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STERICAL CORRELATION OF (+)-ARMEPAVINE AND (+)-LAUDANIDINE

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Abstract—(+)-O-Methylarmepavine and (+)-laudanidine have been sterically correlated through their preparation from a common optically active intermediate. It follows that the asymmetric carbon atom in natural (−)-armepavine has the R configuration.

(−)-ARMEPAVINE is a benzyltetrahydroisoquinoline alkaloid which was isolated from *Papaver armenicum* and later found in *P. floribundum* by Konowalowa *et al.*[1] They also determined its structure as VII (R = H)[2].

This structure of armepavine was confirmed by the synthesis of its racemic form by Marion *et al.*[3] and by Tomita and Yamaguchi.[4] While both groups obtained (±)-armepavine with identical properties, they differed the melting point of (±)-O-methyl-armepavine (VII, R = CH_3), a difference which we will consider again later. (±)-Armepavine has also been synthetized in our laboratories by Giacomazzi, employing the Bischler-Napieralski reaction and protecting the phenolic group by benzoylation.[5]

Armepavine has not been isolated from other plant sources. However, both optical isomers of the base (VII, R = H) and of its O-methyl ether (VII, R = CH_3) have been obtained as direct or indirect degradation products of several alkaloids of the bisbenzylisoquinoline group, when Tomita's reduction method is applied to them.[6]

In spite of the large amount of work done in this field there is no chemical proof of the absolute configuration of the asymmetric carbon atom in the optical isomers of armepavine.

We have now correlated (+)-O-methylarmepavine and (+)-laudanidine by preparing simultaneously both compounds from an optically active intermediate, by a reaction in which the asymmetric carbon atom does not participate.

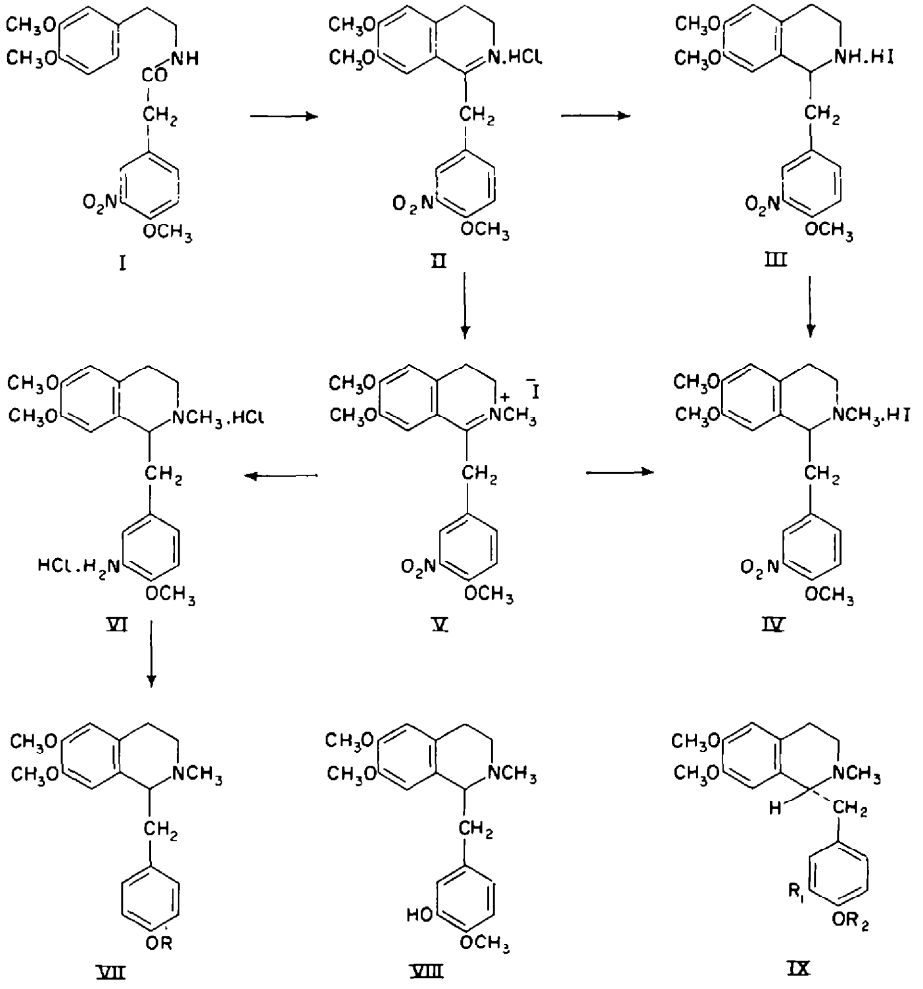
As (−)-O-methylarmepavine has been obtained from natural (−)-armepavine by treatment with diazomethane[1], (−)-armepavine and natural (−)-laudanidine must have the same configuration. On the other hand, methylation of (−)-laudanidine gave (−)-laudanosine[7] the optical isomer of the natural (+)-laudanosine, a base whose

[1] R. Konowalowa, S. Yunussoff and A. Orechoff, *Ber. Dtsch. Chem. Ges.* **68**, 2158, 2277 (1935).
[2] R. Konowalowa, S. Yunussoff and A. Orechoff, *J. Gen. Chem. USSR* **10**, 641 (1940); Chem. Abstr. **34**, 7917 (1940).
[3] L. Marion, L. Lemay and V. Portelance, *Canad. J. Chem.* **15**, 216 (1950).
[4] M. Tomita and H. Yamaguchi, *Pharm. Bull.* **1**, 10 (1953).
[5] A. Giacomazzi, Thesis, Facultad de Ciencias Exactas y Naturales, Buenos Aires, 1959. For other examples of protection of the phenolic group by benzoylation in similar synthesis, B. Frydman, R. Bendisch and V. Deulofeu, *Tetrahedron* **4**, 342 (1958).
[6] M. Tomita, *Fortschr. Chem org. Natursoffe* **9**, 175 (1952) and later papers; I. R. C. Bick and P. S. Clezy, *J. Chem. Soc.* 3893 (1953); D. A. A. Kidd and J. Walker, *Ibid.* 669 (1954)); I. R. C. Bick, P. S. Clezy and M. J. Vernengo, *Ibid.* 4928 (1960).
[7] E. Späth and E. Bernhauser, *Ber. Dtsch. Chem. Ges.* **58**, 200 (1925).

steric configuration has been rigorously determined by Corrodi and Hardegger[8] and which has been correlated with many alkaloids of the tetrahydroisoquinoline, aporphine and tetrahydroberberine groups.

All these connected transformations show that natural (−)-armepavine (IX, $R_1 = R_2 = H$) and natural (−)-laudanidine (IX, $R_1 = OH$, $R_2 = CH_3$) belong to the same steric series, the asymmetric carbon atom having the *R* configuration according to the definition of Cahn *et al.*[9] and as indicated in the formula (IX). In natural (+)-laudanosine, the asymmetric atom has the opposite *S* configuration. It follows that when one of the optical isomers of armepavine or O-methylarmepavine or their methiodides, has been isolated by direct degradation from bisbenzylisoquinoline alkaloids, or by a subsequent reaction, the absolute configuration of the original asymmetric carbon atom is determined.

The simultaneous preparation of (±)-O-methylarmepavine and (±)-laudanidine was found when experimenting with the racemic compound (IV). It was prepared



[8] H. Corrodi and E. Hardegger, *Helv. Chim. Acta* **39**, 889 (1956).
[9] R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia* **12**, 81 (1596).

from 4-methoxy-3-nitro-N-(3,4-dimethoxyphenethyl)-phenylacetamide (I) which gave, when submitted to a Bischler-Napieralski reaction, 1-(4-methoxy-3-nitrobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline, isolated as the hydrochloride (II). The liberated base from II could be reduced to the corresponding tetrahydroisoquinoline (III) with sodium borohydride, which on methylation with formic acid-formaldehyde afforded the N-methyl compound (IV), which crystallized easily as the hydriodide. This hydriodide was also obtained by treating the dihydrobase from II with methyl iodide and reducing the resulting methiodide (V) with the same reagent.

Treatment of the methiodide (V) or of the related tetrahydroisoquinoline (IV) with zinc hydrochloric acid, reduced the nitro group (and the double bond in the case of V) giving 1-(3-amino-4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-isoquinoline dihydrochloride (VI).

When VI was diazotized and the solution of the diazonium salt treated with hypophosphorus acid, (±)-O-methylarmepavine (VII, R = CH_3) was obtained with a m.p. 60–61° in substantial agreement with the m.p. 62·5–63° given by Tomita and Yamaguchi.[4] When kept in solid conditions at room temperature for several months the melting point increased to 87–88·5°. In later preparations we always obtained the compound with the higher melting point, which is in fair agreement with the melting point given by Marion *et al.*[3] for the O-methyl ether of (±)-armepavine. The U.V. spectra of both compounds were identical and they seem to be polymorphic crystals.[10]

We expected to obtain (±)-laudanidine (VIII) by decomposing the same diazonium salt with sulfuric acid, especially because Marion *et al.*[3] had obtained good yields of (±)-armepavine by introducing the phenolic hydroxyl by diazotation of an amino group. In contrast to these expectations, paper chromatography revealed that the only alkaloidal base produced was again O-methylarmepavine. The addition of copper salts, which had been recommended to improve the substitution of the diazonium group by hydroxyl, gave the same results, the diazonium group being always replaced by hydrogen, indicating a strong influence of the other substituents in the phenyl ring.

Partial substitution of the diazonium by hydroxyl, but always with simultaneous substitution by hydrogen, was obtained by preparing the fluoborate of the diazonium cation and decomposing the salt with acetic acid following the method of Haller and Schaffer.[11]

Paper chromatography showed that two bases were produced in this reaction with the R_f values of O-methyl-armepavine and laudanidine, this was confirmed by actual isolation, the O-methyl-armepavine being obtained in larger amount. Having in mind the purpose of this work this was a useful reaction for correlating the steric configuration of both bases if it could be applied to the optically active isomers of compound IV.

After some trials it was found that the base (III) could be separated into optical isomers on treatment with ditoluyl-tartaric acid. In this way (+) and (−)-1-(4-methoxy-3-nitrobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (III) were prepared with $(\alpha)_D^{20°}$ +16·4° and −15·8° (chloroform). On methylation, the isomeric hydriodides (IV) were obtained, the (+)-base (III) giving a levorotatory hydriodide with

[10] A. Giacomazzi (Ref. 5) on treatment of (+)-armepavine with diazomethane obtained (+)-O-methylarmepavine of m.p. 89–90°.

[11] H. L. Haller and P. S. Schaffer, *J. Amer. Chem. Soc.* **55**, 4954 (1933).

$(\alpha)_D^{20°}$ −84·0° (water), the (−)-base (III) a dextrorotatory one with $(\alpha)_D^{20°}$ +94·0°.[12] The difference in the absolute value of the specific rotation of the N-methyl isomers (IV) indicates that the isomers of base III were not optically pure, despite the almost identical values of their rotations.

When the (+)-1-(4-methoxy-3-nitrobenzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline hydriodide (IV) was submitted to the same reaction sequence as the racemic compound, (+)-O-methylarmepavine, $(\alpha)_D^{20°}$ +85·0° and (+)-laudanidine $(\alpha)_D^{20°}$ +80·0° were isolated. The (+)-O-methylarmepavine was optically pure and the (+)-laudanidine contained at least 90% of the dextrorotatory isomer.

The (−)-isomer of IV was transformed into (−) O-methylarmepavine by decomposing the diazonium salt with hypophosphorous acid. Again an optically pure base, $(\alpha)_D^{20°}$ −86·0° was obtained.

In our experience it is not difficult, when recrystallizing one optical isomer of O-methylarmepavine, to get rid of small amounts of the opposite one, which has undoubtedly happened in both cases quoted above.

EXPERIMENTAL

M.p.s are uncorrected. Descending chromatography on Whatman No. 1 was employed with the following systems: (1) Cellosolve:toluene:buffer (5:5:1) upper phase; laudanine, R_f 0·06; O-methylarmepavine, R_f 0·24. (2) n-Butanol:toluene:buffer (3:2:5) upper phase; laudanine, R_f 0·67; O-methylarmepavine, 0·75. The buffer employed was prepared by adding 9·5 ml of 0·2M sodium acetate to 90·5 ml 0·2 M acetic acid.

4-Methoxy-3-nitro-N-(3,4-dimethoxyphenyl)-phenylacetamide (I). 4 Methoxy-3-nitrophenylacetic acid (4 g) was suspended in 20 ml thionyl chloride and heated for 3 hr at 60°, when the acid dissolved. The excess thionyl chloride was evaporated in vacuum and the residue crystallized on standing in a dessicator. Without further purification it was dissolved in 25 ml pure chloroform, the solution cooled to 0° and slowly added to to 6·8 g 3,4-dimethoxyphenylethlyamine dissolved in 20 ml chloroform. After 30 min, 10% NaOH was carefully added until permanemt alkalinity. The aqueous phase was separated and the chloroform was washed well with dil HCl, then with water, dried and evaporated. The remaining oil crystallized easily on cooling and was recrystallized from methanol; 5·8 g (yield 82%) of needles, m.p. 111–113°, were obtained. For analysis it was recrystallized several times from the same solvent, m.p. 113–114°; λ max 227 mμ (log ϵ 3·66); 335 mμ (3·36). (Found C, 60·9; H, 5·9; N, 7·4. $C_{19}H_{22}N_2O_6$ requires: C, 61·2; H, 5·8; N, 7·4%).

1-(4-Methoxy-3-nitrobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline hydrochloride (II) The above amide (10 g) dissolved in 100 ml purified choroform, cooled to 0° and 20 g phosphorous pentachloride added slowly, with good shaking, maintaining the low temp. of the solution. The suspension was kept 4 hr at 5° and then for 5 days at 20–25°. After that time small pieces of ice were added to decompose the excess of the phosphorous pentachloride and the chloroform distilled in vacuum, a yellow oil remaining with the water. On cooling, the oil and some soluble material crystallized. It was then filtered and washed well with water. This product was recrystallized from ethanol without drying and 9 g (yield 85%) needles m.p. 219–220° was obtained. The m.p. remained unchanged by further recrystallizations. λ_{max} 215 mμ (log 4·48); 311 mμ (4·00); 360 mμ (3·83). ((Found: C, 58·0; H, 5·3; N, 7·1; Cl, 9·0. $C_{19}H_{20}N_2O_6$. HCl requires: C, 58·2; H, 5·2; N, 7·1; Cl, 8·7%).

1-(4-Methoxy-3-nitrobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (III) 1-(4-Methoxy-3-nitrobenzyl)-3,4-dihydro-6,7-dimethoxy-isoquinoline hydrochloride (II; 5 g) was dissolved in 10 ml warm 50% ethanol, and the solution alkalinized with ammonia, when the base precipitated as an oil. By dilution with water further portions of the oil separated, which solidified on cooling. After some hours the solid was filtered, dried, dissolved in 80 ml warm ethanol, 2·5 g sodium borohydride added slowly and the mixture heated to boiling for 15 min. By cooling and dilution with 120 ml water a solid separated, which was filtered, dried and crystallized from ethanol; 3·3 g (yield 73%) m.p. 146–148·5° were obtained. Recrystallized several times from ethanol, the m.p. was 148–148·5° (Found: C, 63·6; H, 6·2; N, 7·9. $C_{19}H_{22}N_2O_5$ requires: C, 63·6; H, 6·1; N, 7·8%).

[12] A similar inversion in the sign of rotation on N-methylation has been observed by Corrodi and Hardegger (Ref. 8) when (−)-N-norlaudanosine was transformed into (+)-laudanosine methiodide

1-(4-*Methoxy*-3-*nitrobenzyl*)-3,4-*dihydro*-6,7-*dimethoxyisoquinoline methiodide* (V). The crude dihydroisoquinoline base, prepared from 5 g of the hydrochloride (II) was boiled for 1 hr without further purification with 30 ml methyl iodide, when a yellow solid separated from the solution. After the methylation the excess methyl iodide was evaporated in vacuum and the solid was crystallized from dil ethanol; 4·15 g (yield 65%) of crystals m.p. 203–204° were obtained. By recrystallizing from ethanol the m.p. 206–207° was attained λ_{max} 219 mμ (log ε 4·59); 249 mμ (4·24); 313 mμ (4·01); 364 mμ (4·01). (Found: C, 48·1; H, 4·6; I, 25·4. $C_{19}H_{20}N_2O_5$ requires: C, 48·0; H, 4·8; I, 26·0%). Prolonged heating in ethanol during recrystallization decomposes the methiodide.

1-(4-*Methoxy*-3-*nitrobenzyl*)-1,2,3,4-*tetrahydro*-2-*methyl*-6,7-*dimethoxyisoquinoline hydroiodide* (IV) The methiodide (5 g) were dissolved in 60 ml 90% ethanol, 2·7 g sodium borohydride was slowly added and then refluxed for 15 min. After dilution with 100 ml water, the solution was extracted with ether and the ethereal extracts evaporated in vacuum to give a yellow oil. This oil was dissolved in a small amount ethanol, 6 g sodium iodide was added and dissolved by warming and the mixture was acidified to pH 4 by the addition of acetic acid. By slow cooling yellow cubic crystals precipitated, m.p. 179–181° (4·5 g, yield 81%). On recrystallization from the same solvent they melted 182–183°. λ_{max} 282 mμ (log ε 3·68); 330 mμ (3·35). (Found: C, 48·0; H, 5·0; N, 5·6; I, 25·3. $C_{20}H_{24}N_2O_5 \cdot HI$ requires C, 48·0; H, 5·2; N, 5·3; I, 25·4%).

The same compound was obtained by methylation of the racemic (±)-1-(4-methoxy-3-nitrobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (III) with formic acid-formaldehyde, following the same method that is described in detail below for the methylation of the dextrorotatory isomer. The N-methyl compound was isolated as the hydroiodide, m.p. 179–180° (mixed m.p. 179–180°; U.V. spectrum was identical).

(±)-O-*Methylarmepavine* (VII; R = CH_3). 1-(4-Methoxy-3-nitrobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline methiodide (6 g) was suspended in a mixture of 60 ml water and 120 ml conc HCl, and dissolved by heating in a boiling water bath. Zinc powder (18 g) was added over a 45 min period with good shaking and continuous heating. After cooling the solution was made alkaline with ammonia and extracted well with ether. The combined ethereal extracts were washed with a small amount water and evaporated in vacuum at a low temp. A pale brown oil remained which was dried, and dissolved in 100 ml absolute ether. Absolute methanol (5 ml) was added and a stream of dry hydrogen hydrochloride was passed through the solution, which was kept at 5°. An oil precipitated, which crystallized on standing at 0°. The pale brown crystals were filtered and washed with absolute ether and recrystallized by dissolving in a mixture of 10 ml ethanol and 2 ml 2 N HCl and adding decolourizing carbon. After filtering and cooling 3·3 g (yield 65%) of almost white crystals, m.p. 220° of 1-(3-amino-4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline dihydrochloride (VI) were obtained and employed without any further purification. Reduction of the tetrahydroisoquinoline (IV) gave the same compound.

The dihydrochloride (VI; 100 mg) was dissolved in a mixture of 1 ml water and 0·5 ml conc HCl, and diazotized by employing the calculated amount of sodium nitrite in solution and checking the end point with starch-iodide-paper. The solution was then treated with 1·5 ml of a 30% solution of hypophosphorous acid, It was left at room temp until no more evolution of nitrogen was observed. The solution was made alkaline with solid sodium bicarbonate and extracted with ether. The combined ether extracts were washed with water, dried and evaporated. The remaining oil was dissolved in the smallest amount of pet. ether (b.p. 60–70°). On standing at 5° the solution gave crystals of (±)-O-methylarmepavine m.p. 60–61°. On storing at room temp, the m.p. changed to 87–88·5°. Similar later preparations gave only the (±)-O-methylarmepavine with m.p. 87–88°.

Both forms had the same R_f on paper chromatography and the same U.V. spectra: λ_{max} 227 mμ (log ε 4·24); 283 mμ (3·69). When the high melting variety was mixed with an authentic sample melting 88–89°, no depression was observed.

(±)-O-*Methylarmepavine* (VII; R = CH_3) *and* (±)-*laudanidine* (VIII). The dihydrochloride (VI; 1 g) was dissolved in 10 ml water, 1 ml conc H_2SO_4 was added and the solution was treated with the calculated amount of sodium nitrite in 5 ml water and checking the end point with the usual indicator. The diazonium cation was then precipitated as the fluoroborate by addition of 2 ml 50% fluoroboric acid. The precipitate was filtered, washed with water, ethanol and ether and dried. 1·16 g of a slight yellow product decomposing at 175° was obtained. 500 mg of this product was suspended in 30 ml acetic acid and decomposed exactly as described below for the dextrorotatory isomer. 50 mg of (±)-O-methylarmepavine m.p. 87–88° were obtained and 15 mg of (±)-laudanidine m.p. 159·5–161·5°. λ_{max} 282 mμ (log ε 3·80). The latter product was identified by mixed m.p. with authentic (±)-laudanidine. R_f in several systems and U.V. spectra were also identical.

(−)-1-(4-*Methoxy*-3-*nitrobenzyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (III). To a solution of 2 g of the racemic base dissolved in 60 ml warm acetone, 2·2 g ditoluyl-D-tartaric acid were added, which dissolved on gentle shaking. In 15 min the salt of the base began to separate in crystalline condition and this was filtered after standing overnight and washed with acetone,

m.p. 184–185°; yield 2·3 g. After recrystallization from ethanol, 1·2 g needles m.p. 185·5–186° were obtained.

The purified salt was suspended in water, alkalinized with sodium hydroxide and the base extracted well with chloroform. The chloroform solution after washing and drying was evaporated to dryness, leaving a syrup that was dissolved in a very small amount of warm ethanol. On cooling, 420 mg of yellow prisms, m.p. 120–122°, were obtained. After recrystallization from ethanol, the m.p. was 121–123°; $(\alpha)_D^{20°}$ −15·8° (*c*, 0·25, chloroform). (Found: C, 63·8; H, 6·0; N, 7·9. Calc. for $C_{19}H_{22}N_2O_6$: C, 63·6; H, 6·1; N, 7·8%).

(+)-1-(4-*Methoxy*-3-*nitrobenzyl*)-1,2,3,4-*tetrahydro*-2-*methyl*-6,7-*dimethoxyisoquinoline hydriodide* (IV). (−)-(4-Methoxy-3-nitrobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline, (400 mg), was dissolved in 2 ml 99% formic acid, 2 ml of 40% formaldehyde solution added and heated to 100° for 7 hr.

After cooling, 0·8 ml conc. HCl was added and the solution evaporated to dryness. The residue was dissolved in water and the solution extracted with ether, the extracts being discarded. The aqueous layer was then made alkaline with 10% NaOH and the free base extracted with ether. The ether extracts were washed, dried and evaporated. The residual yellow oil was dissolved in 2·5 ml ethanol; 600 mg sodium iodide added and dissolved by gently warming, and the solution cooled and acidified to pH 4 by the addition of acetic acid. By keeping at 5° and occasional scratching, yellow irregular crystals of the hydriodide formed. They were filtered and recrystallized from ethanol. M.p. 164–167°; $(\alpha)_D^{20°}$ +94·0 (*c*, 0·1, H_2O). (Found: C, 47·8; H, 5·1; I, 25·4. $C_{20}H_{24}N_2O_5 \cdot HI$ requires: C, 48·0; H, 5·03; I, 25·3%).

On further recrystallization from ethanol the optical purity decreased. M.p. 158–167°; $(\alpha)_D^{20°}$ +74·0°.

(+)-O-*Methylarmepavine* (VII; R = CH_3) *and* (−)-*laudanidine* (VIII). The above hydriodide (450 mg), m.p. 164–167°, was suspended in 4·5 ml water, 9 ml conc HCl was added and the solid was dissolved by heating in a boiling water bath and while kept at that temp, 1·35 g zinc powder was added in 45 min. After cooling, the solution was made alkaline with 4% NaOH and extracted well with ether. The collected ether extracts were washed well with water, dried and evaporated. A pale yellow oil (300 mg) remained.

This oil was dissolved in 4 ml 2 N H_2SO_4, cooled to 0°–5° and 10% sodium nitrite solution added, until the usual blue colour was given by the starch-iodide indicator paper. 1 ml of 50% fluoboric acid in water was then added, and the solution was kept at 5° overnight. An oil precipitated, which on scratching solidified to a light yellow solid that was filtered and washed with alcohol and ether. 370 mg were collected; dec. pt. 170°; $(\alpha)_D^{20°}$ +82·0, (*c*, 0·12, H_2O).

This material was suspended in 20 ml glacial acetic acid and heated to boiling. The solid dissolved after 5 hr boiling, the solution was cooled, 40 ml N HCl was added and the solution was extracted with ether, the extracts being discarded. It was then made alkaline by addition of solid sodium hydrogen carbonate and extracted several times with chloroform. The combined chloroform extracts were dried and evaporated to give a residue of 280 mg of a brown oil. This oil was dissolved in 10 ml conc HCl and heated at 70° for 45 min. The solution was cooled, made alkaline and extracted again with chloroform. Evaporation of those chloroform extracts gave a brown oil with strong alkaloidal reaction, that on paper chromatography gave two spots corresponding to O-methylarmepavine and laudanidine,.

This oil was dissolved in benzene and chromatographed on a column of neutral alumina (Woelm, activity II). After washing with benzene, elution with benzene with 0·5% ethanol gave fractions containing O-methylarmepavine; benzene with 2% ethanol was then employed and the laudanidine eluted.

The fraction containing O-methylarmepavine were combined and evaporated. The yellow oil remaining was extracted with boiling pet. ether (60–70°). By cooling, some small drops of oil precipitated which were discarded. The remaining solution on standing at 5°, gave 15 mg of crystals m.p. 59–61°; $(\alpha)_D^{20°}$ +71·0° (*c*, 0·23, chloroform), which after 3 crystallizations from pet. ether yielded practically pure (+)-O-methylarmepavine, m.p. 60–62°; $(\alpha)_D^{20°}$ +85·0°. I.R. spectra in chloroform solution and U.V. spectra were identical to those of (+)-O-methylarmepavine m.p. 88–89°. Treatment with methyl iodide yielded (+)-O-methylarmepavine methiodide, m.p. 136–138° (sintering 127–128°). $(\alpha)_D^{20°}$ +119·0° (Methanol).

The fractions containing laudanidine were combined and evaporated to dryness. The orange oil obtained crystallized on cooling and when recrystallized from ethanol, 24 mg were obtained of small prisms, m.p. 175–177°; $(\alpha)_D^{20°}$ +80·0° (*c*, 0·11, chloroform); 90% of the (+)-isomer). By recrystallization from ethanol the optical purity was not improved, m.p. 176–178°; $(\alpha)_D^{20°}$ +74·0; 84% of the (+)-isomer), Frydman *et al.*[18] found for (+)-laudanidine m.p. 184–185°, $(\alpha)_D^{22°}$ + 94·9°.

[18] B. Frydman, R. Bendisch and V. Deulofeu, *Tetrahedron* **4**, 342 (1958). In this paper the optical rotation of (+)-laudanidine was given, because of a typographical error, with the opposite sign, as −94·8°.

I.R. spectra in chloroform solution and U.V. spectra were identical to those of a sample of pure (+)-laudanidine m.p. 161–162°.

(−)-O-*Methylarmepavine.* The mother liquors from the preparation of the (−)-1-(4-methoxy-3-nitrobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (III) were evaporated to dryness, the solid residue suspended in 4% NaOH and the suspension extracted with chloroform; the solid dissolved. The chloroform solution on evaporation gave 2 g of an oil which was dissolved in 60 ml warm acetone and treated with 2·2 g ditoluyl-L-tartaric acid. The ditoluyl-L-tartrate crystallized easily and the crystals were worked up as indicated for the other isomer. 0·8 g of the dextrorotatory isomer of III were isolated with m.p. 119–122°, $(\alpha)_D^{20°}$ +16·4° (*c*, 0·36). On methylation the hydriodide (IV) was obtained, m.p. 163–167°, $(\alpha)_D^{20°}$ −84·0° (*c*, 0·21) which was transformed into (−)-O-methylarmepavine, m.p. 60·5–62°, $(\alpha)_D^{20°}$ −86·0°, by reduction, diazotation and treatment with hypophosphorous acid, as described for the racemic mixture.

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