The Synthesis of Some Derivatives of 4,5,6,6a,7,12-Hexahydroisoquinolino[8,1-*ab*]carbazole

J. B. Bremner and E. J. Browne

Department of Chemistry, University of Tasmania, G.P.O. Box 252C, Hobart, Tasmania, Australia 7001

Received October 7, 1974

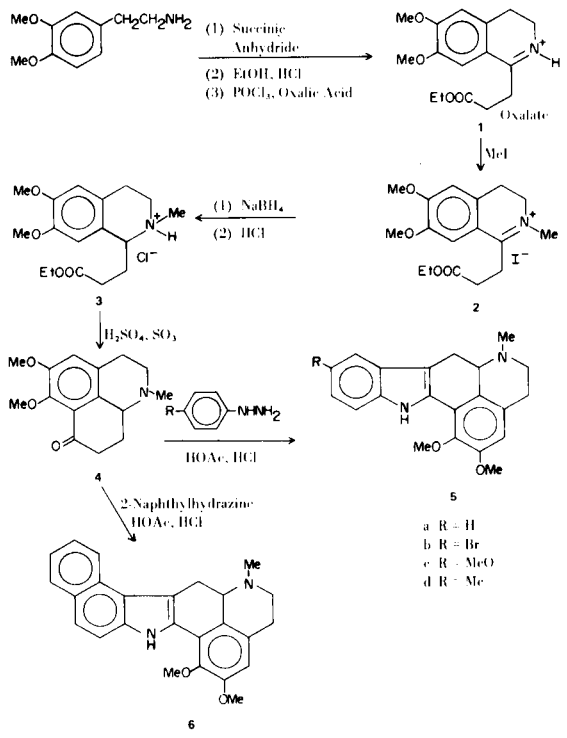
As part of a general project on the chemistry of alkaloid analogues, the synthesis of derivatives **5**, of 4,5,6,6a,7,12-hexahydroisoquinolino[8,1-*ab*]carbazole, which can be considered as ring D indole analogues of the aporphine skeleton, was investigated. Compounds of this type are of interest on two grounds. Firstly it is conceivable some may occur naturally; and secondly, they may display unusual pharmacological properties, since the side-chain configuration of the tryptophan residue is intermediate between that present in lysergic acid diethylamide and the yohimbine-reserpine type alkaloids.

Previous work (1a-b) in this area by Morrison *et al.*, established a route to the ring D indoline analogues *via* an intramolecular Friedel-Crafts reaction, although no attempt was made (2) to oxidise them to **5**. We wished to synthesise this system directly, and by a route capable of introducing a variety of substituents. The Fischer indole synthesis on the cyclic ketone (**4**) seemed to meet these criteria, and the results are described in this Note.

The known ketone (**4**) was obtained by minor variations on standard methods (4, *cf.* 3), as outlined in Scheme 1. Conditions for the indolization reaction (glacial acetic acid; hydrogen chloride) were chosen to minimize further oxidation, and, with phenylhydrazine, pure **5a** was obtained in low yield from the complex reaction mixture by preparative thin layer chromatography; considerable losses occurred during this separation. The structure of **5a** is supported by analytical and spectroscopic data. In particular, the pmr spectrum confirmed the presence of seven aliphatic ring protons, while the three sets of multiplets between 7.05 δ and 7.65 δ, clearly separated from the singlet for the C3-aromatic proton, were assigned to the protons of the indole nucleus.

However, 4-substituted phenylhydrazines and 2-naphthylhydrazine gave very poor or no yields of the corresponding indole derivatives (**5b-d** and **6**), although no attempt was made to investigate other catalysts or non-catalytic thermal indolization procedures. While the Fischer synthesis is favoured by electron-releasing substituents in the 4-position of the arylhydrazine moiety, this may be counterbalanced by an increase in side reactions (5), thus limiting yields.

SCHEME 1



EXPERIMENTAL

Analyses were performed by the Australian Microanalytical Service, Melbourne. Melting points are uncorrected. Pmr spectra were recorded at 20° with a Jeol JNM-4H-100 spectrometer, either

in deuteriochloroform with tetramethylsilane as internal standard, or in deuterium oxide with tetramethylsilane as external standard. Infrared spectra were determined on a Beckman IR-33 spectrometer, and the ultraviolet spectrum (cyclohexane solution) on a Carl Zeiss PMQ-II spectrophotometer. Mass spectra were run at 70 eV using an A.E.I. MS902 spectrometer and an E.A.I. Quad 300 spectrometer. Preparative tlc was performed on Merck silica gel GF_{254}.

Ethyl 3,4-Dihydro-6,7-dimethoxy-1-isoquinolinepropionate Oxalate (**1**).

To 54.3 g. (0.30 mole) of 2-(3,4-dimethoxyphenyl)ethylamine in 300 ml. of dry benzene, was added 31.9 g. (0.32 mole) of succinic anhydride in small portions with stirring over 1 hour. The mixture was refluxed for a further 30 minutes, cooled, and diluted with 200 ml. of light petroleum (b.p. 40-60°), to precipitate the succinamic acid. This acid was dissolved in 500 ml. of dry ethanol containing 5 g. (0.14 mole) of dry hydrogen chloride, and the mixture kept in the dark at 25° for 20 hours. Removal of the solvent *in vacuo* left 89 g. (0.29 mole) of the crude ethyl succinamate as a low melting solid; pmr (deuteriochloroform): δ 1.38 (t, 3H), 2.4-2.6 (m, 6H), 3.4-3.65 (m, 2H), 3.90 (s, 6H), 4.15 (q, 2H), 6.7-6.85 (m, 3H), 6.15 (1H, NH).

This ester (0.29 mole) was dissolved with gentle heating in 400 ml. of dry benzene and, under dry nitrogen, a solution of 50 g. (0.33 mole) of freshly redistilled phosphorus oxychloride in 120 ml. of dry benzene was run in with good mixing over 10 minutes. The mixture was protected from light, and refluxed for 50 minutes. The solvent was removed *in vacuo*, the residue ice cooled, and 100 ml. of dry ethanol added to decompose excess reagent. The mixture was again evaporated to a thick syrup, which was ice cooled, and made alkaline with 200 ml. of saturated aqueous potassium carbonate. The solution was extracted with chloroform (4 x 60 ml.) and dried (magnesium sulphate).

The dry extracts were added with swirling to a solution of 24 g. (0.27 mole) anhydrous oxalic acid in 400 ml. of dry ether, to give a precipitate of the crude oxalate (**1**); smaller amounts were obtained on addition of more ether. The precipitates were recrystallized from dry ethanol and ether to give 42 g. (0.11 mole, 37%) of the oxalate (**1**), m.p. 103-105°, which was used directly for the next step.

Further recrystallization of a sample followed by drying over phosphorus pentoxide at 20° gave pure **1**, m.p. 112-113°; pmr (deuterium oxide); δ 1.62 (t, 3H), 3.35 (t, 2H), 3.55 (t, 2H), 3.85 (t, 2H), 4.27 (t, 2H), 4.33 (s, 3H), 4.39 (s, 3H), 4.54 (q, 2H), 7.50 (s, 1H), 7.78 (s, 1H); ir: 1825 and 1710 cm^{-1} (C=O).

Anal. Calcd. for $C_{18}H_{23}NO_8$: C, 56.69; H, 6.08; N, 3.67. Found: C, 56.81; H, 6.06; N, 3.74.

A run using methanol instead of ethanol as solvent yielded as the main product the methyl ester analogue of **1**, m.p. 111-112°, from methanol and ether.

Anal. Calcd. for $C_{17}H_{21}NO_8$: C, 55.56; H, 5.76; N, 3.81. Found: C, 55.45; H, 5.84; N, 4.03.

Ethyl 3,4-Dihydro-6,7-dimethoxy-1-isoquinolinepropionate Methiodide (**2**).

To 41 g. (0.108 mole) of the oxalate (**1**) was added 150 ml. of saturated aqueous potassium carbonate solution with ice cooling, and the mixture was rapidly extracted with methylene chloride (4 x 50 ml.). To the combined, dried extracts was added 50 g. (0.35 mole) of dry methyl iodide, and the solution refluxed for 6 hours, under nitrogen and protected from light. After removal of the solvent and excess reagent *in vacuo* the methiodide (**2**) (45 g., 0.104 mole) was obtained, most of which was reduced directly. Recrystallization of a portion from dry ethanol gave pale yellow prisms of **2**, m.p. 149-151°; pmr (deuterium oxide): δ 1.55 (t, 3H), 3.35 (t, 2H), 3.51 (t, 2H), 3.92 (t, 2H), 4.25 (s, 3H), 4.29 (s, 3H), 4.35 (t, 2H), 4.44 (q, 2H), 7.44 (s, 1H), 7.69 (s, 1H); ir: 1735 cm^{-1} (C=O).

Anal. Calcd. for $C_{17}H_{24}INO_4$: C, 47.12; H, 5.58; I, 29.3. Found: C, 47.13; H, 5.61; I, 28.9.

Ethyl 6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydro-1-isoquinolinepropionate Hydrochloride (**3**).

To a cooled (ice/calcium chloride) solution of 15 g. (0.035 mole) of the methiodide (**2**) in 110 ml. of dry methanol under nitrogen was added 6.0 g. (0.16 mole) of sodium borohydride in small portions over 2 hours, at less than 5°. The bath was removed and the mixture stirred for a further 1.5 hours. The solvent was removed *in vacuo*, 50 ml. of water added, and the solution extracted with ether (4 x 40 ml.). The dried extracts from three equal runs were combined and the solvent removed to give 25.9 g. (0.084 mole) of the *N*-methylated base derived from **3**. This was dissolved in 150 ml. of dry benzene, the solution ice cooled, and dry hydrogen chloride bubbled through until precipitation of the hydrochloride salt was complete. This was filtered, washed with dry ether, and dried over potassium hydroxide to give the hydrochloride (**3**) (27.3 g., 0.08 mole, 74%), m.p. 187-190° (Lit. (3) 194° from ethanol); pmr (deuterium oxide): δ 1.56 (t, 3H), 2.76 (t, 2H), 2.98 (t, 2H), 3.34 (s, 3H), 3.3-3.7 (m, 4H), 4.23 (s, 6H), 4.39 (q, 2H), 4.80 (t, 1H), 7.16 (s, 1H), 7.75 (s, 1H); ir: 1735 cm^{-1} (C=O).

5,6-Dimethoxy-1-methyl-2,3,7,8,9,9a-hexahydro-1*H*-benzo[*de*]-quinolin-7-one (**4**).

To 8.48 g. (0.025 mole) of the hydrochloride (**3**) under argon, was added 34 g. of 20% oleum over 7 minutes, with stirring. The temperature was kept at 50 to 60° for a further 15 minutes, and the mixture was poured into 600 ml. of ice water and neutralized to *p*H 8 with 50% aqueous sodium hydroxide. The mixture was extracted with methylene chloride (3 x 80 ml.), and the extracts washed with water and dried (sodium sulphate).

Evaporation gave 2.73 g. (43%) of the crude ketone (**4**) which was used directly for the indole synthesis; pmr (deuteriochloroform): δ 2.50 (s, 3H), 2.3-2.8 (m, 6H), 2.95-3.2 (m, 3H), 3.87 (s, 6H), 6.85 (s, 1H).

1,2-Dimethoxy-6-methyl-4,5,6,6a,7,12-hexahydroisoquinolino[8,1-*ab*]carbazole (**5a**).

A solution of 2.5 g. of the ketone (**4**) in 20 ml. of glacial acetic acid saturated with dry hydrogen chloride was heated to 130° under argon. Phenylhydrazine (1.0 ml.) was added dropwise with stirring over 5 minutes, and heating was continued at 130° for a further 15 minutes. The mixture was poured into 700 ml. of ice water and neutralized to *p*H 8 with saturated aqueous potassium carbonate. The crude product (2.5 g.) was filtered and dried. Preparative tlc on five plates (5% ethanol in chloroform) gave 0.35 g. (11%) of the indole (**5a**), $R_f \sim 0.6$. Recrystallization from aqueous ethanol initially gave material melting first at 80°, then setting and remelting at 160°; pmr (deuteriochloroform) indicated the presence of one mole of ethanol: δ 1.15 (t, 3H), 2.55 (s, 3H), 2.4-3.5 (m, 8H), 3.62 (q, 2H), 3.83 (s, 3H), 3.87 (s, 3H), 6.49 (s, 1H), 7.0-7.3 (m, 2H), 7.3-7.65 (m, 2H), 9.35 (1H, NH).

Drying at 70° and 2 mm for 24 hours over phosphorus pentoxide gave solvent-free **5a**, m.p. 159-160°; nmr (deuteriochloroform): δ 2.58 (s, 3H), 2.4-2.9 (m, 3H), 2.9-3.55 (m, 4H), 3.89 (s, 6H), 6.51

(s, 1H), 7.05-7.3 (m, 2H), 7.3-7.5 (m, 1H), 7.5-7.65 (m, 1H), 9.3 (1H, NH); ir: 3400 cm^{-1} (NH); uv λ max (log ε): 228 (4.49), 249 (4.31), 260 sh (4.20), 307 sh (4.18), 320 (4.34), 334 (4.40), 349 (4.25) nm; M^+ 334.1667 (100%); $C_{21}H_{22}N_2O_2$ requires 334.1681.

Anal. Calcd. for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.36. Found: C, 75.62; H, 6.43; N, 8.44.

9-Bromo-1,2-dimethoxy-6-methyl-4,5,6,6a,7,12-hexahydroisoquinolino[8,1-*ab*]carbazole (**5b**).

To a solution under nitrogen of 0.73 g. of the crude ketone (**4**) in 20 ml. of glacial acetic acid saturated with dry hydrogen chloride was added 1.5 g. of 4-bromophenylhydrazine hydrochloride and the mixture then refluxed (bath at 130°) for 20 minutes. The solution was poured onto 300 g. of ice, adjusted to *p*H 8 with saturated aqueous potassium carbonate, and extracted with chloroform (3 x 40 ml.). Removal of the solvent from the dried extracts (sodium sulphate) gave 0.95 g. of a brown gum.

Preparative tlc on three plates (5% ethanol in chloroform) gave 12 mg. of the indole (**5b**), m.p. 153-155°, $R_f \sim 0.6$; pmr (deuteriochloroform): δ 2.60 (s, 3H), 2.4-3.5 (m, 7H), 3.92 (s, 6H), 6.58 (s, 1H), 7.2-7.4 (1H), 7.6-7.8 (1H), 9.1 (1H), 9.4 (1H, NH), ir: 3440 cm^{-1} (NH). The low resolution mass spectrum of **5b**, ($C_{21}H_{21}BrN_2O_2$, M.W. 412.078636 for ^{79}Br) showed a group of peaks at m/e 410, 411, 412, 413, 414 and 415 due to contributions from ^{79}Br, ^{81}Br and ^{13}C and the loss of H and 2H from the molecular ions. The found mass value, 412.07207, (manual peak matching method) for the main peak was in reasonable agreement with the expected mass value of 412.070078 (error, 3.1 ppm) calculated for an unresolved triplet of $C_{21}H_{21}{}^{79}BrN_2O_2$, $^{13}C\,C_{20}H_{20}{}^{79}BrN_2O_2$, and $C_{21}H_{19}{}^{81}BrN_2O_2$. The other found mass values 413.06952, 411.07056 and 410.06338 (single component peak, 412-2H) were also close to the calculated values of 413.070516, 411.069957 and 410.0629858 respectively (errors: 2.4 ppm, 1.5 ppm and 1.0 ppm).

1,2-Dimethoxy-6-methyl-4,5,6,6a,7,12-hexahydroisoquinolino-[8,1-*ab*]benzo[*g*]carbazole (**6**).

To a solution under nitrogen of 0.71 g. of the ketone (**4**) in glacial acetic acid (20 ml.) saturated with dry hydrogen chloride was added 0.7 g. of 2-naphthylhydrazine hydrochloride, and the mixture refluxed for 20 minutes. It was then poured onto 200 g. of ice, adjusted to *p*H 8 with saturated aqueous potassium carbonate, and extracted with chloroform (3 x 50 ml.). The dried extracts (sodium sulphate) were evaporated to give 0.99 g. of a brown gum. This crude mixture was chromatographed on alumina and eluted with chloroform to give fractions (0.25 g.) with intense blue fluorescence at 350 nm.

Preparative tlc (5% ethanol in chloroform) gave 28 mg. of the indole (**6**), $R_f \sim 0.5$, m.p. 154-156° after recrystallization from benzene-light petroleum (b.p. 40-60°); pmr (deuteriochloroform): δ 2.69 (s, 3H), 2.6-3.6 (m, 7H), 3.92 (s, 6H), 6.55 (s, 1H), 7.2-7.7 (m, 4H), 7.8-8.0 (1H), 8.3-8.5 (1H), 9.75 (1H, NH): ir: 3390 cm^{-1} (strong band with a broad base; NH and bound H_2O). M^+ 384.1810 (100%), M^{++} 384.1825 (17.5%); $C_{25}H_{24}N_2O_2$ requires 384.1838.

Anal. Calcd. for $C_{25}H_{24}N_2O_2.H_2O$: C, 74.60; H, 6.51; N, 6.96; O, 11.93. Found: C, 74.66; H, 6.29; N, 6.91; O, 11.60.

Acknowledgements.

We are very grateful to Dr. C. P. Whittle for his assistance with the high-resolution mass spectra and to Dr. G. C. Morrison for a sample of an analogue of **4**.

REFERENCES

(1a) G. C. Morrison, R. O. Waite and J. Shavel, Jr., *J. Org. Chem.*, 33, 1663 (1968); (b) J. Shavel, Jr., and G. C. Morrison, U. S. Patent No, 3,452,023 (1969); *Chem. Abstr.*, 71, 81326b (1969).

(2) G. C. Morrison, private communication.

(3) G. C. Morrison and J. Shavel, Jr., *J. Org. Chem.*, 29, 2486 (1964).

(4) K. Bernauer, J. Borgulya and F. Schneider, German Patent No. 2,038,957 (1971); *Chem. Abstr.*, 74, 112283d (1971).

(5) B. Robinson, *Chem. Rev.*, 69, 227 (1969).