then was treated with anhydrous acetone, which left undissolved 0.20 g. (44%) of 1-methyl-3,4-dihydroxy-4-phenylpiperidine hydrobromide, m. p. 215–216°. The acetone solution was evaporated to dryness under a stream of air, the residue dissolved in 3 ml. of water and, after making basic with potassium hydroxide, the aqueous solution was evaporated to dryness under reduced pressure. The solid residue was extracted with five 10-ml. portions of petroleum ether (b. p. 90–100°). The combined extracts were concentrated to a final volume of 10 ml. whereupon 0.05 g. (15%) of 1-methyl-3,4-dihydroxy-4-phenylpiperidine (VIII), m. p. 159–160°, separated.

(c) A solution of 11.33 g. (0.067 mole) of silver nitrate in 10 ml. of water was added to 2.0 g. (0.008 mole) of the hydrobromide of VI dissolved in 40 ml. of water and the resulting mixture allowed to stand for thirty minutes. It then was made basic with aqueous potassium hydroxide and the precipitated solids removed by filtration. The filtrate and precipitate were each extracted first with four 25-ml. portions of ether and then with four 25-ml. portions of chloroform. The combined extracts were evaporated to dryness and yielded 0.57 g. of a gray oil. This residue was dried at 0.2 mm. for two hours and then extracted with 3 ml. of petroleum ether (b. p. 90–100°). A black residue was removed by filtration; the filtrate was cooled to −70° in a Dry Ice–acetone mixture and 0.40 g. (35%) of 1-methyl-3-hydroxy-4-phenyl-1,2,3,6-tetrahydropyridine (V), m. p. 45–46°, was obtained.

The original solid precipitate and the water filtrate were recombined and extracted with two 50-ml. portions of ether. Solid potassium bromide was added to the mixture until no more silver bromide was precipitated. The solid was removed by filtration and the precipitate extracted with three 100-ml. portions of hot methanol. The ether extract, water filtrate and methanol were combined and evaporated to dryness under reduced pressure on a steam-bath. The solid residue was then extracted with five 50-ml. portions of petroleum ether (b. p. 90–100°); these extracts were concentrated to 50 ml. whereupon 0.35 g. (28%) of 1-methyl-3,4-dihydroxy-4-phenylpiperidine (VIII), m. p. 158–160°, separated.

Summary

The preparation and properties of 1-methyl-4-chloro(and bromo)-4-phenylpiperidines, 1-methyl-3,4-dibromo(and dihydroxy)-4-phenylpiperidines and 1-methyl-3-bromo(and hydroxy)-4-phenyl-1,2,3,6-tetrahydropyridines are described.

Some observations on the preparation of 1-methyl-4-phenyl-4-hydroxypiperidine (I) from the reaction of phenylmagnesium bromide with 1-methyl-4-piperidone are reported. An improved method for the preparation of I from this piperidone and phenyllithium is described.

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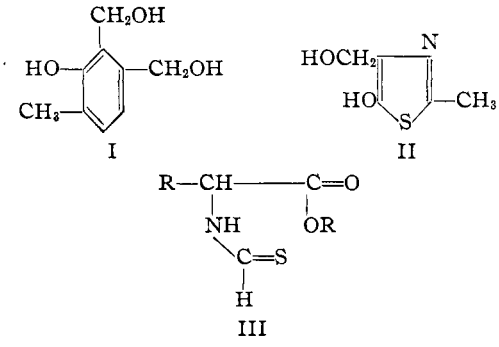
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

2-Methyl-5-ethoxythiazole and Related Compounds[1]

BY D. S. TARBELL, H. P. HIRSCHLER AND R. B. CARLIN

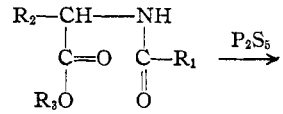
The possibility that analogs of pyridoxine (I) might have antimalarial activity was suggested by some observations of Seeler,[2] and the synthesis of pyridimidine[3] and thiazole[4] analogs of



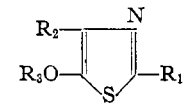
I II III

pyridoxine was therefore undertaken. The 5-hydroxythiazoles were virtually an unknown class of compounds when this work was started, and it therefore seemed of chemical, as well as of antimalarial, interest to investigate the preparation of 2-methyl-4-hydroxymethyl-5-hydroxythiazole II.[5]

One approach to the 5-hydroxythiazole structure would be the treatment of α-amino esters with dithioformic acid[6] followed by cyclization of the α-thioformylamino ester III. However, the reported cyclization[7] of α-acylaminoesters with phosphorus pentasulfide to yield 5-alkoxythiazoles offered an alternative approach. The present paper deals with a study of this cyclization reaction and with the properties of 2-methyl-5-ethoxythiazole.



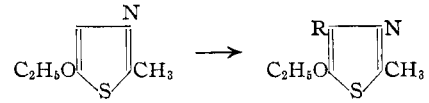
IV, $R_1 = CH_3$, $R_2 = H$, $R_3 = C_2H_5$
V, $R_1 = H$, $R_2 = CH_3$, $R_3 = CH_3$
VI, $R_1 = H$, $R_2 = CH_2OCH_3$, $R_3 = CH_3$



VII, $R_1 = CH_3$, $R_2 = CH_2OCH_3$, $R_3 = CH_3$
VIII, $R_1 = CH_3$, $R_2 = H$, $R_3 = C_2H_5$
IX, $R_1 = H$, $R_2 = CH_3$, $R_3 = CH_3$

It was found that 2-methyl-5-ethoxythiazole VIII could be isolated (as the picrate) in 65% yield from the cyclization of N-acetylglycine ethyl ester IV with phosphorus pentasulfide; the free base was readily obtained from the picrate by the convenient lithium hydroxide method.[8] The cyclization of N-formylalanine methyl ester (V), however, gave only a 22% yield of 4-methyl-5-methoxythiazole IX, and attempted cyclization of N-formyl- and N-acetylserine methyl ether methyl ester (VI and VII) under a variety of conditions gave only decomposition. This behavior was probably caused by the loss of methanol from the serine methyl ether derivatives, followed by polymerization of the acrylate, $CH_2{=}C(NHCOR)COOCH_3$, which would be formed.

2-Methyl-5-ethoxythiazole was found to be a liquid of pyridine-like odor, when pure; it was stable to aqueous alkali, but was decomposed by



VIII X, R = Br XI, R = NO_2

mineral acids when attempts were made to cleave the ether linkage. It formed a picrate,

(1) Part of this work was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Rochester.

(2) Seeler, *Proc. Soc. Exp. Biol. Med.*, **57**, 113 (1944).

(3) (a) McCasland, Tarbell, Carlin and Shakespeare, THIS JOURNAL, **68**, 2390 (1946); McCasland and Tarbell, *ibid.*, **68**, 2393 (1946).

(4) Conover and Tarbell, THIS JOURNAL, in press.

(5) More recently numerous cyclization reactions leading to 5-thiazolone (or 5-hydroxythiazoles) have been studied by Heilbron, A. H. Cook and co-workers (summarized by Heilbron, *J. Chem. Soc.*, 2099 (1949)). The preparation of 2-benzoyl-4-oxymethylene-5-thiazolone and some derivatives is described in "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, pp. 773, 847-848.

(6) *Cf.* Todd, *et al.*, *J. Chem. Soc.*, 361 (1937).

(7) Miyamichi, *J. Pharm. Soc. Japan*, No. **528**, 103 (1926) [*C. A.*, **20**, 2679 (1926); *Chem. Zentr.*, **97**, I, 3402 (1926).

(8) Burger, THIS JOURNAL, **67**, 1615 (1945).