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ALKALOIDS OF THE PAPAVERACEAE—II[1]

COULTEROPINE AND ROMNEINE—NEW ALKALOIDS FROM *ROMNEYA COULTERI*

F. R. STERMITZ, L. CHEN and J. I. WHITE[2]
Department of Chemistry, Utah State University, Logan, Utah

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Abstract—The alkaloid content of *Romneya coulteri* var. *trichocalyx* (Eastwood) Jepson has been investigated. Protopine is the major alkaloid of the species, followed in concentration by two new alkaloids, coulteropine and romneine. The structures of these have been shown to be 1-methoxy-protopine and 6,7-methylenedioxy-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline, respectively.

INTRODUCTION

FEW, if any, plant species can match the *Papaveraceae* in alkaloid content per species. No member of this family has yet been found devoid of alkaloids, and a number of the genera have been studied extensively, particularly the Papaver species. There are, however, a number of genera whose members have as yet not been investigated or have been investigated only cursorily. A systematic survey of some of the rarer genera was therefore begun with the two-fold-goal of (1) seeking new medicinals and (2) searching for new or confirmatory biosynthetic relationships among the various alkaloids. The first paper in this series described[1] the assignment of the basic structure of the argemonine group from *Argemone munita* Dur. & Hilg. subsp. *rotundata* (Rydb.) G. B. Ownb. and the present paper reports the isolation and characterisation of three alkaloids from *Romneya coulteri* var. *trichocalyx* (Eastwood) Jepson. Subsequent papers will deal with additional alkaloids from these two species as well as alkaloids from other *Argemone, Arctomecon and Meconella* species.

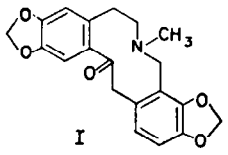
Romneya coulteri Harv., the Matilija poppy, is native to the southern California coastal region and one variety, *R. coulteri* var. *trichocalyx* (Eastw.) Jepson, which was used in the present study, is recognized.[3] The material was from a plot maintained at the Botanical Garden of the University of California, Berkeley, California, and a voucher sample has been deposited in the University of California Herbarium under No. 12,00169.[4] The plant grows into large clumps by extensive root propagation and supports 3–7 stems on a woody base. Relatively large amounts of stems and roots are therefore available. The crude total basic alkaloid fraction represented about 1% of the dried whole plant and showed seven alkaloids on TLC. At least an additional two are present in the non-basic fraction.

[1] For paper I see F. R. Stermitz, S. Y. Lwo and G. Kallos, *J. Amer. Chem. Soc.* **85**, 1551 (1963).
[2] N.S.F. Cooperative Fellow 1963–1964.
[3] L. Abrams, *Illustrated Flora of the Pacific States* Vol. II; p. 226. Stanford University Press (1944).
[4] We are indebted to Dr. Helen-Mar Beard, Senior Botanist, University of California Botanical Garden for assistance in obtaining plant material and preparing the voucher sample.

RESULTS AND DISCUSSION

Protopine

Recrystallization from benzene of the total crude basic alkaloid mixture yielded protopine (I), m.p. 204–205°. The assignment was made on the basis of identical R_f value on TLC, m.p., IR and NMR spectra when compared with an authentic sample. Protopine represented about 30–40% of the total basic alkaloid fraction.

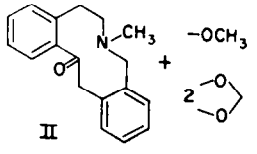


I

Coulteropine

Methanol recrystallization of the benzene soluble residue yielded a white, crystalline, optically inactive compound, m.p. 167–168°, having an analysis corresponding to $C_{21}H_{21}O_6N$. It formed a crystalline hydrochloride, m.p. 149–150°, and methiodide, m.p. 198–200°. Analyses of both derivatives confirmed the $C_{21}H_{21}O_6N$ formula for the free base, which was given the name coulteropine.

The UV spectrum in ethanol showed a maximum at 286 mμ ($\varepsilon = 7100$) and a minimum at 265 mμ. Addition of acid caused little change in the maximum but deepened the minimum to 20% of the maximum height and shifted it to 250 mμ. The chief identifying feature of the IR spectrum (Fig. 1) was the presence of a medium band at 1675 cm^{-1}. The UV spectrum and acid shift are characteristic of protopine-type compounds as are the position and intensity of the 1675 cm^{-1} carbonyl band.[5] Confirmation of these data and assignment of part structure II could be made on the basis of the NMR spectrum given in Fig. 2.



II

The NMR assignments for the methyl, methoxyl, and methylenedioxy group peaks were straightforward and the presence of the N-methyl and O-methyl groups was confirmed by chemical group analysis. In accordance with the literature[6] assignment for protopine, the peak at 3·40 ppm (from tetramethylsilane) in coulteropine would represent the two methylene protons between the nitrogen and aromatic ring, while the broadened absorption at 3·80 ppm should be due to the two methylene protons adjoining the carbonyl group. The correctness of these assignments was proven by equilibrating coulteropine and protopine with base in dioxane-D_2O. This caused disappearance of the 3·80 ppm peak in coulteropine and the 3·76 ppm peak in protopine. The broadness of the absorption in coulteropine as compared to the sharp

[5] F. A. L. Anet, A. S. Bailey and R. Robinson, *Chem. & Ind.* 944 (1953); E. H. Mottus, H. Schwarz and L. Marion, *Canad. J. Chem.* **31**, 1144 (1953); F. A. L. Anet and L. Marion, *Ibid.* **32**, 452 (1954).

[6] N. S. Bhacca, L. F. Johnson and J. N. Shoolery, *NMR Spectra Catalog*, Vol I; Spectrum No. 339. Varian Associates (1962).

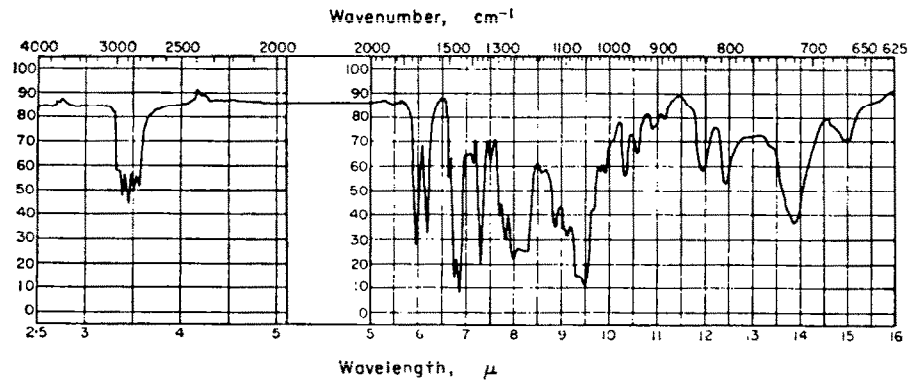


FIG. 1. IR Spectrum of Coulteropine.

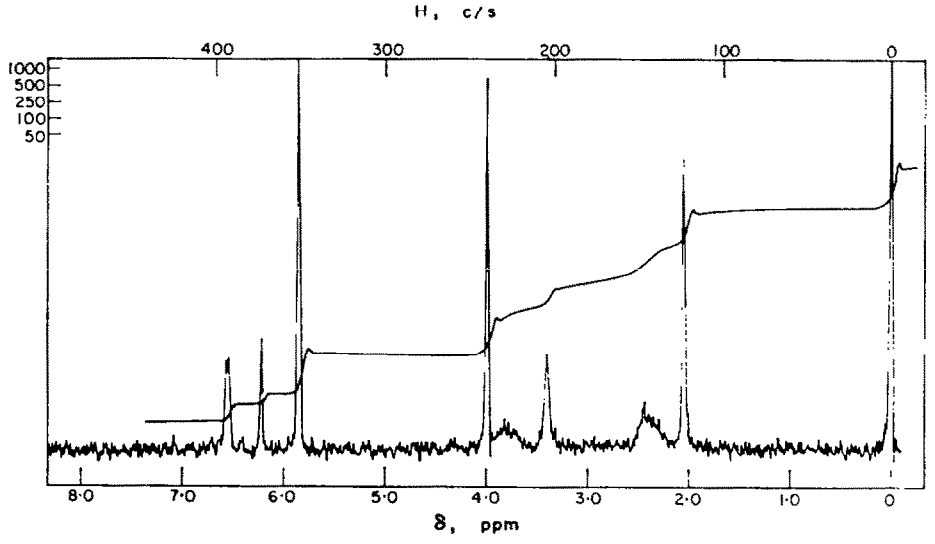


FIG. 2. NMR Spectrum of Coulteropine.

singlet observed with protopine is unexpected. However, cryptopine (which is identical with protopine except that two methoxyl groups are present in ring A instead of the methylenedioxy function) shows a broadening of this peak intermediate to that observed with coulteropine.

Both protopine and cryptopine show well defined, symmetrical multiplets arising from the A_2B_2 system of the protons on the two carbons joining the nitrogen to ring A. However, coulteropine shows an ill-defined broad peak (2·4 ppm) in this region and hence the conformation in the central ring of coulteropine must be different from that in protopine. This must also account for the shift in carbonyl IR frequency and the broadening of the 3·80 ppm peak mentioned above. The three aromatic proton peaks correlate with the required number of substituents. Specific assignments for these peaks will be discussed following interpretation of the mass spectrum.

Confirmation of the mol. wt. and the basic structure of coulteropine as well as assistance in placement of the methoxyl and methylenedioxy groups was gained from analysis of the mass spectrum of protopine and that of coulteropine[7] (Fig. 3). The

mass spectra of protopine and three other protopine-type alkaloids were recently published[8] and an interpretation (assisted by deuteration studies) given. Our spectra and interpretations correlate well with those reported.[8] The mass spectrum thus allows the assignment of one methylenedioxy group each to the A and C rings in II and the placement of the methoxyl group in ring A.

Placement of substituents in rings A and C was made possible by comparison of the aromatic proton absorptions for protopine and coulteropine. Since the methoxyl in coulteropine can be assigned to ring A, coulteropine might be expected to exhibit an almost identical pattern to protopine for the aromatic protons in ring C if the methylenedioxy placement in ring C was identical in the two compounds. Indeed,

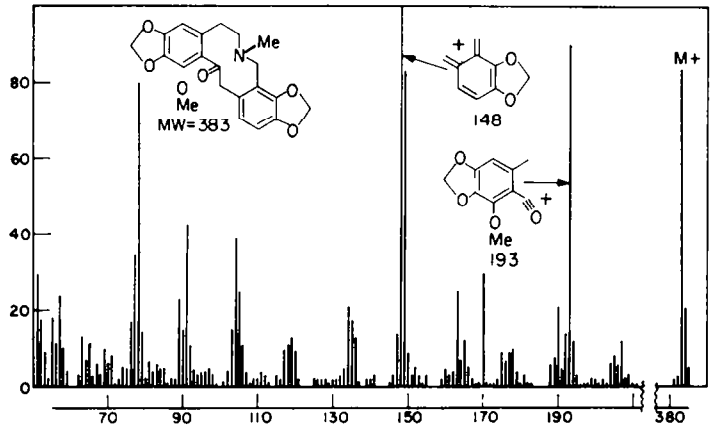


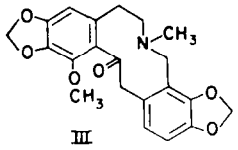
FIG. 3. Mass Spectrum of Coulteropine.

two protons in protopine absorb at 6·62 ppm and 6·65 ppm (with a third proton overlaying the 6·65 ppm peak) while coulteropine shows protons at 6·56 ppm and 6·59 ppm. The AB splitting of the two *ortho* protons in ring C cannot be observed in the known protopine, nor in coulteropine, although some other alkaloids in this series (allocryptopine and muramine, for example) do show this splitting.

The final problem in the structure of coulteropine involved placement of the methoxyl and methylenedioxy groupings in ring A. The most logical placement for comparison with known alkaloids would put the methylenedioxy in positions 2 and 3 and the methoxyl at 1. The least shielded hydrogen in ring A of protopine would be expected to be that in position 1 and this assignment has been previously made[6] for the 6·90 ppm peak. This peak is missing in coulteropine. Substitution of an additional methoxyl in ring A would also be expected to displace the chemical shift of the remaining hydrogen 0·23 to 0·40 ppm upfield (for *para*-methoxyl).[9] The coulteropine peak at 6·22, thus, should represent the 6·62 or 6·65 peak of protopine moved upfield by methoxyl substitution. The observed conformation changes in the coulteropine B ring (as evidenced by IR and NMR spectra) very likely arise from the steric interactions caused by methoxyl at position 1. Substitution of a methoxyl at position 4 would lead to little conformation change as evidenced by models.

[7] We are indebted to Drs. H. Budzikiewicz and C. Djerassi, Stanford University, for these spectra.
[8] L. Dolejs, V. Hanus and J. Slavik, *Coll. Czech. Chem. Comm.* **29**, 2479 (1964).
[9] P. L. Corio and B. P. Daily, *J. Amer. Chem. Soc.* **78**, 3043 (1956); A. A. Bothner-By and R. E. Glick *J. Chem. Phys.* **26**, 1651 (1957).

Thus, coulteropine must have structure III,[10] although other less likely placements of the methylenedioxy grouping on ring C could not be completely ruled out on the basis of our data quoted above. Coulteropine is the first reported protopine-type alkaloid having three oxygenated functional groups in the A ring. Such a grouping occurs occasionally in the biogenetically closely related protoberberine and phthalid-isoquinoline alkaloids.

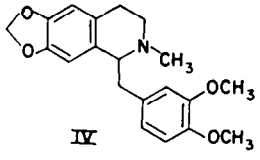


III

Romneine

Evaporation of the methanol solution remaining from coulteropine recrystallization left a brown oil consisting of small amounts of protopine and coulteropine plus a third alkaloid as the major component. This alkaloid was obtained free from other alkaloids by alumina chromatography but remained as an oil. Analysis of the hydrobromide salt (m.p. 224–225°) established the formula $C_{20}H_{23}NO_4 \cdot HBr$ and the corresponding formula for the free base was indicated from the mass spectrum. The UV spectrum of the base, assigned the name romneine, showed λ_{max} 268 mμ, λ_{min} 259 mμ, and exhibited no change on addition of acid or base. The IR spectrum is given in Fig. 4 and the NMR spectrum in Fig. 5. These data, together with the IR spectrum, were interpreted in terms of a benzylisoquinoline structure and the mass spectrum (given in Fig. 6)[11] confirmed this idea.

The placement of the methoxyl and methylenedioxy groupings could not be established absolutely from the spectral data. The total synthesis of (±)-romneine was accomplished by the standard reactions of Fig. 7. The solution IR and NMR spectra of the natural and synthetic compounds proved to be identical, thus establishing structure IV for romneine.



IV

EXPERIMENTAL

All m.ps are uncorrected. Analyses were performed by Galbraith Laboratories, Inc., Nashville, Tennessee. Spectra were taken as follows (spectrometer, solvent): IR-Beckmann Model IR-8, $CHCl_3$; UV-Cary Model 15, EtOH; NMR Varian Model A-60, $CDCl_3$. When organic solutions were dried, Na_2SO_4 was the drying agent. TLC was conducted using silica gel G plates (250 micron) and a developing solvent of 1:1 benzene–MeOH. Visualization was with iodoplatinic acid.

Alkaloid isolation. In a typical extraction, 580 g dried, ground roots was moistened with 400 ml 10% Na_2CO_3aq. 1:1 Butanol–benzene (2 l.) was then added and the mixture shaken vigorously. It was allowed to stand overnight, filtered, and the filter cake washed well with butanol–benzene. The butanol–benzene layer in the filtrate was separated from the aqueous phase and then extracted 3

[10] The structure of coulteropine has been confirmed by X-ray diffraction studies by David R. Harris, Dept. of Applied Statistics and Computer Science, Utah State University. (Unpublished results.)

[11] We are indebted to Dr. A. H. Struck, Perkin-Elmer Corporation, for this spectrum.

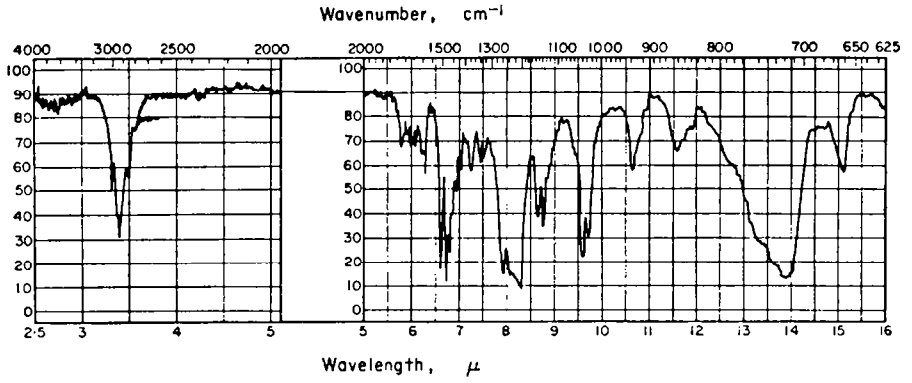


FIG. 4. IR Spectrum of Romneine.

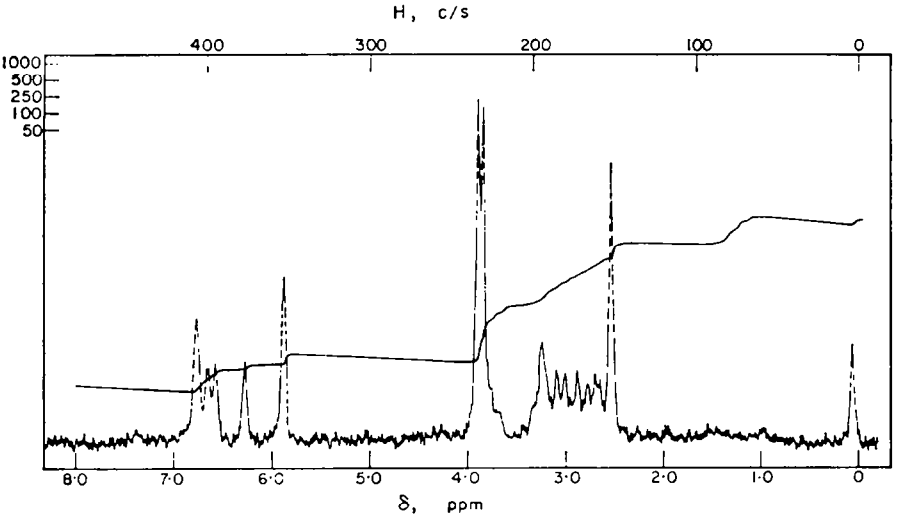


FIG. 5. NMR Spectrum of Romneine.

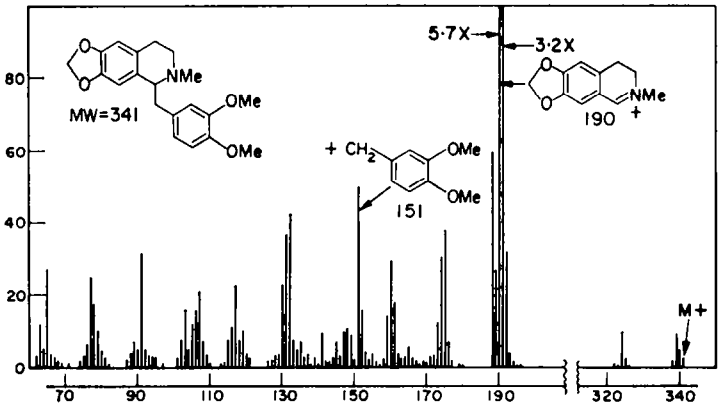


FIG. 6. Mass Spectrum of Romneine.

times with equal volumes of $CHCl_3$. The $CHCl_3$-layer was dried, filtered, and evaporated to dryness to yield 4·5 g crude alkaloid mixture.

Protopine (I). The crude basic alkaloid mixture was triturated with cold benzene and the residue recrystallized from benzene to yield 1·4 g of a white crystalline alkaloid, m.p. 204–205°. The UV, IR and NMR spectra were identical with those of a known sample of protopine as was the TLC R_f value (0·3). Some protopine was also present in the mother liquid and cold benzene extract. On the basis of isolated protopine and TLC on the remaining mixtures, protopine was estimated to represent about 40–50% of the total basic fraction.

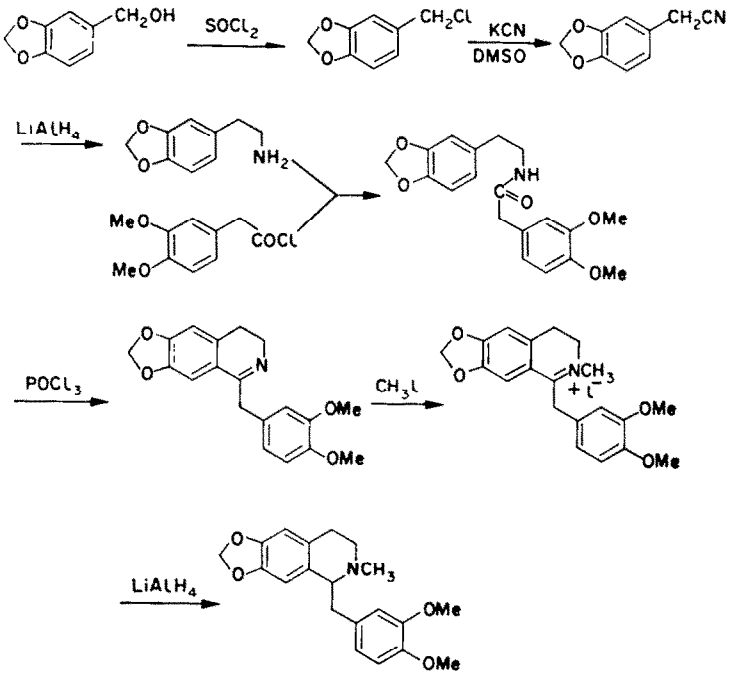


FIG. 7. Total Synthesis of (±)-Romneine.

Coulteropine (III). The mother liquor remaining from the protopine crystallization was evaporated to dryness and the residue recrystallized from MeOH to yield 0·7 g greyish brown crystals, m.p. 156–160°. Repeated recrystallization from benzene yielded white crystals, m.p. 168–170°, and the m.p. did not change on further recrystallization. This alkaloid, given the name coulteropine, represented about 25–30% of the basic fraction based on the isolated material and TLC of the remaining mixtures. The TLC R_f value was 0·8. (Found: C, 65·5; H, 5·30; N, 3·67. $C_{21}H_{21}O_6N$ requires: C, 65·8; H, 5·52; N, 3·65%.)

Coulteropine hydrochloride. m.p. 149–150°. (Found: C, 59·5; H, 5·08; N, 3·15. $C_{21}H_{21}O_6N{\cdot}HCl$ requires: C, 60·00; H, 5·28; N, 3·34%.)

Coulteropine methiodide. m.p. 198–200° from $CHCl_3$–MeOH. (Found: C, 43·6; H, 4·09. $C_{21}H_{21}NO_6{\cdot}CH_3I{\cdot}CHCl_3$ requires: C, 42·9; H, 3·88%.)

Dihydrocoulteropine. A modification of the procedure of Mirza[18] was used. Coulteropine, 0·50 g, was dissolved in 50 ml dry benzene. The solution was added slowly to a suspension of 60 mg LAH in 50 ml ether, and the resultant mixture stirred for 1 hr. It was then treated carefully with 10 ml dil HCl, and the resultant solution brought to pH 5. This was extracted with $CHCl_3$, and the $CHCl_3$-layer dried with Na_2SO_4 and evaporated to leave 0·38 g of a yellow-brown solid, m.p. 169–180°. This was recrystallized several times from benzene–pet. ether to give 0·10 g white crystals, m.p. 193–194°. (Found: C, 65·7; H, 6·10; N, 3·65. $C_{21}H_{23}NO_6$ requires: C, 65·5; H, 5·97; N, 3·63%.)

Romneine (IV). The solution from the cold benzene trituration of the crude alkaloid fraction was

[18] R. Mirza, *Experientia* **8**, 258 (1952).

evaporated to dryness to leave 1·5 g brown residue. This was dissolved in 1:1 benzene–pet. ether and column chromatographed on Woelm Neutral Alumina (Activity grade I) using the same solvent mixture as eluent. Evaporation of the first fractions to be eluted yielded 0·20 g of a brown oil ($[\alpha]_D^{25}$, $CHCl_3$ = −275°) showing only one spot on TLC (R_f = 0·6). Further elutions yielded alkaloid mixtures. Treatment of the brown oil with HBr and recrystallization to a constant m.p. left a white solid hydrobromide salt, m.p. 224–225°. (Found: C, 56·6; H, 5·43; N, 3·63. $C_{20}H_{23}NO_4$·HBr requires: C, 56·9; H, 5·74; N, 3·22%.)

Synthesis of (±)-*Romneine* (Fig. 7). Piperonyl alcohol (10 g) was dissolved in 26 ml ether and 15 ml $SOCl_2$ was added slowly. The solution was stirred an additional 40 min and then evaporated to dryness. The residue was distributed between ether and water, the layers separated and the aqueous layer extracted 3 times with ether. The ether layers were combined, dried, filtered and evaporated. A yellow oil (6·8 g) of crude piperonyl chloride was obtained which showed no OH stretching band in the IR.

The crude piperonyl chloride (6·4 g) was added to a stirred solution of NaCN (2·76 g) in 100 ml dimethylsulfoxide. The solution was stirred for 6 hr at room temp and then partitioned between 50 ml water and 25 ml 1:1 ether–pet. ether. After separation of the layers, the aqueous portion was extracted 4 times with 1:1 ether–pet. ether. The organic layers were combined, dried and evaporated to leave 5·4 g slightly yellow solid piperonyl cyanide, m.p. 37–40° (lit. m.p. 42°).[13] This procedure was similar to that of Friedman and Shechter.[14]

Piperonyl cyanide (3·2 g) was dissolved in 50 ml anhydrous ether and the solution added to a stirred mixture of 1·0 g LAH in 200 ml anhydrous ether. The mixture was heated at reflux for 3·5 hr, cooled, and saturated potassium sodium tartrate solution added. The resultant solution was extracted with portions of ether which were then combined, dried and evaporated to leave 2·5 g brown oil, showing no cyanide bond in the IR.

This crude homopiperonylamine was used without further purification. Homopiperonylamine (1·4 g) was dissolved in a mixture of 20 ml ether and 20 ml 5% KOHaq. To the mixture was added at 0° an equiv. amount 3,4-dimethoxyphenylacetyl chloride (freshly prepared from the corresponding acid and $SOCl_2$) in 20 ml ether. A brown precipitate was obtained which was filtered and washed with dil HClaq. The ethereal layer from the mixture was also washed with acid, dried and combined with the brown precipitate. The total solution was evaporated to dryness and the residue recrystallized from MeOH to yield 1·0 g homoveratroylhomopiperonylamine, m.p. 129–131° (lit. m.p. 136°).[15]

The amide (0·34 g) was dissolved in 2 ml toluene and 2 ml freshly distilled $POCl_3$ was added. The mixture was heated at reflux for 2·5 hr and evaporated to dryness. The residue was dissolved in 25 ml dil HClaq, made basic, and extracted with $CHCl_3$. The solution was dried and evaporated to leave 0·20 g oily residue which was immediately dissolved in 5 ml MeOH and 2 ml MeI. The solution was heated at reflux for 2 hr and then evaporated to dryness. The resultant crude methiodide was dissolved in 10 ml MeOH and 0·5 g $NaBH_4$ was added slowly. After the mixture had remained at room temp overnight, it was extracted with $CHCl_3$. The extract was dried and evaporated to leave 0·075 g brown oil which showed one spot on TLC with the same R_f value as the natural romneine (0·6). The solution IR and NMR spectra of the synthetic and natural compounds were identical. Treatment of the synthetic (±)-romneine with HBr gave a crystalline hydrobromide, m.p. 194–196°. (Found: C, 56·9; H, 5·76; N, 3·03. $C_{20}H_{23}NO_4$·HBr requires: C, 56·9; H, 5·74; N, 3·22%.)

Acknowledgement—This work was made possible by Research Career Development Award 1-K3-6M-16,698 to F.R.S. and Research Grant GM 09300, both from the National Institute of General Medical Sciences, U.S. Public Health Service.

[13] G. Hahn and O. Schales, *Ber.* **67B**, 1486 (1934).
[14] L. Friedman and H. Shechter, *J. Org. Chem.* **25**, 877 (1960).
[15] A. Pictet and A. Gans, *Ber.* **44**, 2480 (1911).