[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

The Hydroxylation of Anhydromethyltetrahydroberberine-A. 13-Hydroxydihydro-*allo*cryptopine

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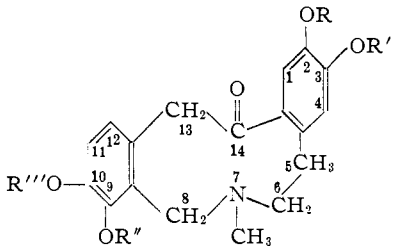
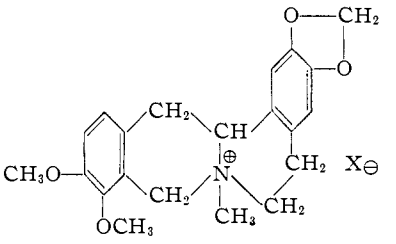
The 10-membered unsaturated ring compound, anhydromethyltetrahydroberberine-A (V), on oxidation with hydrogen peroxide or with aqueous N-bromosuccinimide, gives the α-glycol, 13-hydroxydihydro*allo*cryptopine. The compound, while resembling *allo*cryptopine in some of its properties, is not convertible to the alkaloid by heating in glacial acetic acid containing hydrochloric acid. Attempts to prepare the isomers of this glycol by oxidation with permanganate and with iodine and silver acetate failed.

The classical investigations of W. H. Perkin, Jr., led him to suggest the structures I and II for cryptopine and protopine, respectively.[1] Shortly thereafter, Gadamer[2] proposed the structure III for the related alkaloid β-homochelidonine and at the same time suggested that the name be changed to *allo*cryptopine. This last compound has recently been isolated from *Zanthoxylum coco* under the name of α-fagarine.[3]

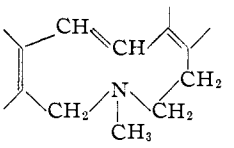


I[4] (R = R′ = —CH_3; R″ and R‴ become —CH_2—)
II (R and R′ = R″ and R‴ = —CH_2—)
III (R and R′ become —CH_2—; R″ = R‴ = —CH_3)

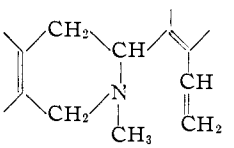
The ten membered ring system proposed for these alkaloids was not unique. Voss and Gadamer[5] and Pyman and Jowett[6] obtained optically inactive products from Hofmann degradation of quaternary salts of *l*-canadine (*l*-tetrahydroberberine, IV); the structure V was proposed for these compounds and although McDavid, Perkin and Robinson[7] criticized this formulation, Pyman,[8] as a result of a comprehensive study of the Hofmann degradation, was able to show that V was in fact one of the products. This compound, which will be called anhydromethyltetrahydroberberine-A or simply base-A, was accompanied by the vinyl base, anhydromethyltetrahydroberberine-B (base-B VI) when obtained from *dl*-tetrahydroberberine. When obtained from *l*-canadine it was accompanied by both the optically inactive and active forms of base-B. Pyman demonstrated that base-A underwent transannular cyclization to give *dl*-tetrahydroberberine quaternary salts very readily, and so the occurrence of the inactive base-B among the products of the Hofmann degradation of the active quaternary salt was explained.



IV



V



VI

Haworth and Perkin[9] attempted to convert the base-A (V) to *allo*cryptopine (III). The realization of this apparently simple change proved difficult because of the ease with which V reverts to IV. Eventually, however, it was found possible to oxidize the base V to the oxide VII with perbenzoic acid. This oxide, on treatment with hydrochloric in acetic acid on a steam-bath, rearranged to *allo*cryptopine. The other alkaloids of the group were synthesized in a similar manner.[10]

The mechanism of the remarkable rearrangement of VII to III is not known. It has been suggested by Manske[11] that the reaction proceeds *via* the glycol, 13-hydroxydihydro*allo*cryptopine (VIII). This, on dehydration, might be expected to give one or both of the enols IXa and b; the former on ketonization would yield *allo*cryptopine, while the latter would give an isomeric compound X. The present communication deals with the preparation and properties of the glycol VIII.

The base-A, as mentioned previously, undergoes cyclization to give quaternary derivatives of tetrahydroberberine with great ease. This reaction may be regarded as a reversal of the Hofmann

(1) (a) W. H. Perkin, Jr., *J. Chem. Soc.*, **109**, 815 (1916); (b) **115**, 713 (1919).

(2) J. Gadamer, *Arch. Pharm.*, **258**, 148 (1918).

(3) (a) C. E. Redemann, B. B. Wisegarver and G. A. Alles, THIS JOURNAL, **71**, 1030 (1949); (b) V. Deulofeu, R. Labriola and J. Dehanghe, *ibid.*, **64**, 2326 (1942).

(4) The numbering is that used by L. F. Small and R. E. Lutz, "Chemistry of the Opium Alkaloids," Supplement No. 103, Public Health Reports, Washington, 1932, p. 101. It is taken from that proposed by J. S. Buck, W. H. Perkin, Jr., and T. S. Stevens, *J. Chem. Soc.*, **127**, 1462 (1925), for the berberine series.

(5) A. Voss and J. Gadamer, *Arch. Pharm.*, **248**, 43 (1910).

(6) F. L. Pyman and H. A. D. Jowett, *J. Chem. Soc.*, **103**, 290 (1913).

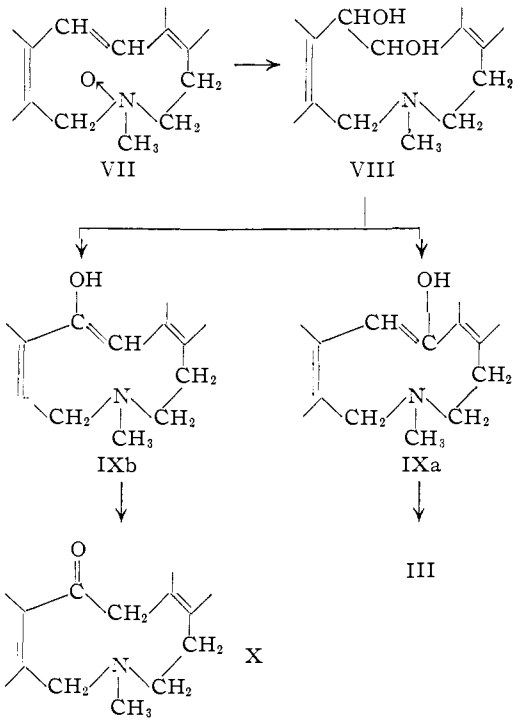
(7) J. W. McDavid, W. H. Perkin, Jr., and R. Robinson, *ibid.*, **101**, 1218 (1912).

(8) F. L. Pyman, *ibid.*, **103**, 817 (1913).

(9) R. D. Haworth and W. H. Perkin, Jr., *ibid.*, 445 (1926).

(10) R. D. Haworth and W. H. Perkin, Jr., *ibid.*, 1769 (1926).

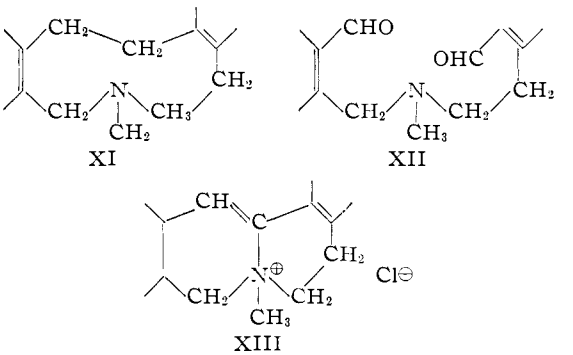
(11) R. F. Manske, "The Alkaloids," Vol. IV, Academic Press, New York, N. Y., 1954, p. 1.



cleavage.[12] The cyclization is rapid in ethanol, less rapid in glacial acetic acid and slow in hydrocarbons, ether, ethyl acetate and dilute hydrochloric acid. This may be demonstrated by the catalytic hydrogenation of the base; in alcohol no hydrogen was absorbed, and after acidification with hydrochloric acid tetrahydroberberine methochloride was isolated in good yield. In 3 *N* hydrochloric acid, on the other hand, one mole of hydrogen was absorbed smoothly and rapidly to give the dihydro compound of base-A (XI)[13] in good yield. In glacial acetic acid about one-half mole of hydrogen was absorbed and both products were isolated from the reaction mixture.

Since base-A was stable in dilute hydrochloric acid, an attempt was made to hydroxylate the double bond with hydrogen peroxide in this solvent. The main product of such reactions was a compound $C_{21}H_{25}O_6N$, m.p. 197° dec., which was in fact shown to be one of the geometrically isomeric glycols represented by VIII. Along with this glycol some other material was isolated which melted at a higher temperature. This was shown to contain small amounts of two compounds, one m.p. 240–243° dec., the other m.p. 206–207°, both apparently isomeric with the glycol, m.p. 197°. The small quantities of these compounds available has prevented their further examination.

The compound $C_{21}H_{25}O_6N$, m.p. 197° dec., was soluble in ethyl acetate, chloroform, benzene and ethanol, less soluble in ether and almost insoluble in water. It crystallized in colorless needles from chloroform–ether or aqueous ethanol. It formed a normal hydrochloride and normal quaternary salts with methyl iodide and methyl and ethyl *p*-toluenesulfonates. With concentrated sulfuric acid it gave an intense bluish violet not unlike that given by *allo*cryptopine itself. It did not absorb hydrogen on attempted hydrogenation. On oxidation with periodic acid a dialdehyde XII, characterized as the methyl *p*-toluenesulfonate and the dioxime, was produced. The dioxime of this aldehyde on refluxing with acetic anhydride gave a dinitrile characterized as the methyl *p*-toluenesulfonate. The absorption spectra of the last three compounds were in accord with the structures allocated. Treatment of the glycol with phosphorus oxychloride gave dihydroanhydroberberine methochloride (XIII); *allo*cryptopine gives the same product under similar conditions.[2] Attempts to acetylate the compound also yielded XIII. These observations provided convincing evidence that the compound, m.p. 197° dec., was in fact one of the isomers of the structure VIII.



A more convenient preparation of the glycol, m.p. 197° dec., was developed. Since hydrochloric acid is oxidized by hydrogen peroxide, it is likely that the oxidation of the base V in this medium proceeds by the addition of hypochlorous acid to the double bond. The fact that in aqueous solution N-bromoamides behave like hypobromous acid, giving bromohydrins with ethylenes, was first observed by Schmidt, v. Knilling and Ascherl.[14a] Since this time many workers have used N-bromoacetamide and N-bromosuccinimide for this purpose.[14b–e] Treatment of the bromohydrins so formed with sodium hydroxide solution gives the corresponding epoxide,[14f] which on hydrolysis yields a glycol. When the hydrochloride of the base-A (V) was treated with N-bromosuccinimide in aqueous suspension, a reaction took place at once; the solution on basification and extraction with chloroform gave the glycol, m.p. 197° dec., in some 50–60% yield. Acidification of the aqueous mother liquors with hydrochloric acid caused the separation of dihydroanhydro-

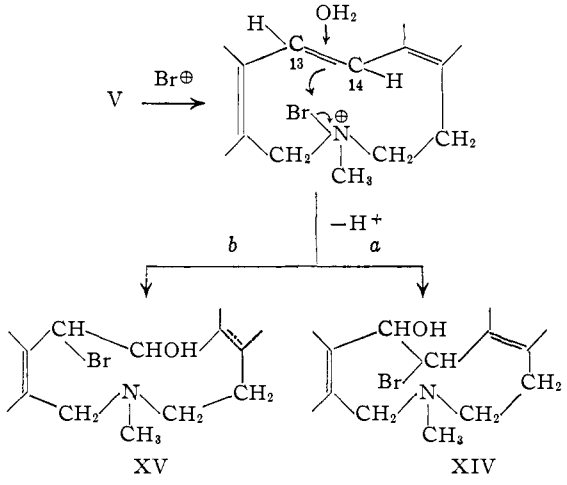
(12) It may be compared with the cyclization of the "des-baseD," obtained from dihydrostrychnidine-A methohydrogen carbonate by the Hofmann cleavage, on attempted catalytic hydrogenation in acetic acid [D. Achmatowicz and R. Robinson, *J. Chem. Soc.*, 941 (1938)]. Here too, the double bond and the tertiary nitrogen are opposed across a medium (9) membered ring [L. H. Briggs, H. T. Openshaw and R. Robinson, *ibid.*, 903 (1946)]. See also E. Gellert, *Chem. and Ind.*, 983 (1955), and H. Bickel, H. Schmid and P. Karrer, *Helv. Chim. Acta*, **38**, 649 (1955). For examples in the conessine field where the nitrogen and double bond are not members of a medium ring, see R. D. Haworth, *et al.*, *J. Chem. Soc.*, 1115 (1953); 967 (1954).

(13) M. Freund and K. Fleischer, *Ann.*, **409**, 246 (1915).

(14) (a) E. Schmidt, W. v. Knilling and A. Ascherl, *Ber.*, **59**, 1279 (1926); (b) S. Winstein and R. E. Buckles, THIS JOURNAL, **64**, 2780 (1942); (c) I. Salamon and T. Reichstein, *Helv. Chim. Acta*, **30**, 1616 (1947); (d) R. A. Raphael, *J. Chem. Soc.*, S44 (1949); (e) P. Bladen and L. N. Owen, *ibid.*, 598 (1950); (f) C. E. Guss and R. Rosenthal, THIS JOURNAL, **77**, 2549 (1955).

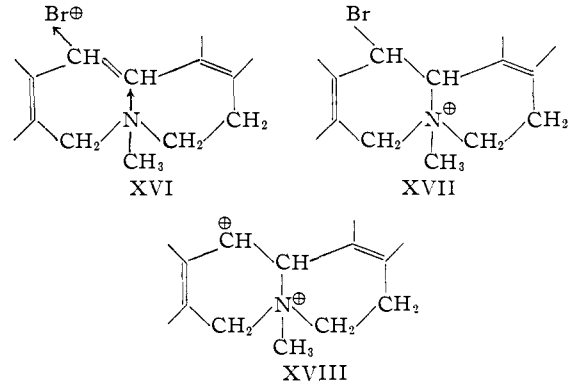
berberine methochloride (XIII) in about 30% yield.

The hydroxyl groups of the glycol VIII may have either the *trans* or the *cis* arrangement. It is not possible, unambiguously, to allocate either configuration to the compound, m.p. 197°, since the mechanism of formation is not clear. As will be shown below the *trans* configuration is favored. If it is assumed that, in the oxidation of V by N-bromosuccinimide, the bromonium ion $Br^{\oplus}$ is the reactive species, then the following series of reactions may be postulated



XV XIV

Process (a) has the virtue of involving the transfer of an atom from N to C_{14} and may be compared with the conversion of the amine oxide (VII) to *allo*cryptopine. It has the disadvantage, however, that the hydrolysis of the bromide in XIV takes place within interacting distance of the nitrogen. However, since the bromine is sandwiched between the N and C_{14}, a consequence of the initial intramolecular bromine transfer, the nitrogen cannot approach at the back of the C_{14}–Br bond. Transannular quaternarization to give a 13-hydroxytetrahydroberberinium salt is therefore impossible, and the displacement of the bromine by water proceeds without interference. Process (b), on the other hand, has the defect of transferring an atom from N to C_{13} in contrast to the known transannular reactions of this series of compounds; it has the virtue, however, that the hydrolysis of the bromine in XV occurs beyond the interacting distance of the nitrogen. There is little to choose between these two pathways; the conversions of either XIV or XV to the glycol VIII have the following points in common. The hydroxyl on the adjacent carbon atom cannot participate in the hydrolysis to any great extent because of the strain of epoxide formation. The hydrolysis of the bromide in the absence of neighboring group participation by either a concerted or carbonium ion mechanism leads to the thermodynamically more stable glycol. Inspection of models shows this to be the *trans* glycol. The formation of the dihydroanhydroberberinium salt XIII may be looked upon as the result of a concerted attack XVI to give XVII, loss of hydrogen bromide from this compound is facilitated by the ability of C_{13} to form, readily, a carbonium ion XVIII, which then loses a proton from C_{14}.[15]



XVI XVII XVIII

Several attempts to hydroxylate the double bond of V by other reagents were made. When the base-A was subjected to oxidation with dilute potassium permanganate in acetone, a crystalline compound was isolated in good (*ca.* 70%) yield. The analysis of this compound suggested that it is isomeric with the glycol (VIII, $C_{21}H_{25}O_6N$). When this compound was treated with picric, picrolonic or *p*-toluenesulfonic acids, salts of the ion $C_{21}H_{24}O_4N^+$ were obtained. The picrate was identical with β-methyltetrahydroberberinium picrate (IV, X = $C_6H_2O_7N_3$). Re-examination of the analytical data in addition to $C_{21}H_{25}O_6N$ they are also in satisfactory agreement with the β-methyltetrahydroberberinium salts of several organic acids [*e.g.*, the tartrate $(C_{21}H_{24}O_4N)_2C_4H_6O_6$]. It is believed, therefore, that while some of the base-A is oxidized to a mixture of simple organic acids, the remainder cyclizes to the β-methyltetrahydroberberinium derivative. When anhydromethyltetrahydroberberine-A was treated with iodine and silver acetate in moist acetic acid,[16] a good yield (70%) of quaternary dihydroanhydroberberine metho-salt XIII was isolated. This reaction probably proceeds in a manner similar to the formation of XIII in the oxidation with N-bromosuccinimide.

The glycol VIII on being heated with hydrochloric acid in acetic acid on a steam-bath, conditions which when applied to the amine oxide VII gave *allo*cryptopine (III) in about 70% yield, gave instead of that alkaloid, dihydroanhydroberberine methochloride (XIII) in good yield. Attempts to convert VIII to III by other methods failed.

Attempts to demonstrate the presence of the isomer X in the product from the rearrangement of the oxide by paper chromatography failed.[17] From the aqueous mother liquors, after removal of the alkaloid, a small amount of dihydroanhydroberberine methochloride was isolated. The isolation of this substance is probably without sig-

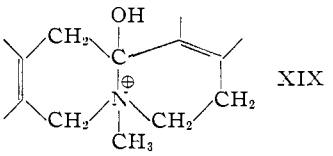
(15) The author is indebted to Dr. Ernest Wenkert (Ames, Iowa) who suggested the above interpretation of the reaction of V with N-bromosuccinimide.

(16) (a) L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson and Q. E. Thompson, THIS JOURNAL, **76**, 5014 (1954); (b) G. W. Kenner, *Ann. Reports Chem. Soc.*, **51**, 178 (1954).

(17) A pair of similarly isomeric alkaloids, namely, cryptopine (I) and cryptocavine (X terminal rings substituted as in I), is described in the literature (see Manske, reference 11, p. 149–155). Dr. Manske, in a private communication to the author, states that it has been found that cryptocavine is identical rather than isomeric with cryptopine.

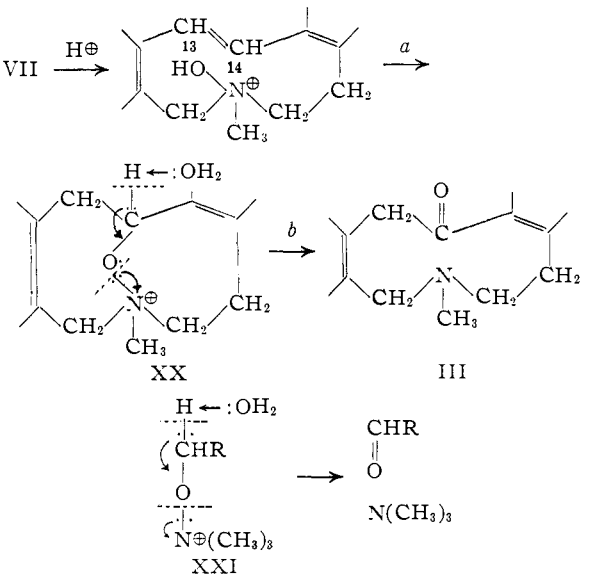
nificance with regard to the mechanism of the conversion of VII to III since Perkin[1] has demonstrated that cryptopine (I) was converted slowly to *iso*cryptopine chloride (XIII terminal rings substituted as in I) on heating with concentrated hydrochloric acid. It would appear unlikely that the rearrangement of the amine oxide to *allo*cryptopine proceeds *via* the glycol VIII as suggested by Manske; the mechanism of this change remains a matter for speculation.

The chemistry of this group of alkaloids and related 10-membered ring compounds is dominated by the ease of the *trans*annular reaction between the tertiary nitrogen and the carbon atom 14. The reversal of the Hofmann degradation in the case of V and the formation of dihydroanhydroberberine metho derivatives from *allo*cryptopine or the glycol VIII with phosphorus oxychloride and from the base-A with N-bromosuccinimide are obvious examples. Furthermore infrared studies on I,[18] II[19,20] and the alkaloids of the ψ-brucine and vomicine series as well as on related synthetic compounds[21] indicate transannular interaction between the carbonyl group and the tertiary nitrogen as first suggested by Kermack and Robinson.[22] Acid salts of the alkaloids and related compounds show no absorption in the carbonyl region, and it is suggested that they exist in the quaternary form XIX.[18-20]

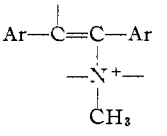


XIX

The above observations provide ample evidence of the proximity of the nitrogen and C_{14}, and this is considered an essential factor in any mechanism which may be proposed for the conversion of VII to *allo*cryptopine (III). The above interpretation of the reaction of V with N-bromosuccinimide is also dependent on this close approach. It is suggested that the rearrangement occurs in the stages (a) the nucleophilic attack of the oxygen on C_{14} with the simultaneous attachment of a proton at C_{13} to give XX and (b) the decomposition of XX to give *allo*cryptopine as shown. The first step is exactly analogous to the formation of XIV by process a; the second finds an exact analogy in the decomposition of trimethylalkoxyammonium salts (XXI) to give aldehydes and the amine hydrohalide.[23a] The mechanism suggested for this step is formally analogous to the well known bimolecular mechanism of the Hofmann cleavage.[23b]



The absorption spectrum of base-A (V) varies with the solvent employed (Table I). In alcohol the spectrum is almost identical with that of tetrahydroberberine methochloride; this would be expected in view of the ready reversal of the Hofmann reaction in this solvent. In solvents which prevent the reverse Hofmann, *i.e.*, cyclohexane or 3 *N* hydrochloric acid, the spectrum of V resembles that of a stilbene as also does the spectrum of the methyl-*p*-toluenesulfonate of V. The C_{13}–C_{14} double bond is, therefore, conjugated with both of the aromatic nuclei, the molecule being approximately planar. It follows that the aromatic nuclei have a *trans* relationship with respect to the double bond, for models show that in the *cis* configuration the molecule cannot be even approximately planar. The spectra of base-B and its quaternary salts show clearly the presence of the styrene chromophore (at 263 mμ). The spectrum of the glycol VIII resembles that of *allo*cryptopine and demonstrates the absence of conjugation between the aromatic nuclei. Dihydroanhydroberberine methochloride shows an intense peak at 350 mμ; this undoubtedly arises from the planar chromophore



Some modifications were introduced in the preparation of the base-A (V) used in this work. Tetrahydroberberine was prepared by the catalytic reduction of berberine hydrochloride in 50% aqueous acetic acid with a platinum catalyst.

(18) F. A. L. Anet, A. S. Bailey and R. Robinson, *Chem. and Ind.*, 944 (1953).

(19) E. H. Mottus, H. Swartz and L. Marion, *Can. J. Chem.*, **31**, 1144 (1953).

(20) F. A. L. Anet and L. Marion, *ibid.*, **32**, 452 (1954).

(21) N. J. Leonard, M. Oki and S. Chiavarelli, THIS JOURNAL, **77**, 6234 (1955).

(22) W. O. Kermack and R. Robinson, *J. Chem. Soc.*, **121**, 427 (1922).

(23) (a) W. R. Dunstan and E. Goulding, *ibid.*, **75**, 792 (1899) J. Meisenheimer, *Ann.*, **397**, 273 (1913); (b) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 429. The steric factors mentioned above should influence chiefly the formation of XX. If these are decisive then the oxidation of stilbene derivatives to ketones by amine oxides should not be a general reaction. Examples of such oxidations are not reported in the literature. When *trans*-stilbene was treated with trimethylamineoxide hydrochloride under a variety of conditions, the hydrocarbon was recovered in almost quantitative yield (96–98%) despite the fact that occasionally a smell reminiscent of an aromatic carbonyl compound developed during the reaction. Dr. Wenkert informs the author that he and Dr. Rolih also failed to obtain any ketone from similar reactions.

TABLE I

ULTRAVIOLET SPECTRA OF *Allo*CRYPTOPINE DERIVATIVES

Compound	Solvent (concn. 10 mg./l.)	λ_{min}, mμ ($E \times 10^{-3}$)	λ_{max}, mμ ($E \times 10^{-3}$)
*Allo*cryptopine hydrochloride (XIX)	Water	253 (1.9)	226 (12)
			285 (4.95)
Tetrahydroberberine methochloride (IV)	Water	260 (1.1)	284 (5.05)
Base A (V)	Cyclohexane	250 (9.4)	285–290 (12)
Base A	0.01 *N* HCl	250 (9.3)	302 (15)
Base A	Alcohol	260 (2.1)	285 (6.2)
Base B (VI)	Alcohol	247 (6.9)	263 (10.4)
		287 (3.5)	301 (4.3)
Base A, methyl *p*-toluenesulfonate	Alcohol	255 (5.9)	302 (12.2)
Base B, methyl *p*-toluenesulfonate	Alcohol	248 (5.4)	265–270 (10.9)
			step out 295–305 (2.6)
Methiodide of glycol VIII	Water	263 (1.3)	290 (6.9)
Dioxime of aldehyde XII	Alcohol	245 (10.3)	270 (21)
		Inflex 290–310 (*ca.* 10)	
Methyl *p*-toluenesulfonate of dialdehyde XII	Alcohol	247 (5.3)	273 (16.8)
		Step out	
		290–310 (11.5)	
Methyl *p*-toluenesulfonate of nitrile from dioxime of XII	Alcohol	240 (5.6)	258 (19.8)
		280 (5.0)	290 (9.1)
Dihydroanhydroberberine methochloride (XIII)	Water	270 (2.2)	240–250 (9.25) step out
		300–320 (9.3)	350 (24.5)
		362 (2.04)	365.5 (2.1)

The conversion of the chloride to the acetate, *via* the acetone compound, prior to the reduction[24] was found to be unnecessary. The tetrahydroberberine so obtained crystallized from alcohol in prisms or needles depending, apparently, on the temperature. Both forms melted at 173°.[25] The methiodide of this base was prepared according to Pyman's instructions,[8] and this was converted to a mixture of α- and β-tetrahydroberberine methochlorides by treatment with dry hydrogen chloride in methanol.[26] The chlorides were converted to the corresponding hydroxides by the use of the ion-exchange resin Amberlite IRA-400 which had previously been treated with sodium hydroxide solution.[27] The resulting solutions were evaporated as recommended by Pyman[8] to give a mixture of base-A (V) and base-B (VI). Since both the α- and β-tetrahydroberberine methochlorides gave identical results when run separately, in subsequent runs the separation of these quaternary salts was not carried out.

Experimental

Tetrahydroberberine.—Berberine hydrochloride (12 g.) was suspended in 50% acetic acid (150 ml.) and hydrogenated in the presence of Adams catalyst. The absorption of the calculated amount of hydrogen (2 mole) took 1.5 hr. At the end of the reduction the solution was colorless with some colorless tetrahydroberberine salt in suspension. The solution was diluted with hot water (200 ml.) and the catalyst removed by filtration. The filtrate was basified with ammonia and the almost white tetrahydroberberine collected after standing 3–4 hr. On recrystallization from ethanol the product separated from the hot solution as colorless needles, or from a cooler solution as colorless prisms, both forms and mixtures of the two melted at 172–173°. Two crops of this melting point were obtained weighing 9 g. (90% calculated on formula B·HCl·$2H_2O$). In glacial acetic acid the reduction was considerably more slow.

α- and β-Tetrahydroberine Methochlorides.—Tetrahydroberberine (5 g.) was heated with methyl iodide as described by Pyman.[8] The excess methyl iodide was evaporated and the residue dissolved in methanol (200 ml.). The methanolic solution was saturated with dry hydrogen chloride and refluxed for 35 minutes. At the end of this time the solution was free from iodide ion. The methanol was evaporated and the residue, after freeing from hydrogen chloride, was dissolved in water (75 ml.). The solution after concentration to 25–30 ml. was allowed to stand. Crystals separated, after recrystallization from water these yielded β-tetrahydroberberine methochloride (3.7 g.) m.p. *ca.* 260°. The original mother liquor gave on concentration α-tetrahydroberberine methochloride (2 g.), m.p. 142°; total yield of mixed tetrahydroberberine methochlorides 5.7 g. (88%).

Anhydromethyltetrahydroberberines A and B.—β-Tetrahydroberberine methochloride (5 g.) was dissolved in distilled water (250 ml.). The cool solution was run through a column of IRA-400 resin (35 g.) [which had been previously treated with 10% sodium hydroxide solution (700 ml.) and washed with distilled water (700 ml.)]. The solution was collected in a container from which carbon dioxide was rigorously excluded. When all the solution had passed through the column, it was followed by distilled water (500 ml.). The original solution and washings were evaporated under reduced pressure as described by Pyman.[8] The residue was extracted with ethyl acetate (*ca.* 100 ml.) and this solution on concentration to about 30 ml. and cooling, deposited silky needles m.p. 135° (2.2 g.). This was almost pure anhydromethyltetrahydroberberine-A. Separation of the residues from the ethyl acetate solution with hydrochloric acid as described by Pyman[8] yielded a further 0.5 g. of A and also anhydromethyltetrahydroberberine-B hydrochloride (1.4 g.).

An exactly similar result was obtained when α-tetrahydroberberine methochloride was used in place of the β-isomer. In later runs the crude mixture of isomers was subjected to the above treatment with results essentially as above.

Methyl *p*-Toluenesulfonates of Bases A and B.—The base in methanol was treated with methyl *p*-toluenesulfonate. The salt precipitated with ether was recrystallized from methanol ether. The derivative of base-A melted at 230–231°, that of base-B at 254–255°.

Anal. Calcd. for $C_{29}H_{33}O_7NS$: C, 64.6; H, 6.1. Found: A: C, 64.4; H, 6.3; B: C, 64.4; H, 6.3.

(24) H. W. Bersch and W. Seufert, *Ber.*, **70**, 1121 (1937).

(25) The melting point of tetrahydroberberine is usually quoted as somewhat lower, thus Voss and Gadamer[5] give 165–166°. Bersch and Seufert[24] report two forms, m.p.'s 167 and 171°. Späth and Polgar [*Monatsh.*, **52**, 117 (1929)] obtained the compound in colorless crystals, m.p. 173°.

(26) A. P. Phillips and R. Baltzly, THIS JOURNAL, **74**, 5231 (1952).

(27) M. F. Grundon and V. Boekelheide, *ibid.*, **75**, 2537 (1953).

Catalytic Hydrogenation of Anhydromethyltetahydroberberine-A. (a) **In Methanol.**—The base (2.4 g.) was dissolved in methanol (50 ml.) and hydrogenated in the presence of Adams catalyst. Apart from the reduction of the catalyst, there was no uptake of hydrogen. The catalyst was removed by filtration and the methanolic solution diluted with water and extracted with ether; no neutral fraction was obtained. The solution was acidified with hydrochloric acid and evaporated to small volume; crystals separated (2.3 g.), m.p. 260–262°, identical with β-tetrahydroberberine methochloride.

(b) **In Glacial Acetic Acid.**—The reduction in this instance stopped when about one-half of the calculated amount of hydrogen had been absorbed. The solution was evaporated to dryness and diluted with water. The solution was then basified with sodium hydroxide solution and extracted with ether. The ethereal solution was washed with water and dried over sodium sulfate. Removal of the ether gave a crystalline product (1.1 g.). After recrystallization from ether–pentane, the product melted at 129°. Freund and Fleischer[13] give m.p. 127–129° for the dihydro derivative of base-A.

The aqueous mother liquors, on acidification with concentrated hydrochloric acid, deposited β-tetrahydroberberine methochloride (1.2 g.).

(c) **In 3 *N* Hydrochloric Acid.**—The reduction was carried out as described above but with 3 *N* hydrochloric acid as solvent. One mole of hydrogen was absorbed rapidly and then the reduction ceased. After removal of the catalyst, the solution was basified with ammonium hydroxide, the precipitated oil was taken into ether, the ethereal solution was washed with water and dried. The residue after removal of the ether weighed 2.2 g. On crystallization from ether–pentane it formed colorless crystals, m.p. 129°.

The Oxidation of Base-A with Hydrogen Peroxide.[28]—The base (1.0 g.) was dissolved in 3 *N* hydrochloric acid (30 ml.), and to this solution was added hydrogen peroxide (1 ml., 30%). The solution was allowed to stand for 10 hr. and was then basified. The precipitated solid was extracted with ethyl acetate, the extract washed with water and dried. On evaporation to about one-half the original volume, the ethyl acetate solution sometimes deposited crystals in small amounts. Recrystallization of this material yielded some of the compound, m.p. 245° dec., obtained by permanganate oxidation of base-A (see below) and sometimes a crystalline material, m.p. 206° dec. Removal of the remainder of the ethyl acetate gave a gum which on recrystallization from chloroform–ether gave colorless crystals (0.35 g.). These, on recrystallization from ethyl acetate–hexane, ethanol–water or benzene, formed colorless needles, m.p. 197° dec. The compound gave an intense blue-violet with concentrated sulfuric acid.

Anal. Calcd. for $C_{21}H_{25}O_6N$: C, 65.2; H, 6.5; N, 3.6. Found: C, 65.6, 65.1, 65.4; H, 6.7, 6.8, 6.4; N, 3.4, 3.5.

The material, m.p. 206°, after recrystallization from ethyl acetate formed colorless needles, m.p. 208–209°. It gave no color with sulfuric acid.[29]

Anal. Calcd. for $C_{21}H_{25}O_6N$: C, 65.2; H, 6.5; N, 3.6; $2OCH_3$, 16.0. Found: C, 65.2; H, 6.7; N, 3.2; OCH_3, 15.6.

Oxidation of the Base-A with N-Bromosuccinimide.—The base (3.5 g.) was dissolved in *N* hydrochloric acid (10 ml.); to this solution was added with shaking a slurry of N-bromosuccinimide (1.9 g.) in water (25 ml.). A rapid reaction took place and the N-bromosuccinimide dissolved at once. The solution was allowed to stand for 30 minutes and then made alkaline with 3 *N* sodium hydroxide solution. The precipitated solid was extracted with chloroform, the chloroform solution after being washed with water was evaporated to small volume (*ca.* 7 ml.) and ether (*ca.* 25 ml.) added. Crystals separated (1.9 g.) which after recrystallization from aqueous ethanol melted at 197° dec. This melting point was not depressed on admixture with the hydrogen peroxide oxidation product, m.p. 197° dec. The methiodides from both the oxidation products, m.p. 197°, did not depress each other's melting points.

Th aqueous solution after the chloroform extraction was acidified with hydrochloric acid and evaporated to half bulk. On standing, some material crystallized which was mixed with inorganic salts. Recrystallization from dilute hydrochloric acid gave a quaternary salt, m.p. 213° dec. (1.0 g.). This salt gave a violet color with concentrated sulfuric acid and a pink color with manganese dioxide in dilute sulfuric acid. The absorption spectrum was identical with that of dihydroanhydroberberine methochloride prepared from *allo*cryptopine by the method of Gadamer.[2]

Derivatives of the Oxidation Product, M.p. 197° dec.—The base gave a hydrochloride which melted at 192–194° dec.

Anal. Calcd. for $C_{21}H_{26}O_6NCl$: C, 59.5; H, 6.1. Found: C, 59.6; H, 6.5.

The methiodide and methyl and ethyl *p*-toluenesulfonates were prepared by treating the base in methanol or chloroform with excess of the reagent at room temperature. The quaternary salts were crystallized from methanol–ethyl acetate. The methiodide formed colorless needles, m.p. 200–202° dec.

Anal. Calcd. for $C_{22}H_{28}O_6NI$: C, 49.9; H, 5.3. Found: C, 50.2; H, 5.5.

The methyl *p*-toluenesulfonate melted at 182° dec.

Anal. Calcd. for $C_{29}H_{35}O_9NS$: C, 60.7; H, 6.1. Found: C, 60.4; H, 6.1.

The ethyl *p*-toluenesulfonate formed prisms, m.p. 182°.

Anal. Calcd. for $C_{30}H_{37}O_9NS$: C, 61.3; H, 6.2. Found: C, 61.0; H, 6.1.

Oxidation of Compound, M.p. 197° dec., with Periodic Acid.—The base (1.25 g.) was dissolved in *N* sulfuric acid (5 ml.) and to this solution was added a solution of periodic acid (0.75 g.) in water (10 ml.). After standing for 24 hr. the solution was basified and the product extracted with ether. The ether was removed, after washing with water and drying over sodium sulfate, leaving an oil (1.2 g.).

The above oil (0.2 g.) was dissolved in a little methanol (0.5 ml.) and methyl *p*-toluenesulfonate was added. After 18 hr. at room temperature ether (5 ml.) was added. The quaternary salt crystallized; after recrystallization from methanol–ether, it melted at 118–120°.

Anal. Calcd. for $C_{29}H_{33}O_9NS$: C, 60.9; H, 5.8; N, 2.5. Found: C, 60.7; H, 6.0; N, 2.4.

The remainder of the oil (1.0 g.) was dissolved in methanol (3 ml.) and to this solution was added a solution of hydroxylamine (from 0.4 g. of the hydrochloride and 6 ml. of *N* sodium hydroxide). After standing for several hours the dioxime separated. After recrystallization from ether–pentane, it formed colorless needles, m.p. 137°.

Anal. Calcd. for $C_{21}H_{25}O_6N_3$: C, 60.7; H, 6.1; N, 10.1. Found: C, 60.6; H, 6.1; N, 10.2.

Dehydration of the Dioxime, M.p. 137°.—The dioxime (0.5 g.) was refluxed with acetic anhydride (5 ml.) for 1.5 hr. The anhydride was evaporated and the residue dissolved in water. On basification with sodium hydroxide an oil separated, and this was extracted with ether. The ethereal solution was washed with water and dried. Removal of the solvent gave an oil; this was converted to the methyl *p*-toluenesulfonate, which after recrystallization from methanol–ether melted at 103–105° with loss of solvent.

Anal. Calcd. for $C_{29}H_{31}O_7N_3S \cdot CH_4O$: C, 60.3; H, 5.8; N, 6.9. Found: C, 59.9; H, 5.9; N, 7.2. Loss on drying at 90° *in vacuo* 5.0%; calcd. 1 CH_4O, 5.3%

Formation of Dihydroanhydroberberine Methochloride from Compound, M.p. 197°.—The base (0.5 g.) was refluxed with phosphorus oxychloride (3 ml.) for 1 hr. The

(28) Haworth and Perkin[9] state that interesting products were obtained by oxidation of base-A with hydrogen peroxide. Professor R. D. Haworth informs the author that this oxidation was carried out in alkaline methanolic solution, the product melted above 200° and analyzed for the formula $C_{21}H_{25}O_8N$. The author wishes to thank Professor Haworth for this information.

(29) A compound, m.p. 206°, obtained by reduction of the mercuric acetate oxidation product of the alkaloid *allo*cryptopine is described by J. Gadamer and H. Kollmar [*Arch. Pharm.*, **261**, 169 (1923)]. The analysis and properties of this compound are not given. By analogy with the products from cryptopine and protopine, however, it should analyze for the formula $C_{21}H_{25}O_6N$. Gadamer believes that these compounds have the second hydroxyl group at position 5. Thus, the compound m.p. 206° would be 5-hydroxydihydro*allo*cryptopine. Prelog and co-workers [*Helv. Chim. Acta*, **35**, 2044 (1952); **36**, 471 (1953)] and also Cope, Fenton and Spencer [THIS JOURNAL, **74**, 5884 (1952)] have described the formation of non-vicinal glycols in the oxidation of medium ring unsaturated compounds with performic acid. The formation of these glycols has been shown by Cope to arise during the solvolysis of the corresponding epoxide.

excess oxychloride was then removed *in vacuo* and the residue dissolved in water (5 ml.). After standing overnight, crystals were deposited; these were collected by filtration (0.42 g.). After recrystallization from dilute hydrochloric acid, the compound appeared as colorless prisms, m.p. 209–210° dec. The color reactions, m.p. and mixed melting point and the ultraviolet absorption spectrum were identical with those of an authentic sample of dihydroanhydroberberine methochloride.[2]

Treatment of the same base with acetic anhydride followed by recrystallization from dilute hydrochloric acid gave the same product.

Oxidation of Base-A with Potassium Permanganate.—The base (1 g.) was dissolved in acetone (500 ml.), and to this solution was added dropwise with stirring, a solution of potassium permanganate (0.31 g.) in acetone (200 ml.). The addition took 2 hr., and the solution was stirred for a further hour. The manganese dioxide was filtered off and washed with a little chloroform. The acetone solution and the chloroform wash were combined and evaporated to small bulk (*ca.* 100 ml.). The product started to separate at this point and the separation became complete on cooling. In all, 0.7 g. was collected. After recrystallization from methanol–ethyl acetate, it formed needles, m.p. 267° (dec. after darkening from *ca.* 245°).

Anal. Calcd. for $C_{21}H_{25}O_6N$: C, 65.1; H, 6.5; N, 3.6; 2 OMe, 16.1. Calcd. for $(C_{21}H_{24}O_4N)_2C_4H_6O_6$: C, 66.5; H, 6.5; N, 3.3; 4 OMe, 15.0. Found: C, 65.8, 65.6; H, 6.3, 6.3; N, 3.7, 3.5; OMe, 15.6.

A solution of the above compound in methanol gave, with picric acid, a picrate, m.p. 245–246° dec. This proved to be identical with an authentic sample of β-tetrahydromethylberberine picrate, m.p. 245° dec.

Anal. Calcd. for $C_{27}H_{26}O_{11}N_4$: C, 55.7; H, 4.5; N, 9.5. Found: C, 55.8; H, 4.6; N, 9.3.

With picrolonic acid a picrolonate was obtained, m.p. 244° (dec. after blackening from 230–235°).

Anal. Calcd. for $C_{31}H_{31}O_9N_5$: C, 60.4; H, 5.0; N, 11.3. Found: C, 60.6; H, 5.2; N, 11.6.

p-Toluenesulfonic acid gave a *p*-toluenesulfonate, m.p. 252°.

Anal. Calcd. for $C_{28}H_{31}O_7NS$: C, 64.6; H, 5.9; N, 2.7. Found: C, 64.4; H, 6.0; N, 2.5.

Oxidation of Base-A with Iodine and Silver Acetate.[16]—Silver carbonate (0.85 g.) was treated with glacial acetic acid (20 ml.) containing water (0.1 ml.). To this was added base-A (1 g.), and then iodine (0.72 g.) was added over 1 hr. The mixture was warmed at 90° for 2 hr. on the steam-bath. After filtration, the acetic acid was removed *in vacuo*. The residue was dissolved in water (*ca.* 15 ml.) and basified with sodium hydroxide solution. The solution was then extracted with chloroform and the aqueous layer acidified with concentrated hydrochloric acid, dihydroanhydroberberine methochloride (0.9 g.) separated. This material was identical in every respect with the previously described samples. The chloroform solution contained a little material, but no pure compound was isolated.

Conversion of the Amine Oxide (VIII) to *Allo*cryptopine (IV).—The amine oxide (1.0 g.), prepared as described by Haworth and Perkin[9] (except that monoperphthalic acid was used in place of perbenzoic acid) was dissolved in glacial acetic acid (5 ml.) and concentrated hydrochloric acid (2.5 ml.) added. The mixture was heated for 1 hr. on a rapidly boiling water-bath. The acids were then evaporated *in vacuo* and the residue dissolved in water and basified with sodium hydroxide. The precipitated solid was extracted with chloroform, the chloroform solution was washed and the chloroform removed. The residue was dissolved in methanol (*ca.* 2 ml.), the methanol solution diluted with ether (*ca.* 15 ml.) and acidified with a solution of hydrogen chloride in methanol. On scratching, a hydrochloride separated, m.p. 188–190° (dec. sinters 170°) (0.77 g. or 70%). The base was obtained by basification of this hydrochloride; it crystallized from ether in small colorless needles, m.p. 160–161°. The melting point was unchanged on admixture with an authentic sample of *allo*cryptopine.

The aqueous solution from the chloroform extraction was acidified with concentrated hydrochloric acid. On standing, dihydroanhydroberberine methochloride (0.1 g.) separated.

When the above procedure was carried out with the glycol VIII, m.p. 197° (0.61 g.), no basic material was obtained. The aqueous solution, on acidification with concentrated hydrochloric acid, deposited dihydroanhydroberberine methochloride (0.5 g.).

Paper Chromatography.—*Allo*cryptopine (0.02 mg.) in dry chloroform was spotted onto chromatogram paper, the spot was developed with butanol–water (86–14) in the usual manner overnight. Examination in ultraviolet light revealed a spot R_f 0.39, which fluoresced blue. Protopine gave a yellowish fluorescent spot R_f 0.24. A mixture of the two alkaloids could be separated on the paper. The synthetic *allo*cryptopine and the total basic fraction obtained from the amine oxide conversion showed only the blue spot R_f 0.39.

Ultraviolet Absorption Spectra.—Were measured with a Beckman model DU quartz spectrophotometer. The spectra were measured at a concentration of 10 mg./l. (cell length 1 cm.).

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The Basic Esters of Some Plant Growth Regulators

BY F. C. G. HOSKIN

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The hydrochlorides and methohalides of the β-diethylaminoethyl esters of several plant growth regulators and of one inhibitor of plant growth hormonal activity have been synthesized. These compounds have been tested as plant growth regulators, as esterase substrates and as spasmolytic agents. In general, they have plant growth hormonal activity equal to or less than the parent acids, are not substrates for the non-specific esterases of rat serum and are much less effective than atropine in reducing acetylcholine-induced spasms.

Most spasmolytic agents are, like atropine, basic esters of carboxylic acids; many are basic esters of α,α-disubstituted acetic acid. In the acid moiety of such compounds there is often a region of high electron density insulated by a single carbon atom from the carbonyl double bond. Most of the plant growth regulators are α-monosubstituted acetic acids in which a region of high electron density is insulated by one or more carbon atoms or by a combination of oxygen and carbon atoms from the carbonyl double bond. The chemical and biological properties and the relationships between these two, for both spasmolytic agents and plant growth hormones, have been the subject of much research.[1,2]

(1) F. C. Nachod and A. M. Lands, *Trans. N. Y. Acad. Sci.*, **16**, 2 (1953).

(2) J. Bonner, Harvey Lectures, Ser. 48, 1 (1954).