A NEW SYNTHESIS OF PHENANTHROINDOLIZIDINE

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Summary

(±)-Phenanthro[9,10-*f*]indolizidine (I), the basic skeleton of the *Tylophora* alkaloids, was synthesized by a modification of the method used for the synthesis of cryptopleurine.

A new synthesis, simpler than the one described earlier[1] or those used for the synthesis of tylophorine[2] and tylocrebrine,[3] was developed by modifying the method described[4] for the synthesis of the phenanthroquinolizidine alkaloid cryptopleurine from *Cryptocarya pleurosperma*.[5] We have synthesized (±)-phenanthro[9,10-*f*]indolizidine (I), i.e. the unsubstituted ring system of the *Tylophora* alkaloids. 9-Phenanthrylmethyl chloride was condensed with benzyl L-prolinate in the presence of anhydrous potassium carbonate in refluxing methanol. During the reaction, transesterification occurred and instead of benzyl *N*-phenanthr-9-ylmethyl-L-prolinate (II) the corresponding methyl ester(III) was isolated. The benzyl ester could be isolated when dimethylformamide was used as the solvent for the *N*-alkylation. Condensation in dioxan gave considerably lower yields. For the cyclization of this *N*-substituted proline derivative to the required pentacyclic structure two routes were attempted. The first method, designed to produce a stereospecific synthesis, proceeded through the corresponding prolinol derivative (IV) (prepared by lithium aluminium hydride reduction of the methyl or benzyl ester), which was converted into the prolyl bromide (V) by the action of phosphorus tribromide. Compound (V) however, failed to cyclize either by the Friedel–Crafts method or by the use of irradiation with ultraviolet light. The second and successful method produced the racemic phenanthroindolizidine. The proline methyl ester derivative was hydrolysed to the acid (VI) which gave the expected racemic phenanthroindolizidone (VII) when heated with polyphosphoric acid at 100° under nitrogen for 5 hr. Catalytic hydrogenation gave only a mixture of compounds, and contained material where, instead of the aryl-

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[1] Govindachari, T. R., Lakshmikantham, M. V., Pai, B. R., and Rajappa, S., *Tetrahedron*, 1960, **9**, 53.

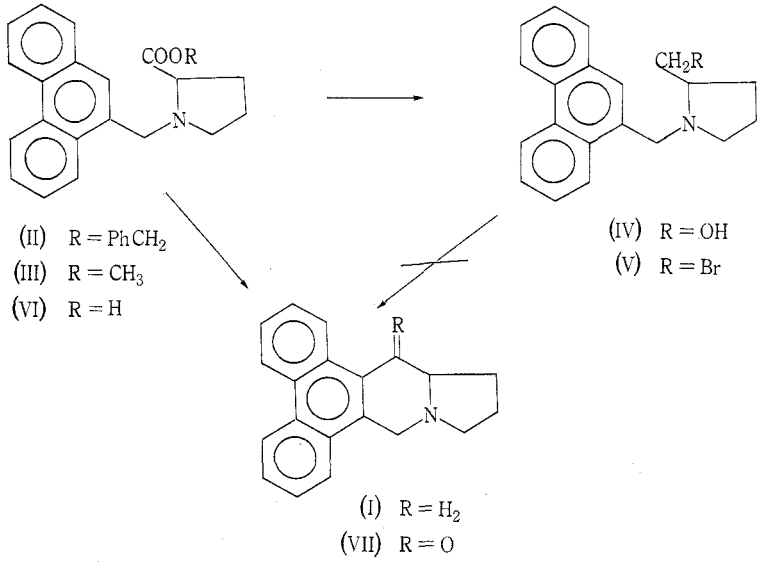
[2] Govindachari, T. R., Lakshmikantham, M. V., and Radadjara, S., *Tetrahedron*, 1961, **14**, 284.

[3] Gellert, E., Govindachari, T. R., Lakshmikantham, M. V., Ragade, I. S., Rudzats, R., and Viswanathan, N., *J. chem. Soc.*, 1962, 1008.

[4] Marchini, T., and Belleau, B., *Can. J. Chem.*, 1958, **36**, 581.

[5] Gellert, E., *Aust. J. Chem.*, 1956, **9**, 489.

carbonyl, the 9,10 double bond of phenanthrene was reduced. Reduction of the amino ketone was finally achieved by the Huang-Minlon modification of the Wolff–Kishner reduction in 20–25% yield.



Experimental

Microanalyses were carried out by Dr E. Challen, University of New South Wales, by Dr S. S. Lele, M. S. University of Baroda, India, and by the Australian Microanalytical Service, Melbourne.

Benzyl N-phenanthr-9-ylmethyl-L-prolinate (II) was prepared by stirring benzyl L-prolinate[6] (1·45 g) with freshly fused K_2CO_3 (1·4 g) in 25 ml of dry dimethylformamide for 15 min; then, after addition of 9-phenanthrylmethyl chloride (1·11 g) the reaction mixture was stirred at 70° for 15 hr. The ester was isolated by pouring the reaction mixture into 200 ml 1N HCl, extracting the aqueous solution with ether to remove non-basic material, basifying with NaOH, and re-extracting with ether exhaustively. Evaporation of the ether and crystallization of the residue from methanol yielded the required benzyl ester, m.p. 97–99°; yield 0·75 g (Found: C, 82·2; H, 6·5; N, 3·4. $C_{27}H_{25}NO_2$ requires C, 82·0; H, 6·3; N, 3·5%). Carbonyl frequency 1745 cm^{-1}.

Methyl N-phenanthr-9-ylmethyl-L-prolinate (III) was prepared by first stirring benzyl L-prolinate hydrochloride (1·45 g) with freshly fused K_2CO_3 (1·4 g) in 50 ml of dry methanol at room temperature for 4 hr, then, after addition of 9-phenanthrylmethyl chloride (1·11 g), refluxing the reaction mixture for 3 hr. Any precipitated NaCl was filtered off, the solution concentrated and allowed to crystallize, m.p. 150–151°; yield 1·6 g (Found: C, 78·8; H, 6·6; N, 4·2. $C_{21}H_{21}NO_2$ requires C, 79·0; H, 6·6; N, 4·4%). Carbonyl frequency 1745 cm^{-1}.

N-phenanthr-9-ylmethyl-L-prolinol (IV) was prepared by adding a solution of either benzyl or methyl *N*-phenanthr-9-ylmethyl-L-prolinate (1 g) in 30 ml of dry ether to a solution of $LiAlH_4$ (0·5 g) in 25 ml of dry ether over a period of 20 min and refluxing the mixture for 4 hr. After decomposing the excess $LiAlH_4$ the ether solution was evaporated to dryness and the residue recrystallized, first from methanol, then from light petroleum (40–60°) to yield colourless needles, m.p. 132°; yield 0·7 g (Found: C, 81·9; H, 7·1; N, 5·1. $C_{20}H_{21}NO$ requires C, 82·4; H, 7·2; N, 4·8%).

[6] Neuman, R. E., and Smith, E. L., *J. biol. Chem.*, 1951, **193**, 97.

The *hydrobromide* of (−)-N-*phenanthr-9-ylmethyl*-L-*prolyl bromide* (V) was prepared by heating the above prolinol (0·5 g) with phosphorus tribromide (1 ml) on a steam-bath for 2 hr. The reaction mixture was poured into ice-water and the precipitate, recrystallized from methanol, melted at 226°; yield 0·4 g; $[\alpha]_D^{25}$ −10±2° in 2% methanol (Found: C, 55·2; H, 4·6; Br, 36·7; N, 3·0. $C_{20}H_{21}Br_2N$ requires C, 55·2; H, 4·9; Br, 36·7; N, 3·2%).

The *hydrochloride* of (−)-N-*phenanthr-9-ylmethyl*-L-*proline* (VI) was prepared by hydrolysis of the corresponding methyl ester (1 g) with conc. hydrochloric acid. The hydrochloride, after recrystallization from methanol–acetone, melted at 198°; yield 0·75 g; $[\alpha]_D^{25}$ −12±2° in 2% methanol. Difficulty was experienced in obtaining the acid from the benzyl ester in this case (Found: C, 70·4; H, 5·7; N, 3·7. $C_{20}H_{20}NO_2Cl$ requires C, 70·3; H, 5·9; N, 4·1%).

The *phenanthroindolizidone* (VII) was prepared from the amino acid hydrochloride (1 g) by stirring it with polyphosphoric acid (15 ml) at 100° for 5 hr in nitrogen atmosphere. The reaction mixture was poured into ice-water and, after basification, extracted with chloroform. The chloroform solution was evaporated to dryness and the residue, recrystallized from benzene, melted at 145°; yield 0·15 g (Found: C, 83·3; H, 5·8; N, 4·8. $C_{20}H_{17}NO$ requires C, 83·6; H, 6·0; N, 4·9%). Carbonyl frequency 1690 cm^{-1}, molecular ion in the mass spectrum, *m/e* 287. As this ketone proved to be unstable, reduction to the phenanthroindolizidine was carried out immediately. The amino ketone (0·1 g) was refluxed with KOH (0·5 g) and hydrazine hydrate (1 ml) in ethylene glycol for 1 hr. After removal of water and excess hydrazine hydrate the mixture was refluxed under nitrogen for 6 hr. The reaction mixture was poured into water and extracted with ether. The residue, after evaporation of the ether, was recrystallized from methanol yielding 20 mg (±)-phenanthro[9,10-*f*]indolizidine, m.p. 172°, identical with the authentic material (lit. m.p. 170°, molecular ion in the mass spectrum, *m/e* 273).

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