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THE STRUCTURE OF THALFOETIDINE*

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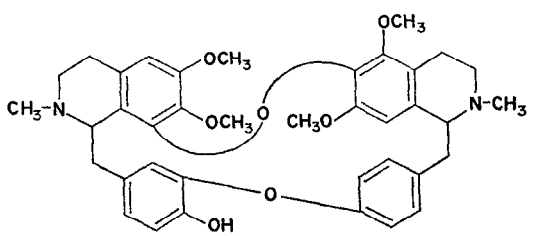
Abstract—The structure of the new bisbenzylisoquinoine alkaloid, thalfoetidine, was established by means of sodium in liquid ammonia cleavage of *O*-ethylthalfoetidine. The nonphenolic base of this degradation was identified as *d*-*O*-ethylarmepavine thus fixing the position of the phenolic hydroxyl group present in the molecule of thalfoetidine. Further a phenolic base was isolated from the above degradation. Its structure was established by synthesis as 1-(4-hydroxybenzyl)-2-methyl-5-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. The two hydroxyl groups of this compound show the position of the ether bridges in the molecule of thalfoetidine. The configuration of thalfoetidine and some related alkaloids is discussed.

INTRODUCTION

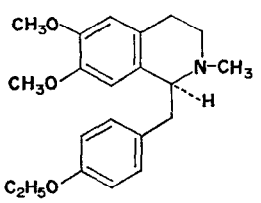
THE ALKALOID thalfoetidine (*A*) was isolated by us from *Thalictrum foetidum* L.[1] Our first attempt to determine its structure led to I, a bisbenzylisoquinoline alkaloid of the thalicberine type with an additional methoxyl group at C-5.[2]

RESULTS AND DISCUSSION

The sodium in liquid ammonia reduction of *O*-methyl- or *O*-ethylthalfoetidine gave *d*-*O*,*O*,*N*-trimethylcoclaurine or *d*-*O*-ethylarmepavine respectively. Both reactions indicated the position of the hydroxyl group of *A*.



I



d-*O*-ethylarmepavine

The same unknown phenolic base (*B*) was isolated from both the above reactions. The structure of this compound is of importance for the structure determination of thalfoetidine (*A*) since the hydroxyl groups fix the position of the ether bridges in this part of *A*. The elemental analysis of phenolic base *B* is in good agreement with the formula $C_{19}H_{23}O_4N$. The i.r. spectrum indicates two hydroxyl groups at 3600 and 3530 cm^{-1}. The NMR spectrum shows a three protons singlet at 2.35 δ from one *N*-methyl group and two three protons singlets from two methoxyl groups at 3·87 δ and 3·56 δ. One aromatic proton

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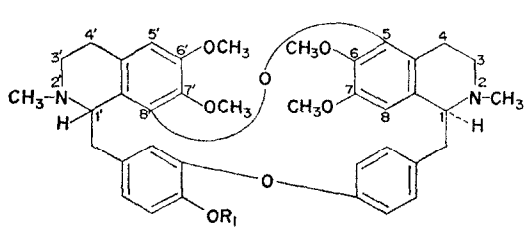
[1] N. M. MOLLOV, V. ST. GEORGIEV, P. P. PANOV and D. JORDANOV, *C. R. Acad. Bulg. Sci.* **20**, 333 (1967).
[2] N. M. MOLLOV and V. ST. GEORGIEV, *Chem. Ind.* 1178 (1966).

absorbs at relatively high-field at 5·73 δ and four aromatic protons as two doublets of *AB* type at 6·97 δ and 6·66 δ ($J = 8$ cycles/sec). Two hydroxyls appear at 5·82 δ as a wide peak. The methylation of *B* with diazomethane converted the latter into *O*-methylthalifendlerine (II)[3] which possesses the general structure of phenolic base *B*.

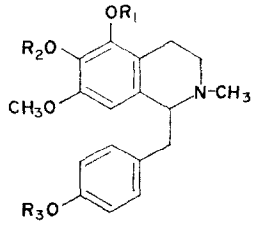
In this earlier stage we suggested for *B* the structure III, and attempted to synthesize III. Meanwhile, Kupchan *et al.*[4] reported the isolation of the alkaloid thalidasine (IV) and that IV is *O*-methylthalfoetidine. They assumed for the phenolic base *B* the structure V, because its reactivity towards Gibbs' reagent make structures III and V most likely. III was prepared by these authors and found to differ from the phenolic base (*B*). The structure V was assumed to be the real one.

As a final proof for the structure of the phenolic base (*B*), thalfoetidine (*A*) and thalidasine (IV), we have synthesized V.



IV $R_1 = CH_3$

XV $R_1 = H$



II $R_1 = R_2 = R_3 = CH_3$

III $R_1 = CH_3$; $R_2 = R_3 = H$

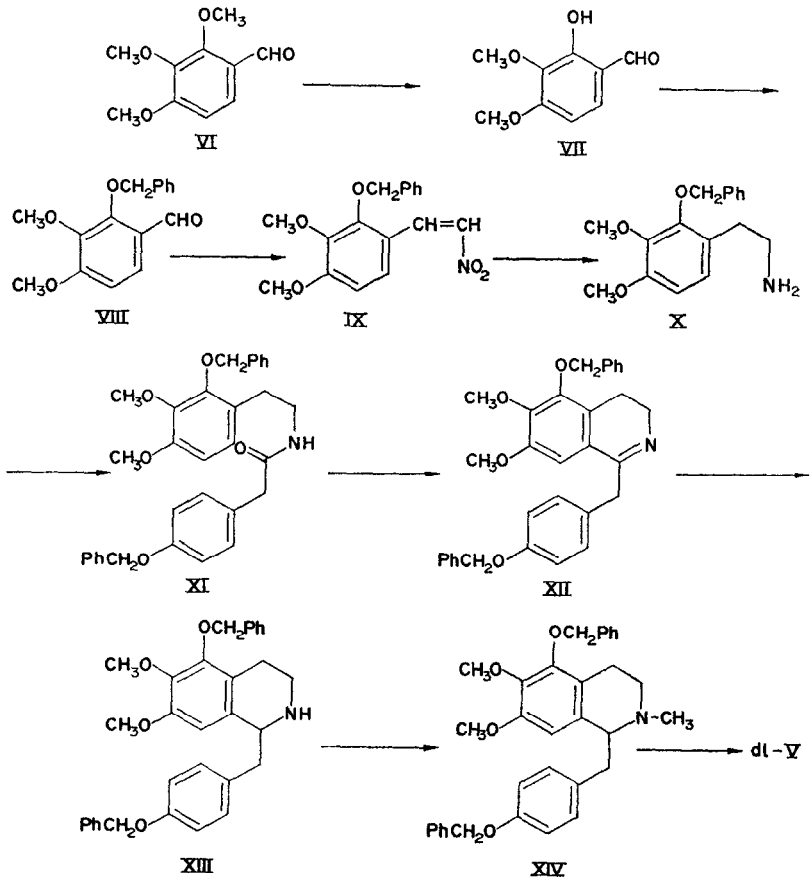
V $R_1 = R_3 = H$; $R_2 = CH_3$

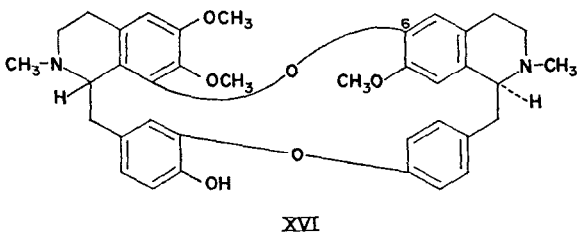
In our approach, we used 2,3,4-trimethoxybenzaldehyde (VI) as a starting substance.[5] The selective demethylation of C-2 methoxyl was made with aniline hydroiodide[6] giving 2-hydroxy-3,4-dimethoxybenzaldehyde (VII) which was converted via a benzyl ether (VIII) into the ω-nitrostyrene (IX) with nitromethane. Reduction of IX with lithium aluminum hydride gave the amine X.

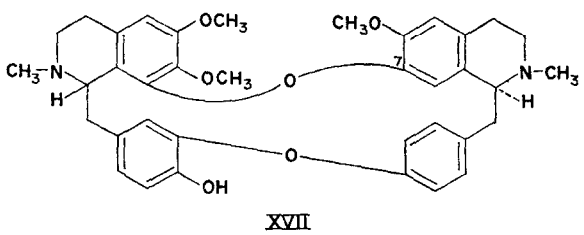
Condensation of X with 4-benzyloxyphenylacetyl chloride gave *N*-(2-benzyloxy-3,4-dimethoxyphenethyl)-4-benzyloxyphenylacetamide (XI) which was cyclized with phosphorus oxychloride to the 3,4-dihydroisoquinoline derivative (XII). The latter after sodium borohydride reduction, *N*-methylation with formaldehyde-formic acid and debenzylation with hydrochloric acid was converted into *dl*-V. The racemate V is a pale yellow amorphous compound, which crystallized as oxalate melting at 214–216° (methanol–acetone).

The IR and NMR spectra of the synthetic compound V are very similar to those of the phenolic base *B* isolated after the sodium in liquid ammonia reduction of *O*-methylthalfoetidine. There is some difference in the resonance absorption of the hydroxyl protons which absorb at 5·73 δ in *B*, while in the synthetic compound they appear at 6·36 δ. The *O*-ethylderivatives of *B* and V are fully identical according to their IR and NMR spectra and TLC behaviour with which the structure of phenolic base(*B*) is confirmed as V, of thalfoetidine (*A*) as XV and of thalidasine as IV.

[3] M. SHAMMA, M. A. GREENBERG and B. S. DUDOCK, *Tetrahedron Letters* 3595 (1965).
[4] S. M. KUPCHAN, T.-H. YANG, G. S. VASILIKIOTIS, M. H. BARNES and M. L. KING, *J. Org. Chem.* **34**, 3884 (1969).
[5] P. PAPADAKIS and W. BOAND, *J. Org. Chem.* **26**, 2075 (1961).
[6] Y. ASAHINA and I. YOSIOKA, *Berichtl.* **69**, 1367 (1936).


OCH3
CH3O
CHO
CH3O
VI
OH
CH3O
CHO
CH3O
VII
OCH2Ph
CH3O
CHO
CH3O
VIII
OCH2Ph
CH3O
CH=CH
NO2
CH3O
IX
OCH2Ph
CH3O
NH2
CH3O
X
OCH2Ph
CH3O
O
NH
CH3O
PhCH2O
XI
OCH2Ph
CH3O
N
CH3O
PhCH2O
XII
OCH2Ph
CH3O
NH
CH3O
PhCH2O
XIII
OCH2Ph
CH3O
N-CH3
CH3O
PhCH2O
XIV
dl-V


OCH3
CH3-N
H
OCH3
O
6
CH3O
N-CH3
H
O
OH
XVI


OCH3
CH3O
CH3-N
H
OCH3
O
7
N-CH3
H
O
OH
XVII

The question about the configuration of IV and XV is connected with the configuration of the benzylisoquinolines obtained during the sodium in liquid ammonia cleavage of these two alkaloids. One part is *d*-*O*,*O*,*N*-trimethylcoclaurine.[7] The ORD curve of the phenolic base (*B*) shows two positive Cotton effects as the benzylisoquinolines from *S*(L)-series. Hence, the configuration of IV and XV have to be *S*,*S*.

The ORD curves of IV and XV are worthy of importance because the compounds are bisbenzylisoquinoline alkaloids with a new type of ether linkage. The ORD curves show two negative Cotton effects about 285 and 249 nm. There is also an extrema at about 260 nm. The trough of the second Cotton effect is about four times larger than that of first (Fig. 1).

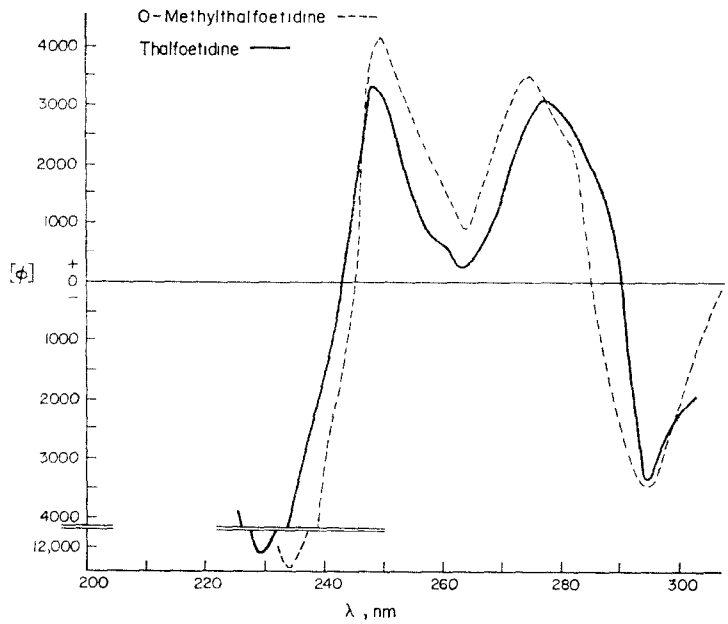


FIG. 1.

The three types of bisbenzylisoquinoline alkaloids thalfoetidine (XV), thalicberine (XVI) and berbamine (XVII) in which the diphenyl ether terminus is at C-5, C-6 and C-7 respectively have different types of ORD curves. While *S*,*S*-berbamine[8] and *S*,*S*-thalicberine have similar ORD curves, the *S*,*S*-thalfoetidine and *S*,*S*-thalidasine have ORD curves which are more close to *R*,*S*-berbamine type alkaloids[8] but are their mirror images.*

EXPERIMENTAL

M.ps are uncorrected and were taken on a Kofler hot-stage block. IR spectra were measured in $CHCl_3$ solution, KBr plates and liquid films with a UNICAM SP 200G Spectrophotometer. NMR spectra were recorded on a JEOL JNM 60 S instrument The chemical shifts are expressed as δ-units and are referred to TMS as internal standard.

* We are grateful to Dr. T. Sticzay from Bratislava, CSSR, who measured the UV and ORD spectra on a JASCO UV/ORD-5 Spectrophotometer.

[7] M. TOMITA and J. KUNITOMO, *J. Pharm. Soc. Japan* **82**, 734 (1962).

[8] A. R. BATTERSBY, I. R. C. BICK, W. KLYNE, J. P. JENNINGS, P. M. SCOPES and M. J. VERNENGO, *J. Chem. Soc.* 2239 (1965).

O-Methylation of thalfoetidine. The alkaloid (100 mg) was methylated in MeOH with ethereal CH_2N_2 for 24 hr at room temp. After working up as usual a crystalline residue (85 mg) with m.p. 108–109° was obtained IR: no band for OH group.

O-Ethylation of thalfoetidine. The compound was obtained by the same manner as above using EtOH and diazoethane.

Cleavage of O-methylthalfoetidine with Na *in liquid ammonia. O*-Methylthalfoetidine in dried toluene was added dropwise alternately with Na to an Na–liquid ammonia solution at dry ice–acetone temperature so that the blue colour of the reaction mixture was maintained. A total of about an equal weight of sodium to alkaloid was used. The mixture was stirred a further 30 min and then allowed to stand overnight. The residual toluene solution was extracted with 5% HCl, washed with Et_2O and made basic with KOH. The alkaline solution was extracted with Et_2O. The Et_2O solution and the aquesus solution were worked up separately.

(*i*) *Ether solution.* It was washed with NaOH (40%), H_2O and dried (Na_2SO_4). The residue after evaporation of the solvent was passed through silica gel column and eluted with Et_2O containing a few drops of ammonia. The eluted *d-O,O,N*-trimethylcoclaurine, m.p. 60–62°, $[\alpha]_D^{26°}$ 108° (c = 0·28; $CHCl_3$) was identified by means of IR spectra and TLC with an authentic sample.

(*ii*) *Alkaline solution. Isolation of the phenolic base B.* The aqueous solution was acidified with HCl made basic with NH_4OH, and extracted with Et_2O. The Et_2O was dried (Na_2SO_4) and the solvent removed. The residue (base *B*) crystallized from hexene-ether as colourless plates, m.p. 68–70°, $[\alpha]_D^{24°}$ 46·8° (c = 0·19; $CHCL_3$). (Calc. for $C_{19}H_{23}NO_4.C_2H_2O_4$: C, 60·13; H, 6·01; N, 3·19. Found: C, 60·31; H, 6·39; N, 3·27%).

O-Methylation of phenolic base B. Methylation was carried out as described giving *O*-methyl-*B*, which was identical by IR, NMR spectra and TLC with *O*-methylthalifendlerine obtained from an authentical sample of thalifendlerine.*

Cleavage of O-ethylthalfoetidine with Na *in liquid ammonia. O*-Ethylthalfoetidine was reductively cleaved by the procedure described above. The nonphenolic base was identified by its IR spectrum, TLC and optical rotation as *d-O*-ethylarmepavine. The phenolic base from this cleavage is the same as in the above mentioned experiment.

2-*Hydroxy*-3,4-*dimethoxybenzaldehyde* (*VII*). A mixture of 2,3,4-trimethoxybenzaldehyde[5] (2 g) and aniline (1 g) was stirred at room temp. for 30 min. EtOH (20 ml) was added and the solution evaporated *in vacuo* to yield a yellow oil. The latter was dissolved in hot light petroleum, from which pale yellow prismatic crystals separated, m.p. 69–70°. IR: 1620 cm^{-1} (C=N) ($CHCl_3$). NMR: 4·03, 3·95 (9H, O-Me), 7·97 and 6·85 (2H, quadr. J = 9 cycles/sec, ortho-aromatic), 7·60–7·20 (5H, aromatic), 9·13 (1H, methyne).

Aniline hydroiodide (9 g) and the above anil (11 g) were well mixed and heated for 1 hr at 100°. EtOH was added and the mixture evaporated *in vacuo* to dryness. The residue was extracted with benzene. After removal of the solvent, a solid was obtained, dissolved in 150 ml conc. HCl and refluxed for 2 hr. After cooling the solution was extracted with Et_2O. The Et_2O was dried (Na_2SO_4) and evaporated under reduced pressure to give amorphous VII (1·4 g). IR: 1640 cm^{-1} (CHO) (KBr). NMR: 3·68, 3·84 (6H, O-Me), 7·45 and 6·70 (2H, quadr. J = 9 cycles/sec, ortho-aromatic), 7·40 (1H, OH), 10·35 (1H, CHO) (in DMSO-d_6).

2-*Benzyloxy*-3,4-*dimethoxybenzaldehyde* (*VIII*). The mixture of 1·8 g of VII, 2·9 g benzyl chloride, 3 g K_2CO_3 and 50 ml dimethylformamide was refluxed for 2 hr, cooled and extracted with benzene. The resultant extract was washed with 5% aq. NaOH and H_2O, dried and taken to dryness to yield a brown-red oil (2·6 g). IR: 1670 cm^{-1} (CHO) (film).

ω-Nitro-2-*benzyloxy*-3,4-*dimethoxystyrene* (*IX*). A mixture of 2·6 g of the benzaldehyde (VIII), 3 ml nitromethane, 10 ml HOAc and 1·6 g NH_4OAc was heated at 100° for 2 hr. After the reaction, the brown liquid was poured into H_2O, extracted with Et_2O, the extract dried, the solvent removed and the crude IX recrystallized from MeOH. 1·6 g of the ω-nitrostyrene were obtained as yellow needles, m.p. 93–95°. NMR: 3·95, 3·92 (6H, O-Me), 5·20 (2H, OCH_2Ph), 7·23 and 6·77 (2H, quadr. J = 9 cycles/sec, *ortho*-aromatic), 7·40 (5H, aromatic), 8·10 (2H, J = 12 cycles/sec, CH=CH) (in $CDCl_3$). (Calc. for $C_{17}H_{17}NO_5$: C, 64·75; H, 5·43; N, 4·44. Found: C, 65·17; H, 5·57; N, 4·65%.)

2-*Benzyloxy*-3,4-*dimethoxy*-β-*phenethylamine* (*X*). The styrene (IX) was reduced with $LiAlH_4$ in Et_2O, the mixture being refluxed with stirring for 6 hr. After working up in the usual way, the amine X was isolated as a pale yellow oil (0·9 g), whose HCl-ide crystallized as colourless needles with m.p. 136–138°. IR: 3300 cm^{-1} (NH_2) (film).

N-(2-*benzyloxy*-3,4-*dimethoxyphenethyl*)-4-*benzyloxyphenylacetamide* (*XI*). The HCl-ide of X in H_2O was treated with 4-benzyloxyphenylacetyl chloride, 40% KOH and Et_2O. The mixture was stirred for 2 hr at room temp. and the aqueous layer separated and repeatedly extracted with Et_2O. The combined extracts were dried and evaporated giving the amide XI as a colourless crystalline powder, m.p. 62–64° (methanol) (0·47 g). IR: 1645 cm^{-1} (amide) (KBr). NMR: 3·37, 2·68 (4H, quadr. A_2B_2 type, —CH_2—), 3·45 (2H, —CH_2—), 3·95 (6H, O-Me), 5·13 (4H, OCH_2Ph). (Calc. for $C_{32}H_{33}NO_5$: C, 75·04; H, 6·51; N, 3·13. Found: C, 75·12; H, 6·50; N, 2·74%.)

* We thank Professor M. Shamma of Pennsylvania State University, U.S.A. for the generous gift of thalifendlerine, as well as its IR and NMR spectra.

1-(4-*Benzyloxybenzyl*)-5-*benzyloxy*-6,7-*dimethoxy*-3,4-*dihydroisoquinoline* (*XII*). The amide XI was ring closed with $POCl_3$ in dry toluene at 110° for 1·5 hr in N_2. The mixture was diluted with *n*-hexene and the hexene layer decanted and the resultant residue repeatedly washed with *n*-hexene. The residue was dissolved in $CHCl_3$ and shaken with a saturated $NaHCO_3$ during 20 min under N_2. The $CHCl_3$ layer was removed, washed (H_2O), dried (Na_2SO_4) and evaporated. 0·4 g of XII was obtained as a brown-red oil. IR: 1620, 1560 cm^{-1} (C=N) (film).

1-(4-*Benzyloxybenzyl*)-5-*benzyloxy*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (*XIII*). XII was reduced with $NaBH_4$ in MeOH at 80° for 1 hr. The mixture was worked up as usual giving a pale yellow oil (0·6 g). IR: 3400 cm^{-1} (NH) (film). NMR: 3·88, 3·82 (6H, O-Me), 5·05 (4H, OCH_2Ph).

1-(4-*Benzyloxybenzyl*)-2-*methyl*-5-*benzyloxy*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (*XIV*). A mixture of crude XIII, 98% formic acid and 37% formalin was heated in an oil-bath at 100° for 4 hr. After the reaction, the solution was cooled, basified with 10% NH_4OH and extracted with Et_2O. After drying, the Et_2O was removed giving a pale yellow oil (0·4 g). IR: 2790 cm^{-1} (N-CH_3) (film). NMR: 2·45(3H, N-Me), 3·83, 3·51 (6H, O-Me), 5·00 (4H, OCH_2Ph).

1-(4-*Hydroxybenzyl*)-2-*methyl*-5-*hydroxy*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (*dl-V*). XIV was hydrolysed with conc. HCl in EtOH (1:1 v/v) at 100° for 2 hr under N_2. Part of the solvent was evaporated *in vacuo* and 5% NaOH added. The resulting solution was extracted with Et_2O, the latter dried and removed under reduced pressure. The *dl*-base V was obtained as a pale yellow powder (0·15 g). IR: 2790 cm^{-1} (N-Me), 3540, 3470 cm^{-1} (OH). NMR: 2·50 (3H, N-Me), 3·83, 3·51 (6H, O-Me), 5·62 (1H, C-8 proton), 6·93 and 6·66 (4H, quadr. J = 8 cycles/sec, *ortho*-aromatic), 6·36 (2H, OH). The racemate V was converted into the oxalate which crystallized from MeOH–acetone as colourless prisms, m.p. 214–216° (decompn.). (Calc. for $C_{19}H_{23}NO_4.C_2H_2O_4$: C, 60·13; H, 6·01. Found: C, 60·53; H, 6·90 %).