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

Reduction Products of the Rubremetinium Cation[1]

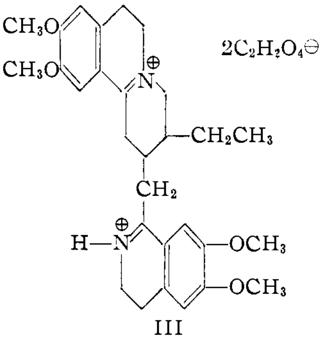
BY RAYMOND F. TIETZ AND WILLIAM E. MCEWEN

RECEIVED APRIL 1, 1953

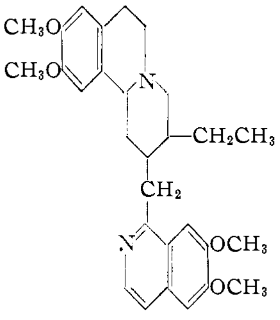
Several reduction products of the rubremetinium cation have been described in the literature. Since there are some inconsistencies in the data, all of the reported reduction procedures have been repeated and the reduction products re-examined. Isotetrahydrodehydroemetine was found to be identical with "α-dihydrorubremetine." Tetrahydrodehydroemetine was obtained both by direct hydrogenation of rubremetinium chloride and by the two-stage reduction of the salt, involving first treatment with lithium aluminum hydride, then catalytic hydrogenation. β-Dihydrorubremetine was isolated only when the catalytic hydrogenation of rubremetinium chloride was interrupted after the absorption of one mole of hydrogen. Catalytic hydrogenation of dehydrohalorubremetine gave mainly the previously reported racemic tetrahydrodehydrohalorubremetine plus a small amount of an optically active base. The infrared spectra of the racemic and active products were identical. Two moles of hydrogen were taken up in each of the catalytic hydrogenations of rubremetinium chloride, "o-dihydrodehydroemetine" and dehydrohalorubremetine. The ultraviolet spectra of all the above-mentioned reduction products of the rubremetinium cation were found to be closely related.

One of the more interesting reactions of the alkaloid emetine (I)[2] is its conversion to the rubremetinium cation by means of a variety of mild oxidizing agents, such as ferric chloride,[3] iodine,[4] bromine[5] and mercuric acetate.[6] Other relatives of emetine which can similarly be dehydrogenated to the rubremetinium cation include O-methylpsychotrine (II),[7] isoemetine (differs from emetine in the configuration of C_1'),[8] tetradehydroemetine hydrogen oxalate (III),[6,9] and isotetradehydroemetine.[10] Emetamine (IV),[7a,b,11] however, gives a similar but not identical cation on mild oxidation.[7c]

On the basis of a molecular formula reported to be $C_{29}H_{33}N_2O_4Cl$,[3-5] the orange-red color, the quaternary nature of both nitrogen atoms, the nonidentity of rubremetinium chloride and the similar oxidation product of emetamine (IV), the catalytic hydrogenation of rubremetinium chloride to a dihydro derivative which was readily reoxidized by air, and the red pine shaving reaction given by tetrahydrodehydroemetine,[7c,12] a reduction product of the rubremetinium cation, structure V was proposed for rubremetinium chloride.[13]



III



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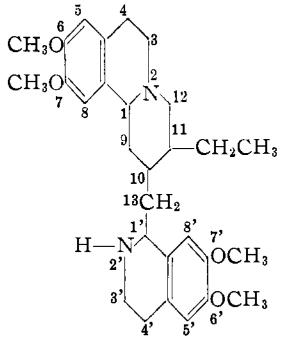
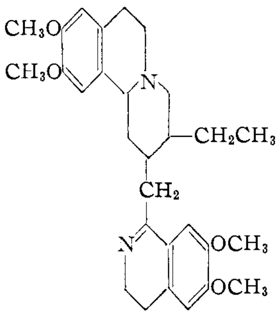
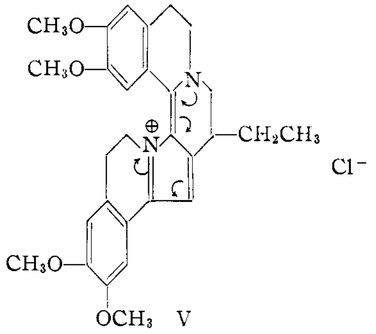


I



II



V

Karrer and Ruttner[14] objected to structure V on the grounds that it represented an illogical product of a dehydrogenation reaction. They also reported that lithium aluminum hydride reduction of rubremetinium bromide gave a dihydro derivative, o-dihydrodehydroemetine, which catalytically added one mole of hydrogen to give a mixture of two tetrahydro derivatives, tetrahydrodehydroemetine, m.p. 134°, $[\alpha]^{18}\text{D}$ +42° (ethanol solution) and isotetrahydrodehydroemetine, m.p. 194°, $[\alpha]^{18}\text{D}$ −380° (ethanol solution). Structure V would be expected to give only a dihydro derivative as a result of mild reduction.

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[1] This paper was presented before the Organic Division of the American Chemical Society, Atlantic City, N. J., Sept. 14–19, 1952.

[2] (a) M. Pailer and K. Porschinski, *Monatsh.*, **80**, 94 (1949); (b) A. R. Battersby and H. T. Openshaw, *J. Chem. Soc.*, 3207 (1949).

[3] F. H. Carr and F. L. Pyman, *ibid.*, **105**, 1591 (1914).

[4] P. Karrer, *Ber.*, **49**, 2057 (1916).

[5] H. Staub, *Helv. Chim. Acta*, **10**, 826 (1927).

[6] A. R. Battersby and H. T. Openshaw, *J. Chem. Soc.*, S67 (1949).

[7] (a) F. L. Pyman, *ibid.*, 111, 419 (1917); (b) W. H. Brindley and F. L. Pyman, *ibid.*, 1067 (1927). These authors also reported that O-methylpsychotrine can be converted to the rubremetinium cation by means of chromic acid; (c) P. Karrer, C. H. Eugster and O. Ruttner, *Helv. Chim. Acta.*, **31**, 1219 (1948); (d) M. I. Moyer and W. E. McEwen, THIS JOURNAL, **73**, 3075 (1951); (e) H. T. Openshaw and H. C. S. Wood, *J. Chem. Soc.*, 391 (1952).

[8] F. L. Pyman, *ibid.*, **113**, 222 (1918).

[9] Openshaw and Wood[7e] have assigned this structure on a tentative basis.

[10] R. N. Hazlett and W. E. McEwen, THIS JOURNAL, **73**, 2578 (1951).

[11] A. Ahl and T. Reichstein, *Helv. Chim. Acta*, **27**, 366 (1944).

[12] P. Karrer, *Ber.*, **50**, 582 (1917). Whereas Pyman named the salts as derivatives of the hypothetical base rubremetine, $C_{29}H_{32}N_2O_4$, Karrer employed the name dehydroemetine.

[13] A. R. Battersby, H. T. Openshaw and H. C. S. Wood, *Experientia*, **5**, 114 (1949).

[14] P. Karrer and O. Ruttner, *Helv. Chim. Acta*, **33**, 291 (1950).

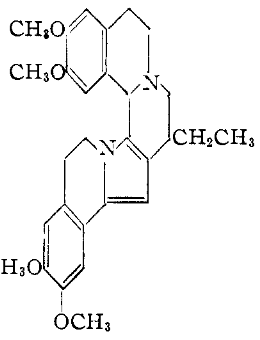
In the meantime, Battersby and Openshaw[15] reported the total synthesis of *d,l*-rubremetinium bromide. Since the salt was obtained by mercuric acetate oxidation of racemic O-methylpsychotrine or one of its diastereoisomers, however, this synthesis did not serve to establish the complete structure of the rubremetinium cation.

The situation with regard to structure V became further confused when it was found[10] that rubremetinium chloride reacted with hot aqueous alcoholic alkali to give a crystalline product, dehydrohalorubremetine,[16] which did not give back rubremetinium chloride on reaction with hydrochloric acid. On catalytic hydrogenation it appeared to absorb nearly two moles of hydrogen to give a racemic product, "tetrahydrodehydrohalorubremetine," the ultraviolet absorption spectrum of which was very similar to those of tetrahydrodehydroemetine and isotetrahydrodehydroemetine. Since the hydrogenation was carried out on crude dehydrohalorubremetine, and since the yield of completely purified racemic tetrahydrodehydrohalorubremetine was low, however, the designation as a tetrahydro derivative was admittedly insecurely based.

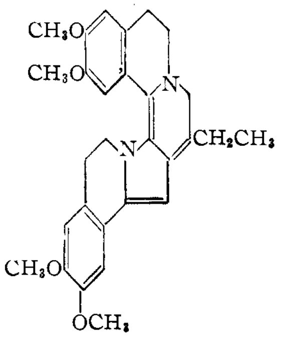
Recently Openshaw and Wood[7e] have reported new data which served to support structure V. Hydrogenation of rubremetinium chloride in ethanol solution, in the presence of sodium acetate and platinum oxide catalyst, resulted in the absorption of one mole of hydrogen. The hydrogenation mixture consisted of two stereoisomeric dihydrorubremetines, the α-isomer being strongly levorotatory, $[\alpha]^{15}\text{D}$ −395° (*c* 0.165 in acetone) and the β-isomer even more strongly dextrorotatory, $[\alpha]^{15}\text{D}$ +406° (*c* 0.148 in acetone). When the original mixture was crystallized from methanol, a "partial racemate" separated as a complex containing one molecule of each isomer and two molecules of methanol, m.p. 128° and $[\alpha]^{12}\text{D}$ +21.2° (*c* 0.176 in acetone). From the mother liquor the pure α-isomer, m.p. 198°, was obtained. The complex split up on crystallization from ethanol, and the less soluble β-isomer, m.p. 202°, separated first. If methanol solutions of the two pure isomers were mixed, the "partial racemate" was again precipitated.

Openshaw and Wood[7e] extended their arguments in support of structure V for the rubremetinium cation by assigning to α- and β-dihydrorubremetine the structure VI. They carried out additional qualitative tests which provided strong support for the presence of a pyrrole ring in the isomeric dihydrorubremetines. They further suggested that dehydrohalorubremetine possesses structure VII, "in which the sole remaining asymmetric center of rubremetine has been destroyed."

Meanwhile the preparation and catalytic reduction of dehydrohalorubremetine had been repeated in these laboratories on a larger scale than previously employed.[10] The crude dehydrohalorubremetine was found to absorb about 1.8 moles of hydrogen. The major product was the previous[10] racemic tetrahydrodehydrohalorubremetine. In addition, a small amount of another crystalline base, m.p. 165.8–166.0°, $[\alpha]^{23}\text{D}$ +11.4° (*c* 2.10 in acetone), was isolated. These two compounds accounted for almost all of the isolable material. Both compounds gave correct analyses for $C_{29}H_{34}N_2O_4$. Both had identical infrared absorption spectra in nujol mull. The ultraviolet spectra of both substances, while very similar, were not identical (Fig. 1). The racemic product gave a correct analysis for one active hydrogen, but the experimental value was about half of the theoretical value for one active hydrogen in the case of the optically active product. Both compounds gave analyses for terminal methyl groups slightly in excess of the theoretical value for one $C{-}CH_3$ group. Despite the relatively minor discrepancies, it appears probable that the two substances are the active and racemic forms of the same compound.



VI



VII

In view of the confusing and apparently inconsistent data summarized above, we set out to repeat the other reduction procedures for rubremetinium chloride described in the literature. On hydrogenation of rubremetinium chloride by the method of Openshaw and Wood,[7e] we found that 1.5 moles of hydrogen was absorbed in 29 hours. After addition of fresh catalyst, an additional 0.5 mole of hydrogen was absorbed in another 110 hours. It is significant that there was a sharp break in the rate of absorption of hydrogen after slightly more than one mole had been consumed. The first mole was absorbed in only one hour, the second mole in a period greater than 100 hours. This probably explains why Openshaw and Wood[7e] thought that the hydrogenation had stopped after the absorption of only one mole of hydrogen. The solution still possessed a faint red tint after one mole of hydrogen had been consumed, the last trace of reddish color disappearing when about 1.2 moles of hydrogen had been absorbed. This suggests that at least a small portion of the rubremetinium cation had been reduced to the tetrahydro stage by the time one mole of hydrogen was taken up.

Two products were obtained from the hydrogenation mixture. One, m.p. 196.2–197.2°, $[\alpha]^{26}\text{D}$ −392° (*c* 0.255 in absolute ethanol), corresponds in physical properties to "α-dihydrorubremetine"[7e] and to isotetrahydrodehydroemetine.[14] The second product, m.p. 132.0–132.8°, $[\alpha]^{22}\text{D}$ +18° (*c* 0.275 in acetone), $[\alpha]^{26}\text{D}$ +41.9° (*c* 0.691 in abso-

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[15] A. R. Battersby and H. T. Openshaw, *Experientia*, **VI**, 378 (1950).

[16] The name is objectionable when considered in relation to Pyman's hypothetical rubremetine. Yet it suggests the origin of the compound and will be retained for that reason.

lute ethanol), corresponds closely to tetrahydrodehydroemetine.[14] No products corresponding in properties either to β-dihydrorubremetine or to the complex containing methanol of crystallization were obtained. This indicates, therefore, that the reported[7e] β-dihydrorubremetine is indeed a dihydro derivative and that the reported complex consists of one molecule each of β-dihydrorubremetine and isotetrahydrodehydroemetine plus two molecules of methanol. The report of Openshaw and Wood[7e] on the relatively poor solubility of β-dihydrorubremetine in ethanol parallels one of our observations. During the hydrogenation of rubremetinium chloride in ethanol, a heavy precipitate appeared shortly after the absorption of one mole of hydrogen. This precipitate gradually disappeared as the second mole of hydrogen was consumed. By interrupting the hydrogenation at the point where one mole of hydrogen had been absorbed and collecting the precipitate which had formed, we were able to identify it as β-dihydrorubremetine, m.p. 201.5–202.5°, $[\alpha]^{21}\text{D}$ +402° (c 0.189 in acetone). In a separate experiment this was shown to absorb one mole of hydrogen on catalytic hydrogenation at atmospheric pressure and room temperature.

Reduction of rubremetinium chloride, first by treatment with lithium aluminum hydride, then catalytically with hydrogen, according to the method of Karrer and Ruttner,[14] also gave two products. One, m.p. 195.0–195.6°, corresponds to isotetrahydrodehydroemetine. This was shown to be identical with the "α-dihydrorubremetine" mentioned above, as evidenced by a mixed m.p. test and the identity of the ultraviolet spectra.[7e,14] The second product, m.p. 131.4–132.4°, corresponds to tetrahydrodehydroemetine. It was shown by a mixed m.p. test and the identity of the ultraviolet spectra to be identical with the substance of similar melting point obtained by the direct hydrogenation of rubremetinium chloride.

Although we found agreement with Karrer and Ruttner on the properties of the reduction products, we found one point of divergence on the experimental details. Whereas Karrer and Ruttner reported that "o-dihydrodehydroemetine," the product of lithium aluminum hydride "reduction," took up one mole of hydrogen on catalytic hydrogenation, we observed the uptake of two moles of hydrogen. Therefore we suspect that "o-dihydrodehydroemetine" is the product of an elimination reaction.

Thus there are several reduction products of the rubremetinium cation. All possess very similar ultraviolet absorption spectra (Fig. 1).[7e,14] Tetrahydrodehydroemetine and isotetrahydrodehydroemetine doubtless correspond to the general structure VI. Both are apparently formed from the rubremetinium cation by the uptake of two moles of hydrogen. Satisfactory structures for the rubremetinium cation and its reduction products must, of course, be capable of explaining these facts.

Woodward's structure (VIII)[17] for the rubremetinium cation is widely known, although the structure has not been published. The unique feature of this structure is that the optical activity of the cation is attributable to molecular dissymmetry resulting from crowding at the starred positions of VIII. The molecular formula for rubremetinium chloride on the basis of structure VIII would be $C_{29}H_{31}N_2O_4Cl$ rather than the previously accepted formula, $C_{29}H_{33}N_2O_4Cl$. It is clear that structure VIII nicely accommodates the relationship between the rubremetinium cation and the tetrahydro derivatives, tetrahydrodehydroemetine and isotetrahydrodehydroemetine (VI).

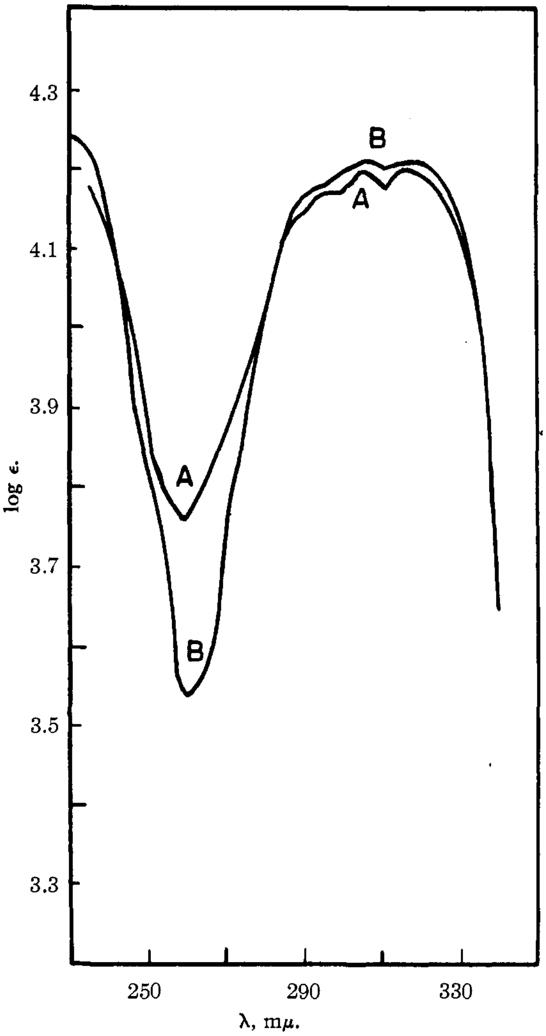
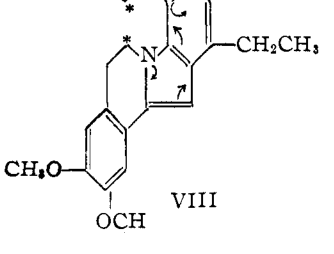


Fig. 1.—Ultraviolet absorption spectra in ethanol solution of (A) racemic tetrahydrodehydrohalorubremetine and (B) dextrorotatory tetrahydrodehydrohalorubremetine.



VIII

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(17) Private communication from R. B. Woodward, November 28, 1950.

Three facts suggest that dehydrohalorubremetine is a Hofmann degradation product of the rubremetinium cation (VIII): (1) Extensive racemization accompanies formation of dehydrohalorubremetine. (2) A Zerewitinoff determination shows that there is one active hydrogen present in racemic "tetrahydrodehydrohalorubremetine." (3) Both racemic and active "tetrahydrodehydrohalorubremetine," appear to possess two $C-CH_3$ groups. Although the analyses correspond only to slightly more than one $C-CH_3$ group, it is known that considerably less than the theoretical value is ordinarily found in the Kuhn–Roth determination. Compare, for example, the data on the Kuhn–Roth determination of $C-CH_3$ in the case of tetrahydrodesdimethylapoerysotrine.[18,19]

The hydrogenation data for dehydrohalorubremetine are inconsistent with a Hofmann degradation product, however, and therefore further discussion of this point will be postponed until additional experimental facts have been uncovered.

Experimental[20,21]

Dehydrohalorubremetine.—This material was prepared as previously described.[10] The m.p. behavior of the crude material depends on the rate of heating and on the temperature at which the sample is introduced into the m.p. bath. With a very slow rate of increase of temperature and introduction of the sample at 130°, the material melts at 150–157°, with sintering several degrees lower.

Hydrogenation of Dehydrohalorubremetine.—The crude dehydrohalorubremetine obtained from 19.2 g. of rubremetinium chloride hexahydrate was dried in a vacuum desiccator for one week over anhydrous calcium chloride. A 2.03 g. sample of the material was taken from the 13.00-g. batch of dried material and added to 75 cc. of absolute ethanol together with 0.20 g. of Adams catalyst. The suspension was hydrogenated at atmospheric pressure for 40 hours, 93 cc. (S.T.P.) of hydrogen being consumed. An additional 0.20 g. of catalyst was added, the hydrogenation was started again, and, after 150 hours, an additional 144 cc. (S.T.P.) of hydrogen had been consumed. About 100 cc. of ethanol was added to the greenish-white suspension, the mixture warmed to effect solution of the organic material and filtered. The filtrate was concentrated to 75 cc. *in vacuo*. A colorless solid crystallized, m.p. 165–168°.

The remaining 11.00 g. of dehydrohalorubremetine was suspended in 200 cc. of ethanol together with 0.50 g. of Adams catalyst. The mixture was hydrogenated in a Parr apparatus for 75 hours at room temperature and a pressure of 50 lb. per sq. in. initially. The greenish-white suspension which resulted was treated as described above for the 2.03-g. sample. The colorless precipitate which was obtained had a m.p. of 164–169°.

The two crops of solid material were combined as were the ethanol mother liquors, and the material was subjected to six stages of a fractional crystallization by the "triangle scheme." The least soluble fraction consisted of pale yellow needles, m.p. 179.2–180.2°. The material showed no rotation in alcohol, benzene or acetone solution.

Anal. Calcd. for $C_{29}H_{34}N_2O_4$: C, 73.39; H, 7.22; N, 5.90; CH_3O, 26.16; one terminal methyl, 3.17; one active H, 0.21. Found: C, 73.59, 73.70; H, 7.36, 7.55; N, 5.80, 5.94; CH_3O, 25.3, 25.8; terminal methyl, 3.44, 4.13; active H, 0.18, 0.17.

From one of the more soluble fractions there was obtained colorless crystalline material, m.p. 167.8–169.0°, $[\alpha]^{19}\mathrm{D}$ +15.1° (*c* 1.06 in acetone).

Anal. Found: C, 72.77, 72.73; H, 7.06, 7.11; N, 7.6, 7.7; CH_3O, 25.9, 25.1; terminal methyl, 3.7, 3.4; active H, 0.05, 0.08.

The more insoluble intermediate fractions, those melting close to 180°, were combined, and a 3.50-g. sample was placed in a Soxhlet extractor. After 48 hours of continuous ether extraction, at such a rate of refluxing that the ether solution siphoned into the reservoir three times per hour, there remained in the thimble 2.20 g. of colorless solid, m.p. 180.2–181.8°. This showed no rotation in acetone solution.

The more soluble fractions, those melting in the vicinity of 170°, were combined, a 1.80-g. sample placed in a Soxhlet extractor and extracted with ether. As soon as any solid material began to crystallize in the reservoir, the solution was removed and fresh ether substituted. The first three extracts gave material of the same m.p., but the following extracts gave material of gradually ascending m.p. The first three extracts yielded 0.50 g. of material, m.p. 165.8–166.0°, $[\alpha]^{23}\mathrm{D}$ +11.4° (*c* 2.10 in acetone).

Anal. Calcd. for $C_{29}H_{34}N_2O_4$: C, 73.39; H, 7.22; N, 5.90. Found: C, 73.36, 73.42; H, 7.01, 7.20; N, 5.92, 6.10.

"*o*-Dihydrodehydroemetine."—In a one-liter 3-necked flask fitted with a mercury-sealed stirrer, an inlet tube and a reflux condenser fitted with a calcium chloride tube were placed 2.30 g. of pulverized, thoroughly dried, rubremetinium chloride and 400 cc. of anhydrous ether. A stream of dry nitrogen was passed over the suspension and 0.60 g. of lithium aluminum hydride was added. The suspension was refluxed for 2.5 hours, the solution becoming decolorized except for a few specks of unreacted rubremetinium chloride. The excess lithium aluminum hydride was destroyed by addition of wet ether. The ether solution was filtered and dried over anhydrous sodium sulfate. The solution was concentrated to a small volume, whereupon 1.10 g. of yellow crystals precipitated, m.p. 156.5–157.5° (reported[14] m.p. 157–158°).

Isotetrahydrodehydroemetine.—To a solution of 0.96 g. of the yellow material, m.p. 156.5–157.5°, in 50 cc. of glacial acetic acid was added 0.10 g. of Adams catalyst. During 12 hours of hydrogenation at atmospheric pressure, 110 cc. (S.T.P.) of hydrogen was taken up. A separate experiment showed that 20 cc. (S.T.P.) of hydrogen was required for reduction of the catalyst.

The solution was filtered and the acetic acid distilled *in vacuo*. The residue was treated with dilute sodium carbonate solution and extracted with ether. The ether solution, dried over anhydrous sodium sulfate, was concentrated to a small volume. About 0.10 g. of colorless isotetrahydrodehydroemetine crystallized, m.p. 183.4–186.6°. Recrystallization, first from ether, then absolute methanol, gave colorless needles, m.p. 195.0–195.6° (reported[14] m.p. 194°).

Tetrahydrodehydroemetine.—The ether mother liquor was concentrated further. The solid material which crystallized was recrystallized from fresh ether, giving colorless tetrahydrodehydroemetine, m.p. 131.4–132.4° (reported[14] m.p. 134°), $[\alpha]^{26}\mathrm{D}$ +47.5° (*c* 0.464 in absolute ethanol), $[\alpha]^{25}\mathrm{D}$ +24° (*c* 0.368 in acetone). Karrer and Ruttner[14] reported $[\alpha]^{18}\mathrm{D}$ +42° (in absolute ethanol).

Hydrogenation of Rubremetinium Chloride.—To 4.00 g. of rubremetinium chloride, dried in a vacuum desiccator over anhydrous calcium chloride for several days, was added 3.5 g. of sodium acetate trihydrate, 55 cc. of absolute ethanol and 0.15 g. of Adams catalyst. The mixture was hydrogenated at atmospheric pressure for 29 hours, 286 cc. (S.T.P.) of hydrogen being consumed. (Of this quantity of hydrogen, the first 220 cc. was absorbed in the course of an hour, a thick suspension being formed in the process.) An additional 0.10 g. of Adams catalyst was added and the hydrogenation continued for 120 hours, an additional 106 cc. (S.T.P.) of hydrogen being consumed. There was no uptake of hydrogen during the last 12 hours of this period.

The yellow solution was filtered and the filtrate concentrated to dryness *in vacuo*. Dilute sodium hydroxide solution was added to the residue, and the mixture was extracted with ether. The ether solution, dried over anhydrous sodium sulfate, was evaporated to dryness. Crystallization of the residue from absolute ethanol afforded 2.63 g. of pale yellow crystals. Recrystallization from absolute methanol gave colorless material, m.p. 127.5–130.6°, 2.14 g. This was placed in a Soxhlet extractor and extracted with

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[18] K. Folkers, F. Koniuszy and J. Shavel, Jr., THIS JOURNAL, **73**, 589 (1951).

[19] M. Carmack, B. C. McKusick and V. Prelog, *Helv. Chim. Acta*, **34**, 1601 (1951).

[20] Analyses by Weiler and Strauss, Oxford, England. Infrared spectra by Samuel P. Sadtler and Son, Inc., Philadelphia, Pa.

[21] All m.p.'s are corrected.

125 cc. of ether for a period of 8 hours. A second and a third extraction, each involving 125 cc. of ether and carried out for an 8-hour period, brought all of the material in the thimble into solution. Concentration of the second ether extract afforded 0.77 g. of colorless crystals, m.p. 132.0–132.8°, $[\alpha]^{22}$D +18.2° (*c* 0.275 in acetone), $[\alpha]^{26}$D +41.9° (*c*, 0.691 in absolute ethanol). A mixed m.p. with tetrahydrodehydroemetine, described above, showed no depression.

The mother liquor from the methanol recrystallization was concentrated to a small volume, whereupon 0.19 g. of colorless needles, m.p. 196.2–197.2°, $[\alpha]^{26}$D −392° (*c* 0.255 in absolute ethanol), was obtained. Openshaw and Wood[7e] report a m.p. of 197–198°, $[\alpha]^{15}$D −395° (*c* 0.165 in acetone) for α-dihydrorubremetine. A mixed m.p. with isotetrahydrodehydroemetine, described above, showed no depression.

In a separate experiment, the hydrogenation of rubremetinium chloride was halted after the absorption of only one mole of hydrogen. The greenish-white suspension was filtered, and the filter cake extracted with hot absolute ethanol. Concentration and cooling of this solution afforded 0.40 g. of pale yellow crystals, m.p. 177–187°. Recrystallization from absolute ethanol gave colorless needles, m.p. 201.5–202.5°, $[\alpha]^{21}$D +402° (*c* 0.189 in acetone). Openshaw and Wood[7e] reported a m.p. of 201–202° for β-dihydrorubremetine and $[\alpha]^{16}$D +406.3° (*c* 0.148 in acetone). By working up the various mother liquors there was obtained a total of 0.45 g. of purified β-dihydrorubremetine. The β-dihydrorubremetine readily absorbed one mole of hydrogen in absolute ethanol containing 10% by volume of glacial acetic acid over Adams catalyst.

LAWRENCE, KANSAS

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, STANFORD UNIVERSITY]

Synthesis of Piperazines by Reductive Cyclization[1,2]

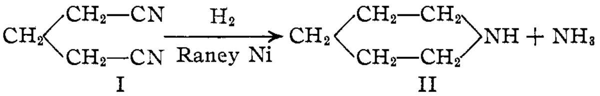
BY HARRY S. MOSHER, JOHN CORNELL, JR.,[3] OWEN L. STAFFORD[4] AND THORNDYKE ROE, JR.

RECEIVED JUNE 8, 1953

It has been shown that catalytic reduction of di-(cyanomethyl)-amine and its N-substituted derivative gives piperazine and mono-N-substituted piperazines. The N-acetyl, N-benzoyl, N-carbethoxy, N-diethylcarbamyl, N-methyl, N-ethyl and N-benzyl derivatives of di-(cyanomethyl)-amine (IV) have been prepared and reduced to the corresponding piperazines (V). This constitutes a new synthesis of piperazines which may be valuable in special cases since it inherently gives the mono-N-substituted products.

The formation of cyclic imines by the reduction of dinitriles is a particular intramolecular case of the formation of secondary amines which takes place during the reduction of nitriles. The term *reductive cyclization* has been applied to reactions of this kind in which the cyclic nitrogen bases are formed by reductive methods, and there are many known examples of the production of nitrogen ring compounds by this process.[5]

The best known example is the reduction of trimethylene cyanide I to give piperidine II as the major product along with a small yield of cadaverine III.[6] Mignonac[7] has postulated a satisfactory mechanism for the formation of secondary amines in the reduction of nitriles which can readily be applied to the above case.



$$CH_2\left\langle\begin{matrix}CH_2\text{—}CN\\CH_2\text{—}CN\end{matrix}\right. \xrightarrow[\text{Raney Ni}]{H_2} CH_2\left\langle\begin{matrix}CH_2\text{—}CH_2\\CH_2\text{—}CH_2\end{matrix}\right\rangle NH + NH_3$$

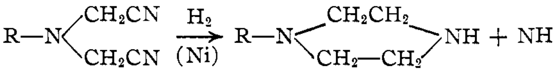
I II

and $H_2N\text{—}(CH_2)_5NH_2$

III

This process of reductive cyclization has been especially useful in the synthesis of piperidine,[5b] pyrrolidines,[5a] pyrrazolidines[5c] and octahydropyrrocolines[5c] but we have found no reference in the literature where this process has been used for the preparation of an heterocyclic compound containing more than one hetero atom in the ring.[8]

We therefore undertook a study of the reduction of di-(cyanomethyl)-amine and N-substituted di-(cyanomethyl)-amines to determine whether the reductive cyclization predicted by the following equation would be realized.



$$R\text{—}N\left\langle\begin{matrix}CH_2CN\\CH_2CN\end{matrix}\right. \xrightarrow[\text{(Ni)}]{H_2} R\text{—}N\left\langle\begin{matrix}CH_2CH_2\\CH_2\text{—}CH_2\end{matrix}\right\rangle NH + NH_3$$

IV V

The first experiments on the high pressure Raney nickel catalyzed reduction of ethyldi-(cyanomethyl)-amine (IV, R = $-C_2H_5$) were unsuccessful.[9] It has been stated by Reihlen and co-workers[10] that α-aminonitriles on catalytic reduction readily eliminate hydrogen cyanide which poisons

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(1) Presented in part at the International Congress of Pure and Applied Chemistry, New York, September, 1951.

(2) Abstracted from the Thesis submitted by J. H. C. in partial fulfillment of the requirements for the Ph.D to Stanford University, June, 1952.

(3) Parke Davis and Company Research Fellow 1950–1952.

(4) Parke Davis and Company Research Fellow 1950–1951.

(5) The references are far too numerous to review here but the following will indicate some of the most important work in this field: (a) H. Adkins, "The Reaction of Hydrogen with Organic Compounds over Copper–Chromium Oxide and Nickel Catalysts," Univ. of Wisc. Press, Madison, Wis., 1937; (b) H. S. Mosher, "Piperidines" in Elderfield's "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 650–655; (c) N. J. Leonard, *et al.*, THIS JOURNAL, **71**, 1758 (1949), *et seq.;* (d) K. Smeykal and H. Dierichs, German Patent 730,235, Dec. 10, 1942; (e) J. Paden and H. Adkins, THIS JOURNAL, **58**, 2487 (1936).

(6) Reference 5a, pp. 53–55.

(7) G. Mignonac, *Ann. chim.*, [11] **2**, 225 (1934).

(8) (a) The only examples which might be considered to fall in this category are the reductions of the monoximes of α,β-diketones to give pyrazines reported by C. Winans and H. Adkins, THIS JOURNAL, **55**, 4167, 4170 (1933), and H. Adkins and E. Reeves, *ibid.*, **60**, 1328 (1938). Since the expected α-aminoketones spontaneously cyclize to pyrazines this seems to be a very special case. (b) P. L. Barrick, U. S. Patent 2,516,289 (July 25, 1950) reports the preparation of piperazines by the reduction of the monoxime of α,β-diketones using palladium catalysts at 20–150° and 50–200 p.s.i. (c) NOTE ADDED TO PROOF.—Since this paper was submitted, a patent (U. S. 2,605,263, July 29, 1952, by Martin J. Culver and Louis H. Bock) has come to our attention in which the reduction of di-(cyanomethyl)-amine to piperazine with hydrogen in the presence of acidified Raney nickel or cobalt is described.

(9) See R. B. Taylor, Ph.D. Thesis, The Pennsylvania State College, Feb. 1945, pp. 43–44, 133–136, and T. Roe, M.S. Thesis, Stanford University, Dec. 1949.

(10) H. Reihlen, G. von Hessling, W. Hühn and E. Weinbrenner, *Ann.*, **493**, 20–32 (1932).