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MACRANTALINE AND MACRANTORIDINE, NEW ALKALOIDS FROM A TURKISH SAMPLE OF *PAPAVER PSEUDO-ORIENTALE*

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Key Word Index—*Papaver pseudo-orientale*; Papaveraceae; alkaloids; macrantaline, 1(-2′-hydroxymethylene-3′,4′-dimethoxybenzyl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline; macrantoridine, 1-(2′-carboxy-3′,4′-dimethoxybenzyl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline; salutaridine; structural determination.

Abstract—The major alkaloids of the aerial parts of a Turkish sample of *Papaver pseudo-orientale* are salutaridine and a new alkaloid, macrantaline, UV, IR, PMR, MS and CD have been used to establish the structure of macrantaline as 1-(2′-hydroxymethylene-3′,4′-dimethoxybenzyl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline. The corresponding 2′-methyl substituted analogue prepared from (−)-α-narcotine and also from macrantaline proved to have identical properties, including CD spectra, thus confirming the structure and establishing the absolute configuration of macrantaline. A new minor alkaloid, macrantoridine, yielded macrantaline on lithium aluminium hydride reduction and differs from the latter in that the 2′-substituent is a carboxyl instead of hydroxymethylene. UV, IR, PMR, MS and CD data are reported for macrantoridine.

INTRODUCTION

The medicinally important alkaloids morphine and codeine are obtained from the Opium Poppy, *Papaver somniferum*, but the major alkaloid, morphine, and its readily prepared diacetyl derivative, heroin, feature prominently, throughout the world, as drugs of abuse. Despite its addictive properties, morphine is used medicinally, particularly for terminal pain because of its powerful analgesic properties. Much of the isolated morphine is in fact converted into codeine which is more widely used medicinally as an analgesic and antitussive. Hence other plant sources, particularly of codeine, have been sought and *P. bracteatum* is a possible commercial alternative since some strains produce high yields of thebaine [1] which can readily be converted into codeine [2, 3]. According to the chemical literature, the alkaloids of *P. bracteatum* have appeared to be variable and it has been proposed that different chemical strains exist and in particular that some strains produce thebaine (1) as the major alkaloid [4–12] while others produce isothebaine (3) as the major alkaloid [4, 5, 13]. Other minor alkaloids reported from *P. bracteatum* include the types which are summarised as follows: (a) morphinane—oripavine [14], codeine [11], neopine [11], isomeric *N*-oxides of thebaine [15]; (b) morphinandienone—salutaridine [13, 16]; (c) aporphine—bracteoline [17], nuciferine [13]; (d) pro-aporphine—orientalinone (bracteine) [14, 16]; (e) tetrahydroprotoberberine and related alkaloids—orientalidine (bractavine) [13, 18], mecambridine (oreophiline [13, 16]; (f) rhoeadine—alpinine [11], epialpinine [20], alpinigenine [5, 8, 12, 19, 21]; (g) papaverrubine—[22]; (h) others—protopine [13], coptisine [13], oxysanguinarine [13]; bractamine [14].

It is apparent however, that in some instances, alkaloids which have been reported from *P. bracteatum*, may, in all probability, have been obtained from the closely related species *P. orientale*, which according to the chemical literature, is also said to be variable in its alkaloidal content. Distinct chemical strains of *P. orientale* are reported in which the major alkaloid is either thebaine (1) [23, 24] or isothebaine (3) [24, 28] or oripavine (2) [12, 21]. Alkaloids which in some instances have been isolated as minor products are summarised as follows: (a) morphinane—thebaine [12, 21, 26]. oripavine [23]; (b) morphinandienone—salutaridine [27–29]; (c) aporphine—nuciferine [27], bracteoline [28], isothebaine [12, 21]; (d) pro-aporphine—orientalinone [28, 29], dihydroorientalinone [29]; (e) tetrahyroprotoberberine and related alkaloids—mecambridine (oreophiline) [27, 28, 30]; orientalidine bractavine [27, 28, 30, 31], PO-4 [30–32], alborine (PO-5) [30, 32]; (f) papaverrubine— [22, 28]; (g) others—protopine [24, 26], orientaline [33], oxysanguinarine [27], Or_1 and Or_2 [28].

The botanical confusion which exists between these two species has been discussed at some length [12] and it has been stated that as a result of intensive field study, combined with cytology and chemical analysis of the *Papaver* section Oxytona (i.e. Macrantha), a re-evaluation of the species within this group has been effected. In fact, 3 species are recognised, *P. bracteatum* Lindl. (diploid 2n = 14), *P. orientale* L. (tetraploid, 2n = 28) and *P. pseudo-orientale* (Fedde) Medw. (hexaploid, 2n = 42). It is claimed that a single alkaloid characterises each of these 3 species and that *P. bracteatum* contains thebaine (1) as the major alkaloid with alpinigenine as a minor alkaloid in some samples [12, 21] while *P. orientale*

contains oripavine (2) as the dominant alkaloid with either thebaine or isothebaine as minor alkaloids. The third species, *P. pseudo-orientale*, is stated to contain isothebaine (3) as the major alkaloid with thebaine and/or oripavine being present as minor components in some samples. A detailed chemical investigation of *P. pseudo-orientale* [21] from Iran, has shown that isothebaine is the major alkaloid of the dried latex and that the minor alkaloids include (a) morphinandienone—salutaridine; (b) aporphine—bracteoline; (c) tetrahydroprotoberberine and related alkaloids—orientalidine, aryapavine (a new alkaloid), PO-4, alborine (PO-5); (d) others—Or_1, Or_2. The alkaloid content of this sample of *P. pseudo-orientale* is very similar in composition to that previously reported from plants stated to be *P. orientale* [27, 28, 30]. It has been concluded, therefore, that much of the conflicting evidence on alkaloid composition which appears in the literature cited above, is now explicable in terms of these 3 species currently recognised in the section Oxytona [12]. However, recent publications [34, 35] have shown that a Turkish poppy, identified as *P. pseudo-orientale* contains the morphinandienone alkaloid salutaridine (4) and a novel 1-benzyltetrahydroisoquinoline alkaloid named macrantaline, as major alkaloids.

The present paper establishes the structure of macrantaline together with that of a closely related minor alkaloid named macrantoridine, and comments on the taxonomic and biosynthetic implications of these findings.

RESULTS AND DISCUSSION

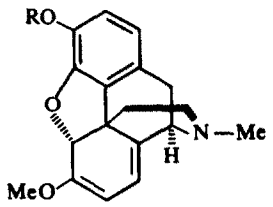
The total crude alkaloid from the aerial parts of *P. pseudo-orientale* obtained from Sivas in Turkey was divided into phenolic and non-phenolic portions from which the alkaloids were separated by column chromatography. The major alkaloid from the phenolic portion was identified as the morphinandienone, salutaridine (4) by comparison of its UV, IR, PMR, MS and TLC properties with an authentic sample, while the non-phenolic portion yielded macrantaline, a novel alkaloid, as the major alkaloid. The elemental analysis of macrantaline indicated an empirical formula of $C_{22}H_{17}NO_6$ but the electron-impact MS (EIMS) showed a peak of only 0.06% relative abundance for the expected $M^{+\cdot}$ at *m/e* 401. The very low intensity of the $M^{+\cdot}$, the presence of a base peak at *m/e* 220 and a peak at *m/e* 205 was consistent with the structure of a 1-benzyltetrahydroisoquinoline alkaloid [36, 37] with *N*-Me, MeO and methylenedioxy substituents in the AB rings. Confirmation of the MW was obtained from a field desorption MS (FDMS) which showed peaks at *m/e* 402 ($M^{+\cdot}$ + 1; 9%) and *m/e* 401 ($M^{+\cdot}$; 17%). In addition to the base peak at *m/e* 220 another prominent peak at *m/e* 181 (38%) could be attributed to the substituted benzyl portion of macrantaline. The methylenedioxy and *N*-Me substituents were also indicated by the presence of a two-proton singlet appearing at δ 5.89 and a 3-proton singlet at δ 2.19 in the PMR spectrum. Three methoxyl groups were also present as evidenced by 3 singlets, each for 3 protons, appearing at δ 4.15, 3.91 and 3.87. A one proton singlet which appeared at δ 6.31 would be consistent with an unsubstituted A-ring proton while the remaining aromatic signals accounted for two adjacent protons which appeared as an AB quartet at δ 6.97. The PMR spectrum was also consistent with a 1-benzyltetrahydroisoquinoline structure, since the H-1 proton was indicated by a one-proton quartet at δ 3.85 and the methylene and B ring protons could be accounted for by a 6-proton multiplet which occurred between δ 2.45–3.45. The MS and PMR evidence suggested therefore that ring C contained two OMe groups and one other substituent. The possibility that this was a hydroxymethylene was indicated by a two-proton AB quartet which appeared in the PMR spectrum at δ 4.45 and 4.89 and also by the presence of OH absorption in the IR spectrum at 3150 cm^{-1}. Further evidence for the hydroxymethylene substituent of macrantaline was obtained from the PMR spectrum of the mono-acetyl derivative which was generally very similar except for the presence of a two-proton singlet at δ 5.29 instead of the AB quartet at δ 4.45 and 4.89. By analogy with known alkaloids and because of biosynthetic consideration, a plausible structure for macrantaline as 1-(2′-hydroxymethylene-3′,4′-dimethoxybenzyl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (5) can be postulated. Confirmation of this proposal was obtained by comparison of the Pd/C hydrogenation product of acetyl macrantaline with 1-(2′-methyl-3′,4′-dimethoxy-benzyl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (6) prepared from (−)-α-narcotine (7). $LiAlH_4$ reduction of (−)-α-narcotine [38–40] yielded narcotinediol (8) and Pd/C hydrogenation of the diacetylated product yielded compound 6 [39] which proved to be identical in its TLC behaviour, UV and PMR spectra with the product obtained from macrantaline. The CD spectrum of macrantaline exhibited positive Cotton effects at 287, 232 and 222 nm. It has been observed previously that the CD curves of narcotine-diols (8) do not fit the general pattern, possibly because of the extra OMe at C-8 [41], and hence it could be misleading to relate the observed Cotton effects for macrantaline to those of other 1-benzyl tetrahydroisoquinolines [42–44]. However, the fact that 1-(2′-methyl-3′,4′-dimethoxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline prepared either from (−)-α-narcotine or from macrantaline had the same CD spectrum, established that macrantaline possesses the 1S absolute configuration.

A novel minor alkaloid, isolated from the phenolic fraction, has been named macrantoridine. Its PMR spectrum was very similar to that of macrantaline but with 3 distinct differences, *viz.* an additional one proton signal, which was exchangeable with D_2O, appeared at δ 11.25, indicating a OH function, the AB quartet at δ 11.25 and 4.45 was absent showing that the hydroxymethylene was not present and the two proton AB quartet for H-5′ and 6′ was replaced by a 2 proton singlet. Signals which could account for the presence of one N-Me group, 3 OMe groups and an aromatic H with no coupling were observed. EIMS revealed a base peak at *m/e* 220 but with no apparent $M^{+\cdot}$ suggesting the 1-benzyl tetrahydroisoquinoline nature of the alkaloid. FDMS established the $M^{+\cdot}$ by the presence of a peak at *m/e* 415. The PMR and MS data indicated therefore, that macrantoridine possibly possessed an identically substituted AB ring system to that of macrantaline and than an additional 14 amu were present in a C ring substituent. The presence of an OH group was further substantiated by the broad absorption at 3460 cm^{-1} in the IR spectrum, but its non-phenolic nature was established by the absence of any bathochromic shift in the UV spectrum when alkali was present.

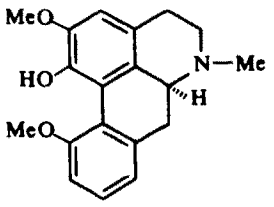
The possibility that macrantoridine was the Me ester of macrantaline was discounted by the absence of a signal in the PMR spectrum for a Ar—CH_2O— moiety and also by the presence of an OH group which was most likely attached to ring C. The possibility that the additional 14 amu in macrantoridine could be accounted for by the presence of carboxylic group instead of the hydroxymethylene, thus accounting for the alkaloid's presence in the phenolic fraction, was at first discounted since the IR spectrum did not show carbonyl absorption in the region expected for an aromatic carboxylic acid. However, a study of Dreiding models indicated that, if a carboxyl substituent were present at the 2-'position, then its proximity to the tertiary N would most likely result in the presence of a strong intramolecular H-bond. It appeared possible that the absorption band at 1660 cm^{-1} observed in the IR spectrum of macrantoridine might possibly be attributed to the carbonyl of a carboxylic acid which is strongly H bonded [45]. Confirmation that this was indeed the case was obtained by the addition of MeI to macrantoridine since the product proved to have an IR spectrum which showed the presence of a strong carbonyl absorption peak at 1720 cm^{-1}. Chemical confirmation for the structure of macrantoridine as **9** was obtained by $LiAlH_4$ reduction since the product proved to have identical R_f values, in 3 TLC systems, and to have an identical PMR spectrum with natural macrantaline (**5**). The CD spectrum of macrantoridine has Cotton effects of opposite sign to those in the spectrum of macrantaline at 215 and 294 nm and it is tempting to speculate that these two alkaloids may well differ in their stereochemistry at C-1. However, as pointed out above, it can be misleading to make such interpretations, not least for macrantoridine because the proximity of the 2'-carboxyl group to the tertiary N could well result in a different conformation from that of macrantaline. At present, therefore, the stereochemistry of macrantoridine must not be regarded as being established.

The revised taxonomic position of section Oxytona (Macrantha) [12] and the related chemical investigations [12, 21] indicates that *P. bracteatum*, *P. orientale* and *P. pseudo-orientale* are not as varied in their alkaloid content as suggested from the literature. In fact, it appears that the alkaloids isolated from a number of different samples are remarkably consistent in the major alkaloids present, *viz.* thebaine (**1**), oripavine (**2**) and isothebaine (**3**) respectively. The finding of salutaridine (**4**) and the new alkaloid macrantaline (**5**) as major alkaloids in a Turkish sample of *P. pseudo-orientale* is a clear indication therefore that the picture is not as simple as proposed [12, 21] and that different chemical strains of *P. pseudo-orientale* do exist. The samples of these 3 species which appeared to be so uniform in their alkaloid content were mainly collected in Iran and of the 10 samples of *P. pseudo-orientale* investigated, 8 were Iranian and only two were Turkish. In addition to the plant material reported in the present paper, it has been shown that another chemical strain of Turkish *P. pseudo-orientale* exists in which orientalidine (**12**) and isothebaine (**3**) are major alkaloids [34, 35, 46]. Furthermore there is good evidence to suggest that different chemical strains of the other two species exist since Turkish samples of *P. bracteatum* have salutaridine (**4**) as a major alkaloid, in addition to thebaine, and thebaine or isothebaine as well as oripavine are the major alkaloids in some Turkish samples of *P. orientale* [46].

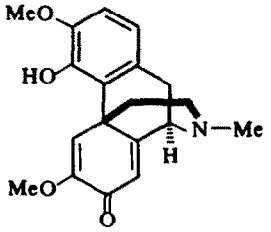
The new alkaloids macrantaline (**5**) and macrantoridine (**9**) are interesting from a biosynthetic viewpoint since they contain the same A ring substitution pattern as mecambridine (**10**), aryapavine (**11**) and orientalidine (**12**) alkaloids known to be present in Iranian *P. pseudo-orientale* [21]. Macrantaline also contains two OMe and hydroxymethylene substituents in ring C and its close similarity to mecambridine suggests that macrantaline is a precursor of the latter. Presumably macrantaline accumulates in this particular sample of Turkish *P. pseudo-*



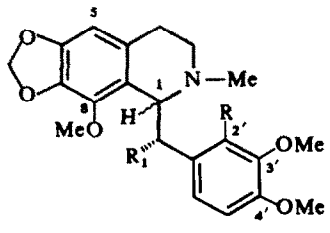
1 R = Me
2 R = H



3



4



5 R = CH_2OH, R_1 = H, C-1Hα
6 R = Me, R_1 = H, C-1Hα
8 R = CH_2OH, R_1 = OH, C-1Hα
9 R = COOH, R_1 = H

orientale because of the lack of enzyme systems responsible for its cyclisation to the tetrahydroprotoberberine alkaloid, mecambridine. Although narcotine (7) has not been isolated from section Oxytona, its close relationship to macrantoridine (9) is an indication that the latter may well serve as a precursor of narcotine by oxidation of the benzylic methylene and lactone formation. Salutaridine (4) is a known biosynthetic precursor of thebaine (1) and again it would appear that this particular sample of *P. pseudo-orientale* lacks the enzyme system responsible for the conversion of the morphinan–dienone to the morphinane-type alkaloid.

EXPERIMENTAL

Wild plants growing at an altitude of 1750–2000 m at Yildizdag, near Sivas, Turkey, were collected by Mr. Helim Sariyar in June 1975 and the identity as *P. pseudo-orientale* (Fedde) Medw. was confirmed by Dr. P. Goldblatt of the Missouri Botanical Garden, U.S.A. A voucher specimen is retained in the Herbarium of the Faculty of Pharmacy, Istanbul. IR were determined in KBr or in Nujol and the 60 MHz PMR were obtained using $CDCl_3$ solns with TMS as internal reference. EIMS were determined with a high resolution spectrometer operating at 70 eV and at 190°. TLC was carried out with Si gel G in systems: (A) C_6H_6–Me_2CO–MeOH (7:2:1); (B) C_6H_6–EtOH–18 M NH_4OH (80:20:0.3); (C) C_6H_6–EtOAc–MeOH (1:1:1) and with Al_2O_3 G (Merck) in systems: (D) C_6H_6–$CHCl_3$–Me_2CO (1:1:0.2); (E) *n*-C_7H_{16}–$CHCl_3$–Et_2O (4:5:1); (F) C_6H_6–$CHCl_3$–Me_2CO (2:1:0.2). The hR_f values obtained were: macrantaline, (A) 72; (B) 74; (C) 72; (D) 49; (E) 50; (F) 41; salutaridine, (A) 26; (B) 36; (C) 41; (D) 15; (E) 17; (F) 7; macrantoridine, (A) 6; (B) 8; (C) 19. Detection was either by the pale orange colour produced by Dragendorff's reagent or by 60% H_2SO_4 followed by heat; macrantaline turned yellow, then brown and finally violet, salutaridine turned orange and then brown and macrantoridine turned red-violet.

Isolation and characterisation of alkaloids. Total dried aerial parts, at the capsule stage (1.2 kg) were extracted with MeOH and the isolation procedure, as previously described [35], yielded 7.08 g (0.59%) of total crude alkaloid. The total alkaloid was dissolved in $CHCl_3$ (800 ml) and shaken with successive portions of 5% NaOH (8 × 100 ml). The $CHCl_3$ soln was washed, dried and concd to dryness *in vacuo* to yield 3.85 g (0.32%) of non-phenolic alkaloids. The combined 5% NaOH extracts were acidified with 25% H_2SO_4, re-basified with 25% NH_4OH and extracted with successive portions of $CHCl_3$ (4 × 100 ml). The combined $CHCl_3$ extracts were washed, dried and concd to dryness *in vacuo* to yield 2.55 g (0.21%) of phenolic alkaloids. The non-phenolic and phenolic fractions were each chromatographed in an identical manner on columns of neutral Al_2O_3 eluting with *n*-C_7H_{16}–Et_2O–$CHCl_3$ (5:5:1) followed by *n*-C_7H_{16}–Et_2O–$CHCl_3$ (1:6:3:) and then $CHCl_3$. Fractions were combined in the basis of their TLC similarities and evapd to dryness to yield the following major alkaloids, crystallised from the appropriate solvents: phenolic fraction, salutaridine 1.5 g (0.12%), macrantoridine, 48 mg (0.004%); non-phenolic fraction, macrantaline, 0.92 g (0.08%).

Salutaridine (4) crystallised from MeOH, mp 200°, identical TLC, UV, IR, PMR and MS properties to authentic alkaloid.

Macrantaline (5) [1-(2'-hydroxymethylene-3',4'-dimethoxybenzyl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline] crystallised from MeOH, mp 140–141°; UV λ_{max}^{MeOH} 385, 238 (*sh*), (log ε 3.64, 4.04), λ_{min}^{MeOH} 256 nm (log ε 2.95; IR (KBr) ν_{max} 3150 (intra-molecular H-bonded OH), 2960, 2900, 2860, 1630 (CH=CH), 1500, 1430, 1280, 1050 cm^{-1}; EIMS, *m/e* 401 ($M^{+\cdot}$; 0.06%), 400 ($M^{+\cdot}$ − 1; 0.17%), 220 (100%), 205 (12.5%); FDMS (MeOH), *m/e* 402 ($M^{+\cdot}$ + 1; 9%), 401 ($M^{+\cdot}$; 17%), 220 (100%), 181 (38%). PMR, δ 6.97 (2H, *AB q*, J_0 = 7 Hz; H-5', H-6'), 6.31 (1H, *s*; H-5), 5.89 (2H, *s*; *ar*—O—CH_2—O—*ar*), 4.89 and 4.45 (2H, *AB q*, *J* = 10 Hz; *ar*—CH_2O—), 4.15 (3H, *s*; C-8 MeO), 3.91 and 3.87 (2 × 3H, *s*; 2 × MeO), 3.85 (1H, *q*, partly hidden; H-1), 2.45–3.45 (6H, *m*; 2 × H-3, 2 × H-4, *ar*-CH_2), 2.19 (3H, *s*; N Me). CD (MeOH) Δε 287 nm (+0.80), 244 nm (−5.84), 232 nm (+3.22), 222 nm (−1.17), 210 nm (+17.52). Elemental analysis, found C, 65.99%; H, 6.72%; N, 3.54%; $C_{22}H_{27}NO_6$ calculated for C, 65.84%; H, 6.73%, N, 3.49%.

Acetylmacrantaline. Crystallised from Et_2O, mp 105° IR (KBr) ν_{max} 1735 cm^{-1} (CO); PMR, δ 6.96 (2H, *AB q*, J_0 = 7 Hz; H-5', H-6'), 6.32 (1H, *s*; H-5), 5.87 (2H, *s*;—O—CH_2O—*ar*), 5.29 (2H, *s*; *ar*—CH_2O), 3.92 (2H, *s*; C-8 MeO), 3.85 (6H, *s*; 2 × MeO, 2.30 (3H, *s*; NMe), 2.04 (3H, *s*; MeCO).

1-(2'-Methyl-3',4'-dimethoxybenzyl)-2-methyl-6,7-methylenedioxy-8-methoxy 1,2,3,4-tetrahydroisoquinoline (6). *(a) From (−)-α-narcotine.* (−)-α-Narcotine (1 g) dissolved in THF (250 ml) was added slowly to a suspension of $LiAH_4$ (2 g, 50 ml THF) and the mixture refluxed for 5 hr. More $LiAH_4$ (1.5 g) was added and refluxing continued for a further 15 hr [40]. The reaction was stopped by the addition of moist EtOAc, filtered, shaken first with dil. NH_4OH, then with H_2O, dried and concd *in vacuo* to an amorphous solid (0.27 g). Preparative-TLC of an aliquot (100 mg) using Si gel G and system G, EtOAc–*iso* PrOH–18 M NH_4OH (100:2:1) yielded α-narcotine diol (32 mg) (8), δ 7.41, 7.03 (2H, *AB q*, J_0 = 10 Hz; H-5', H-6'), 6.46 (1H, *s*; H-5), 5.97 (2H, *s*; *ar*—O—CH_2—O—*ar*), 4.93, 4.55 (2H, *AB q*, *J* = 12 *HZ*; *ar*—CH_2O), 4.13 (3H, *s*; MeO), 3.9 (6H, *s*; 2 × MeO), 2.02 (3H, *s*; NMe). Narcotine-diol (27 mg) was dissolved in C_5H_5N (0.5 ml), Ac_2O (0.1 ml) added and the mixture allowed to stand 18 hr. Evaporation to dryness *in vacuo* yielded the amorphous diacetate, hR_f (G) 61, which was dissolved in EtOH (120 ml) and hydrogenated with Pd/C (50 mg), for 10 hr at 1.4 kg/cm^2 and 95° [40]. The reaction mixture was filtered and concd to dryness yielding an amorphous residue (12 mg) which showed the presence of only one Dragendorff + ve spot on TLC, hR_f (G) 43; UV λ_{max}^{MeOH} 213, 233 (*sh*), 282 nm; PMR, δ 6.93, 6.70 (2H, *AB q*, J_0 6.6 Hz; H-5', H-6'), 6.32 (1H, *s*; H-5), 5.87 (2H, *s*; *ar*—O—CH_2—O—*ar*), 3.88, 3.82, 3.79 (3 × 3H, *s*; 3 × MeO), 2.3 and 2.32 (2 × 3H, *s*; NMe and *ar* Me). CD (MeOH) Δε 286 nm (+0.85), 243 nm (−2.50), 218 nm (+2.80). (b) *From macrantaline.* Acetyl macrantaline (0.15 g) was dissolved in EtOH (120 ml) and hydrogenated with Pd/C (50 mg) for 10 hr at 1.4 kg/cm^2 and 95°. The reaction mixture was filtered, concd to dryness *in vacuo* to yield an amorphous solid (83 mg) which showed the presence of only one Dragendorff + ve spot on TLC, hR_f (G) 43. The TLC, PMR and CD properties of this product were identical with those of 1-(2'-methyl-3',4'-dimethoxybenzyl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (6) prepared from narcotine.

Macrantoridine (9) crystallised from $CHCl_3$–*n*-C_7H_{16}, mp 114°; UV λ_{max}^{MeOH} 236, 284 nm (log ε 3.91, 3.45), λ_{max}^{MeOH} 258 nm (log ε 2.96), no bathochromic shift with NaOH; IR (KBr) ν_{max} 3460 (broad, OH). 1660 (broad, intramolecularly bonded (COOH), 1625 (CH=CH), 1600, 1485, 1280, 1042 cm^{-1}; EIMS (MeOH), *m/e* 220 (100%), 205 (10%), 147 (2%), $M^{+\cdot}$ absent; FDMS, *m/e* 416 ($M^{+\cdot}$ + 1; 100%), 415 ($M^{+\cdot}$; 3%), 220 (92%), 195 (8%). PMR δ 11.25 (1H, *s*, exchanges with D_2O; OH), 6.83 (2H, *s*: H-5', H-6'), 6.35 (1H, *s*; H-5), 5.95 (2H, *s*; *ar*—O—CH_2—O—*ar*), 4.19, 3.97, 3.87 (3 × 3H, *s*; 3 × MeO) *ca* 4.1 (1H, *m*, partly hidden; H-1), 2.5–3.5 (6H, *m*; 2 × H-3, 2 × H-4, *ar*—CH_2), 2.30 (3H, *s*; NMe). CD (MeOH) Δε 294 nm (−0.81), 242 nm (−10.0), 215 nm (−47.6), 205 (+). *Methiodide.* MeI added to macrantoride (2 mg) in $CHCl_3$ and allowed to stand for 2 days, evaporation of the solvent *in vacuo* gave an amorphous residue which could not be induced to crystallise. TLC, System C, indicated the presence of unchanged macrantoridine, hR_f 19 and a major polar Dragendorff + ve compound at hR_f 8. UV (MeOH) of the total product was identical to macrantoridine but the IR spectra ($CHCl_3$) showed the presence of an intense peak at 1720 cm^{-1} (CO). *Reduction.* $LiAH_4$ (5 mg) was added to macrantoridine (20 mg) in THF (10 ml) and refluxed for 16 hr. The reaction was stopped by the addition of moist EtOAc, filtered, then shaken successively with dil. NH_4OH and H_2O, dried and concd to dryness *in vacuo* to an

amorphous solid (4 mg). TLC indicated the presence of only one Dragendorff + ve spot which had indentical hR_f values in systems A, B and C to macrantaline. The UV, EIMS and PMR spectrum of the reduction product were identical with those of macrantaline (**5**).

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REFERENCES

1. Fairbairn, J. W. and Hakim, F. (1973) *J. Pharm. Pharmacol.* **25**, 353.
2. Garard, J. P., Krauz, F. and Rull, T. (1965) *Bull. Soc. Chim. Fr.* 486.
3. Barber, R. B. and Rapoport H. (1976) *J. Med. Chem.* **19**, 1175.
4. Neubauer, D. and Mothes, K. (1963) *Planta Med.* **11**, 387.
5. Böhm, H. (1965) *Planta Med.* **13**, 215.
6. Sharghi, N. and Lalezari, I. (1967) *Nature* **213**, 1244.
7. Smith, D. W., Beasley, Sr., T. H., Charles, R. L. and Zeigler, H. W. (1973) *J. Pharm. Sci.* **62**, 1691.
8. Lalezari, I., Shafiee A. and Nasseri-Nouri, P. (1973) *J. Pharm. Sci.* **62**, 1718.
9. Lalezari, I. Nasseri-Nouri, P. and Asgharian, R. (1974) *J. Pharm. Sci.* **63**, 1331.
10. Böhm, H. (1974), *Pharmazie* **29**, 70.
11. Kuppers, F.J.E.M., Salemink, C.A., Bastart, M. and Paris, M. (1976) *Phytochemistry* **15**, 444.
12. Goldblatt, P. (1974) *Ann. Missouri Bot. Gard.* **61**, 264.
13. Preininger, V. and Santavy, F. (1970) *Pharmazie* **25**, 356.
14. Kiselev, V. V. and Konovalova, R. A. (1948) *J. Gen. Chem. (USSR)* **18**, 142.
15. Phillipson J. D., Handa, S. S. and El-Dabbas, S. W. (1976) *Phytochemistry* **16**, 1297.
16. Heydenreich, K. and Pfeifer, S. (1966) *Pharmazie* **21**, 121.
17. Heydenreich, K. and Pfeifer, S. (1967) *Pharmazie* **22**, 124.
18. Heydenreich, K. and Pfeifer, S. (1965) *Pharmazie* **20**, 521.
19. Guggisberg, A., Hesse, M., Schmid, H., Böhm, H., Rönsch, H. and Mothes, K. (1967) *Helv. Chim. Acta* **50**, 621.
20. Shamma, M., Weiss, J. A., Pfeifer, S. and Dohnert, H. (1968) *Chem. Commun.* **212**.
21. Shafiee, A., Lalezari, I., Nasseri-Nouri, P. and Asgharian, R. (1975) *J. Pharm. Sci.* **64**, 1570.
22. Pfeifer, S. (1962) Pharmazie **17**, 298.
23. Konovalova, R. A., Yunusov, S. Yu. and Orechoff, A. P. (1935) *Chem. Ber.* **68B**, 2158.
24. Neubauer, D. and Mothes, K. (1961) *Planta Med.* **9**, 466.
25. Dawson, R. F. and James, C. (1956) *Lloydia* **19**, 59.
26. Kleinschmidt, G. (1961) *Arch. Pharm.* **294**, 254.
27. Preininger, V. and Santavy, F. (1966) *Acta Univ. Palacki Olomuc., Fac. Med.* **43**, 5.
28. Delenk-Heydenreich, K. and Pfeifer, S. (1969) *Pharmazie* **24**, 635.
29. Battersby, A. R. and Brown, T. H. (1966) *Chem. Commun.* 170.
30. Preininger, V., Simanek, V. and Santavy, F. (1969) *Tetrahedron Letters* 2109.
31. Preininger, V., Cross, A. D., Murphy, J. W., Santavy, F. and Toube, T. (1969) *Coll. Czech. Chem. Commun.* **34** 875.
32. Preininger, V., Hruban, L., Simanek, V. and Santavy, F. (1970) *Coll. Czech. Chem. Commun.* **35**, 124.
33. Battersby, A. R., Brown, R. T., Clements, J. H. and Iverach, G. C (1965) *Chem. Commun.* 230
34. Sariyar, G. (1975) Dissertation, University of Istanbul, Faculty of Pharmacy.
35. Sariyar, G. (1976) *J. Fac. Pharm. Istanbul* **12**, 171.
36. Ohashi, M., Wilson, J. M., Budzikiewicz, H., Shamma, M., Slusarchyk, W. A. and Djerassi, C. (1963) *J. Am. Chem. Soc.* **85**, 2807.
37. Tomita, M., Furukawa, H., Kikuchi, T., Kato, A. and Ibuka, T. (1966) *Chem. Pharm. Bull.* **14**, 232.
38. Mirza, R. and Robinson, R. (1950) *Nature* **166**, 271.
39. Ohata, M., Tani, H., Morozumi, S. and Kodaira, S. (1966) *Chem. Pharm. Bull.* **12**, 1080.
40. Battersby, A. R. and Spenser, H. (1965) *J. Chem. Soc.* 1087.
41. Snatzke, G., Wollenberg, G., Hrbek, J., Santavy, F., Blaha, K., Klyne, W. and Swan, R. J. (1969) *Tetrahedron* **25**, 5059.
42. Snatzke, G. and Wollenberg, G. (1966) *J. Chem. Soc.* 1681.
43. Craig, J. C., Martin-Smith, M., Ray, C. K. and Stenlake J. B. (1966) *Tetrahedron* **22**, 1335.
44. Grethe, G., Lee, H. L., Uskovic, M. R. and Brossi, A. (1970) *Helv. Chim. Acta* **53**, 874.
45. Brooks, C. J. W., Eglington, G. and Morman, J. F. (1961) *J. Chem. Soc.* 661.
46. Baytop, T. and Sariyar, G. (1977). *J. Fac. Pharm. Istanbul* **13**, in press.