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Nitrenes. Part I. Modified Syntheses of β -Carboline Derivatives through Nitrene Intermediates †

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Reduction of 6-chloro-2-methyl- (IV) and 2-chloro-6-methyl-3-nitro-4-phenylpyridine (V) with triethyl phosphite gave 3-chloro-1-methyl- (VI) and 1-chloro-3-methyl-β-carboline (VII) respectively. Dechlorination of these gave 1-methyl-β-carboline (harman) (VIII) and 3-methyl-β-carboline (IX) respectively in good yield.

CADOGAN AND HIS CO-WORKERS 1,2 recently demonstrated that reduction of nitro-compounds, for instance 2nitrobiaryls, by triethyl phosphite gives carbazoles in high yields. Sundberg et al.^{3,4} also reported that this reaction is an elegant new route to an indole synthesis. The reaction mechanism has been attributed to the participation of a nitrene,^{5,6} but this reaction has not yet been applied to the syntheses of natural products. We therefore report a convenient new route to the harman series of simple β -carboline alkaloids by application of this reaction.

Nitration of 6-methyl-4-phenyl-2-pyridone⁷ (I)afforded the expected compound (II) together with its isomer (III). The formation ratio (1:1) was established by the n.m.r. spectrum. Since the above mixture of (II) and (III) could not be separated by fractional recrystallisation or chromatography because of its insolubility in most organic solvents, it was treated with triethyl phosphite without separation, but the expected β carboline derivative was not formed. Therefore, the



mixture of (II) and (III) was chlorinated with phosphoryl chloride to give a mixture of the corresponding chloroderivatives (IV) and (V), whose separation was also so difficult that both were treated with triethyl phosphite. Silica gel chromatography of the reaction products recovered one of the starting materials (IV), whose structure was confirmed by the appearance in its n.m.r. spectrum of a signal from the 3-proton at low field due to the inductive effect of chlorine atom. On the other hand, our expected β -carboline derivative (VII) was obtained in the above reaction. Further treatment of the recovered compound (IV) with triethyl phosphite under stronger conditions afforded the other β-carboline derivative (VI). The n.m.r. signal of the methyl group in the former compound (VII) appeared at τ 7.38 and the methyl group in the latter compound (VI) appeared at τ 7.25. Furthermore, the signals of one aromatic proton in the benzene ring is at $\tau 2.40$ in the former (VII) and $\tau 2.22$ in the latter (VI). The methyl group of (VI) appeared at low field because of ring-current anisotropy and one aromatic proton is shifted to lower field owing to the inductive effect of the neighbouring chlorine atom.

Recovery of only compound (IV) seems to be attributable to the steric hinderance of the methyl group at the ortho-position to the nitro-group, as a result of which the accessibility of the reagent to compound (IV) is hindered and compound (V) therefore reacts more readily with triethyl phosphite to give (VII). Therefore, use of an excess of the reagent and heating for a long time were tried in the case of the recovered compound (IV) to give a mixture of both compounds (VI) and (VII), no starting material being recovered in this case. Finally, dechlorination of the compound (VII) with zinc powder and sulphuric acid 8 afforded the compound (IX) successfully, but dehalogenation of 3-chloroharman (VI) by this method failed. Furthermore, dehalogenation of (VI) by various procedures, namely catalytic hydrogenation using palladium-carbon as a catalyst and fusion with copper powder, also gave only starting material, but reduction of (VI) with lithium aluminium hydride at room temperature afforded the expected compound (VIII), whose n.m.r. spectrum was identical with that of harman. Accordingly, convenient syntheses of β carboline derivatives, including a simple alkaloid, harman, have been accomplished through a nitrene without using tryptamine.

EXPERIMENTAL

N.m.r. spectra were determined on a Hitachi H-60 spectrometer with deuteriochloroform as solvent and tetramethylsilane as internal reference.

Mixture of 6-Methyl-5-nitro-4-phenyl-2-pyridone (II) and 6-Methyl-3-nitro-4-phenyl-2-pyridone (III).-To 6-methyl-4-phenyl-2-pyridone⁷ (I) (16 g.) was added concentrated

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nitric acid (d 1·42) (18 ml.) and the mixture gradually became a reddish brown viscous liquid with generation of heat. When the resultant mixture was warmed mildly on a water-bath, a brief but severe reaction occurred with evolution of nitrogen dioxide. After 2 hours' heating, the cooled reaction mixture was poured into ice-water (200 g.), yellow crystals separating. Collection by filtration and recrystallisation from dilute ethanol afforded a mixture (8·3 g., 43·6%) of (II) and (III) as yellow-brown needles, m.p. 195—197° (Found: C, 62·25; H, 4·45; N, 11·85. Calc. for $C_{12}H_{10}N_2O_3$: C, 62·6; H, 4·4; N, 12·15%). Attempted separation of this mixture failed. The mixture showed τ 7·59 [singlet, Me of (III)], 7·49 [singlet, Me of (II)], 3·85 [singlet, 5-H of (II)], and 3·61 [singlet, 3-H of (III)].

Mixture of 2-Chloro-6-methyl-5-nitro-4-phenylpyridine (IV) and 2-Chloro-6-methyl-3-nitro-4-phenylpyridine (V).--The above mixture of (II) and (III) (4.6 g.) and phosphoryl chloride (15.3 g.) were heated at 130° in an oil-bath for 3 hr. After cooling, removal of the excess of reagent by distillation under reduced pressure gave a black oil, to which a small amount of water was added, and the resultant mixture was basified with sodium carbonate solution and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4) , and evaporated to give black crystals $(5 \cdot 1 \text{ g})$ which were chromatographed on silica gel using chloroform. Removal of the first eluate gave a mixture $(2.9 \text{ g}_{.}, 58\%)$ of (IV) and (V). Recrystallisation from methanol afforded colourless prisms, m.p. 136-137° (Found: C, 58.2; H, 3.9; N, 11.2. Calc. for $C_{12}H_9ClN_2O_2$: C, 58.0; H, 3.65; N, 11.3%), whose separation was so difficult that the mixture was used in the following reaction. N.m.r.; τ 7.43 [singlet, Me of (IV)], 7.40 [singlet, Me of (V)], 2.80 [singlet, 5-H of (V)], and 2.72 [singlet, 3-H of (IV)].

1-Chloro-3-methyl- β -carboline (VI).—A mixture (5.5 g.) of (IV) and (V) was mixed with triethyl phosphite (19 g.), and the resultant mixture was heated at 160° in an oilbath for 15 hr. under a current of hydrogen. After the reaction, the excess of reagent was removed by distillation under reduced pressure to give a syrup, which was chromatographed on silica gel using benzene as solvent.

The first eluate afforded 2-chloro-6-methyl-5-nitro-4-phenylpyridine (IV) (0.9 g.), which was recrystallised from methanol to give colourless needles, m.p. 138–139° (Found: C, 58.4; H, 4.0; N, 11.25%); τ 7.45 (3H, singlet, 6-CH₃) and 2.72 (1H, singlet, 3-H).

The second eluate afforded 1-chloro-3-methyl- β -carboline (VII) (1.5 g.), which was recrystallised from n-hexane to give colourless needles, m.p. 170–171° (Found: C, 66.5; H, 4.4; N, 12.85. C₁₂H₉ClN₂ requires C, 66.55; H, 4.2; N, 12.95%); τ 7.38 (3H, singlet, 3-CH₃) and 2.40 (1H, singlet, 4-H).

3-Chloro-1-methyl- β -carboline (3-Chloroharman) (VI).---(a) A mixture of compound (IV) (800 mg.) and triethyl phosphite (10 g.) was heated under the same conditions as above and treated as usual. The second eluate from silica gel chromatography afforded 3-chloroharman (VI) (120 mg.), which was recrystallised from benzene-n-hexane to give yellow-brown needles, m.p. 206° (Found: C, 66.55; H, 4.45; N, 13.0%); τ 7.25 (3H, singlet, 1-CH₃) and 2.22 (1H, singlet, 4-H).

* Natural harman has m. p. 228—230 after one recrystallisation.9 $\,$

(b) A mixture of (IV) and (V) (6.5 g.) and triethyl phosphite (33.2 g.) was heated at 170—180° in an oil-bath for 24 hr. in a current of hydrogen, and the reaction mixture was treated by the same way as for (VII). The second and fourth benzene eluates afforded 1-chloro-3-methyl- β -carboline (VII) (2.1 g.) and 3-chloro-1-methyl- β -carboline (VI) (150 mg.) respectively, identical (i.r., n.m.r., and mixed m.p.) with the samples prepared above. The third eluate is under examination.

3-Methyl-β-carboline (IX).—A mixture of the above compound (VII) (100 mg.), ethanol (16 ml.), zinc powder (100 mg.), and concentrated sulphuric acid (2 drops) was heated on a water-bath for 2 hr. After cooling, the rection mixture was filtered to remove the excess of zinc powder, which was washed with chloroform. The washings and the filtrate were combined and the solvent was distilled off to give a clear solution, which was made basic with ammonia and extracted with chloroform. The extract was washed with water, dried (Na₂SO₄), and evaporated to give brown crystals, which when recrystallised from benzene afforded 3-methyl-β-carboline (IX) (60 mg., 71%) as yellow-brown needles, m.p. 208° (Found: C, 78·8; H, 6·0; N, 15·65. C₁₂H₁₀N₂ requires C, 79·1; H, 5·55; N, 15·4%); τ 7·30 (3H, singlet, 3-CH₃) and 2·21 (1H, singlet, 4-H).

Recrystallisation of the *picrate* of (IX) from ethanol gave yellow needles, m.p. 258° (decomp.) (Found: C, 52.8; H, 3.4; N, 17.15. $C_{18}H_{13}N_5O_7$ requires C, 52.55; H, 3.2; N, 17.05%).

1-Methyl- β -carboline (Harman) (VIII).—To a cooled solution of 3-chloro-1-methyl- β -carboline (VI) (50 mg.) in absolute ether (5 ml.) was added dropwise a suspension of lithium aluminium hydride (150 mg.) in absolute ether (10 ml.), and the mixture was stirred at room temperature for 4 hr. After the reaction the excess of the reagent was decomposed with saturated Rochelle salt solution and the precipitate was removed by filtration and washed with ether (20 ml.). The filtrate and ethereal washing were combined together, washed with water, dried, and evaporated to give crystals (20 mg.), which were chromatographed on neutral alumina using benzene as solvent. The benzene eluent afforded harman (VIII) (9 mg., 21.5%). The chloroform eluent gave the starting material (VI) (15 mg.).

Recrystallisation of harman (VIII) from ether-hexane afforded colourless needles, m.p. 228° (sinters at 220°),* $v_{max.}$ (CHCl₃) 1630, 1605, 1570, and 1500 cm.⁻¹, τ (CDCl₃) 7·20 (3H, singlet, 1-CH₃), 2·40—2·80 (3H, aromatic protons), 2·16 and 1·64 (1H and 1H, doublets, J 5 c./sec., 3-H and 4-H), 1·90 (1H, doublet, J 6 c./sec., 5-H), and 0·88 (1H, broad, NH).

The i.r. (in $CHCl_3$) and n.m.r. (in $CDCl_3$) spectra of our sample (VIII) were superimposable on those of natural harman.

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