Studies on the Syntheses of Heterocyclic Compounds. Part DLXXXIX.† A Simple Route to Pyridocarbazoles

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Synthesis of 4-acetoxy-3-methyl-6*H*-pyrido[4,3-*b*]carbazole (11) and the isomeric pyrido[3,4-*b*]carbazole (14) are described. The key step involves condensation of indolylmagnesium bromide with 3-acetoxy-5-acetoxymethyl-4-hydroxymethyl-2-methylpyridine (2).

WE have previously reported a one-step synthesis of the dihydropyridocarbazole derivatives (9) and (10) from indole and 4,5-bisbromomethyl-3-hydroxy-2-methylpyridine hydrobromide (1).[1] These compounds were easily converted into pyridocarbazole derivatives [(11) and (14), respectively] closely similar to olivacine (12) and ellipticine (13), which show antitumour activity. However, compound (9), which leads to the olivacine-type compound, was obtained only as a minor product; we have therefore sought an alternative synthesis of dihydropyridocarbazoles. At this stage, we supposed this type of reaction to proceed stepwise *via* an ionic intermediate. We report here a synthesis of the pyridocarbazole derivatives (11) and (14) in accord with the foregoing consideration.

It is well known that the selectivity of a reaction decreases when the reactivity of the reagent is increased.[2-5] We therefore used indolylmagnesium bromide instead of indole in the hope that more of the desired condensation product (3) would be obtained than in the reaction [1] previously reported.

Condensation of indolylmagnesium bromide with 3-acetoxy-5-acetoxymethyl-4-hydroxymethyl-2-methylpyridine (2) in tetrahydrofuran and chloroform, followed by acetylation without purification, indeed gave the desired product (3) in 10% yield and its structural isomer (6) in 20% yield. Isolation of the product without acetylation afforded the hydroxy-compound (7) (corresponding to (6)], formed by deacetylation with the Grignard reagent. The isomer (4) was not separated. Acetylation of compound (7) gave the acetate (6).

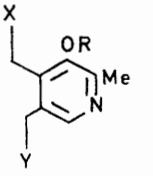
The i.r. spectrum ($CHCl_3$) of both compounds (3) and (6) showed a band due to indole NH at 3480 cm^{-1}, and acetoxy carbonyl bands at 1760 and 1735 cm^{-1}. The n.m.r. spectra of both compounds lacked a signal due to an indole β-proton but an indole NH signal was observed. The signal for the methyl group occurred at δ 2·42 for (3) and 2·39 for (6). The mass spectra of each compound showed a molecular ion at *m/e* 352. At this stage, the two isomers (3) and (6) were not distinguishable.

In order to resolve this point, the following reactions were investigated. Both condensation products (3) and (6) were converted into the corresponding known pyridocarbazole derivatives [(11) and (14),[1] respectively] by heating with 47% hydrobromic acid on a water-bath for 10 h, followed by acetylation without purification.

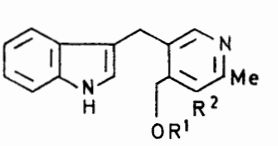
† Part DLXXXVIII, T. Kametani, M. Takemura K. Takahashi, M. Takeshita, M. Ihara, and K. Fukumoto, *Heterocycles*, 1974, **2**, 653.

[1] T. Kametani, Y. Ichikawa, T. Suzuki, and K. Fukumoto, *Heterocycles*, 1974, **2**, 171; *Tetrahedron*, 1974, **20**, 3713.

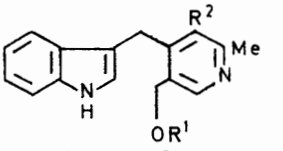
These conversions were also achieved *via* the alcohols (5) and (8) by cyclisation and acetylation. Many other



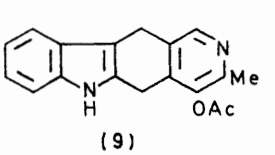
(1) R = H, X = Y = Br
(2) R = Ac, X = OH, Y = OAc



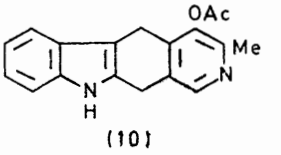
(3) R^1 = Ac, R^2 = OAc
(4) R^1 = Ac, R^2 = OH
(5) R^1 = H, R^2 = OH



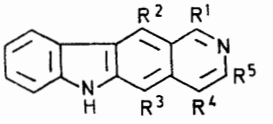
(6) R^1 = Ac, R^2 = OAc
(7) R^1 = Ac, R^2 = OH
(8) R^1 = H, R^2 = OH



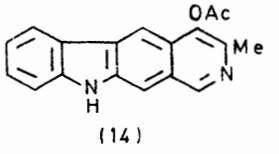
(9)



(10)



(11) R^1 = R^2 = R^3 = H, R^4 = OAc, R^5 = Me
(12) R^1 = R^3 = Me, R^2 = R^4 = R^5 = H
(13) R^1 = R^4 = R^5 = H, R^2 = R^3 = Me



(14)

cyclisation conditions were investigated, but all resulted in failure.

The yield in the reaction of indole with 4,5-bisbromomethyl-3-hydroxy-2-methylpyridine hydrobromide (1) was improved in the synthesis of the dihydropyridocarbazoles (9) and (10) by using freshly distilled dimethylformamide as solvent and prolonging the reaction time. The corresponding pyridocarbazoles (11) and (14) were

[2] M. G. Evans and M. Polanyi, *Trans. Faraday Soc.*, 1936, **32**, 1340.
[3] R. P. Bell, *Proc. Roy. Soc., Ser. A*, 1936, **154**, 414.
[4] E. Warhurst, *Quart. Rev.*, 1951, **5**, 44.
[5] M. J. S. Dewar, 'The Molecular Orbital Theory of Organic Chemistry,' McGraw-Hill, New York, 1969.

obtained in nearly quantitative yield by keeping the dihydropyridocarbazoles (9) and (10) at room temperature for a long time.

EXPERIMENTAL

M.p.s were determined on a Yanagimoto microapparatus (MP-S2). The i.r. spectra were measured with a Hitachi EPI-3 spectrophotometer and u.v. spectra for methanolic solutions with a Hitachi EPS-3 recording spectrophotometer. Mass spectra were measured with a Hitachi RMU-7 spectrometer. N.m.r. spectra were measured for solutions in deuteriochloroform (tetramethylsilane as internal standard) with JNM-PMX60 and Hitachi H-60 instruments.

3-Acetoxy-5-acetoxymethyl-4-hydroxymethyl-2-methylpyridine (2).—A mixture of 4,5-bis(hydroxymethyl)-3-hydroxy-2-methylpyridine hydrochloride (30 g), acetic anhydride (30 ml), pyridine (2 ml), and chloroform (300 ml) was stirred in an ice-bath for 8 h. The excess of acetic anhydride was decomposed with 10% ammonia, and the mixture was washed with saturated sodium chloride solution and then dried (Na_2SO_4). The solvent was distilled off under reduced pressure to afford a syrup, which was triturated with ether. Recrystallisation of the solid from ether afforded *needles*, m.p. 93—95° (Found: C, 56·95; H, 6·05; N, 5·55. $C_{12}H_{15}NO_5$ requires C, 56·9; H, 5·95; N, 5·55%), $\nu_{max.}$ ($CHCl_3$) 1760 (C=O) and 1735 cm^{-1} (C=O), δ ($CDCl_3$) 2·00 (3H, s, CH_3), 2·37 (6H, s, 2 × OAc), 4·76 (2H, s, $ArCH_2$·OH), 5·18 (2H, s, $ArCH_2$·OAc), and 8·30 (1H, s, pyridine α-proton).

Reaction of Indolylmagnesium Bromide with the Pyridine Derivative (2).—(*a*) A solution of indole (0·6 g) in ether (30 ml) was added to a solution of ethylmagnesium bromide [from ethyl bromide (1·5 g) and magnesium turnings (0·2 g)] at −10° within 10 min. The mixture was stirred for 30 min at room temperature and then chloroform (30 ml) was added in order to dissolve the complex. To the solution, cooled at −10°, was added a solution of the pyridine derivative (2) (990 mg) in tetrahydrofuran (20 ml). The mixture was then refluxed on a water-bath for 3 h and decomposed with ammonium chloride (500 mg) in water (5 ml). The solvent was distilled off *in vacuo*. To the residue were added acetic anhydride (0·5 ml) and pyridine (0·5 ml), and the mixture was set aside at room temperature for 12 h. The excess of acetic anhydride was decomposed with 10% ammonia, and the mixture was extracted with chloroform. The extract was washed with saturated sodium chloride solution, dried (Na_2SO_4), and evaporated to give a brown syrup, which was chromatographed on silica gel (10 g). Elution with trichloroethane afforded a solid (250 mg), recrystallisation of which from chloroform–n-hexane gave *3-acetoxy-5-acetoxymethyl-4-(indol-3-ylmethyl)-2-methylpyridine* (6) as brownish needles (225 mg), m.p. 173—175° (Found: C, 68·15; H, 5·85. $C_{20}H_{20}N_2O_4$ requires C, 68·15; H, 5·7%), $\nu_{max.}$ ($CHCl_3$) 3480 (NH), 1760 (C=O), and 1735 cm^{-1} (C=O), δ ($CDCl_3$) 1·84 (3H, s OAc), 2·03 (3H, s, OAc), 2·39 (3H, s, CH_3), 4·02 (2H, s, $Ar^1CH_2Ar^2$), 5·03 (2H, s, Ar^2CH_2·OAc), 6·50 (1H, s, indole α-proton), 6·95—7·65 (4H, m, ArH), 8·33 (1H, s, pyridine α-proton), and 8·60—8·90br (1H, s, NH, exchanged with D_2O), *m/e* 352 (M^+). Elution with trichloroethane–methanol (99 : 1 v/v) then gave the isomer (3) (115 mg) as a brownish syrup which could not be crystallised; $\nu_{max.}$ ($CHCl_3$) 3480 (NH), 1760 (C=O), and 1735 cm^{-1} (C=O), δ ($CDCl_3$) 1·94 (3H, s, OAc), 2·08 (3H, s, OAc), 2·42 (3H, s, CH_3), 4·10 (2H, s, $Ar^1CH_2Ar^2$), 5·12 (2H, s, Ar^2CH_2·OAc), 6·55 (1H, s, indole α-proton), 6·95—7·65 (4H, m, ArH), 8·30 (1H, s, pyridine α-proton), and 8·50—8·70br (1H, s, NH, exchanged with D_2O), *m/e* 352 (M^+).

(*b*) A solution of indole (0·94 g) in tetrahydrofuran (50 ml) was added to a suspension of ethylmagnesium bromide [from ethyl bromide (1·09 g) and magnesium turnings (0·24 g)] at 0° within 30 min, and the mixture was stirred for 1 h at the same temperature. A solution of the pyridine derivative (2) (2 g) in tetrahydrofuran (100 ml) was then added within 30 min; the mixture was stirred at room temperature for an additional 1 h, then decomposed with ammonium chloride (1 g) and water (10 ml). The solvent was removed *in vacuo* and the residue was extracted with 10% hydrochloric acid. The resulting solution was basified with 10% ammonia and then extracted with chloroform. The chloroform layer was dried (Na_2SO_4) and evaporated to leave a brownish oil, which was chromatographed on silica gel (10 g) to afford the hydroxy-compound (7) (105 mg) as a brownish syrup, $\nu_{max.}$ ($CHCl_3$) 3480 (NH) and 1735 cm^{-1} (C=O), δ ($CDCl_3$) 1·86 (3H, s, OAc), 2·42 (3H, s, CH_3), 4·12 (2H, s, $Ar^1CH_2Ar^2$), 5·05 (2H, s, Ar^2CH_2·OAc), 6·00—6·20br (1H, s, OH, exchanged with D_2O), 6·50 (1H, s, indole α-proton), 6·95—7·65 (4H, m, Ar*H*), 7·95 (1H, s, pyridine α-proton), and 8·30—8·60br (1H, s, NH, exchanged with D_2O).

Without further purification, the syrup (7) (50 mg) was treated with acetic anhydride (0·5 ml) and pyridine (0·5 ml) to afford the acetylated product (6) (51 mg), identical (spectral data) with the product obtained by method (*a*).

4-Acetoxy-3-methyl-6H-pyrido[4,3-b]*carbazole* (11).—(*a*) A mixture of compound (3) (20 mg), potassium hydroxide (100 mg), water (1 ml), and ethanol (2 ml) was refluxed in an oil-bath for 6 h and then neutralised with 10% hydrochloric acid. The solvent was evaporated off under reduced pressure and to the residue was added 47% hydrobromic acid. The mixture was heated under reflux on a water-bath for 8 h. The pH of the mixture was adjusted to 7 with 10% ammonia and the solvent was evaporated off. To the residue were added acetic anhydride (1 ml) and pyridine (1 ml). The mixture was set aside at room temperature for 3 h, treated with 10% ammonia to decompose the excess of anhydride, and extracted with chloroform. The extract was washed with saturated sodium chloride solution and dried (Na_2SO_4); the solvent was distilled off and the residue was chromatographed on silica gel (2 g) with chloroform as eluant. Evaporation of the eluate afforded 4-acetoxy-3-methyl-6*H*-pyrido[4,3-*b*]carbazole (11) (10 mg), which afforded yellow needles, m.p. 270—272° (decomp.) (from methanol) (lit.,[1] 271—272°), identical (i.r., n.m.r., and u.v. spectra) with an authentic sample.[1]

(*b*) A solution of compound (3) (18 mg) in 47% hydrobromic acid solution (2 ml) was heated on a water-bath for 10 h. The same treatment as in (*a*) then afforded the pyridocarbazole (11) (13 mg), identical (spectral data) with the sample prepared by the method (*a*).

4-Acetoxy-3-methyl-10H-pyrido[3,4-b]*carbazole* (14).—(*a*) A mixture of compound (6) (20 mg), potassium hydroxide (100 mg), water (1 ml), and ethanol (2 ml) was treated as in the above method (*a*) to give 4-acetoxy-3-methyl-10*H*-pyrido[3,4-*b*]carbazole (14) (11 mg), m.p. 284—285° (decomp.) (lit.,[1] 284—285°), identical (i.r., n.m.r., and u.v. spectra) with those reported.[1]

(*b*) Treatment of compound (6) (20 mg) as in the above method (*b*) afforded the pyridocarbazole (14) (14 mg), identical (spectral data) with the authentic sample.

4-Acetoxy-5,11-dihydro-3-methyl-6H-pyrido[4,3-b]*carbazole* (9) *and* *4-Acetoxy-5,11-dihydro-3-methyl-10H-pyrido*[3,4-b]-

carbazole (10).—A mixture of indole (2·9 g) and 4,5-bisbromomethyl-3-hydroxy-2-methylpyridine hydrobromide (1) (9 g) in freshly distilled *NN*-dimethylformamide (50 ml) was refluxed in a current of nitrogen for 6 h. After cooling, acetic anhydride (10 ml) and pyridine (1 ml) were added and the mixture was set aside overnight at room temperature. The excess of acetic anhydride was decomposed with saturated aqueous sodium hydrogen carbonate solution, and the mixture was diluted with water (900 ml) and then extracted with chloroform. The extract was washed with saturated sodium chloride solution and dried (Na_2SO_4). The solvent was distilled off under reduced pressure to afford a syrup, which was chromatographed on silica gel (250 g). Elution with trichloroethane afforded a solid, recrystallisation of which from ethanol gave (9) (650 mg) as needles, m.p. 238—240° (lit.,[1] 238—240°), identical (spectral data) with an authentic sample.

Elution with trichloroethane–methanol (199 : 1 v/v) also gave a solid, which was recrystallised from ethanol to afford (10) (2 g) as pale yellow needles, m.p. 246—247° (lit.,[1] 245—247°), identical (spectral data) with an authentic sample.

4-*Acetoxy*-3-*methyl*-6H-*pyrido*[4,3-b]*carbazole* (11) *and* 4-*Acetoxy*-3-*methyl*-10H-*pyrido*[3,4-b]*carbazole* (14).—Compounds (9) and (10) (each 500 mg) were kept at room temperature for one month, and then recrystallised from methanol to give compounds (11) (460 mg) and (14) (455 mg), respectively, identical (spectral data) with authentic samples.

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