Hydrogenations with Palladium Precipitated in the Presence of the Substrate

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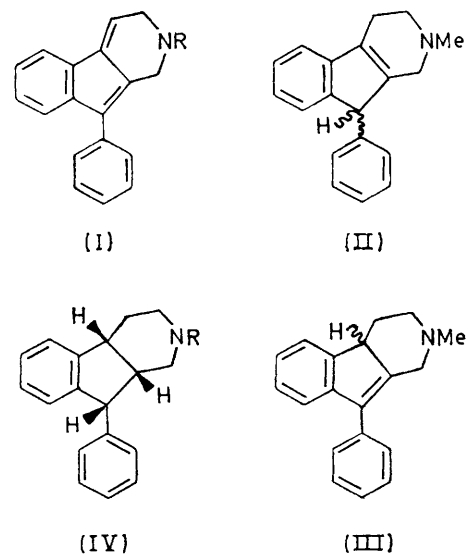
Catalytic hydrogenation of 2,3-dihydro-2-methyl-9-phenyl-1*H*-indeno[2,1-*c*]pyridine (I; R = Me) or of the 2,3,4,9-tetrahydro-analogue [phenindamine (II)] with palladium precipitated *in situ* afforded smoothly a quantitative yield of stereospecifically pure all-*cis*-2,3,4,4a,9,9a-hexahydro-2-methyl-9-phenyl-1*H*-indeno[2,1-*c*]-pyridine (IV; R = Me). *N*-Debenzylation also occurs under these conditions. Use of conventional catalysts and conditions gave intractable mixtures.

THE hexahydroindenopyridines (IV; R = Me and H) were required for biological investigation. Compound (IV; R = Me) has been prepared previously [1] by hydrogenation of the diene (I; R = Me) or of phenindamine (II) over platinum oxide under high-pressure conditions. In our hands the reported procedure gave multicomponent mixture containing 20% of the desired product (IV; R = Me) and variable quantities of over-reduced materials (cyclohexyl derivatives). After numerous unsuccessful variations of hydrogenation conditions, the reduction of compounds (I; R = Me), (II), and (III) by use of the catalysts described by Paul *et al.*[2] and Brown and Brown [3] gave high yields of compound (IV; R = Me) only upon application of pressures of 10—20 atm and reaction times in excess of 24 h at 60°. However when palladium was precipitated in the presence of the diene (I; R = Me), and the pH of the mixture was adjusted to 2, the reduction was complete within 1—3 h at 60° and 4 atm (of H_2), and compound (IV; R = Me) was obtained in >90% yield as a single isomer. Lower hydrogenation pressures or temperatures required longer reaction periods. The product has been shown to be the all-*cis*-2,3,4,4a,9,9a-hexahydro-2-methyl-9-phenyl-1*H*-indeno[2,1-*c*]-pyridine.[4]



(I) (II) (IV) (III)

[1] J. T. Plati and W. Wenner, *J. Org. Chem.*, 1949, **14**, 543; 1950, **15**, 209; 1955, **20**, 1412; B.P. 642,346.
[2] R. Paul, P. Buisson, and N. Joseph, *Compt. rend.*, 1951, **232**, 627; *Ind. Eng. Chem.*, 1952, **44**, 1006.
[3] H. C. Brown and C. A. Brown, *J. Amer. Chem. Soc.*, 1962, **84**, 1493, 1495.
[4] A. L. Ham and P. R. Leeming, *J. Chem. Soc.* (*C*), 1969, 523.

Hydrogenation of compound (I; R = $PhCH_2$) was also carried out at 60° and 4 atm; cleavage of the benzyl group occurred to give compound (IV; R = H) in 99% yield.

It was found that the hydrogen evolved during the *in situ* preparation of the catalyst could reduce the diene (I; R = Me) to a mixture of compounds (II) and (III) from which phenindamine (II) could be isolated as the tartrate salt, identified by comparison with an authentic sample. Compound (IV; R = Me) was not formed until a pressure of hydrogen was applied.

The fact that the hydrogenation of compounds (I) and (II) proceeds under less extreme conditions when the palladium catalyst is precipitated *in situ* suggests that some imprint of shape is imparted to the surface of the quasi-colloidal metal particles which facilitates the transfer of hydrogen from the surface of the metal to the substrate.

EXPERIMENTAL

2-*Benzyl*-2,3-*dihydro*-9-*phenyl*-1H-*indeno*[2,1-c]*pyridine* (I; R = $PhCH_2$) *Hydrobromide*.—This *compound* was prepared as yellow crystals by the procedure described by Plati and Wenner [1] with benzylamine in place of methylamine; m.p. 188—190° (from propan-2-ol) (Found: C, 72·3; H, 4·65; Br, 18·6; N, 3·15. $C_{25}H_{22}BrN$ requires C, 72·2; H, 5·35; Br, 19·2; N, 3·35%).

2,3,4,9-*Tetrahydro*-2-*methyl*-9-*phenyl*-1H-*indeno*[2,1-c]-*pyridine* (II) *Tartrate*.—A solution of the diene (I; R = Me) (3·4 g) in 50% aqueous ethanol (50 ml) was mixed with palladium(II) chloride (0·1 g) in water (2 ml). Sodium borohydride (1 g) in water (5 ml) was added with stirring and cooling, after which 0·2N-hydrochloric acid in 50% aqueous ethanol (80 ml) was introduced dropwise. When evolution of hydrogen had ceased the catalyst was filtered off, and the residue obtained on evaporation was extracted with chloroform. The extracts were shaken with 10% sodium carbonate solution under nitrogen. The dried organic layer was evaporated to a solid residue, from which the tartrate salt was prepared in ethanolic solution of tartaric acid to give phenindamine (II) (3·2 g), identical with commercial material.

all-cis-2,3,4,4a,9,9a-*Hexahydro*-2-*methyl*-9-*phenyl*-1H-*indeno*[2,1-c]*pyridine* (IV; R = Me) *Hydrochloride*.—(a) *From diene* (I; R = Me). To 2,3-dihydro-2-methyl-9-phenyl-1*H*-indeno[2,1-*c*]pyridine hydrobromide (34 g) in 50% aqueous ethanol (400 ml), a solution of palladium(II) chloride (1 g) and sodium chloride (0·66 g) in water (10 ml) was added with stirring. Sodium borohydride (1 g) in water (10 ml) was then added with stirring; a black precipitate of palladium formed instantly, together with exothermic and vigorous evolution of hydrogen. The pH of the mixture was adjusted to 2 with conc. hydrochloric acid, and hydrogenation was conducted in a Parr apparatus at 60° and 4 atm (H_2) until uptake was complete (3 h). The catalyst was filtered off, the solution evaporated *in vacuo*, and the solid residue freed from inorganic salts by extraction into dichloromethane. Evaporation left an oil (35 g) which solidified slowly. The free base liberated from this solid by basification (Na_2CO_3) was converted into the hydrochloride with ethereal hydrogen chloride. The precipitate was recrystallised from ethanol–ethyl acetate to give white needles (30·2 g), m.p. 268—270° (Found: C, 76·25; H, 7·35; N, 4·85. Calc. for $C_{19}H_{22}ClN$: C, 76·1; H, 7·4; N, 4·7%).

(b) *From phenindamine* (II). Phenindamine tartrate (2-methyl-9-phenyl-2,3,4,9-tetrahydro-1*H*-indeno[2,1-*c*]-pyridine tartrate) (4·1 g) was reduced as in (a) to give the hydrochloride of (IV; R = Me) (3·2 g), m.p. 267—270°.

Reduction of 2,3,4,4a-*Tetrahydro*-2-*methyl*-9-*phenyl*-1H-*indeno*[2,1-c]*pyridine* (III) *Hydrochloride*.—The tetrahydro-derivative (III) (3 g) was similarly reduced to give the hydrochloride of (IV; R = Me), m.p. 268—270°.

all-cis-2,3,4,4a,9,9a-*Hexahydro*-9-*phenyl*-1H-*indeno*[2,1-c]-*pyridine* (IV; R = H).—The diene (I; R = $PhCH_2$) (4·2 g) was reduced by the same procedure. The *hydrochloride* of (IV; R = H), prepared from the crude base, was recrystallised from ethyl acetate–ethanol to give white crystals, m.p. 275—277° (Found: C, 75·6; H, 7·1; N, 5·0. $C_{18}H_{20}ClN$ requires C, 75·7; H, 7·05; N, 4·9%), $\lambda_{max.}$ 253 (ε 457), 259 (734), 265·5 (944), and 272·5 nm (887), δ ($CDCl_3$; deuteriated base) 4·43 p.p.m. (d, 9-H, $J_{9,9a}$ 6 Hz).

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