

ALKALOIDS OF *MAHONIA NEPALENSIS* D.C.

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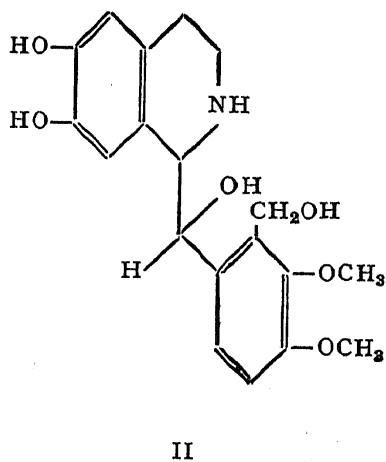
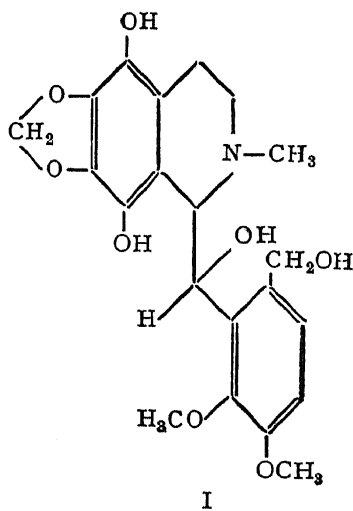
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FROM *Mahonia nepalensis* D.C., Chatterjee¹ reported the isolation of an yellow base umbellatine, $C_{21}H_{21}O_8N$, m.p. 205–07° (decomp.) and a red base neprotine, $C_{19}H_{23}O_6N$. Earlier Chatterjee had reported the isolation of umbellatine from *Berberis umbellata*² and *Berberis insignis*.³ On the basis of degradation work umbellatine was assigned the structure I⁴ and neprotine the structure II.⁵



Both these structural formulæ have unusual features and a re-examination of the alkaloids of *Mahonia nepalensis* appeared desirable. Following the procedure of Chatterjee two bases were isolated by us, a yellow base, m.p. 205–07° (decomp.) and a red base, m.p. 206° (decomp.).

The yellow base was characterised by preparation of a crystalline sulphate and a picrate whose melting points were in good agreement with those of the corresponding derivatives of Chatterjee's umbellatine. Analysis of the yellow base after drying at 110° *in vacuo* gave values in agreement with the molecular formula $C_{20}H_{19}O_5N, 3 H_2O$. Reduction of the 'hydrochloride' of the yellow base in alcohol solution in presence of Adams catalyst yielded

a hydrochloride, m.p. 215–17°, from which a colourless base, m.p. 172°, analysing for the formula $C_{20}H_{21}O_4N$ was obtained. The identity of the last compound with *dl*-tetrahydroberberine was established by mixed melting point determination with an authentic sample. Reduction of the hydrochloride of the yellow base with lithium aluminium hydride yielded a base, m.p. 164°, identical with dihydroberberine (m.p. and mixed m.p.). The yellow base gave an acetone compound, m.p. 168°, identical with berberine acetone compound (m.p. and mixed m.p.). A sample of berberine regenerated from berberine sulphate (B.D.H.) after one crystallisation from alcohol yielded crystals, m.p. 145° (decomp.). A second crystallisation from alcohol gave crystals, m.p. 205–07°.* The latter gave no depression in melting point with the yellow base from *Mahonia nepalensis*. It is therefore proved that umbellatine is identical with berberine.

It is curious that the m.p. 205–07° has not so far been recorded in literature for berberine. Katti and Shintre⁶ isolated from *Coscinium fenestratum* Coleb an alkaloid, m.p. 205°, whose identity was not established. Pillai and Varrier⁷ in a reinvestigation of this plant obtained an alkaloid whose identity with berberine was established by conversion to the acetone compound from which the form of berberine, m.p. 145°, was regenerated. It is also strange that melting or decomposition points have not been recorded for many of the salts of berberine. It is true that berberine and its salts undergo considerable colour change before melting, but it was observed in the present work that the hydrochloride, the sulphate and the picrate all melt with decomposition after a considerable preliminary darkening of colour. The melting points of berberine and its derivatives and the corresponding compounds from the yellow base of the *Mahonia nepalensis* are recorded in Table I.

Chatterjee has reported that the red base obtained from *Mahonia nepalensis* charred without melting. From the present work it was found that the red base melted at 206–08° (decomp.) and yielded a picrate, m.p. 210–11° (cf. Chatterjee 208–10°). The red base analysed for the formula $C_{20}H_{21}O_5N$, $3 H_2O$. Reduction of the 'hydrochloride' of the red base proceeded with absorption of two moles of hydrogen, yielding a tetrahydro base $C_{20}H_{23}O_4N$, m.p. 206–07°, which after methylation with diazomethane, yielded a compound m.p. 146°, identical with *dl*-tetrahydropalmatine. Ethylation of the

* Prof. K. Venkataraman (private communication) obtained a base, m.p. 205–06°, from *Coscinium fenestratum*, which gave an acetone compound identical with that from berberine. He also noted that berberine from commercial berberine sulphate melted at 145° after one crystallisation and at 205–207° after a second crystallisation from alcohol.

tetrahydrobase with diazoethane yielded an ethyl ether, m.p. 124°. A sample of *l*-corypalmine was ethylated, oxidised with iodine and reduced with zinc and hydrochloric acid to yield *dl*-O-ethyltetrahydrojatrorrhizine, m.p. 124°, identical with the ethyltetrahydroneprotine above. It is thus established that neprotine is identical with the known alkaloid jatrorrhizine. The relevant melting point data is presented in Table II.

TABLE I

	The yellow base (present work) m.p.	Umbellatine (Chatterjee's work) m.p.	Berberine m.p.
Base ..	205-07° (decomp.)	206-07° ⁸ (decomp.)	145° ⁹
Hydrochloride ..	206° (decomp.)	..	205-07° (decomp.)
Sulphate ..	274° (decomp.)	274° ⁸ (decomp.)	274° (decomp.)
Picrate ..	234° (decomp.)	232° ⁸ (decomp.)	232° (decomp.)
Acetone compound ..	168°	..	168° ¹⁰
Product from treatment with dimethyl sulphate	284° (decomp.)	265° ⁸	284° (decomp.)
Tetrahydrobase ..	171°	213-15° ⁸	171° ¹¹
Dihydro base ..	164°	⁸ Charred without melting	164° ¹²

TABLE II

	The red base (present work) m.p.	Neprotine (Chatterjee's work) m.p.	Jatrorrhizine m.p.
Base ..	206° (decomp.)	Charring ¹ without melt- ing	..
Hydrochloride ..	206-08° (decomp.)	Charrs ¹ above 200° without melting	206° (decomp.)
Nitrate ..	225° (decomp.)	..	225° ¹⁴ (decomp.)
Picrate ..	210-211° (decomp.)	208-10° ¹³ (decomp.)	..
Tetrahydrobase ..	206°	..	206° ⁵
O-Ethyltetrahydro base	124°	..	120° ¹⁵
O-Methyltetrahydro base	146°	..	146° ¹⁶

EXPERIMENTAL

Plant material was supplied by Messrs. Ghosh and Co., Darjeeling.

Isolation of the alkaloids of Mahonia nepalensis D.C.—Air-dried powdered roots and stem bark of the plants (2.5 kg.) were treated with alcohol (5:1). After two days, the yellow solution was drawn off and distilled on a water-bath. The brown residue was treated with water (500 c.c.), filtered, and the filtrate was treated with hydrochloric acid (congo red) and allowed to stand overnight. Crystals of the yellow base hydrochloride separated and were filtered and well washed, until the washings were yellow in colour. The brown filtrate was concentrated on a water-bath to 400 c.c. and filtered twice. On leaving this solution overnight, a second crop of yellow crystals appeared. The solution was decanted carefully into a shallow dish, evaporated partially and was left to crystallise. After two days red granules appeared and the dish was left undisturbed for a week till the quantity of granules stopped increasing. The red granules were filtered, washed and dried. Further spontaneous evaporation of the filtrate gave only a sticky brown mass which could not be crystallised.

Yellow base hydrochloride.—The foregoing yellow hydrochloride was crystallised first from hot water containing a few drops of hydrochloric acid. Recrystallisation from alcohol gave the *hydrochloride* (4.8 g./kg. of plant material) as yellow silky needles, m.p. and mixed m.p. with berberine hydrochloride, 206° (decomp.).

Yellow base.—The purified hydrochloride (4 g.) was dissolved in hot water and a dilute solution of sodium carbonate was added until alkaline, whereupon the yellow colour of the solution changed to dark brown, and on cooling, yellow silky needles of the free alkaloid (3 g.) were obtained. Repeated crystallisation from alcohol gave the *base*, m.p. 205–07° (decomp.). Found: C, 59.0; H, 5.9; N, 3.4. $C_{20}H_{19}O_5N \cdot 3 H_2O$ requires C, 59.0; H, 6.4; N, 3.4%. The melting point was undepressed by admixture with the higher melting form of berberine prepared as below:—

Berberine sulphate (B.D.H.) was suspended in water and basified by adding saturated sodium carbonate solution. The solid was filtered and crystallised once from alcohol when yellow crystals of berberine, m.p. 145° were obtained. A second crystallisation from alcohol changed the m.p. to 205–07°.

The *sulphate* was prepared as usual and crystallised from alcohol had m.p. and mixed m.p. with berberine sulphate (B.D.H.) 274° (decomp.).

Picrate.—The picrate was prepared as usual and was crystallised from alcohol. It had m.p. and mixed m.p. with berberine picrate, 234° (decomp.).

The acetone compound.—The yellow base hydrochloride (0.2 g.) dissolved in water (15 c.c.) was treated with sodium hydroxide solution (10%; 4 c.c.) and heated to 50°. Acetone (10 c.c.) was added and the solution set aside when lemon-yellow needles of the acetone compound separated, which melted at 168°. Mixed with berberine-acetone compound, there was no depression in the melting point.

Treatment of the yellow base with dimethyl sulphate.—An excess of dimethyl sulphate was added drop by drop to a solution of the yellow base (0.1 g.) in 10% potassium hydroxide solution with constant shaking. After half hour, yellow, silky fine needles separated. The shaking and the addition of dimethyl sulphate were continued and the mixture was kept alkaline. After one hour, the crystals were filtered, well washed with water, dried and then recrystallised from alcohol as silky yellow needles, m.p. 284°, undepressed by admixture, with the product, m.p. 284°, obtained from berberine by a similar procedure (Found: C, 55.0; H, 4.2%).

Dihydrobase.—To a suspension of lithium aluminium hydride (0.8 g.) in ether (100 c.c.), the yellow base hydrochloride (0.5 g.) was added during the course of 15 minutes, and the stirring was continued for 12 hours. The complex was decomposed as usual and repeatedly extracted with ether. After the removal of ether, the dihydrobase was obtained as yellow crystals (0.25 g.). After recrystallisation from ether, the *dihydro compound* had m.p. and mixed m.p. with dihydroberberine, 164° (Found: C, 70.8; H, 5.3. $C_{20}H_{19}O_4N$ requires C, 71.2; H, 5.6%).

Tetrahydrobase.—A solution of the yellow base hydrochloride (0.5 g.) in absolute alcohol (40 c.c.) containing platinum oxide (0.2 g.) was hydrogenated at 50 lb./sq. in. After the removal of solvent, the hydrochloride was obtained as a white powder, which crystallised from alcohol, had m.p. 215–17°. The free base was obtained after basification with liquor ammonia. After recrystallisation from alcohol, the *tetrahydro compound* was obtained as white needles, m.p. and mixed m.p. with tetrahydroberberine, 172° (Found: C, 70.6; H, 6.2. $C_{20}H_{21}O_4N$ requires C, 70.8; H, 6.2%).

Oxidation of the yellow base with potassium permanganate.—The base hydrochloride (0.5 g.) was dissolved in warm water (20 c.c.) and treated with potassium carbonate (0.15 g.) and then oxidised by slowly running in a solution of potassium permanganate (2.5 g. in 50 c.c. of water). The decolourisation of the permanganate was very rapid at first and then slowed down

appreciably after 30 c.c. of the solution had been added. The contents were warmed on a water-bath for 3 hours, and left aside overnight. The mixture was filtered and the residual manganese dioxide was extracted twice with hot water and the combined filtrate concentrated to 30 c.c. The solution was acidified with concentrated hydrochloric acid (congo red) and extracted continuously with ether for several hours. After the removal of solvent, the gummy residue left behind was sublimed *in vacuo*. The sublimate was dissolved in ethanol (5 c.c.) and anhydrous ethyl amine (3 c.c.) was added and the solution was evaporated on a water-bath. The residue was heated at 180° for 5 minutes and then sublimed *in vacuo*. The sublimate was crystallised from dilute alcohol to yield N-ethylhemipinimide as white, slender needles, m.p. and mixed m.p. with an authentic specimen, 90°.

The red base hydrochloride.—The red hydrochloride from the extraction of *Mahonia nepalensis* D.C. was crystallised from hot water containing a few drops of hydrochloric acid; the crystals were filtered and recrystallised from alcohol. Orange red prisms, m.p. 206–08° (decomp.), were obtained on slow crystallisation (0.2 g./kg. of plant material) (Found: C, 58.8; H, 5.5. $C_{20}H_{22}O_5NCl \cdot H_2O$ requires C, 58.6; H, 5.9%).

The red base.—The purified hydrochloride (0.8 g.) was dissolved in hot water and a dilute solution of sodium carbonate was added until alkaline, when the brown colour of the solution changed to blood red and on cooling, garnet red needles of the free alkaloid were obtained. It was recrystallised from alcohol to give the *red base* (0.6 g.), m.p. 206° (decomp.) (Found: C, 59.1; H, 6.1. $C_{20}H_{21}O_5N \cdot 3H_2O$ requires C, 58.7; H, 6.6%). The *nitrate* prepared by the usual method and crystallised from alcohol had m.p. 225° (decomp.). The *picrate* prepared by the usual method was crystallised from alcohol and had m.p. 210–11°.

Oxidation of the red base with potassium permanganate.—The red base (0.2 g.) on oxidation and working up in the usual way yielded hemipinic acid characterised as N-ethylhemipinimide, m.p. 90°.

Tetrahydro base—A solution of the red base hydrochloride (0.5 g.) in absolute alcohol (30 c.c.) containing platinum oxide (0.2 g.) was hydrogenated at 50 lb./sq. in. After the removal of solvent, *tetrahydrobase hydrochloride* was obtained as a yellow powder which crystallised from alcohol as yellow needles, m.p. 206° (Found: C, 61.0; H, 6.7. $C_{20}H_{24}O_4NCl \cdot H_2O$ requires C, 60.7; H, 6.5%).

The free tetrahydrobase was obtained by basification of the above hydrochloride with liquor ammonia and was crystallised from alcohol, as white

needles, m.p. 206–07° (Found: C, 70·7; H, 6·7; N, 4·1. $C_{20}H_{23}O_4N$ requires C, 70·5; H, 6·7; N, 4·1%).

O-Methyltetrahydrobase.—To a solution of the tetrahydrobase above (50 mg.) in absolute methanol (15 c.c.), a solution of diazomethane in ether (50 c.c.) (prepared from 5 g. of nitrosomethylurea) was added. Next day, the solvent was evaporated and the residue was crystallised from absolute ether to give *tetrahydropalmatine*, m.p. and mixed m.p. with an authentic specimen, 146° (Found: C, 70·8; H, 5·7. $C_{21}H_{25}O_4N$ requires C, 70·9; H, 6·0%).

O-Ethyl tetrahydrobase.—The tetrahydrobase (50 mg.) was ethylated in the same way as above using diazoethane. The product was crystallised from absolute ether, to give the ethyl ether as white needles, m.p. and mixed m.p. with *dl*-*O*-ethyltetrahydrojatrorrhizine (see below) 124°.

dl-*O*-Ethyltetrahydrojatrorrhizine.—*l*-Corypalmine (50 mg.) was ethylated in the same way as above using diazoethane. The product was dissolved in chloroform-methanol, treated with iodine in excess, and heated on a steam-bath with a little sodium acetate. The solvent and excess iodine were then removed and the residue treated on a steam-bath with zinc and dilute hydrochloric acid until all of it had dissolved to a colourless solution. An excess of ammonia was added and the liberated base extracted with ether and the ether extract evaporated. The residue was crystallised repeatedly from ether to give colourless needles melting at 124°.

SUMMARY

Chemical investigation of the alkaloids of *Mahonia nepalensis* D.C. has established the identity of 'umbellatine' with berberine and 'neprotine' with jatrorrhizine.

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REFERENCES

1. Chatterjee .. *J. Amer. Pharm. Assoc.*, 1944, **33**, 210.
2. ——— .. *J. Ind. Chem. Soc.*, 1940, **17**, 289.
3. ——— .. *J. Amer. Pharm. Assoc.*, 1941, **30**, 247.
4. ——— .. *Ibid.*, 1949, **38**, 149.
5. ——— and Guha .. *Ibid.*, 1951, **40**, 233.

6. Katti and Shintre .. *Arch. Pharm.*, 1930, **268**, 314.
7. Pillai and Varrier .. *Curr. Sci.*, 1943, **12**, 228.
8. Chatterjee .. *J. Ind. Chem. Soc.*, 1942, **19**, 233.
9. Perkin .. *J. Chem. Soc.*, 1889, **55**, 63.
10. Gadamer .. *Arch. Pharm.*, 1905, **243**, 42.
11. ————— .. *Ibid.*, 1901, **239**, 1901.
12. Schmid and Karrer .. *Helv. Chim. Acta*, 1949, **32**, 960.
13. Chatterjee and Guha .. *J. Amer. Pharm. Assoc.*, 1950, **39**, 181.
14. Feist .. *Arch. Pharm.*, 1907, **245**, 586.
— and Sandstede .. *Ibid.*, 1918, **256**, 1.
15. Späth and Mosettig .. *Ber.*, 1925, **58**, 2133.
16. Govindachari, Rajadurai, Subramanian and Viswanathan .. *J. Chem. Soc.*, 1957, **575**, 2943.