Carcinogenic Nitrogen Compounds. Part LXXVII.[1] A Novel Synthesis of β-Carbolines

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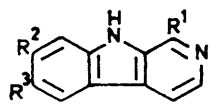
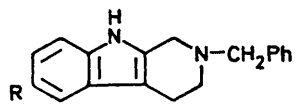
N-Benzyl-3-piperidone phenylhydrazone undergoes Fischer indolisation at position 4, the cyclisation product being readily converted into β-carboline by palladium–charcoal; this represents a convenient new route to alkaloids of the harman group. Potentially carcinogenic angular benzo-β-carbolines have also been prepared in this way.

β-CARBOLINE (norharman) (I; $R^1 = R^2 = R^3 = H$) is the basic nitrogen heterocycle from which numerous biologically active alkaloids, ranging from the simple harman (I; $R^1 = Me$, $R^2 = R^3 = H$) and harmine (I; $R^1 = Me$, $R^2 = OMe$, $R^3 = H$) to the complex yohimbine, reserpine, *etc.*, are derived. Its preparation by indolisation of cyclohexanone 3-pyridylhydrazone [2] is complicated by the fact that cyclisation occurs at both positions 2 and 4 of the pyridine nucleus, giving 5,6,7,8-tetrahydro-β-carboline as a minor product only. We have now found that *N*-benzyl-3-piperidone phenylhydrazone, when heated with a solution of hydrogen chloride in acetic acid at room temperature, readily



(I)



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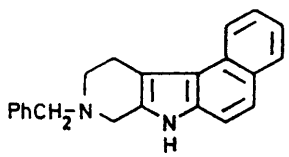
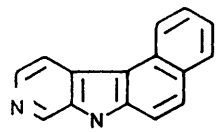


(III)

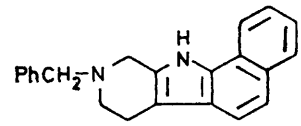
affords 2-benzyl-1,2,3,4-tetrahydro-β-carboline (II; R = H), which had already been prepared *via* another route;[3] simultaneous debenzylation and dehydrogenation of this compound to give β-carboline was achieved, as in the case of a previously reported synthesis of γ-carboline,[4] by treatment with palladium–charcoal. 6-Methyl-β-carboline (I; $R^1 = R^2 = H$, $R^3 = Me$), a positional isomer of harman, and 6-methoxy-β-carboline (I; $R^1 = R^2 = H$, $R^3 = OMe$), a positional isomer of norharmine, were similarly synthesised from the appropriate *N*-benzyl-3-piperidone arylhydrazones.

In view of the carcinogenic activity of 8,9-benzo-γ-carboline,[5] the isomeric benzo[*g*][β]carboline (IV) and benzo[*i*][β]carboline (VI) were synthesised *via* the corresponding *N*-benzyltetrahydro-compounds (III) and (V).

The preferential attack at position 4 in the indolisation of arylhydrazones from *N*-benzyl-3-piperidone (a readily available reagent) in the presence of acetic acid–hydrogen chloride at room temperature makes this a



(IV)



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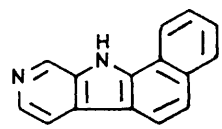

(VI)

simple and convenient route of access to numerous pharmacologically active derivatives of β-carboline, which we are further exploiting.

An n.m.r. spectrum of β-carboline (in Me_2SO) had already been reported;[6] a new determination at 100 MHz (Me_2SO–$CDCl_3$; Varian A-100 spectrometer) provided a complete elucidation of the signals: τ 1·13br (s, 1-H), 1·68br (s, 3-H), 1·85 (dt, 8-H), 2·02 (doublet-like m, 4-H), 2·35—2·60 (m, 5- and 6-H), and 2·70—2·90 (m, 7-H); the N*H* signal (at 20° in Me_2SO) appeared at τ −1·55 (s).

Results of carcinogenesis tests with compounds (IV) and (VI) will be reported elsewhere.

EXPERIMENTAL

Several β-carboline derivatives gave unreliable results for C analysis.

β-Carboline.—A mixture of *N*-benzyl-3-piperidone (3·8 g), phenylhydrazine (3 g), and water (6 ml) was maintained at room temperature for 24 h, then treated with saturated aqueous potassium carbonate; the resin which formed solidified slowly and was recrystallised from hexane to give *N*-benzyl-3-piperidone phenylhydrazone as pale yellow needles (4·5 g), m.p. 82° (Found: N, 14·9. Calc. for $C_{18}H_{21}N_3$: N, 15·%). Indolisation was effected at room temperature by treatment with acetic acid (15 ml) saturated with hydrogen chloride; the precipitate was made basic,

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[2] R. A. Abramovitch and K. A. H. Adams, *Canad. J. Chem.*, 1962, **40**, 864; see also E. Späth and K. Eiter, *Ber.*, 1940, **73**, 719.

[3] M. Onda and M. Sasamoto, *Chem. and Pharm. Bull. Japan*, 1957, **5**, 305.

[4] N. P. Buu-Hoï, O. Roussel, and P. Jacquignon, *J. Chem. Soc.*, 1964, 708.

[5] A. Lacassagne, N. P. Buu-Hoï, F. Zajdela, O. Périn-Roussel, P. Jacquignon, F. Périn, and J.-P. Hoeffinger, *Compt. rend.*, 1970, **271**, *D*, 1474.

[6] R. A. Abramovitch and I. D. Spenser, *Canad. J. Chem.*, 1964, **42**, 954.

and 2-benzyl-1,2,3,4-tetrahydro-β-carboline (II; R = H) crystallised from aqueous methanol as leaflets, m.p. 140—141° (lit.,[3] 140—141°) (Found: N, 10·6. Calc. for $C_{18}H_{18}N_2$: N, 10·7%); *picrate*, orange-yellow prisms, m.p. 191—192° (from methanol) (Found: N, 14·2. $C_{24}H_{21}N_5O_7$ requires N, 14·3%). An intimate mixture of (II; R = H) (1 g) and 5% palladium–charcoal (0·5 g) was heated slowly to >200° in a sublimation apparatus and the sublimate was recrystallised from benzene to give β-carboline, needles (*ca.* 25% overall yield calc. from *N*-benzyl-3-piperidone), m.p. 199—200°; picrate, yellow needles, m.p. 260° (from ethanol) (lit.,[2] 199—200° for base and 260° for picrate). The purity of the β-carboline was verified by t.l.c.

6-*Methyl*-β-*carboline*.— 2-*Benzyl*-1,2,3,4-*tetrahydro*-6-*methyl*-β-*carboline* (II; R = Me), prepared similarly with *p*-tolylhydrazine, formed pale yellow leaflets, m.p. 163—164° (from aqueous methanol) (Found: H, 7·1; N, 9·8; M^+, 276. $C_{19}H_{20}N_2$ requires H, 7·2; N, 10·1%; *M*, 276); picrate, bright yellow prisms, m.p. 203° (decomp. >190°), from chlorobenzene. Treatment with palladium–charcoal in boiling pseudocumene (45 min) afforded 6-*methyl*-β-*carboline* as needles (overall yield *ca.* 25%), m.p. 189—190° (sublim. >170°) (from benzene) (Found: H, 5·7; N, 15·1%; M^+, 182. $C_{12}H_{10}N_2$ requires H, 5·5; N, 15·4%; *M*, 182); *picrate*, orange-yellow prisms, m.p. 252° (decomp. >235°) (from ethanol–benzene) (Found: N, 16·6. $C_{18}H_{13}N_5O_7$ requires N, 17·0%). If the latter reaction was prolonged (3 h), a 6,6′-dimethyl-*x*,*x*′-bi-β-carbolinyl was obtained as pale yellow leaflets, m.p. 346 (from benzene) (Found: C, 79·2; H, 5·3; N, 15·7%; M^+, 362. Calc. for $C_{24}H_{18}N_4$: C, 79·5; H, 5·0; N, 15·5%; *M*, 362).

6-*Methoxy*-β-*carboline*.— 2-*Benzyl*-1,2,3,4-*tetrahydro*-6-*methoxy*-β-*carboline* (II; R = OMe), prepared from *p*-methoxyphenylhydrazine, formed needles, m.p. 141° (from benzene) (Found: H, 6·9; N, 9·4. $C_{19}H_{20}N_2O$ requires H, 6·9; N, 9·6%); *picrate*, orange prisms, m.p. 192° (from benzene) (Found: N, 13·5. $C_{25}H_{23}N_5O_8$ requires N, 13·4%). Treatment with palladium–charcoal in boiling xylene (90 min) afforded 6-*methoxy*-β-*carboline*, leaflets, m.p. 202° (from benzene) (Found: C, 72·4; H, 5·2; N, 13·8. $C_{12}H_{10}N_2O$ requires C, 72·7; H, 5·1; N, 14·1%), along with small amounts of a 6,6′-dimethoxy-*x*,*x*′-bi-β-carbolinyl, pale yellow leaflets, m.p. 314° (from xylene) (Found: C, 73·2; H, 4·5; N, 14·0. Calc. for $C_{24}H_{18}N_4O_2$: C, 73·1; H, 4·6; N, 14·2%).

Benzo[g][β]*carboline* (IV).—The 2-*benzyl*-1,2,3,4-*tetrahydro-derivative* (III), obtained in 23% yield from α-naphthylhydrazine, formed needles, m.p. 157—158° (from ethanol) (Found: C, 84·5; H, 6·5; N, 8·8. $C_{22}H_{20}N_2$ requires C, 84·6; H, 6·4; N, 9·0%); *dipicrate*, brown-red prisms, m.p. 213° (decomp. >175°) (from ethanol) (Found: N, 14·4. $C_{34}H_{26}N_8O_{14}$ requires N, 14·55%). Treatment with palladium–charcoal in boiling pseudocumene (2 h) furnished the *benzocarboline* (IV), needles, m.p. 259—260° (sublim. >230°) (from xylene) (Found: C, 82·4; H, 4·9; N, 12·7. $C_{15}H_{10}N_2$ requires C, 82·6; H, 4·6; N, 12·8%); *picrate*, orange-yellow needles, m.p. 274° (decomp. >255°) (from ethanol) (Found: N, 15·6. $C_{21}H_{13}N_5O_7$ requires N, 15·7%).

Benzo[i][β]*carboline* (VI).—The 2-*benzyl*-1,2,3,4,-*tetrahydro-derivative* (V), obtained (35% yield) from β-naphthylhydrazine, formed needles, m.p. 143—144° (from cyclohexane) (Found: C, 84·3; H, 6·5; N, 9·1%); *picrate*, yellow prisms, m.p. 204° (decomp. >190°) (from chlorobenzene) (Found: N, 12·6. $C_{28}H_{23}N_5O_7$ requires N, 12·9%). Similar treatment with palladium–charcoal gave the *benzocarboline* (VI), prisms, m.p. 235° (sublim. >210°) (from toluene) (Found: C, 82·3; H, 4·8; N, 12·8%); *picrate*, orange-yellow prisms, m.p. 269—270° (from toluene) (Found: N, 15·4%).

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