423. *The Synthesis of Laudanosoline 4′,6-Dimethyl Ether.*

By M. K. Jain.

A thirteen-step unambiguous synthesis of laudanosoline 4′,6-dimethyl ether is described, starting from isovanillin.

For research on the biogenesis of morphine and aporphine alkaloids by oxidative coupling of phenolic compounds,[1] we required a laudanosoline 4′,6-dialkyl ether (I; R′ = H) as the phenolic precursor.[2] We now report a synthesis of the dimethyl ether.

In preliminary work we failed to repeat the reported selective demethylation [3] of laudanosine (I; R = R′ = Me). We therefore used the route shown in formulæ (III)—(VII). The acid chloride (III; R = CH_2Ph, Z = Cl) and amine (IV; R = CH_2Ph) were prepared from isovanillin and vanillin, respectively, by conventional methods, but preparation of appreciable amounts of the acid (IV; R = CH_2Ph, Z = OH) required modification of the usual method.[4] The method involves condensation of *O*-benzylisovanillin with

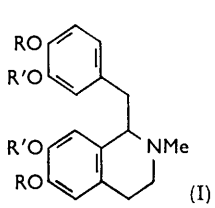
[1] Barton and Cohen, " Festschrift Arthur Stoll," Birkhaüser, Basle, 1957, p. 117; Barton, Deflorin, and Edwards, *J.*, 1956, 530.

[2] It is significant that the alkaloid coclanoline, isolated from *Cocculus laurifolius* DC with the quaternary aporphines laurifoline (II; R = OH, R′ = H, X = Cl) and magnoflorine (III; R = H, R′ = OH, X = I), has been shown to have the structure (I; R = Me, R′ = H). We had independently synthesized this compound (laudanosoline 4′,6-dimethyl ether) in 1956 before that report came to our notice (Tomita and Kikkawa, *Pharm. Bull. Japan*, 1956, **4**, 230; *Chem. Abs.*, 1957, **51**, 8116; *J. Pharm. Soc. Japan*, 1957, **77**, 195; *Chem. Abs.*, 1957, **51**, 9648). The occurrence of these bases in the same plant has biogenetic significance and supports the hypothesis on which the present work was based.

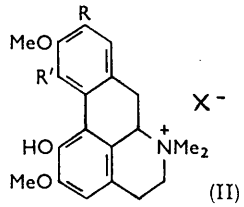
[3] Schöpf and Thierfelder, *Annalen*, 1939, **537**, 143.

[4] Robinson and Sugasawa, *J.*, 1931, 3163.

hippuric acid, and alkaline hydrolysis of the resulting oxazolone to a mixture of 3-benzyloxy-4-methoxyphenylpyruvic and benzoic acid. These acids could not be separated by the recorded method, but after treatment of the mixture with alkaline hydrogen peroxide

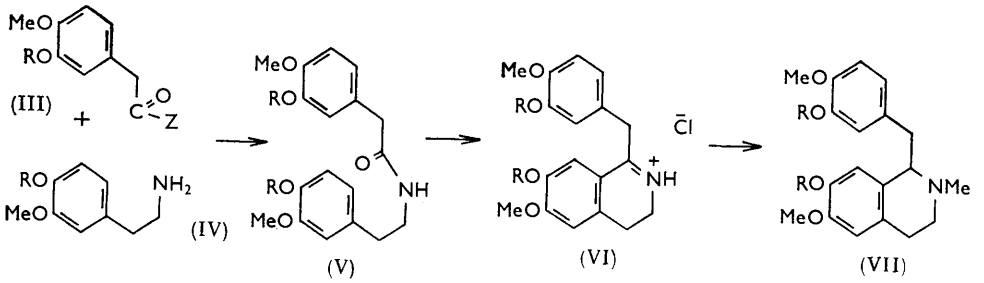


(I)



(II)

the resulting phenylacetic acid (III; R = CH_2Ph, Z = OH) was separated by chromatography (fractional crystallization of the acids and fractional distillation of their esters were unfruitful). No oxazolone was obtained when hippuric acid was replaced by acetylglycine. Reduction by lithium aluminium hydride of ω-nitrostyrenes, which have a negligible solubility in ether, generally involves use of a Soxhlet technique [5] that is time-consuming. It was found that 4-benzyloxy-3-methoxy-ω-nitrostyrene was fairly soluble in tetrahydrofuran and reduction in that solvent hastened the reaction without reducing the yield. The acid chloride (III; R = CH_2Ph, Z = Cl), freshly prepared, was treated at once with the amine (IV; R = CH_2Ph) in the Schotten–Baumann manner, yielding the amide (V; R = CH_2Ph). Bischler–Napieralski cyclization then afforded a 3,4-di-



hydroisoquinoline hydrochloride (VI; R = CH_2Ph). The derived free base was immediately quaternized under nitrogen, and the resulting methiodide was reduced with sodium or potassium borohydride [6] to the tetrahydroisoquinoline (VII; R = CH_2Ph), characterized as the picrate. Attempts to remove the benzyloxy-groups by hydrogenolysis failed under a variety of conditions but the ether was hydrolyzed with 25% hydrochloric acid in dilute acetic acid at 110—115° to laudanosoline 4',6-dimethyl ether, characterized as the picrate. With diazomethane this afforded a non-phenolic base identical with laudanosine (VII; R = Me) prepared from papaverine.[7]

Experimental

Unless indicated otherwise, m. p.s were measured on a Kofler block. Ultraviolet absorption spectra refer to EtOH solutions and were obtained with a Unicam S.P. 500 spectrophotometer. Infrared spectra were kindly determined by Dr. G. Eglinton and colleagues. Microanalyses were carried out by Mr. J. M. L. Cameron and his associates.

3-Benzyloxy-4-methoxyphenylacetic Acid (III; R = CH_2Ph, Z = OH).—4-(3-Benzyloxy-4-methoxybenzylidene)-2-phenyloxazolone, prepared from *O*-benzylisovanillin [7a] by the method of Robinson and Sugasawa,[4] had m. p. 159—160° (lit.,[4] 155°). A mixture of the oxazolone (50 g.; a larger scale of working gives lower yields) and 10% sodium hydroxide (500 ml.) was

[5] Cf. Erne and Ramirez, *Helv. Chim. Acta*, 1950, **33**, 912.
[6] Cf. Mirza, *J.*, 1957, 4400, and references cited therein.
[7] Awe and Unger, *Ber.*, 1937, **70**, 472.
[7a] Späth, Orechoff, and Kuffner, *Ber.*, 1934, **67**, 1214.

refluxed under nitrogen until evolution of ammonia ceased (6—7 hr.), then saturated with carbon dioxide (pH 8—8·5), and cooled to 5°. 6% Aqueous hydrogen peroxide (250 ml.) was then added at such a rate that the temperature of the reaction mixture did not rise 5° (45 min.). After storage at 0° for 14 hr. the mixture was acidified with concentrated hydrochloric acid, and the precipitated gummy acids were exhaustively extracted with chloroform. The extracts, when washed, dried, and evaporated under diminished pressure, afforded an oil (*ca.* 45 g.) which was chromatographed in the minimum amount of benzene on silica gel (B.D.H.) (900 g.). Benzene containing 10% of ether eluted first benzoic acid, then oils (in two fractions), and finally 3-benzyloxy-4-methoxyphenylacetic acid. This acid was best eluted by benzene containing 15% of ether, but the last fractions eluted were oils. The acid obtained recrystallized from benzene as rhombic plates (13 g.), m. p. 127—129° (lit.,[4] 125°).

4-Benzyloxy-3-methoxyphenethylamine (IV; R = CH_2Ph).—4-Benzyloxy-3-methoxy-ω-nitrostyrene, prepared from *O*-benzylvanillin [8] by Lange and Hambourger's method,[9] was reduced by lithium aluminium hydride [10] in dry tetrahydrofuran, in 74% yield. (Tetrahydrofuran is preferable to dioxan as it has a lower b. p.) The resulting crude 4-benzyloxy-3-methoxyphenethylamine was dried *in vacuo* and used as such in the next step. It gave a picrate, m. p. 174—175° (vac.), and an oxalate, m. p. 162—163°.

3-Benzyloxy-N-(4-benzyloxy-3-methoxyphenethyl)-4-methoxyphenylacetamide (V; R = CH_2Ph).—3-Benzyloxy-4-methoxyphenylacetic acid (3·2 g.), suspended in dry ether (100 ml.), was warmed with oxalyl chloride (5 ml.), dissolving in *ca.* 1 hr. The excess of oxalyl chloride and the solvent were removed under diminished pressure. The residual acid chloride solidified (m. p. 50—55°) and was used immediately.

A solution of the acid chloride (from 2·95 g. of acid) in dry tetrahydrofuran (30 ml.) was added during 1 hr. to 4-benzyloxy-3-methoxyphenethylamine (2·65 g.) in tetrahydrofuran (50 ml.) and aqueous sodium hydroxide (0·55 g. in 2 ml.). After an additional ½ hr., tetrahydrofuran was removed. The residue was taken up in water (100 c.c.), the pH adjusted to 10, and the solution extracted with chloroform. The combined chloroform extracts, when washed successively with water, 6N-hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried, and evaporated *in vacuo*, gave the solid *amide* (5·2 g.) that crystallized from ethyl acetate as needles (3·9 g.), $\nu_{max.}$ (in Nujol) 3270, 1640, 1535, 1264, and 1230 $cm.^{-1}$ (Found: C, 74·8; H, 6·3; N, 2·9. $C_{32}H_{33}NO_5$ requires C, 75·1; H, 6·5; N, 2·7%).

7-Benzyloxy-1-(3-benzyloxy-4-methoxybenzyl)-3,4-dihydro-6-methoxyisoquinoline Hydrochloride (VI; R = CH_2Ph).—The above acetamide (5 g.), dry toluene (80 ml.), and freshly distilled phosphoryl chloride (1·5 ml.) were heated at 115—120° for 45 min. The solvent and excess of phosphoryl chloride were removed on a steam-bath under reduced pressure. The residue was washed repeatedly by decantation with dry light petroleum (b. p. 60—80°) and crystallized from ethanol (charcoal), giving the *dihydroisoquinoline hydrochloride* (4·18 g.) as rhombic plates, m. p. 198—200° (decomp.) (Found: C, 72·3; H, 5·8; N, 3·0; Cl, 6·85. $C_{32}H_{32}ClNO_4$ requires C, 72·5; H, 6·1; N, 2·6; Cl, 6·7%).

7-Benzyloxy-1-(3-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (VII; R = CH_2Ph).—The dihydroisoquinoline hydrochloride (1 g.), suspended in ether, was shaken with aqueous sodium hydrogen carbonate. The aqueous phase was repeatedly extracted with more ether as rapidly as possible. The combined ether extracts were dried (K_2CO_3) and evaporated under reduced pressure at low temperature, giving free base. This was dissolved in dry benzene (20 ml.), the air was replaced by oxygen-free nitrogen, methyl iodide (1 ml.) was added, and the mixture left in the dark at room temperature for 20 hr. The deposited methiodide, m. p. 196—198°, was collected, washed with a little dry ether, and immediately reduced, as follows:

To the methiodide (from 4 g. of dihydroisoquinoline hydrochloride), suspended in " AnalaR " methanol (100 ml.), sodium borohydride (3 g.) was added during 1 hr. with stirring under nitrogen. Next morning the methanol was removed *in vacuo*, the residue taken up in dilute sodium hydroxide solution, and the turbid mixture exhaustively extracted with ether to afford, after the usual working up, the oily *tetrahydro-compound* (2·35 g.) which crystallized from benzene–light petroleum (b. p. 60—80°) as needles, m. p. 89° (2 g.) (Found: C, 78·1; H, 6·9; N, 3·1. $C_{33}H_{35}NO_4$ requires C, 77·8; H, 6·9; N, 2·75%). The picrate formed plates, m. p. 149·5°,

[8] Dickinson, Heilbron, and Irving, *J.*, 1927, 1888.
[9] Lange and Hambourger, *J. Amer. Chem. Soc.*, 1931, **53**, 3865.
[10] Cf. Gensler and Samour, *J. Amer. Chem. Soc.*, 1951, **73**, 5555.

from methanol (Found: C, 63·7; H, 5·0; N, 7·8. $C_{39}H_{38}N_4O_{11}$ requires C, 63·4; H, 5·2; N, 7·6%).

Potassium borohydride could replace sodium borohydride in the above reaction.

Laudanosoline 4′,6-Dimethyl Ether (VII; R = H).—A solution of 7-benzyloxy-1-(3-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (211 mg.) in 3N-acetic acid was slowly dropped into 25% aqueous hydrochloric acid heated in a bath maintained at 130—135°. The benzyl chloride distilled as it was formed. The residual mixture was evaporated to dryness *in vacuo* on a water-bath. The residue was evaporated repeatedly with ethanol. The residual foam was made alkaline with aqueous sodium hydrogen carbonate, and the resulting laudanosoline 4′,6-dimethyl ether extracted with ether. This failed to crystallize. It gave a violet colour with alcoholic ferric chloride. Its picrate, m. p. 190—192°, was prepared from acetone–alcohol (Found: C, 53·5; H, 4·8; N, 10·1. Calc. for $C_{25}H_{26}N_4O_{11}$: C, 53·75; H, 4·7; N, 10·0%). Methylation with diazomethane afforded a product identical with laudanosine,[7] as shown by mixed m. p.s, and superimposable ultraviolet and infrared spectra, and similar comparison of the picrates.

The author is indebted to Professor D. H. R. Barton, F.R.S., for his interest, and to Dr. K. H. Overton for discussions. The work was carried out during the tenure of a Research Fellowship from the Panjab University (India).

THE UNIVERSITY, GLASGOW, W.2.
[Present address: DEPARTMENT OF PHARMACY,
PANJAB UNIVERSITY, CHANDIGARH-3 (INDIA).]

[*Received, November 9th,* 1961.]