that at least some of the guanylic acid molecules are adjacent to each other.[31]

The ribonuclease-resistant fraction probably represents that portion of the nucleic acid upon which the phosphatase acts to produce the materials just discussed (G, F, J and K). Comparison of their respective analytical data reveals the major difference to be the phosphorus content. This is consistent with the fact that only singly-esterified phosphates are removed by phosphatase. In the main, therefore, the ribonuclease-resistant fractions and the phosphatase treated material may be considered to be similar.

The relationship of the enzyme-treated materials to the parent nucleic acid is for the most part quite complex. The inability of ribonuclease to completely hydrolyze nucleic acid is one of the more pertinent problems. Linkages other than the usual sugar-phosphate type occur more frequently in the resistant fraction based on the titration results. The phosphate esters of the hydroxyl groups of the pyrimidine ring may be resistant to the enzyme. Although these types might be present in the digestible portion of the nucleic acid, they would not necessarily have to be cleaved by the enzyme, since they could be removed as a part of a larger portion. Implicit in this suggestion is the idea that the resistant fraction is an integral part of a larger molecule, part of which is attacked by enzymes. It is conceivable that the resistant fraction is a separate entity, distinct from the digestible portion.

Acknowledgment.—The authors wish to thank Dr. George B. Brown for continued interest and support, Dr. Fred Karush for helpful discussions, Krikor Seraidarian for purine and pyrimidine analyses and Roscoe C. Funk, Jr., for nitrogen and phosphorus analyses.

NEW YORK 25, N. Y. RECEIVED NOVEMBER 15, 1950

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

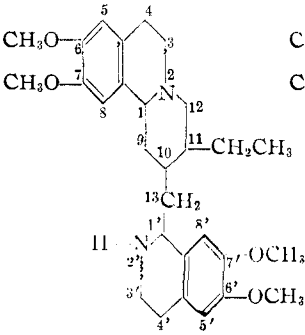
Studies on Emetine[1]

BY ROBERT N. HAZLETT AND WILLIAM E. McEWEN

Attempts have been made to prepare some new diastereoisomers of emetine and to obtain further evidence concerning the structures of various dehydrogenation products of emetine. Mercuric acetate dehydrogenation of emetine gave a crystalline isotetradehydroemetine together with the known tetradehydroemetine. Catalytic hydrogenation of tetradehydroemetine hydrogen oxalate afforded emetine, isoemetine and two new diastereoisomers. Hydrogenation of either isotetradehydroemetine or isotetradehydroemetine hydrogen oxalate gave emetine as the only isolable product. The production of isoemetine determines the position of one of the ethylenic double bonds in tetradehydroemetine, and the striking similarity of the ultraviolet absorption spectra of tetradehydroemetine hydrogen oxalate and isotetradehydroemetine hydrogen oxalate indicates a close structural relationship between the two isomers. Some new reactions of rubremetinium chloride are described as well as some new Hofmann degradation results on acetylemetine.

Emetine (I)[2,3] having four dissimilar asymmetric carbon atoms is one of sixteen theoretical optical isomers. In addition to emetine only one of these isomers, isoemetine, is known.[4,5] Since isoemetine together with emetine is obtained on reduction of O-methylpsychotrine (II),[4] and since ozonolysis or perphthalic acid oxidation of N-benzoyl-O-methylpsychotrine affords N-benzoylcorydaldine (III),[6] it is known that O-methylpsychotrine has an ethylenic double bond at C_{13}–C_1' and that isoemetine differs from emetine in the configuration of C_1'. The main object of this work was to prepare further optical isomers of emetine starting with known degradation products of emetine. It is to be expected that knowledge of these stereoisomers will facilitate studies on the total synthesis of emetine and on the stereochemistry of the emetine series of compounds.

By dehydrogenation of emetine with four moles of mercuric acetate, Battersby and Openshaw[7] obtained a moderate yield of a substance, formed by the removal of four hydrogen atoms. This compound, tetradehydroemetine, was characterized as the hydrogen oxalate. The substance absorbed two moles of hydrogen on a microhydrogenation,



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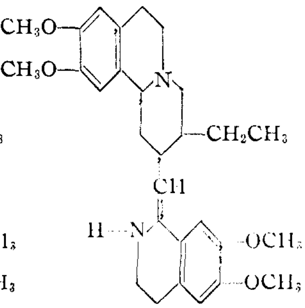

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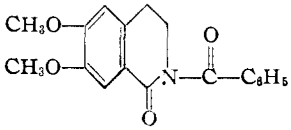

III

gave rubremetinium chloride on further mercuric acetate dehydrogenation followed by addition of hydrochloric acid, and its ultraviolet absorption spectrum suggested that two ethylenic double bonds

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(1) This, together with the work published in THIS JOURNAL, 71, 1949 (1949), was submitted by Robert N. Hazlett in partial fulfillment of the requirements for the Ph.D. degree at The University of Kansas, 1950.

(2) M. Pailer and K. Porschinski, *Monatsh.*, **80**, 94 (1949).

(3) A. R. Battersby and H. T. Openshaw, *J. Chem. Soc.*, 3207 (1949).

(4) F. L. Pyman, *ibid.*, **111**, 419 (1917).

(5) F. L. Pyman, *ibid.*, **113**, 222 (1918).

(6) P. Karrer, C. H. Eugster and O. Ruttner, *Helv. Chim. Acta*, **31**, 1219 (1948).

(7) A. R. Battersby and H. T. Openshaw, *J. Chem. Soc.*, 567 (1949).

were in conjugation with each other and with a benzene ring.

Since any two ethylenic double bonds meeting the above specifications would necessarily obliterate two or more of the asymmetric centers of emetine, it seemed likely that hydrogenation of tetradehydroemetine hydrogen oxalate on a macro scale would permit isolation of some additional diastereoisomers of emetine. This proved to be the case. Four products were obtained: emetine, isolated as the hydrobromide; isoemetine, isolated as the benzoyl derivative; a new diastereoisomer, herein named neoemetine, isolated as the hydrogen oxalate, and further characterized as the hydrobromide; and a second new diastereoisomer, herein named emetine-IV, isolated as the hydrogen oxalate.

By way of further characterization of the emetine diastereoisomers, the infrared spectra of the hydrogen oxalates of all four substances were determined (Fig. 1). The hitherto unreported emetine hydrogen oxalate was prepared from an authentic specimen of the alkaloid. Isoemetine hydrogen oxalate was prepared by catalytic reduction of O-methylpsychotrine hydrogen oxalate according to the method of Karrer, Eugster and Ruttner,[6] the O-methylpsychotrine being obtained by Pyman's method[4] of dehydrogenating emetine with alcoholic iodine. It can be seen that a number of absorption peaks occur at the same wave length in the four spectra (3.0, 3.5, 4.4, 5.8, 6.2, 6.6, 7.9, 8.2 and 8.9 μ). In addition, several other portions of two or more of the spectra are very similar. Whatever alterations in the four spectra exist might reasonably be expected of diastereoisomers.[8]

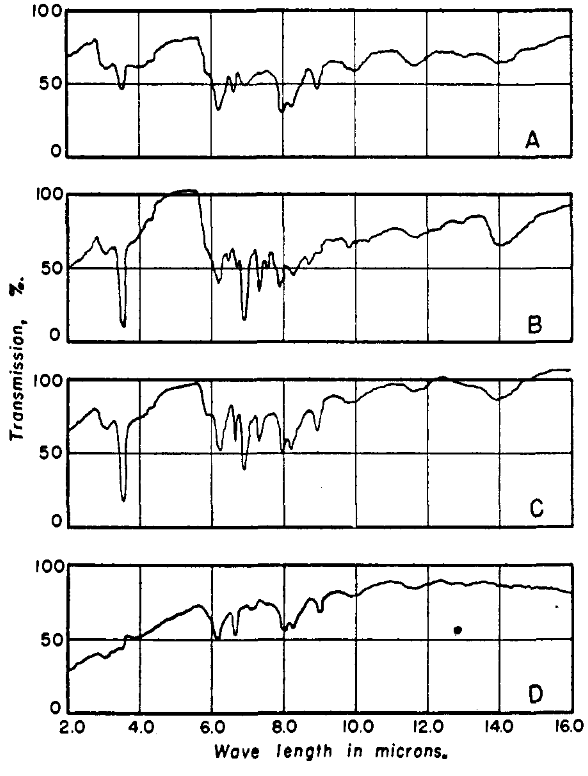

Fig. 1.—Infrared spectra in nujol suspension: A, emetine-IV hydrogen oxalate trihydrate; B, neoemetine hydrogen oxalate dihydrate; C, emetine hydrogen oxalate monohydrate; D, isoemetine hydrogen oxalate pentahydrate.

The fact that isoemetine was isolated as a reduction product of tetradehydroemetine hydrogen oxalate is significant in that it places the position of one of the ethylenic double bonds at C_{1}'–C_{13}. The other ethylenic double bond is then most likely located at either C_{9}–C_{10} or C_{10}–C_{11}. In an attempted barium permanganate oxidation of tetradehydroemetine hydrogen oxalate no products were obtained which permitted a decision on this matter.

In a variation of the procedure for working up the reaction mixture from the dehydrogenation of emetine with four moles of mercuric acetate, an additional substance containing four fewer hydrogen atoms was isolated as a crystalline product. This substance, herein named isotetradehydroemetine, was further characterized as the N-methyl dimethiodide, the N-benzoyl methiodide and the hydrogen oxalate.

Catalytic hydrogenation of isotetradehydroemetine in 50% acetic acid proceeded with absorption of approximately two moles of hydrogen and yielded emetine, isolated as the hydrobromide and further identified as the benzoyl derivative, this being the only isolable product. Catalytic hydrogenation of isotetradehydroemetine hydrogen oxalate in ethanol also proceeded with absorption of nearly two moles of hydrogen and afforded emetine, partially isolated as the hydrogen oxalate and partially as the hydrobromide, and further characterized as the benzoyl derivative, as the only isolable substance.

The ultraviolet absorption spectra of both tetradehydroemetine hydrogen oxalate[9] and isotetradehydroemetine hydrogen oxalate were determined (Fig. 2). The striking similarity of the two spectra indicates that there can be no major differences in the unsaturated systems of the two isomers. The fact that both tetradehydroemetine and isotetradehydroemetine gave emetine on reduction prohib-

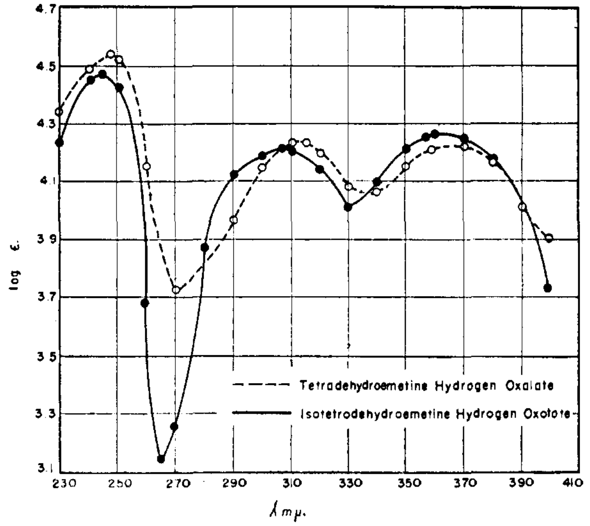

Fig. 2.—Ultraviolet absorption spectra in water.

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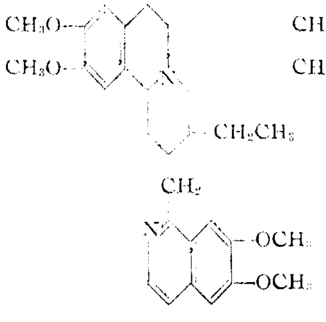
[8] H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949, p. 3.

[9] Battersby and Openshaw[7] reported only the maxima.

its their being optical isomers differing only in the configuration of either or both of the possible remaining asymmetric centers, C_1 and C_{11}. One possibility exists that the two substances are geometrical isomers about the double bond at C_1'–C_{13}. Another possibility is that one isomer has the second double bond at C_9–C_{10}, while the other has the second double bond at C_{10}–C_{11}. The observation that isotetradehydroemetine, like tetradehydroemetine,[7] afforded a rubremetinium salt on further mercuric acetate dehydrogenation implies that the mechanism of this dehydrogenation reaction must permit either an isomerization of the double bond system or a *cis–trans* interconversion.

Mainly on the basis of a molecular formula reported to be $C_{29}H_{33}N_2O_4Cl$,[10,11,12] the brilliant orange-red color, the quaternary nature of one nitrogen atom and the lack of basicity of the other,[10] the non-identity of rubremetinium chloride and the similar dehydrogenation product of emetamine (IV[4,13]),[6,14] and the red pine shaving reaction given by tetrahydrodehydroemetine,[15] a reduction product of rubremetinium chloride, structure V has been proposed[15] for rubremetinium chloride. Objections have been raised to structure V on the grounds that it represents an illogical terminal product of a dehydrogenation reaction.[16] Further, since a lithium aluminum hydride reduction of rubremetinium chloride affords a dihydro derivative, which catalytically adds one mole of hydrogen to give a mixture of two isomeric tetrahydro derivatives, tetrahydrodehydroemetine and isotetrahydrodehydroemetine, it has been suggested[16] that rubremetinium salts have the partial structure VI.[17]



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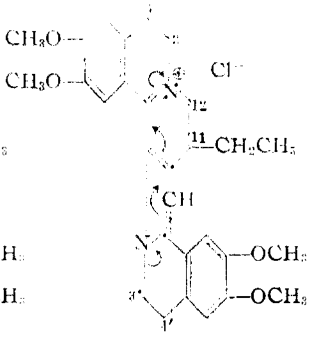

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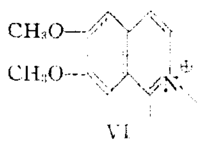
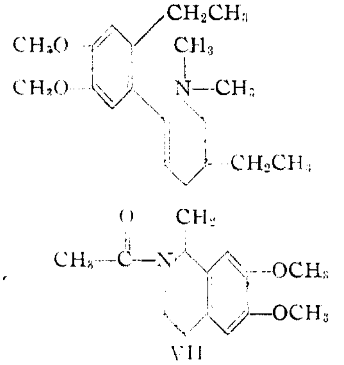


VI

Another objection which can be raised to structure V is that the tetrahydro derivatives, tetrahydrodehydroemetine and isotetrahydrodehydroemetine, are resistant to low pressure catalytic hydrogenation. If structure V were correct, the tetrahydro derivatives would have a pyrroline structure rather than a pyrrole structure, and it is known that such a structure in phyllopyrroline, for example, is readily hydrogenated to the corresponding pyrrolidine in a low pressure catalytic hydrogenation.[18]

We have uncovered some new information concerning rubremetinium chloride which also cannot be interpreted adequately on the basis of structure V. Heating rubremetinium chloride with aqueous alcoholic sodium hydroxide gave an unstable product, herein named dehydrohalorubremetine, formed by an over-all dehydrochlorination reaction. The substance did not give back rubremetinium chloride on being heated with hydrochloric acid. The crude dehydrohalorubremetine readily added two moles of hydrogen in a low pressure catalytic hydrogenation to give a mixture of reduced products, probably a mixture of diastereoisomers. A pure crystalline compound, herein named tetrahydrodehydrohalorubremetine,[19] was obtained by a fractional crystallization. The substance appeared to be racemic, and its ultraviolet absorption spectrum (Fig. 3) is very similar to that of levorotatory isotetrahydrodehydroemetine[16]; hence tetrahydrodehydrohalorubremetine might actually be racemic isotetrahydrodehydroemetine. The compound did not form an acyl derivative with benzoyl chloride or *p*-toluenesulfonyl chloride. It would be premature to speculate on the nature of these transformations until more conclusive evidence concerning the structure of rubremetinium chloride becomes available.



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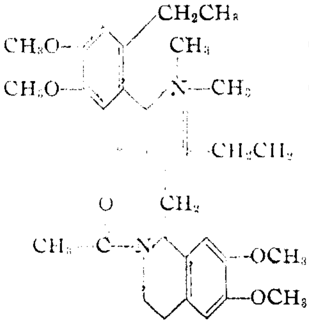

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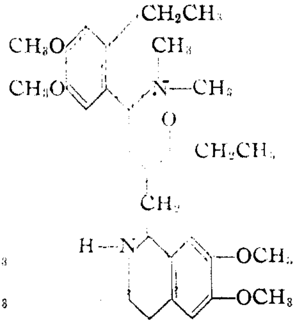

IX

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[10] F. H. Carr and F. L. Pyman, *J. Chem. Soc.*, **105**, 1591 (1914).

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

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

[13] A. Ahl and T. Reichstein, *ibid.*, **27**, 366 (1944).

[14] W. H. Brindley and F. L. Pyman, *J. Chem. Soc.*, 1067 (1927).

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

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

[17] P. Karrer and H. Schmid, *ibid.*, **32**, 960 (1949), have shown that isoquinoline methiodide affords a dihydro derivative on lithium aluminum hydride reduction.

[18] R. Willstätter and Y. Asahina, *Ann.*, **385**, 188 (1911).

[19] The available analytical data do not provide absolute proof that the molecular formulas of dehydrohalorubremetine and tetrahydrodehydrohalorubremetine differ by four hydrogen atoms, particularly since the hydrogenation was carried out on crude dehydrohalorubremetine.

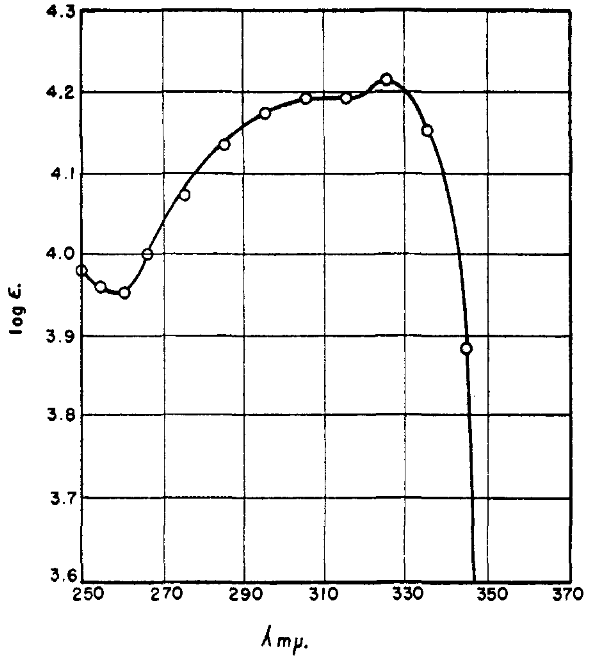

Fig. 3.—Ultraviolet absorption spectrum of tetrahydrodehydrohalorubremetine in ethanol.

A scheme for obtaining an intermediate suitable for resynthesis of emetine and its diastereoisomer differing in the configuration of C_1 failed to materialize when a Hofmann degradation gave unexpected results. Using the method of Pailer[20] N-acetylemetine iodomethylate was degraded to a methine base, catalytically reduced, reacetylated, converted to the iodomethylate, again subjected to a Hofmann degradation and reacetylated. At this point two isomeric bases (VII and VIII) must have been present, because ozonolysis of the crude product gave 2-ethyl-4,5-dimethoxybenzaldehyde (isolated as the semicarbazone) together with a base, $C_{30}H_{44}N_2O_5$, which could only have the structure IX. The desired product for the projected synthesis, the nitrogen containing cleavage component of the ozonolysis of VII, could not be isolated.

Acknowledgments.—The authors wish to express their appreciation to the Office of Naval Research whose generous support made this work possible. Thanks are also due to Mr. Jack A. Williams and Mr. Nariman B. Mehta, who gave some valuable experimental assistance in parts of this work.

Experimental[21]

Oxidation of Emetine with Four Moles of Mercuric Acetate.—A solution of 20.0 g. of emetine hydrochloride heptahydrate in 200 cc. of water was heated on the steam-bath and treated dropwise with mechanical stirring during seven hours with a solution of 38.0 g. of mercuric acetate, 4.0 g. of potassium acetate and 20.0 cc. of acetic acid in 400 cc. of water. Heating was continued for an additional hour, the precipitate of mercurous acetate removed from the cooled mixture and washed with water until the washings were colorless. The combined filtrate and wash was heated to boiling, treated with hydrogen sulfide for one hour, filtered and the mercuric sulfide washed thoroughly with hot water. The filtrate plus wash was made alkaline with excess sodium carbonate, and the resulting milky suspension continuously extracted with ether.

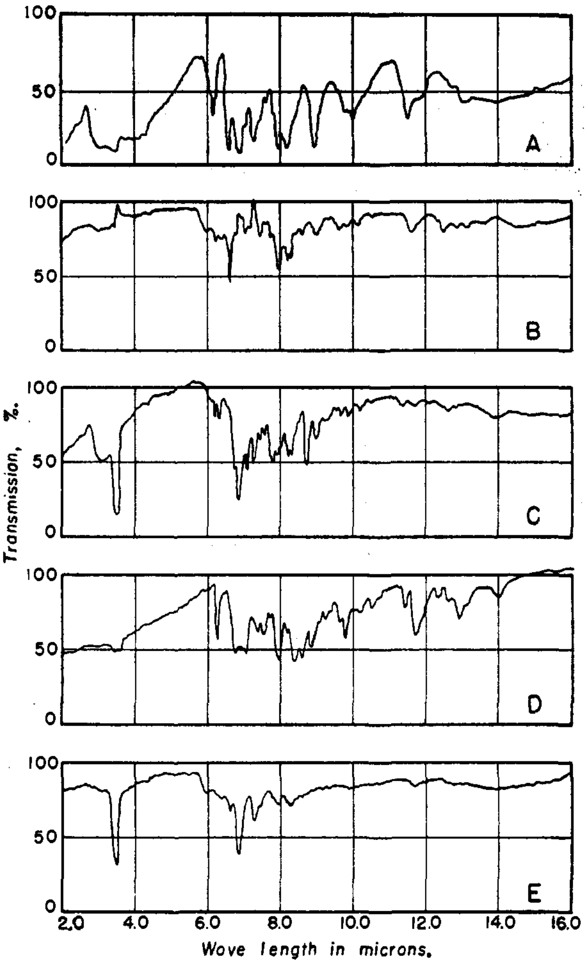

Fig. 4.—Infrared spectra in nujol suspension: A, emetine hydrochloride heptahydrate; B, isotetradehydroemetine; C, rubremetinium chloride hydrate; D, dehydrohalorubremetine; E, tetrahydrodehydrohalorubremetine.

Isolation of Isotetradehydroemetine.—On thorough drying of the ether solution over anhydrous potassium carbonate, a colorless organic base precipitated, which was filtered and extracted from the drying agent with hot absolute ethanol. Isotetradehydroemetine crystallized from the alcohol solution, colorless needles, 3.86 g. (28%), m.p. 152–155°. Two additional crystallizations raised the m.p. to 153–155°, $[\alpha]_D + 30.6°$ (*c*, 1.04 in benzene).

Anal. Calcd. for $C_{29}H_{36}N_2O_4$: C, 73.08; H, 7.62; N, 5.88. Found: C, 72.72, 72.91; H, 7.88, 7.93; N, 5.96, 6.07.

Isolation of Tetradehydroemetine Hydrogen Oxalate.—The ether mother liquor was evaporated and the residue dissolved in hot ethanolic oxalic acid solution. Tetradehydroemetine hydrogen oxalate readily crystallized from this solution, 6.25 g. (32%), m.p. 153–155° (dec.), $[\alpha]_D +82.0°$ (*c*, 2.7 in water). Battersby and Openshaw[7] report a m.p. of 151–153° (dec.), $[\alpha]_D +84.5°$ (*c*, 1.9 in water).

N-Methylisotetradehydroemetine Dimethiodide.—A solution of 1.00 g. of isotetradehydroemetine and 3.0 cc. of methyl iodide in dry benzene was refluxed for two hours, an orange solid beginning to precipitate after several minutes. After removal of the solvent *in vacuo*, the residual solid was crystallized from absolute ethanol, 1.35 g.; m.p. behavior: sinters at 163–167°, effervesces at 175°. Two further crystallizations did not alter this m.p. behavior. The substance becomes gummy on exposure to air, but hardens again on drying.

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[20] M. Pailer, *Monatsh.*, **79**, 127 (1948).

[21] Analyses by Oakwold Laboratories, Alexandria, Va. Infrared spectra by Samuel P. Sadtler and Sons, Inc., Philadelphia, Pa. All m.p.'s are corrected. The rotations were measured at room temperature.

Anal. Calcd. for $C_{32}H_{48}N_2I_2O_4$: N, 3.64; I, 32.75. Found: N, 3.80, 3.83; I, 32.84, 32.83.

N-Benzoylisotetradehydroemetine Methiodide.—A suspension of 0.85 g. of isotetradehydroemetine in 100 cc. of ether was shaken with 0.4 cc. of benzoyl chloride and 5.0 cc. of 10% sodium hydroxide solution, the organic base eventually going into solution. The aqueous layer was extracted with four additional portions of ether, and the combined ether extracts, dried over anhydrous sodium sulfate, afforded an orange gum on evaporation. This was dissolved in 6.0 cc. of dry benzene, treated with 1.0 cc. of methyl iodide and heated on the steam-bath in a pressure bottle for six hours. Evaporation of the solvent gave a residue which was crystallized from water, 0.23 g., m.p. 165–185° (dec.) after drying *in vacuo*.

Anal. Calcd. for $C_{37}H_{43}N_2IO_5$: N, 3.88; I, 17.56. Found: N, 4.19; I, 17.16.

Isotetradehydroemetine Hydrogen Oxalate.—Warm ethanolic solutions of 3.86 g. of isotetradehydroemetine and 2.50 g. of oxalic acid dihydrate were mixed, and a gummy precipitate formed in a few minutes. The alcohol was decanted, and on refluxing the residue with fresh absolute ethanol, crystallization was initiated. After several days standing, 4.41 g. of product was obtained. One recrystallization from absolute ethanol gave a product of m.p. 166° (dec.) after drying *in vacuo*, $[\alpha]_D$ +7.3° (*c*, 1.84 in water).

Anal. Calcd. for $C_{29}H_{36}O_4N_2 \cdot 2C_2H_2O_4 \cdot 2H_2O$: C, 57.21; H, 6.40; N, 4.05; H_2O, 5.2. Found: C, 57.61; H, 6.58; N, 4.16; gain in weight of a heat-vacuum dried sample on standing exposed to the air for one day, 6.0. (The usual procedure for moisture determination gave abnormally high results indicating loss of organic material.)

Hydrogenation of Tetradehydroemetine Hydrogen Oxalate.—A suspension of 2.00 g. of tetradehydroemetine hydrogen oxalate in 75 cc. of absolute ethanol was hydrogenated at one atmosphere pressure over 0.15 g. of Adams catalyst. In the course of one hour 149 cc. of hydrogen was consumed (1.96 moles per mole of tetradehydroemetine hydrogen oxalate), the suspension becoming thicker as the reaction progressed.

Isolation of Neoemetine Hydrogen Oxalate.—The insoluble organic material plus catalyst was filtered, and the organic material separated from the platinum by extraction with hot methanol. Colorless neoemetine hydrogen oxalate crystallized from the methanol solution, 0.43 g. (22%). After two additional crystallizations from methanol, the substance showed a m.p. of 154–157° (dec.) after drying *in vacuo*. $[\alpha]_D$ +37.0° (*c*, 1.38 in water). The pure salt is very poorly soluble in absolute ethanol, hot or cold.

Anal. Calcd. for $C_{29}H_{40}N_2O_4 \cdot 2C_2H_2O_4 \cdot 2H_2O$: C, 56.88; H, 6.95; N, 4.02; H_2O, 5.2. Found for air-dried sample: C, 56.37, 56.50; H, 6.85, 6.92; N, 4.26, 3.88; loss in weight on drying *in vacuo* at 56°, 5.3.

Isolation of Emetine-IV Hydrogen Oxalate.—The ethanol mother liquor was concentrated *in vacuo* to 20 cc. The cooled solution deposited emetine-IV hydrogen oxalate, 0.58 g. (29%). Three recrystallizations from ethanol afforded material of m.p. 168° (dec.) after vacuum drying, $[\alpha]_D$ +27° (*c*, 1.26 in water). The pure salt is very soluble in hot and moderately soluble in cold absolute ethanol. Rapid cooling of a hot ethanol solution is required to obtain a crystalline precipitate.

Anal. Calcd. for $C_{29}H_{40}N_2O_4 \cdot 2C_2H_2O_4 \cdot 3H_2O$: H_2O, 7.6. Found: loss in weight on heating an air-dried sample at 110° *in vacuo*, 7.6. Calcd. for $C_{29}H_{40}N_2O_4 \cdot 2C_2H_2O_4$: C, 59.98; H, 6.71; N, 4.24. Found (for vacuum-heat dried sample): C, 59.63; H, 6.80; N, 4.40.

Isolation of Emetine Hydrobromide.—The ethanol mother liquor from the emetine-IV hydrogen oxalate was evaporated to dryness at reduced pressure. The residue was dissolved in water, made alkaline with 10% sodium hydroxide solution, and extracted with ether. Evaporation of the ether solution, dried over anhydrous potassium carbonate, afforded 0.37 g. of amorphous solid. This was dissolved in 5.0 cc. of hot 3% hydrobromic acid solution, and emetine hydrobromide crystallized out, 0.10 g. (5%). After one crystallization from water, colorless material was obtained, m.p. 229–231° (dec.), $[\alpha]_D$ +12.5° (*c*, 1.80 in water). Carr and Pyman[10] report a m.p. of 250–265° for emetine hydrobromide, but we have found that an authentic sample of the salt, prepared from the commercially available emetine hydrochloride heptahydrate, has a m.p. of 229–233° when heated slowly as in the above determination. Carr and Pyman[10] report $[\alpha]_D$ +12.1° (*c*, 1.39 in water).

Isolation of Benzoylisoemetine.—The hydrobromic acid mother liquor was combined with a similar mother liquor from another run, made basic with 10% sodium hydroxide solution and extracted with ether. Evaporation of the ether extract, dried over anhydrous potassium carbonate, afforded an amorphous residue of 0.44 g. This was heated with 1.0 g. of benzoic anhydride on the steam-bath for one hour. The reaction mixture was worked up according to Pyman's method[4] for the benzoylation of isoemetine. Benzoylisoemetine was obtained, 0.09 g. (3%), m.p. 204–205°, $[\alpha]_D$ +50° (*c*, 1.97 in chloroform). A mixed m.p. with an authentic sample of benzoylisoemetine showed no depression. Pyman[4] reports a m.p. of 206–207°, $[\alpha]_D$ +48.9° (*c*, 2.12 in chloroform) for benzoylisoemetine.

Neoemetine Hydrobromide.—A solution of 0.40 g. of neoemetine hydrogen oxalate in water was made basic with 10% sodium hydroxide solution and extracted with ether. Evaporation of the ether solution, dried over anhydrous potassium carbonate, afforded an amorphous residue which was dissolved in 3.0 cc. of 10% hydrobromic acid solution. After long standing, neoemetine hydrobromide, 0.15 g., crystallized. After one crystallization from water, the salt showed a m.p. of 200–235° (dec.), $[\alpha]_D$ +30° (*c*, 1.70 in water) for a sample dried *in vacuo*.

Anal. Calcd. for $C_{29}H_{40}N_2O_4 \cdot 2HBr \cdot 3H_2O$: H_2O, 7.8. Found: air-dried sample lost 8.1% on drying *in vacuo* at 110°. Calcd. for $C_{29}H_{40}N_2O_4 \cdot 2HBr$: Br, 24.88. Found: Br, 24.64.

Isoemetine Hydrogen Oxalate.—This compound was prepared by the method of Karrer, Eugster and Ruttner[6]; m.p. 176–180°, $[\alpha]_D$ +11° (*c*, 1.48 in water). Karrer, *et al.*, report a m.p. of 175–180°, $[\alpha]_D$ +11.0° (*c*, 1.36 in water). Pyman[6] reports a m.p. of 150–165°, $[\alpha]_D$ +11.3° (*c*, 1.36 in water). The O-methylpsychotrine used in this preparation was prepared from emetine by the method of Pyman.[4]

Emetine Hydrogen Oxalate.—Emetine was liberated from an aqueous solution of 2.00 g. of emetine hydrochloride heptahydrate by treatment with 10% sodium hydroxide solution and then taken up in ether. Evaporation of the ether solution, dried over anhydrous potassium carbonate, gave an amorphous residue which was dissolved in 20 cc. of a 5% oxalic acid solution. A gummy precipitate which formed was recrystallized three times from absolute ethanol, m.p. 166° (dec.) after drying *in vacuo*, $[\alpha]_D$ +7.8° (*c*, 1.43 in water).

Anal. Calcd. for $C_{29}H_{40}N_2O_4 \cdot 2C_2H_2O_4 \cdot H_2O$: C, 58.39; H, 6.83; N, 4.13; H_2O, 2.6. Found for air-dried sample: C, 58.38, 58.54; H, 7.02, 7.15; N, 4.52, 4.74; loss in weight on heating at 110° *in vacuo*, 2.7.

Hydrogenation of Isotetradehydroemetine.—A solution of 1.00 g. of isotetradehydroemetine in 25 cc. of 50% acetic acid was hydrogenated at one atmosphere pressure over 0.02 g. of Adams catalyst. A total of 95.3 cc. of hydrogen (1.85 moles of hydrogen per mole of isotetradehydroemetine) was consumed in the course of an hour. The solution was filtered, the filtrate made basic with sodium hydroxide solution, and the liberated organic bases taken up in ether. Evaporation of the ether solution, dried over anhydrous potassium carbonate, afforded 0.93 g. of colorless solid, which was dissolved in ethanolic oxalic acid solution. A small amount of material which precipitated was fractionally crystallized from ethanol, giving traces of two hydrogen oxalate salts, m.p. 159° (dec.) and m.p. 148° (dec.).

The alcohol mother liquors were combined and evaporated to dryness at reduced pressure. The residue was dissolved in water, made basic with 10% sodium hydroxide solution and the liberated bases taken up in ether. Evaporation of the ether solution, dried over anhydrous potassium carbonate, left a gum which was dissolved in 25 cc. of 5% hydrobromic acid, boiled with decolorizing charcoal and filtered. The filtrate deposited 0.51 g. (38%) of emetine hydrobromide, m.p. 228–232° (dec.), $[\alpha]_D$ +12.0° (*c*, 0.83 in water).

A portion of the above salt was converted to benzoylemetine, m.p. 184–185°, $[\alpha]_D$ −65° (*c*, 1.97 in chloroform). A mixed m.p. with an authentic sample of benzoylemetine[4] showed no depression. Carr and Pyman[10] report a m.p.

of 185–186° and $[\alpha]_D$ −62.3° (*c*, 2.37 in chloroform) for benzoylemetine.

Hydrogenation of Isotetradehydroemetine Hydrogen Oxalate.—A suspension of 1.50 g. of isotetradehydroemetine hydrogen oxalate in absolute ethanol was hydrogenated at one atmosphere pressure over 0.25 g. of Adams catalyst. A total of 100 cc. of hydrogen (1.75 moles of hydrogen per mole of isotetradehydroemetine hydrogen oxalate) was consumed in the course of eight hours, the organic material gradually going into solution. The solution was filtered, and on refrigeration, 0.41 g. of emetine hydrogen oxalate crystallized. One recrystallization from absolute ethanol afforded material of m.p. 167° (dec.) after drying *in vacuo*, $[\alpha]_D$ +11° (*c*, 1.80 in water). This salt was converted to benzoylemetine, m.p. 184–185°, $[\alpha]_D$ −65° (*c*, 1.51 in chloroform). A mixed m.p. with an authentic sample of benzoylemetine[4] showed no depression.

The original alcohol mother liquor was evaporated to dryness at reduced pressure, the residue dissolved in water, made basic with 10% sodium hydroxide solution and extracted with ether. Evaporation of the ether solution, dried over anhydrous potassium carbonate, left a solid, which was dissolved in 10 cc. of 5% hydrobromic acid solution. Emetine hydrobromide crystallized, m.p. 228–230° (dec.), $[\alpha]_D$ +11° (*c*, 1.82 in water), 0.24 g. This salt was also further identified by conversion to benzoylemetine. The total yield of emetine (hydrogen oxalate plus hydrobromide) amounted to 43%.

All attempts to obtain isoemetine, as the benzoyl derivative, from the hydrobromic acid mother liquor failed.

Mercuric Acetate Oxidation of Isotetradehydroemetine Hydrogen Oxalate.—A solution of 1.00 g. of isotetradehydroemetine hydrogen oxalate in 10 cc. of water was mixed with a solution of 2.20 g. of mercuric acetate, 0.20 g. of potassium acetate and 1.0 cc. of acetic acid in 15 cc. of water and refluxed for two and a half hours. An additional 1.00 g. of mercuric acetate was added and the refluxing continued for another two hours. The cooled orange solution was filtered and the precipitate washed with water, alcohol and acetone. The combined filtrate and wash solutions were concentrated to remove the alcohol and acetone, then treated with hydrogen sulfide. Following removal and washing of the mercuric sulfide with hot alcohol, the combined filtrate and wash solution was concentrated to 10 cc. *in vacuo*. Addition of 2.0 cc. of concentrated hydrochloric acid caused precipitation of 0.37 g. (45%) of rubremetinium chloride, which exhibited the m.p. behavior described by Battersby and Openshaw.[7]

Reaction of Rubremetinium Chloride with Aqueous Alcoholic Sodium Hydroxide.—A mixture of 1.00 g. of rubremetinium chloride, 25 cc. of water, 10 cc. of ethanol and 2.0 g. of sodium hydroxide was refluxed on the steam-bath for four hours. A yellow-brown solid which precipitated was collected, washed with water and dried on a clay plate, 0.70 g. Crystallization of 0.50 g. of this material from 85% ethanol afforded 0.28 g. of dehydrohalorubremetine, small, orange-yellow needles, which exhibited the following m.p. behavior: sinters at 165–170°, melts without flowing 170–175°, flows to a red liquid 175–179°.

Anal. Calcd. for $C_{29}H_{32}N_2O_4$: C, 73.70; H, 6.83; N, 5.93. Found: C, 73.23; H, 6.95; N, 6.17.

Dehydrohalorubremetine reddened fairly rapidly on standing exposed to laboratory air. Whereas freshly prepared material absorbed hydrogen readily over Adams catalyst (see below), an old preparation resisted hydrogenation. Best hydrogenation results were obtained by using the crude product from the aqueous alcoholic sodium hydroxide treatment, dried on a clay plate, without recrystallization. On treatment of the material with hot 6 *M* hydrochloric acid solution, with addition of enough acetone to effect solution, and then cooling, a yellow solid precipitated, which gradually turned dark brown on standing. No rubremetinium chloride was obtained.

Hydrogenation of Dehydrohalorubremetine.—A suspension of 1.15 g. of dehydrohalorubremetine in 50 cc. of absolute ethanol was hydrogenated at one atmosphere pressure over 0.12 g. of Adams catalyst. The yellow-brown suspension gradually changed in color to greenish-white as the hydrogenation progressed. Altogether 106 cc. of hydrogen (1.95 moles per mole of dehydrohalorubremetine) was consumed in the course of about eight hours. Enough absolute ethanol was added, with heating on the steam-bath, to dissolve all of the organic material, and the solution was filtered. A fractional crystallization of the product from absolute ethanol finally afforded 0.20 g. of colorless needles as the most insoluble fraction, m.p. 178.8–179.5° (to a red liquid).

Anal. Calcd. for $C_{29}H_{36}N_2O_4$: C, 73.08; H, 7.61; N, 5.88. Found: C, 72.82, 73.19; H, 7.37, 7.23; N, 6.01, 6.29.

The intermediate fractions in the fractional crystallization did not give well defined crystals, but the temperature at which melting began varied from 171.0 to 177.0° for the various fractions. None of the material exhibited any rotation in alcohol or benzene.

The compound, m.p. 178.8–179.5°, failed to give either a benzoyl derivative or a *p*-toluenesulfonyl derivative. The substance is readily soluble in dilute hydrochloric acid.

Preparation of the Unsaturated Bases (VII and VIII).—The mixed bases were prepared by the method of Pailer[20]: The iodomethylate of N-acetylemetine was subjected to a Hofmann degradation, the resulting methine base hydrogenated, reacetylated, converted to the iodomethylate, again subjected to a Hofmann degradation and again acetylated.

Ozonolysis of the Mixed Bases (VII and VIII).—A solution of 3.52 g. (0.0065 mole) of the mixed bases in 20 cc. of dry ethyl acetate was treated with 3.8 l. of oxygen containing a total of 0.007 mole of ozone. The solution of the ozonides was hydrogenated in a Parr apparatus at 3 atmospheres pressure over 0.05 g. of Adams catalyst. The solution was filtered and the solvent distilled *in vacuo*. The residue was dissolved in 50 cc. of 15% hydrochloric acid and the purple solution continuously extracted with ether. The orange ether solution was washed with small amounts of sodium bicarbonate solution and 10% sodium hydroxide solution. Evaporation of the ether solution left a yellow oil which was converted to the semicarbazone of 2-ethyl-4,5-dimethoxybenzaldehyde, m.p. 195–197°, 0.15 g. The m.p. was raised to 199–200° by two crystallizations from absolute ethanol. Pailer[20] reports a m.p. of 200–201°.

Acidification of the sodium bicarbonate solution afforded a small amount of 2-ethyl-4,5-dimethoxybenzoic acid, m.p. 140–141° after crystallization from Skelly C solvent. Späth and Pailer[22] report a m.p. of 144°.

The original acid solution was made basic with sodium hydroxide solution, and the turbid, brown mixture was continuously extracted with ether. The ether solution, dried over anhydrous potassium carbonate, afforded 2.13 g. of orange residue on evaporation. A solution of 1.00 g. of this material in 25 cc. of dry benzene was passed through a 4″ column of mixed alumina, super-cel filter-aid (1:1). The dried adsorbent was extruded, cut into two portions and each eluted with absolute ethanol. The following fractions were obtained: (1) 0.39 g. of orange glass from the upper 1.5″ of the column; (2) 0.21 g. of amorphous yellow solid from the lower 2.5″ of the column; (3) 0.25 g. of amorphous colorless solid from the benzene solution which passed through the column. No crystalline derivatives were obtained from any of these fractions. Fraction (3), m.p. 39–44°, was dried *in vacuo* for two days at room temperature.

Anal. Calcd. for $C_{30}H_{44}N_2O_5$ (IX): C, 70.28; H, 8.65; N, 5.47. Found: C, 70.62; H, 8.56; N, 5.48.

In another run, 3.80 g. of the mixed bases (VII and VIII) was ozonized and worked up as described above, except that the ether extract of the basic solution was shaken with 5.0 cc. of acetic anhydride and 50 cc. of 10% sodium hydroxide solution, with water cooling. Evaporation of the ether solution, dried over anhydrous potassium carbonate, afforded 1.10 g. of red gum. This was dissolved in 25 cc. of dry benzene and passed through an 8″ column of alumina. The dried adsorbent was extruded, cut into three portions and each eluted with absolute ethanol, giving the following fractions: (1) 0.08 g. of orange glass from the upper 0.5″ of the column; (2) 0.58 g. of amorphous orange solid from the next 5.0″ of the column; (3) 0.30 g. of colorless glass from the bottom 2.5″ of the column.

The third fraction was dissolved in 20 cc. of dry ether, dry hydrogen chloride was passed in, and the colorless, hygroscopic hydrochloride was collected, m.p. 55–65°. To a solution of 0.10 g. of this hydrochloride in 5 cc. of water was added 0.10 g. of chlorauric acid. A tan precipitate

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(22) E. Späth and M. Pailer, *Monatsh.*, **78**, 348 (1948).

which formed was filtered, washed with dilute hydrochloric acid and dried *in vacuo* at 56°, m.p. 104–108° (dec.).

Anal. Calcd. for $C_{32}H_{47}N_2O_6AuCl_4$: C, 42.95; H, 5.29; N, 3.13; Au, 22.03. Found: C, 42.99, 42.91; H, 5.44, 5.19; N, 3.53, 3.41; Au, 21.70, 21.88.

No crystalline derivatives were obtained from fractions (1) and (2) of the chromatographic separation.

Chromatographic Separation of the Unsaturated Bases (VII and VIII).—A solution of 1.75 g. of the mixed bases in 25 cc. of dry benzene was passed through an 8" column of alumina. A partial elution was carried out with first 10 cc. of dry benzene, then 20 cc. of a 3% solution of ethanol in benzene. The column was extruded, dried and sectioned. The following fractions were obtained: (1) all of the color was located in the upper 0.25" of the column, and this was discarded; (2) 0.18 g. of colorless glass from the next 2" of the column; (3) 0.61 g. of colorless glass from the lower 5.75" of the column; (4) 0.86 g. of colorless glass from the original solvent and eluent solvents.

Ozonolysis of fraction (3) and working up as described before gave 0.11 g. (40%) of 2-ethyl-4,5-dimethoxybenzaldehyde semicarbazone and 0.03 g. (13%) of 2-ethyl-4,5-dimethoxybenzoic acid. The other, nitrogen containing cleavage product of the ozonolysis could not be obtained in crystalline form or as a crystalline derivative.

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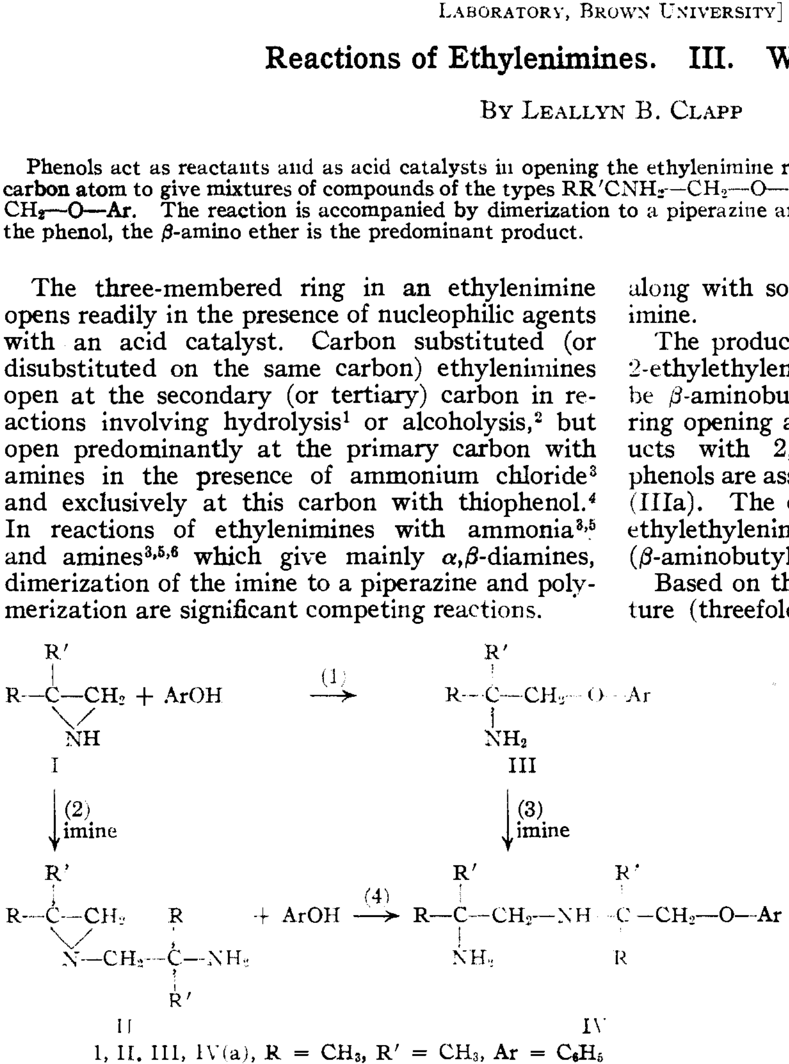
Reactions of Ethylenimines. III. With Phenols

BY LEALLYN B. CLAPP

Phenols act as reactants and as acid catalysts in opening the ethylenimine ring, $RR'\text{—}\overbrace{CH\text{—}CH_2}^{NH}$, at the unsubstituted carbon atom to give mixtures of compounds of the types $RR'CNH_2\text{—}CH_2\text{—}O\text{—}Ar$ and $RR'\text{—}CNH_2\text{—}CH_2\text{—}NH\text{—}CRR'\text{—}CH_2\text{—}O\text{—}Ar$. The reaction is accompanied by dimerization to a piperazine and polymerization. With a large excess of the phenol, the *β*-amino ether is the predominant product.

The three-membered ring in an ethylenimine opens readily in the presence of nucleophilic agents with an acid catalyst. Carbon substituted (or disubstituted on the same carbon) ethylenimines open at the secondary (or tertiary) carbon in reactions involving hydrolysis[1] or alcoholysis,[2] but open predominantly at the primary carbon with amines in the presence of ammonium chloride[3] and exclusively at this carbon with thiophenol.[4] In reactions of ethylenimines with ammonia[3,5] and amines[3,5,6] which give mainly *α*,*β*-diamines, dimerization of the imine to a piperazine and polymerization are significant competing reactions.



I, II, III, IV(a), R = CH_3, R' = CH_3, Ar = C_6H_5
(b), R = C_2H_5, R' = H, Ar = C_6H_5

When a phenol is the nucleophilic agent as well as the acid catalyst for the ring cleavage, products in which the imine to phenol ratio is 1:1 (III) and 2:1 (IV), respectively, are formed on an approximately equal basis (using threefold of phenol), along with some piperazines and polymers of the imine.

The product of the reaction of one molecule of 2-ethylethylenimine with one of phenol proved to be *β*-aminobutyl phenyl ether (IIIb), a result of ring opening at the primary carbon and the products with 2,2-dimethylethylenimine and other phenols are assumed to have an analogous structure (IIIa). The compound from two molecules of 2-ethylethylenimine with one of phenol was *β*-(*β*-aminobutyl)-aminobutyl phenyl ether (IVb).

Based on the imine present in the reaction mixture (threefold in phenol) the total yields of the two isolated products containing phenols diminish with acid strength from about 60% for phenol itself to 17% for 2,6-dimethylphenol. However, the yields do not follow acid strength alone in reactions with acids which are not homologs of phenol; nucleophilic character appears also to be an important factor in the over-all picture. For example, thiophenol in reacting with 2,2-dimethylethylenimine gives a 92% yield[4] of the *β*-amino sulfide whereas *o*-, *m*- and *p*-nitrophenol and *p*-bromophenol, acids of comparable strength, act only as catalysts for the polymerization of this imine and give no yields of adducts at all. The still stronger carboxylic acids, such as benzoic, again give good yields of the corresponding *β*-amino esters.[7]

Having an ortho position occupied in a phenol does not decrease the yields of amino ethers, but, as expected, if both ortho positions are occupied, the yields are much lower. The yields of products from 2,5-dimethylphenol and *p*-methoxyphenol, respectively, with 2,2-dimethylethylenimine are nearly equal and about half those from *o*- and *p*-cresol.

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