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Studies in Protoberberine Alkaloids: Part I—New Synthesis of Tetrahydroberberine & Epiberberine

T. R. GOVINDACHARI & K. NAGARAJAN
CIBA Research Centre, Goregaon East, Bombay 63
and
R. CHARUBALA & B. R. PAI
Department of Chemistry, Presidency College, Madras 5

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Alkali induced disproportionation of 7,8-dimethoxy-2-(3',4'-methylenedioxyphenethyl)isoquinolinium bromide (XIII) and 2-(3',4'-dimethoxyphenethyl)-7,8-methylenedioxyisoquinolinium bromide (XVII) affords the corresponding dihydroisoquinolines which on cyclization with alcoholic hydrochloric acid give tetrahydroberberine (VIII) and tetrahydroepiberberine (IX) respectively.

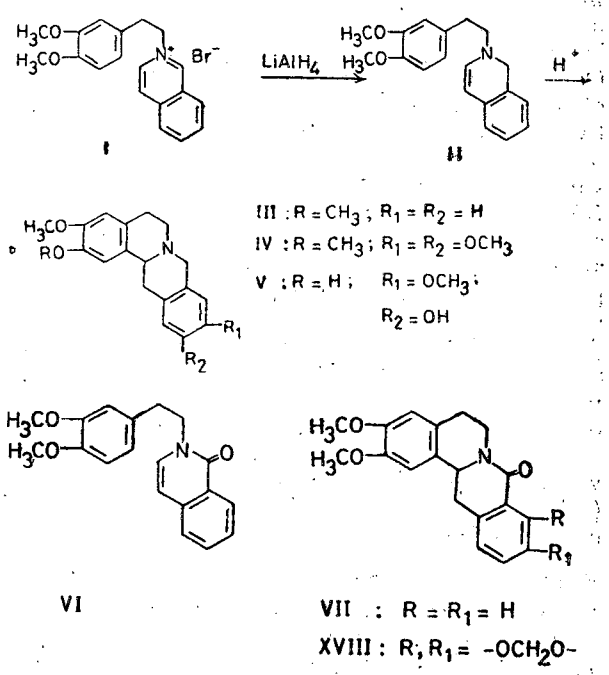
THE more important methods of synthesis of the berberine system have been reviewed by Pelz[1]; probably the simplest and most direct of these is that due to Huffmann and Miller[2] who reduced the quaternary isoquinolinium bromide (I) with lithium aluminium hydride and cyclized the resultant 1,2-dihydroisoquinoline derivative (II) with mineral acid to III.

This method was extended by Battersby *et al.*[3] for the synthesis of norcoralydine (IV) and coreximine (V). An interesting and important variation of this method is due to Dyke and Brown[4] who treated the isoquinolinium salt (I) at room temperature with cold aqueous sodium hydroxide solution; the resultant pseudo base disproportionated in the presence of excess alkali, to a mixture of the 1,2-dihydroisoquinoline II and an isocarbostyril VI; the mixture of II and VI, on treatment with acid, gave III and VII respectively. Dyke and Brown used this method for the synthesis of several other berberine analogues, but not for the synthesis of tetrahydroberberine (VIII) itself nor for the more difficultly accessible tetrahydroepiberberine (sinactine) (IX) and tetrahydrocoptisine (stylopine) (X).

In connection with studies on the stereochemistry of 13-methyl protoberberine alkaloids, we required some quantities of epiberberine. As the method of Dyke and Brown seemed to be the most elegant of all methods available for the synthesis of protoberberine alkaloids, we planned first to standardize this procedure for tetrahydroberberine and then to extend it to epiberberine and stylopine.

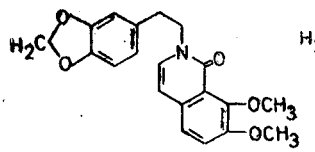
Tetrahydroberberine (VIII) was synthesized as follows:

7,8-Dimethoxyisoquinoline[5] (XII) was allowed to react with β-3,4-methylenedioxyphenethyl bromide (XI) to give the isoquinolinium bromide (XIII). This on treatment with hot alkali gave the pseudo base which disproportionated to a mixture of isocarbostyril (XIV) and dihydroisoquinoline (XV) (TLC analysis). The crude mixture was extracted

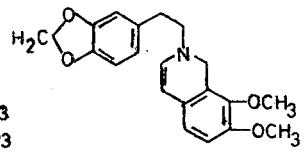


with methylene chloride and, after removal of the solvent *in vacuo*, was treated with alcoholic hydrochloric acid. The product on working up as detailed in the experimental section, gave tetrahydroberberine (VIII), m.p. 168-70°, identical with an authentic sample; the oxo compound that should have arisen by cyclization of the isocarbostyril could not be isolated in this case. The yield of tetrahydroberberine itself was not satisfactory.

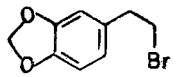
Tetrahydroepiberberine (IX) was made essentially on the same lines. 7,8-Methylenedioxyisoquinoline (XVI) was made by Pomerantz-Fritsch cyclization[6] of *o*-piperonylidene-aminoacetal. This was quaternized with β-(3,4-dimethoxyphenethyl) bromide. The resultant 2-(3',4'-dimethoxyphenethyl)-



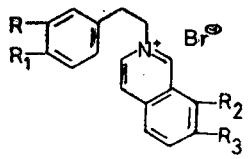
XIV



XV

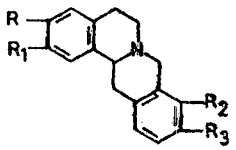


XI



XIII : R, R_1 = $-OCH_2O-$;
R_2 = R_3 = OCH_3

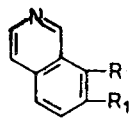
XVII : R = R_1 = OCH_3 ;
R_2, R_3 = $-OCH_2O-$



VIII : R, R_1 = $-OCH_2O-$; R_2 = R_3 = OCH_3

IX : R = R_1 = OCH_3 ; R_2, R_3 = $-OCH_2O-$

X : R, R_1 = R_2, R_3 = $-OCH_2O-$



XII : R, R_1 = OCH_3

XVI : R, R_1 = $-OCH_2O-$

7,8-methylenedioxyisoquinolinium bromide (XVII) was subjected to hot alkaline disproportionation followed by acid treatment, when tetrahydroepiberberine (IX) and the corresponding oxo-derivative (XVIII) were obtained. In the NMR spectrum of XVIII, the methylenedioxy protons were seen as two closely spaced doublets centred at 6·1 and 6·2 ppm ($J = 1·5$ cps), establishing their non-equivalence. Lithium aluminium hydride reduction of XVIII gave more of IX. Our sample of tetrahydroepiberberine was identical (TLC in different solvent systems and IR in chloroform) with a sample kindly provided by Prof. R. D. Haworth[7]. However, the material from Prof. Haworth was insufficient for determination of mixed melting point. Hence, the synthetic tetrahydroepiberberine was oxidized with mercuric acetate in acetic acid and the product obtained was characterized as epiberberinium picrate, m.p. 220° (decomp.). This was identical with epiberberinium picrate [reported[8] m.p. 222° (d)] recently prepared by Dominguez[8], by photolysis of cryptopine.

Experimental Procedure

***Synthesis of Tetrahydroberberine* (VIII)**

7,8-*Dimethoxy*-2-(3′,4′-*methylenedioxyphenethyl*)*isoquinolinium bromide* (XIII) — A mixture of 7,8-dimethoxyisoquinoline (XII) (0·8 g), 3,4-methylenedioxyphenethyl bromide (1 g) and methanol (8 ml) was heated under reflux for 8 hr. Removal of methanol and addition of ether precipitated the quaternary salt which was crystallized from methanol-benzene; yield 1 g; m.p. 198-200° (Found: C, 57·18; H, 5·15. $C_{20}H_{20}BrNO_4$ requires C, 57·41; H, 4·78%).

Tetrahydroberberine (VIII) — The quaternary salt (XIII, 1 g) was dissolved in water (10 ml) and aq. sodium hydroxide (40%; 20 ml) added. The mixture was heated for 30 min under reflux. The resultant oil was extracted several times with methylene chloride. The combined extracts were then evaporated and the residue dissolved in 50% ethanolic hydrochloric acid (10 ml) and the solution set aside. After 5 days at room temperature, the mixture was concentrated *in vacuo*. The residue was taken up in water, basified with ammonia and extracted with chloroform. The chloroform extract was dried; upon removal of the solvent, a dark gum was left behind. This was then chromatographed over alumina using chloroform as eluant. The fractions giving solid product were combined and evaporated. The residue was crystallized from methanol to give tetrahydroberberine (VIII); yield 100 mg; m.p. 168-70° (Found: C, 70·49; H, 6·27. $C_{20}H_{21}NO_4$ requires C, 70·79; H, 6·19%).

This was identical (m.p., m.m.p. and IR spectrum in solution) with a sample of tetrahydroberberine obtained by sodium borohydride reduction of berberinium chloride.

***Synthesis of Tetrahydroepiberberine* (IX)**

2,3-*Methylenedioxybenzylidene-aminoacetal*—A solution of *o*-piperonal (10 g) and aminoacetal (10 g) in dry benzene (60 ml) was heated under reflux in an apparatus, provided with a Dean-Stark water separator till the theoretical amount of water was collected. The solvent was removed and the residual oil was distilled *in vacuo* to give the Schiff's base as a yellow oil; yield 11 g.

7,8-*Methylenedioxyisoquinoline* (XVI) — To sulphuric acid (72%; 143 g), cooled to 0°, was added with stirring ice-cold 2,3-methylenedioxybenzylidene aminoacetal (10 g) at such a rate that the temperature did not exceed 5°. The mixture was then saturated with dry hydrogen chloride at 0° and kept at the same temperature for 10 days and at room temperature for 3 days. The dark solution was then poured into ice, the aqueous solution extracted thrice with ether and then basified with sodium hydroxide solution. The liberated base was extracted with chloroform; the chloroform extract was washed with water and dried; removal of chloroform gave a crystalline residue which was recrystallized from benzene-hexane to give XVI; yield 3·2 g; m.p. 90° (Found: C, 69·23; H, 4·00. $C_{10}H_7NO_2$ requires C, 69·36; H, 4·04%).

2-(3',4'-*Dimethoxyphenethyl*)-7,8-*methylenedioxyisoquinolinium bromide* (XVII) — A mixture of 7,8-methylenedioxyisoquinoline (0·71 g) and 3,4-dimethoxyphenethyl bromide (1·0 g) in absolute methanol (8 ml) was refluxed on a water-bath for 8 hr. Removal of methanol and addition of ether precipitated the quaternary salt which was crystallized from methanol-benzene; yield 1·3 g; m.p. 250° (Found: C, 57·16; H, 4·83. $C_{20}H_{20}BrNO_4$ requires C, 57·41; H, 4·78%).

Tetrahydroepiberberine (IX) *and tetrahydrooxoepiberberine* (XVIII) — The above salt (XVII, 3 g) was dissolved in water (20 ml) and aqueous sodium hydroxide solution (40%; 20 ml) added. The mixture was heated under reflux for 30 min and the resultant oil extracted thrice with methylene chloride; the combined extracts were washed and evaporated, and the residue dissolved in conc. hydrochloric acid (7 ml). After 5 days at room temperature, the mixture was concentrated *in vacuo*; the residue was triturated with acetone and filtered. The insoluble yellow residue was tetrahydrooxoepiberberine (XVIII) and was crystallized from methanol; yield 0·5 g; m.p. 198-200° (Found: C, 67·70; H, 5·61. $C_{20}H_{19}NO_5$ requires C, 67·98; H, 5·38%).

The acetone filtrate was evaporated to dryness; the residue was washed with ether and then crystallized from methanol to give tetrahydroepiberberine hydrochloride; yield 0·5 g; m.p. 257-8° (d) (Found: C, 63·89; H, 5·63. $C_{20}H_{21}NO_4.HCl$ requires C, 63·83; H, 5·85%).

(±)-*Tetrahydroepiberberine* (IX) was also prepared from the oxo compound (XVIII) as follows: The oxo compound (XVIII) (0·75 g) was added to a stirred suspension of lithium aluminium hydride (0·3 g) in dry ether (30 ml). The mixture was heated under reflux for 1½ hr and then left at room temperature overnight. Excess hydride was decomposed with water and ether decanted off. The ether extract was dried and evaporated to leave an oil (0·3 g) to which conc. hydrochloric acid was added. This afforded tetrahydroepiberberine hydrochloride; m.p. 257°, identical with the previous preparation.

Epiberberine — Tetrahydroepiberberine (0·5 g) dissolved in aqueous acetic acid (10%; 40 ml) was treated with a solution of mercuric acetate (0·2 g) in the same solvent (40 ml) and the solution gently heated for 72 hr. The separated mercurous acetate was filtered, the filtrate saturated with hydrogen sulphide and the precipitated mercuric sulphide removed by filtration. The brown filtrate was concentrated by distillation under reduced pressure and mixed with a large excess of conc. hydrochloric acid. Epiberberinium chloride which separated was collected and dried (75 mg). The picrate was prepared by treating a dil. solution of the chloride with aq. picric acid and crystallized from methanol; m.p. 220-22° [Found: C, 55·36; H, 3·89; N, 10·22. $(C_{20}H_{18}NO_4)^+(C_6H_2N_3O_7)^-$ requires C, 55·24; H, 3·71; N, 9·9%].

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