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

Structure of "Oxyprotopine" and Related Alkaloid Products

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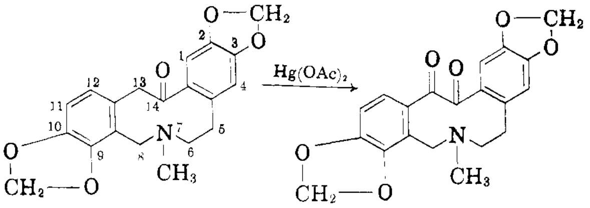
The structure of "oxyprotopine," the mercuric acetate oxidation product of the alkaloid protopine, has been established as 13-ketoprotopine. Structures have also been assigned to related alkaloid products.

Our interests in mercuric acetate oxidation of tertiary amines[2] and in transannular nitrogen-carbonyl interaction in medium-sized ring amino-ketones[3] merged in a reinvestigation of the product "oxyprotopine," obtained by the mercuric acetate oxidation of the alkaloid protopine (I).[4] The $C_{20}H_{17}NO_6$ product, corresponding to a net loss of two hydrogens and gain of one oxygen with respect to protopine, was assigned the 5,14-diketo structure by Gadamer and Kollmar.



I II

(a, 2,3-Di-CH_3O- in place of 2,3-OCH_2O-,
b, 9,10-Di-CH_3O- in place of 9,10-OCH_2O-)

The evidence for their assignment cannot be considered convincing. Positions 6 and 8 were excluded as possibilities for the carbonyl group which was introduced on the basis of the reducibility of the $C_{20}H_{17}NO_6$ product with sodium amalgam to a "tetrahydroöxyprotopine," which was not fully characterized. Position 13 was excluded because of the failure of "oxyprotopine" to condense with *o*-phenylenediamine, although it might well be argued that the 13,14-diketone system would be expected to resist quinoxaline formation not only because of steric resistance to coplanarity but also because of decreased reactivity of the C-14 carbonyl due to transannular interaction (CH_3—$N^{\delta+}$----$C{=}O^{\delta-}$).[5] Moreover, the light yellow color of the $C_{20}H_{17}NO_6$ compound is strongly suggestive of a 13,14-diketone system, and the C-13 position presents the most highly activated methylene group for oxidative attack by mercuric acetate.

On the assumption that Gadamer's "oxyprotopine" was actually 13-ketoprotopine (II) rather than the 5-keto isomer, we assembled data which established structure II as correct. The ultraviolet absorption spectrum, determined in 95% ethanol (λ_{max} 317 mμ, log ϵ 3.93; 288 mμ, log ϵ 3.97), showed close similarity to that of the open analog, 3,3′,4,4′-bis-methylenedioxybenzil (λ_{max}^{EtOH} 324 mμ, log ϵ 4.12; 281 mμ, log ϵ 3.98),[6] and was good evidence for the skew-benzil system. Scale molecular models support the preferred residence of a 13,14-diketone system as in II in skew conformations.

Chemical proof of the adjacency of the carbonyl groups in "oxyprotopine" was provided by the following sequence. "Oxyprotopine" was reduced with a large excess of lithium aluminum hydride to a tetrahydro compound, $C_{20}H_{21}NO_6$, with properties similar to those reported by Gadamer and Kollmar[4] for their "tetrahydroöxyprotopine" and an infrared spectrum consistent with the diol structure III.[7]

The diol could be oxidized with periodic acid, and the resulting oxidation product was convertible to a dioxime. Satisfactory representation of the reaction sequence is found solely in the formulas III, IV, and V.

These results show clearly that the $C_{20}H_{17}NO_6$ product of the mercuric acetate oxidation of protopine is 13-ketoprotopine[8] and suggest that the

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[1] Standard Oil Foundation, Inc. (Indiana) Fellow, 1955–56.

[2] For leading references, see N. J. Leonard, W. J. Middleton, Paul D. Thomas, and D. Choudhury, *J. Org. Chem.*, **21**, 344 (1956); N. J. Leonard and A. S. Hay, *J. Am. Chem. Soc.*, **78**, 1984 (1956).

[3] For leading reference, see N. J. Leonard and M. Ōki, *J. Am. Chem. Soc.*, **77**, 6245 (1955).

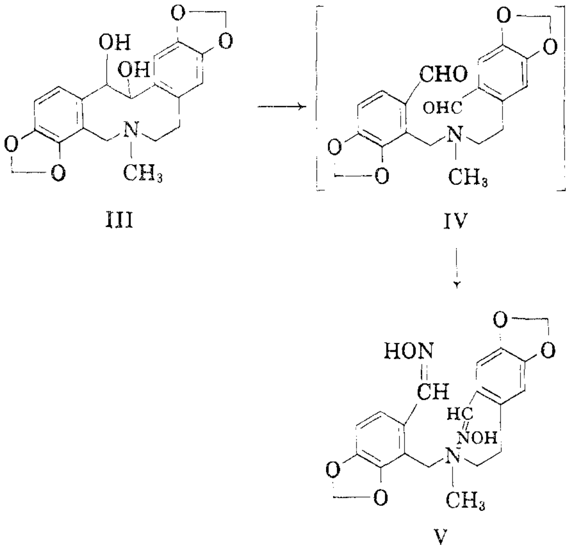
[4] J. Gadamer and H. Kollmar, *Arch. Pharm.*, **261**, 153 (1923).

[5] The low carbonyl reactivity in protopine and cryptopine was ascribed to such N—C_{CO} interaction by W. O. Kermack and R. Robinson, [*J. Chem. Soc.*, **121**, 427 (1922)], and J. Gadamer [*Arch. Pharm.*, **258**, 148 (1920)]; J. Gadamer and F. von Bruchhausen [*Arch. Pharm.*, **260**, 97 (1922)] suggested that in the salt form the ten-membered ring of these alkaloids is transformed to two six-membered rings, with the nitrogen quaternary; *cf.* F. A. L. Anet, A. S. Bailey, and Sir Robert Robinson, *Chemistry and Industry*, 944 (1953); E. H. Mottus, H. Schwarz, and L. Marion, *Can. J. Chem.*, **31**, 1144 (1953); F. A. L. Anet and L. Marion, *Can. J. Chem.*, **32**, 452 (1954).

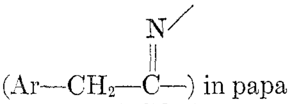
[6] N. J. Leonard, R. T. Rapala, H. L. Herzog, and E. R. Blout, *J. Am. Chem. Soc.*, **71**, 2997 (1949).

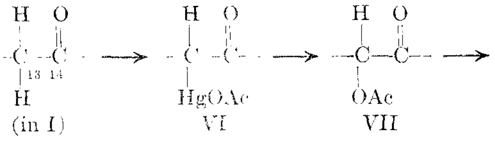
[7] The preservation of the oxygen functions in the presence of excess lithium aluminum hydride simultaneously ruled against location of the mercuric acetate–introduced carbonyl at either C-6 or C-8, in confirmation of the original Gadamer and Kollmar suggestion.

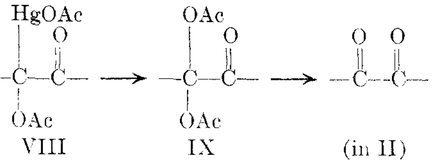
[8] Deuterium exchange reactions with protopine and "oxyprotopine" gave corroberative evidence for this structure assignment (see experimental).



products[4] of similar oxidation of the alkaloids cryptopine (Ia) and allocryptopine (Ib) are 13-ketocryptopine (IIa) and 13-ketoallocryptopine (IIb), respectively.

The course of the oxidation at C-13 may well involve a mercury-containing intermediate. The oxidation of cyclohexene with Hg^{++} has been shown to proceed through an intermediate mercurial.[9] Acetoxymercuration of the C-13,14 system (enol ?) could proceed in a manner (VI, VII) similar to that suggested by Barton and Rosenfelder[10] for the action of mercuric acetate on isodehydrocholesteryl *p*-nitrobenzoate. Parallel intermediates have been suggested for the conversion of the similarly activated methylene  $(Ar{-}CH_2{-}\overset{\overset{N\diagup}{\|}}{C}{-})$ in papaverine[11] to CHOH (papaverinol) and CO (papaveraldine), and the closely related 2-benzylpyridine has been shown to yield 2-pyridylphenylcarbinol on oxidation with mercuric acetate.[12] A repetition of the process (VI, VII) involving acetoxymercuration and replacement of HgOAc by OAc, represented schematically by VIII and IX, would lead logically to the C-13,14 diketone (II).





Direct α-acetoxylation of less highly activated ketones has been realized under somewhat more vigorous conditions with mercuric acetate.[13,14]

EXPERIMENTAL[15]

Oxidation of protopine with mercuric acetate.[4] To a solution of 2.0 g. (5.7 mmoles) of protopine ($\lambda_{max}^{95\%\ EtOH}$ 293 mμ, log ε 3.93) in 20 ml. of water and 0.35 ml. of acetic acid, warmed to 75°, was added during 35 minutes a solution of 9.1 g. (29 mmoles) of mercuric acetate in 25 ml. of 1% acetic acid. After heating and stirring for an additional 30 min., the solution was cooled and filtered, whereupon 2.4 g. of mercurous acetate was collected. An additional 1.9 g. was obtained on heating for 4.5 hr. The excess mercuric acetate was then decomposed by heating with an excess of 98% formic acid. The filtered solution was basified with potassium carbonate and strong potassium hydroxide solution, followed by extraction with chloroform. The dried extracts were evaporated, yielding 1.5 g. of a yellow powder. The product was chromatographed on alumina. A yellow crystalline solid (380 mg., 18%), m.p. 227–230°, was obtained in the ether-acetone eluates. Further elution gave only oily material. The solid was recrystallized from acetone, m.p. 229–230° (reported,[4] 225°).

Anal. Calc'd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.38; H, 4.61; N, 3.56.

The infrared spectrum (chloroform) showed carbonyl absorption at 1668 cm.$^{-1}$ with a shoulder at *ca.* 1680 cm.$^{-1}$.

The nitrate salt was made in water and was recrystallized from methanol-water, m.p. 270–271° (dec.) (reported,[4] 274–275°).

Anal. Calc'd for $C_{20}H_{18}N_2O_9$: C, 55.81; H, 4.22. Found: C, 55.47; H, 4.49.

The infrared spectrum (Nujol) showed two bands in the O—H stretching region: 3620 cm.$^{-1}$ and 3480 cm.$^{-1}$ The carbonyl stretching band appeared at 1701 cm.$^{-1}$ The spectrum appears consistent with the transannular bonded form of the salt as a solid.

Deuterium exchanges. A solution of 100 mg. of protopine with 1.0 g. of sodium methoxide in 3 ml. of deuterium oxide was heated under reflux for 42 hr. The aqueous solution was extracted five times with chloroform, and the chloroform extracts were dried. Evaporation of the chloroform yielded 85 mg. of a tan powder which melted at 206–208° after drying overnight in an Abderhalden. The infrared spectrum (chloroform) showed three weak bands in the C—D stretching region. A few minor changes appeared in other sections of the protopine spectrum.

Anal. Calc'd for $C_{20}H_{17}D_2NO_5$: D, 10.5 atom %. Found: 8.5 atom %.

Under the same conditions 100 mg. of 13-ketoprotopine yielded a tarry solution from which 50 mg. of a tan powder was extracted, m.p. 220–223° (dec.). The infrared spectrum showed no appreciable absorption in the C—D stretching region and was otherwise very similar to that of pure ketoprotopine.

Anal. Found: 3.5 atom % D.

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(9) D. A. Shearer and G. F. Wright, *Can. J. Chem.*, **33**, 1002 (1955); see also H. J. Lucas, F. R. Hepner, and S. Winstein, *J. Am. Chem. Soc.*, 61, 3102 (1939).

(10) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 2381 (1951).

(11) J. Gadamer, *Arch. Pharm.*, **253**, 274 (1915).

(12) R. Anker, A. Cook, and I. Heilbron, *J. Chem. Soc.*, 917 (1945).

(13) W. Treibs and H. Bast, *Ann.*, **561**, 165 (1949).

(14) P. R. Jefferies, A. K. Macbeth, and B. Milligan, *J. Chem. Soc.*, 705 (1954).

(15) Eastman protopine was used without further purification. Melting points are corrected. Deuterium analyses were performed by Mr. Joseph Nemeth by the falling drop method.

Under these similar conditions, including the arbitrary reaction time, only II among the possible dicarbonyl structures could be expected to take up less deuterium than I, and the relative figures for deuterium content can be taken therefore as qualitatively significant.

Reduction of 13-ketoprotopine with lithium aluminum hydride.[16] To a slurry of 150 mg. (4 mmoles) of lithium aluminum hydride in 30 ml. of dry ether was added rapidly 230 mg. (0.63 mmole) of 13-ketoprotopine in 30 ml. of dry benzene. After stirring for 11 hours at 25° the mixture was decomposed with 10 ml. of $6N$ hydrochloric acid. The aqueous phase was basified with saturated potassium carbonate solution and extracted with methylene chloride. The dried extracts were evaporated to a gray powder, from which 122 mg. (52%) of colorless prisms (III) were obtained on crystallization from acetone, m.p. 257–259° (dec.). Gadamer[4] reported a melting point of 255–256° for "tetrahydroöxyprotopine."

Anal. Calc'd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.67; H, 5.85; N, 3.66.

The infrared spectrum in Nujol showed strong OH absorption at 3260 cm.$^{-1}$ and no carbonyl absorption.

Oxidation of tetrahydroketoprotopine with periodic acid.[17] A solution of 81 mg. (0.22 mmole) of the diol in 0.4 ml. of $1N$ H_2SO_4 was treated with a solution of 50 mg. of periodic acid in 0.8 ml. of water. The resulting solution was allowed to stand at 25° for 27 hr. Basification with saturated potassium carbonate solution was followed by ether extraction. The dried extracts were evaporated to give 64 mg. of a gray powder. The infrared spectrum in Nujol showed carbonyl absorption at 1678 cm.$^{-1}$, characteristic of an aromatic aldehyde (IV).

The powder was treated with 0.5 ml. of methanol followed by 0.5 ml. of $1N$ sodium hydroxide solution and 30 mg. of hydroxylamine hydrochloride. About 50 mg. of dioxime was obtained after 3 hr. at 25°. The dioxime (V) was washed with hot 90% ethanol and dried in vacuum at room temperature (to avoid decomposition), m.p. 209°.

Anal. Calc'd for $C_{20}H_{21}N_3O_6.H_2O$: C, 57.55; H, 5.55; N, 10.07. Found: C, 57.45; H, 5.15; N, 9.50.

The ultraviolet spectrum in 95% ethanol showed maxima at 272 mμ (log ϵ 4.26) and 306 mμ (log ϵ 4.09). The values reported by Russell[17] for the dimethoxy analog (Vb) are: 270 mμ (log ϵ 4.32) and inflexion at 290–310 mμ (log ϵ 4.00).

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[16] R. Mirza, *Experientia*, **8**, 258 (1952).

[17] P. B. Russell, *J. Am. Chem. Soc.*, **78**, 3115 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF OREGON]

Ester Derivatives of Mucic Acid[1]

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The reaction of "mucic acid lactone" with ethanol and methanol produced monoesters of mucic acid, which were purified and characterized as the tetraacetyl derivatives. Monoethyl mucate was also prepared, in impure form, by partial hydrolysis of the diethyl ester. Tetraacetylmucic acid and one mole of diazomethane gave mainly the dimethyl ester. Mucic acid or tetraacetylmucic acid and one mole of silver nitrate gave the respective disilver salts.

A derivative of mucic acid in which the hydroxyl groups and one carboxyl group are esterified, such as monoethyl tetraacetylmucate, was desired as the starting point for a projected synthesis of inositol.[1] The monoesters of dicarboxylic acids are usually prepared by treatment of the appropriate cyclic anhydride with one mole of alcohol, but this type of compound is not available in the case of mucic acid. Therefore, the preparation of monoethyl mucate was first attempted by partial hydrolysis of the diethyl ester.

A mixture of one mole of diethyl mucate with one mole of potassium hydroxide became neutral in a very short time. Rapid evaporation of the solution to dryness and treatment of the residue with the calculated amount of 1 M hydrochloric acid gave a white solid, m.p. 177–179°, with a neutralization equivalent of 200 and a saponification equivalent of 117. Saponification produced mucic acid quantitatively. It appears, accordingly, that the solid was a mixture of 84% monoethyl mucate and 16% mucic acid. Unfortunately, this product could not easily be purified by recrystallization; water would cause some hydrolysis, and all other liquids tried were not sufficiently good solvents.

Monoethyl mucate could be prepared, in somewhat purer form, from Fischer's[4] "mucic acid lactone." This viscous liquid, obtained from an aqueous solution of mucic acid by rapid evaporation to dryness, is, likely, a mixture of lactones and intermolecular esters. From a solution of this substance in anhydrous ethanol there separated, in the course of several days, crystals of monethyl mucate mixed with a little mucic acid, of neutralization equivalent 211. Further purification was effected by first converting this product to the tetraacetyl derivative, which could be purified by crystallization from ethanol, m.p. 181–183°.

Monomethyl mucate was obtained similarly from a solution of mucic acid in anhydrous methanol. Acetylation of the crude ester and crystalliza-

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[1] Abstracted from a thesis submitted by M. D. Bealor in partial fulfillment of the requirements for the Ph.D. degree, University of Oregon, June 1956.

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[4] Fischer, *Ber.*, **24**, 2141 (1891).