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The Isolation of Neoprotoveratrine and Protoveratrine from *Veratrum viride* Ait.

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RECEIVED MAY 13, 1952

Neoprotoveratrine, a new hypotensively active tetraester of protoverine has been isolated from *Veratrum viride* Ait. On hydrolysis, neoprotoveratrine,  $C_{41}H_{63}O_{15}N$ , yielded the alkamine protoverine as well as  $\alpha$ -methylbutyric acid,  $\alpha$ -methyl- $\alpha,\beta$ -dihydroxybutyric acid, and 2 moles of acetic acid. The isolation of protoveratrine from *Veratrum viride* for the first time is also described.

Neoprotoveratrine ( $C_{41}H_{63}O_{15}N$ ), a new hypotensively active tetraester of protoverine<sup>1</sup> and protoveratrine<sup>3,4</sup> have been isolated from *Veratrum viride*. Previous investigations by Fried, *et al.*,<sup>5,6</sup> have yielded the hypotensively active germines: germinine, germitrine and neogermitrine. Our investigation of the "amorphous bases"<sup>7</sup> employing the technique of Craig's countercurrent distribution yielded germitrine as the main hypotensive principle, thus confirming the findings of Fried, *et al.*<sup>5</sup> Neoprotoveratrine and protoveratrine accounted for approximately 12% of the hypotensive activity.

The basic chloroform extract of the ground roots and rhizomes was fractionated to remove the inactive constituents, yielding the hypotensively active "amorphous bases." This fraction, when dissolved in ether, yielded a crystalline mixture that was resolved by a 24-plate countercurrent distribution (Fig. 1) into two main fractions. The material recovered from tubes 0-12 was crystallized from acetone yielding cubic crystals whose physical

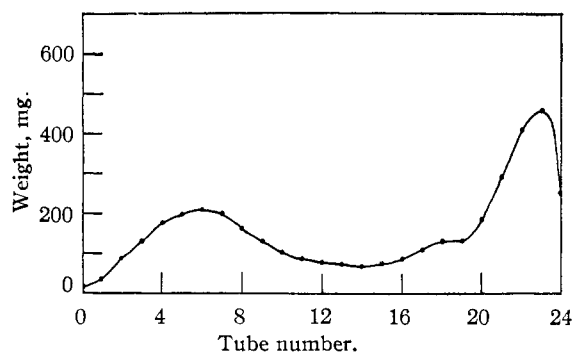


Fig. 1.—Countercurrent distribution of protoveratrine-neoprotoveratrine mixture, benzene-2*M* acetate buffer (pH 5.5).

(1) We have now identified the alkamine of the tetraester escholerine<sup>2</sup> as protoverine.

(2) M. W. Klohs, F. Keller, S. Koster and W. Malesh, *THIS JOURNAL*, **74**, 1871 (1952).

(3) First isolated by Salzberger from *Veratrum album*.

(4) G. Salzberger, *Arch. Pharm.*, **228**, 462 (1890).

(5) Joseph Fried, Howard L. White and O. Wintersteiner, *THIS JOURNAL*, **72**, 4621 (1950).

(6) J. Fried and P. Numerof, *Abst. 119th Meeting A.C.S., Cleveland, Ohio, April, 1951*, p. 12L.

(7) Pharmacological tests<sup>8</sup> on various fractions revealed that the hypotensive activity was concentrated in these "amorphous bases."

(8) The authors are indebted to Drs. George L. Maisin and J. W. Stutzman, Boston University School of Medicine, for the pharmacological tests. The results of these tests<sup>9</sup> and details of the assay procedure<sup>10</sup> have been published elsewhere.

(9) J. W. Stutzman, George L. Maisin and G. W. Kusserow, *Proc. Soc. Exptl. Biol. Med.*, **71**, 725 (1949).

(10) George L. Maisin and J. W. Stutzman, *Arch. Intern. pharmacodynamie*, **85**, 357 (1951).

constants agreed with those of an authentic sample of protoveratrine obtained from *Veratrum album* by the method of Craig and Jacobs.<sup>11</sup>

The material recovered from tubes 18-24 crystallized readily from acetone. To test for homogeneity, a redistribution was made on a 50-plate countercurrent machine. The experimental curve with a peak at tube 32,  $K = 1.78$  (Fig. 2), was in good agreement with the theoretical. The material recovered from the tubes in the peak area was recrystallized from acetone yielding well-defined cubic crystals melting with bubbling and decomposition at 255.4-255.8°,  $[\alpha]^{24}_D -39 \pm 2^\circ$  in pyridine. The marked similarity to protoveratrine has prompted the name neoprotoveratrine for this new alkaloid.

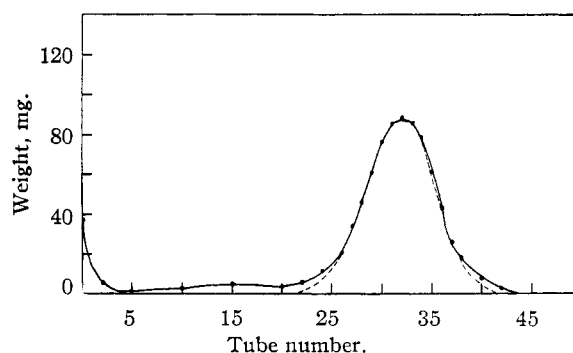


Fig. 2.—Countercurrent distribution of crude neoprotoveratrine, chloroform-carbon tetrachloride 60:40-*M*/2 acetate buffer (pH 5.0) —●—●—●, experimental; - - -, calculated.

The analysis of neoprotoveratrine and its picrate, as well as equivalent weight determinations, were in accord with the theoretical values for  $C_{41}H_{63}O_{15}N$ . In concentrated sulfuric acid neoprotoveratrine slowly developed a greenish-blue color in contrast to protoveratrine which turns violet on standing. In this regard, it is noteworthy that Salzberger originally reported protoveratrine to give a clear solution, changing from green to blue and then violet. The infrared spectrum of neoprotoveratrine (Fig. 3) differed from that of protoveratrine in the region 8.4-9.2 $\mu$  which may be attributed to a difference in the C-O-C vibration of the ester bonds.

Saponification of neoprotoveratrine yielded an alkamine which proved to be identical with protoverine obtained by the saponification of protoveratrine. The acidified mother liquor on extraction with ether yielded acetic acid and  $\alpha$ -methyl-

(11) Lyman C. Craig and Walter A. Jacobs, *J. Biol. Chem.*, **143**, 427 (1942).

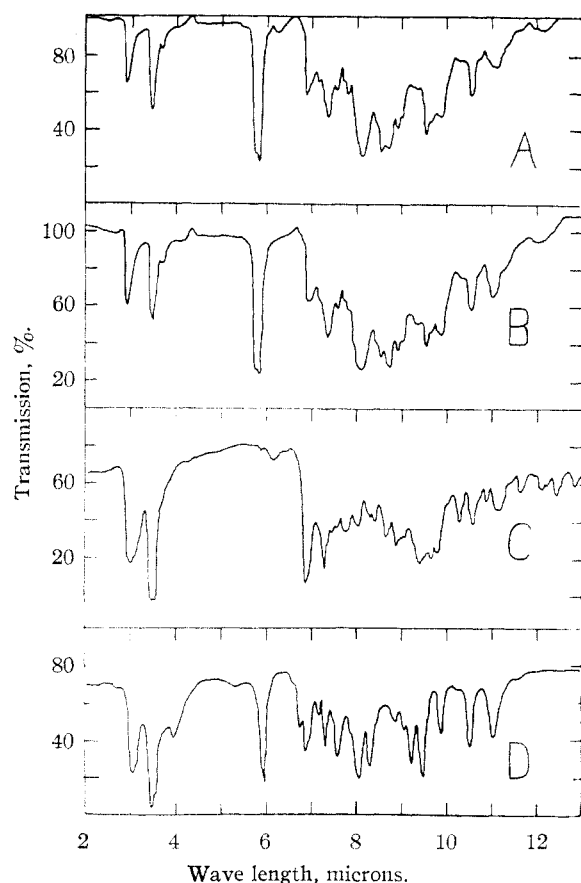


Fig. 3.—Infrared spectra: A, protoveratrine in chloroform; B, neoprotoveratrine in chloroform; C, protoverine in Nujol mull; D,  $\alpha$ -methyl- $\alpha,\beta$ -dihydroxybutyric acid in Nujol mull.

butyric acid, identified as their *p*-phenylphenacyl esters. An additional extraction with *n*-butanol yielded a third acid, m.p. 99–100°,  $[\alpha]_D^{25} + 8 \pm 2^\circ$  (*c* 0.57 in 95% ethanol). The analysis and neutralization equivalent indicated the empirical formula  $C_6H_{10}O_4$ . A negative test for a carbonyl group and a positive test with periodic acid was indicative of a vicinal glycol. Periodic acid cleavage yielded acetaldehyde and pyruvic acid which were identified as their 2,4-dinitrophenylhydrazones. The acid therefore appears to be  $\alpha$ -methyl- $\alpha,\beta$ -dihydroxybutyric acid. A volatile acid determination on neoprotoveratrine gave 2.95 equivalents of acid. Since  $\alpha$ -methyl- $\alpha,\beta$ -dihydroxybutyric acid proved to be non-volatile under the conditions of the volatile acid determination, neoprotoveratrine is a tetraester of protoverine with 2 moles of acetic acid and a mole each of  $\alpha$ -methylbutyric acid and  $\alpha$ -methyl- $\alpha,\beta$ -dihydroxybutyric acid. This is in agreement with the empirical formula  $C_{41}H_{83}O_{15}N$  derived by analyses and equivalent weight determinations.

**Pharmacology.**—The pharmacology of neoprotoveratrine, referred to as alkaloid V-B, and protoveratrine has previously been described.<sup>12–14</sup>

(12) George L. Maison, Eleanor Gotz and J. W. Stutzman, *J. Pharmacol. Exptl. Therap.*, **103**, 74 (1951).

(13) Edward D. Swiss, *ibid.*, **104**, 76 (1952).

(14) Lois Mosey and A. Kaplan, *ibid.*, **104**, 67 (1952).

## Experimental

**Extraction of the Roots and Rhizomes of *Veratrum viride* Ait.**—Ground dried roots and rhizomes<sup>15</sup> of *Veratrum viride* Ait. (66 kg.) were extracted with three 300-kg. portions of chloroform-ammonium hydroxide (1 liter of ammonium hydroxide per 50 kg. of chloroform); the extractions were carried out in stainless steel tanks equipped with a drain. Each extraction was made by stirring for 20 hours and the extracts drained through filter pads into a stainless steel vacuum still. The combined extracts were concentrated to 18 kg. at 175–225 mm. pressure and then further concentrated in glass stills at 100–120 mm. pressure to approximately 3 kg. of a brown, viscous liquid. The concentrate was slowly poured with vigorous stirring into 17.3 l. of aqueous 5% acetic acid and the resulting insoluble tarry materials were removed by filtering through cotton towelling and further clarified by passing through an asbestos pad. A solution of ammonium sulfate (1725 g.) in 1.6 l. of water was added to the filtrate with stirring and allowed to stand for one hour. The precipitated fraction (fraction A) thus obtained consisted mainly of secondary amine alkaloids with negligible hypotensive activity and was set aside. The filtrate was cooled to 4° in a jacketed tank and made basic with ammonium hydroxide; the maximum temperature during this step was 12°. The free bases were immediately extracted successively with one 10-l. and two 5-l. portions of chloroform. The combined extracts were dried over anhydrous sodium sulfate and then concentrated to dryness at 100–120 mm. pressure. The residue (420 g.) was extracted with benzene (4.2 l.) by stirring for one hour at room temperature and was then filtered. The precipitate was washed with benzene (2.1 l.) and set aside (Fraction B). The filtrate and wash were combined and concentrated to dryness at 100–120 mm. pressure yielding a tan-colored resin (308 g.). By dissolving the resin in acetone (1.52 l.) and refrigerating for 4 hours at 10° a white semi-crystalline material (fraction C), consisting mainly of isorubijervine, was removed by filtration and washed with cold acetone (0.6 l.). The combined filtrate and wash were concentrated to dryness at 100–120 mm. pressure yielding the "amorphous bases" (249 g.).

**Separation of Neoprotoveratrine and Protoveratrine Mixture from the "Amorphous Bases."**—The amorphous mixture (50 g.) was dissolved as much as possible in one liter of dry ether and filtered. On standing overnight, a white crystalline powder was obtained from the filtrate. The crystalline material (6 g.) was dissolved with heating in 300 ml. of acetone and concentrated on the steam-bath to approximately 150 ml. Crystallization began immediately. The crystalline material was recovered by filtration and the mother liquor concentrated further to yield additional crystalline product. This procedure was continued until the crystals no longer gave the characteristic spot test with concentrated sulfuric acid for neoprotoveratrine or protoveratrine. The crystalline fractions were then combined (3.5 g.).

**Separation of Neoprotoveratrine and Protoveratrine by 24-Plate Countercurrent Distribution.**—Eight and one-half grams of the above crystals was distributed using Craig's fundamental procedure employing 25 one-liter separatory funnels. Benzene-2*M* acetate buffer pH 5.5, 450 ml. in each phase, was used for the solvent system. On completion of the distribution, the contents of each funnel was made basic with aqueous 2 *M* sodium carbonate solution. The layers were separated and the aqueous phases extracted with chloroform until a negative test was obtained with Wagner reagent. The benzene and the chloroform extracts from each funnel were combined and washed with water (50 ml.). The extracts were then dried over anhydrous sodium sulfate and evaporated to dryness under vacuum. The weight of material obtained from each funnel is plotted as a function of the funnel number in Fig. 1.

**Protoveratrine.**—On crystallizing the material (1.64 g.) recovered from tubes 0–12 from acetone, prisms formed (1.01 g.), m.p. 255° (dec.),<sup>16</sup>  $[\alpha]_D^{25} - 8.3 \pm 2^\circ$  (*c* 1.0 in

(15) The roots and rhizomes were collected during the summer of 1950 in the province of Quebec, Canada.

(16) All melting points are corrected. They were determined in a Hershberg m.p. apparatus using total immersion N.B.S. calibrated thermometers. The melting points of protoveratrine, neoprotoveratrine and neoprotoveratrine picrate were taken in evacuated capillaries. In all cases, the rate of heating was 1° per minute.

$\text{CHCl}_3$ ). The infrared spectrum was identical with that of an authentic sample of protoveratrine from *Veratrum album*. For analysis, the sample was dried at  $110^\circ$  (2 mm.) for 16 hours.

*Anal.* Calcd. for  $\text{C}_{38}\text{H}_{61}\text{O}_{13}\text{N}$ : C, 62.28; H, 8.18. Found: C, 61.98; H, 8.16.

In a volatile acid determination 14.40 mg. required 5.45 ml. of 0.009125  $N$   $\text{Na}_2\text{S}_2\text{O}_3$  or 2.59 equivalents.

**Neoprotoveratrine.**—On crystallizing the material (1.84 g.) recovered from tubes 18–24 from acetone, prisms formed (1.14 g.), m.p.  $253^\circ$  (dec.). To establish homogeneity, the alkaloid (0.99 g.) was distributed on a Craig Countercurrent Machine (glass) using chloroform–carbon tetrachloride 60:40 and  $M/2$  sodium acetate buffer pH 5.0 as the solvent system; 50 ml. being employed for each phase. The material in each tube was recovered as previously described and the results plotted (Fig. 2). The material recovered from tubes 26–38 was recrystallized three times from acetone yielding 0.34 g., m.p.  $255.4$ – $255.8^\circ$ ,  $[\alpha]^{24}_D -39 \pm 2^\circ$  ( $c$  1.0 in pyridine);  $-3.8 \pm 2^\circ$  ( $c$  1.0 in  $\text{CHCl}_3$ ). For analysis, the sample was dried at  $110^\circ$  (2 mm.) for 36 hours.

*Anal.* Calcd. for  $\text{C}_{41}\text{H}_{65}\text{O}_{15}\text{N}$ : C, 60.80; H, 7.84; N, 1.73; equiv. wt., 809.9. Found: C, 60.87; H, 7.99; N, 2.03; equiv. wt., 810.<sup>17</sup>

In a volatile acid determination 14.65 mg. required 5.72 ml. of 0.009317  $N$   $\text{Na}_2\text{S}_2\text{O}_3$  or 2.95 equivalents.

**Neoprotoveratrine Picrate.**—Neoprotoveratrine (75 mg.) was dissolved in 5% acetic acid (2 ml.) and a saturated aqueous solution of picric acid was added dropwise until no further precipitate formed. The precipitate was collected and crystallized twice from dilute acetone; m.p.  $233^\circ$  (dec.). For analysis the sample was dried at  $110^\circ$  (2 mm.) for 16 hours.

*Anal.* Calcd. for  $\text{C}_{41}\text{H}_{63}\text{O}_{15}\text{N} \cdot \text{HOC}_6\text{H}_2(\text{NO}_2)_3$ : C, 54.32; H, 6.22. Found: C, 54.01; H, 6.37.

**Hydrolytic Cleavage of Neoprotoveratrine to Protoverine,  $\alpha$ -Methylbutyric Acid, Acetic Acid and  $\alpha$ -Methyl- $\alpha$ , $\beta$ -dihydroxybutyric Acid.**—Neoprotoveratrine (0.5 g.) was suspended in 1  $N$  methanolic  $\text{NaOH}$  (5 ml.) and heated on the steam-bath for ten minutes. The solution was then cooled and adjusted to pH 2.0 with 12  $N$   $\text{H}_2\text{SO}_4$  and buffered at pH 8.5 by addition of a saturated solution of sodium carbonate. The solution was transferred to a Wehrli extractor fitted with a 25-ml. receiver, diluted to 20 ml. with distilled water and extracted continuously for 24 hours with chloroform. At the end of this time, clumps of slender needles had formed in the receiver. The crystals were collected by filtration (145 mg.) and recrystallized 3 times from methanol yielding prisms, m.p.  $192.6^\circ$ ,  $[\alpha]^{24}_D -21.7 \pm 2^\circ$  ( $c$  1.7 in pyridine). For analysis the sample was dried at  $130^\circ$  (2 mm.) to constant wt.

*Anal.* Calcd. for  $\text{C}_{27}\text{H}_{45}\text{O}_9\text{N}$ : C, 61.67; H, 8.25. Found: C, 61.54; H, 8.26.

Protoverine obtained by treating protoveratrine in the same manner yielded needles which on three recrystallizations from methanol formed prisms, m.p.  $190.5^\circ$ ,  $[\alpha]^{24}_D -20 \pm 2^\circ$  ( $c$  1.0 in pyridine). For analysis, the sample was dried to constant wt. at  $130^\circ$  (2 mm.).

*Anal.* Calcd. for  $\text{C}_{27}\text{H}_{45}\text{O}_9\text{N}$ : C, 61.67; H, 8.25. Found: C, 61.61; H, 8.29.

**Acetonylprotoverine.**—The protoverine (100 mg.) from neoprotoveratrine was converted to the hydrochloride of the acetone compound by the method of Jacobs and Craig.<sup>18</sup> The resulting material (yield 99 mg.) was recrystallized twice from methanol–acetone, yielding needles, m.p.  $272^\circ$ . For analysis the sample was dried at  $130^\circ$  (2 mm.) to constant weight.

*Anal.* Calcd. for  $\text{C}_{30}\text{H}_{48}\text{O}_9\text{NCl}$ : C, 59.82; H, 8.04. Found: C, 59.82; H, 8.25.

Protoverine treated in the same manner yielded needles, m.p.  $273^\circ$ ; for analysis the sample was dried at  $130^\circ$  (2 mm.) to constant weight.

*Anal.* Found: C, 59.62; H, 7.81.

Acetonylprotoverine hydrochloride (50 mg.) was converted to acetonylprotoverine by the method of Jacobs and Craig.<sup>18</sup> The resulting material was recrystallized from

methanol yielding platelets, m.p.  $243^\circ$ . For analysis the sample was dried at  $130^\circ$  (2 mm.) to constant weight.

*Anal.* Calcd. for  $\text{C}_{30}\text{H}_{47}\text{O}_9\text{N}$ : C, 63.67; H, 8.38. Found: C, 63.77; H, 8.25.

**The Identification of Acetic,  $\alpha$ -Methylbutyric and  $\alpha$ -Methyl- $\alpha$ , $\beta$ -dihydroxybutyric Acids.**—The aqueous layer remaining after extraction of the alkaline was adjusted to pH 3.0 with concd.  $\text{H}_2\text{SO}_4$  and extracted four times with equal volumes of ether. The combined ether extracts were evaporated under a slow current of air. Five ml. of water was then added and the pH adjusted to 6.2 with a saturated sodium carbonate solution. Ethanol (20 ml.) and  $p$ -phenylphenacyl bromide (0.5 g.) were added and the mixture refluxed for two hours. The ethanol was then removed under vacuum at room temperature and the remaining solution extracted with benzene. The benzene extracts were dried over sodium sulfate and evaporated to dryness. The solids were dissolved in 10 ml. of a mixture consisting of equal portions of benzene and petroleum ether ( $69$ – $74^\circ$ ) and chromatographed on a silicic acid–Celite 3:1 (8 g.) column.<sup>19</sup> Elution of the column with the same solvent mixture yielded in the first ten fractions (5-ml. cuts) unreacted  $p$ -phenylphenacyl bromide, m.p.  $125^\circ$ . The next ten fractions yielded a substance which after recrystallization from dilute alcohol melted at  $69.8$ – $70.1^\circ$ . The infrared spectra of this substance and  $p$ -phenylphenacyl- $\alpha$ -methyl butyrate were identical. For analysis the sample was dried at  $25^\circ$  (2 mm.) over  $\text{P}_2\text{O}_5$  for 24 hours.

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{20}\text{O}_3$ : C, 77.01; H, 6.80. Found: C, 77.33; H, 7.05.

Continued elution with the same solvent mixture yielded a third fraction which on recrystallizing from 95% ethanol melted at  $110.2$ – $111.2^\circ$ . The infrared spectra of this substance and  $p$ -phenylphenacyl acetate were identical. A mixed melting point gave no depression. For analysis the sample was dried at  $25^\circ$  (2 mm.) over  $\text{P}_2\text{O}_5$  for 24 hours.

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{14}\text{O}_3$ : C, 75.58; H, 5.55. Found: C, 75.40; H, 5.63.

The aqueous layer remaining after the ether extractions was then extracted five times with equal volumes of  $n$ -butanol. The combined extracts were evaporated to dryness under a current of air, depositing a cream-colored solid. For purification, this was crystallized from benzene, m.p.  $99$ – $100^\circ$ ,  $[\alpha]^{24}_D +8 \pm 2^\circ$  ( $c$  0.57 in 95% ethanol). For analysis the sample was dried to constant weight at  $25^\circ$  (2 mm.) over  $\text{P}_2\text{O}_5$ .

*Anal.* Calcd. for  $\text{C}_8\text{H}_{10}\text{O}_4$ : C, 44.71; H, 7.46; neut. equiv., 134.13. Found: C, 45.32; H, 7.34; neut. equiv., 132.8.

The acid failed to form a 2,4-dinitrophenylhydrazone and gave a positive test with periodic acid reagent, indicating the presence of a vicinal glycol. For identification of the cleavage products, the compound (56 mg.) was placed in a ten-ml. distilling flask equipped with an extra side arm, through which a slow stream of air was passed. The outgoing vapors were bubbled through a solution of freshly prepared 2,4-dinitrophenylhydrazine. An excess of periodic acid was added through a dropper placed in the neck of the flask and the temperature was slowly raised to  $50^\circ$  and maintained at that temperature for one hour. A yellow 2,4-dinitrophenylhydrazone began to precipitate almost immediately. On recrystallization from alcohol, this material yielded orange needles, m.p.  $148.0$ – $148.5^\circ$ . The metastable form of acetaldehyde 2,4-dinitrophenylhydrazone has been reported as melting at  $147^\circ$ .<sup>20</sup> Infrared spectra of this compound and an authentic sample of acetaldehyde 2,4-dinitrophenylhydrazone were identical. The periodic acid solution was extracted with ether. On evaporation, the residue formed a 2,4-dinitrophenylhydrazone which on repeated crystallization from alcohol yielded orange cubes, m.p.  $216^\circ$ . A mixed melting point of this compound with an authentic sample of the 2,4-dinitrophenylhydrazone of pyruvic acid gave no depression.

**Acknowledgments.**—We are indebted to Dr. Adalbert Elek for the carbon and hydrogen analyses and S. M. Nagy for the volatile acid determina-

(17) By titration with perchloric acid in glacial acetic acid solution.

(18) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **149**, 276 (1942).

(19) J. G. Kurchner, A. H. Prater and A. J. Haagen-Smit, *Ind. Eng. Chem., Anal. Ed.*, **18**, 31 (1946).

(20) W. M. D. Bryant, *This Journal*, **58**, 2335 (1936).

tions. We also wish to express our thanks to M. Robinson, B. Creapeau and C. Stimmel in the Riker Analytical Department for the optical rotations,

infrared spectra and equivalent weight determinations.

LOS ANGELES, CALIFORNIA

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

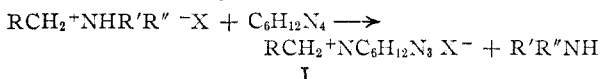
## A New Synthesis of Indole-3-aldehydes. The Reaction of Hexamethylenetetramine with Some Mannich Bases

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RECEIVED MARCH 31, 1952

When gramine, the Mannich base from indole, dimethylamine and formaldehyde, is heated in acetic acid or dilute propionic acid with hexamethylenetetramine and the reaction mixture is poured into water, indole-3-aldehyde is formed. The process provides a very convenient synthesis, and it can be applied to Mannich bases related to substituted indoles. Certain phenolic Mannich bases can be converted to aldehydes in the same way, but in poorer yields. Mannich bases derived from ketones evidently do not undergo the reaction.

A large number of amines of the type  $\text{RCH}_2\text{-NR}'\text{R}''$  prepared by the Mannich reaction are active alkylating agents, and many of them react with primary or secondary amines by a process of amine exchange<sup>2</sup> in which the residue  $\text{RCH}_2\text{-}$  is transferred to another nitrogen atom. It would seem likely that such reactive Mannich bases, either in acid solution or in the form of their quaternary salts, might react with hexamethylenetetramine to give salts of the type (I) encountered in the Sommelet<sup>3</sup> synthesis.



The success of such an interchange then would make possible the conversion of a tertiary amine or a quaternary salt to an aldehyde, since salts of the type I are easily hydrolyzed to yield aldehydes.<sup>3</sup>

The conversion of primary and secondary amines containing a radical of the benzyl type by means of a modified Sommelet reaction has been described.<sup>4,5</sup> The success of this process led to the formulation of a mechanism for the ordinary Sommelet reaction consisting in the *initial formation of a primary amine* which is dehydrogenated and hydrolyzed to an aldehyde.<sup>5</sup> In accordance with this mechanism benzyl dimethylamine was found not to give benzaldehyde. Thus it would seem likely that the conversion of gramine to indole-3-aldehyde could occur *only* if amine interchange is the *initial* step.

In a test of the proposed interchange gramine ( $\beta$ -dimethylaminomethylindole, a Mannich base of indole) and hexamethylenetetramine were heated in glacial acetic acid solution for five minutes and the solution was diluted with cold water. From the solid material which separated, 3-indolealdehyde was obtained in 25% yield. A considerable amount of resinous material was formed also. A number of experimental variations were studied, and it was found possible to obtain the pure aldehyde (m.p. 191–193°) in 53% yield by carrying

out the reaction over a period of one hour in 66% propionic acid. The use of indole Mannich bases derived from secondary amines other than dimethylamine, such as diethylamine and piperidine, offered no advantage.

Since gramine is easily obtained from indole by means of the Mannich reaction, this sequence provides a very convenient synthesis of indole-3-aldehyde. It is also very attractive for the synthesis of certain substituted indole-3-aldehydes. In the present work 2-carbethoxyindole-3-aldehyde and 2-phenylindole-3-aldehyde were obtained in best yields (60–70% and 70–80%, respectively) when the reactions were carried out in refluxing glacial acetic acid over periods of only three and five minutes, respectively. However 2-methylindole-3-aldehyde could be obtained in only trace amounts under any experimental conditions tried. Evidently the character of a substituent in the  $\alpha$ -position has a profound influence on the course of the reaction.

Although the new synthesis was suggested by the analogy to the Sommelet reaction, it is conceivable that under the conditions used the Mannich bases are hydrolyzed to indole, formaldehyde and the secondary amines, and that the aldehyde is formed from indole. The process would then be similar to the Duff<sup>6,7</sup> synthesis, in which a phenolic aldehyde is prepared from a phenol, hexamethylenetetramine and glyceroboric acid. However, when indole was substituted for its Mannich base none of the aldehyde was formed; hence the process cannot be regarded as a variant of the Duff reaction.

Another method of converting an amine to an aldehyde, as a derivative, is that devised by Fisher<sup>8</sup> in which an  $\alpha$ -aminoaldehyde or ketone<sup>9,10</sup> is transformed into an osazone by the action of phenylhydrazine. It was of interest to find whether gramine would react in a similar way to give the phenylhydrazone of indole-3-aldehyde. An attempt yielded only resinous materials.

The new reaction has been applied to phenolic Mannich bases, such as 1-dimethylaminomethyl-

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(2) H. R. Snyder and J. H. Brewster, *THIS JOURNAL*, **70**, 4230 (1948).

(3) M. Sommelet, *Compt. rend.*, **157**, 852 (1913).

(4) J. Graymore and D. R. Davies, *J. Chem. Soc.*, 293 (1945).

(5) S. Angyal and R. C. Rassack, *Nature*, **161**, 723 (1948); *J. Chem. Soc.*, 2700 (1949).

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