Synthesis of 9-Aminoellipticine (9-Amino-5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) and Related Compounds

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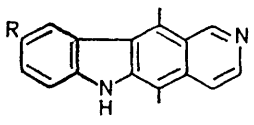
Attempts to prepare 9-nitroellipticine from 2-{1-[3-(1-methoxyethyl)-4-pyridyl]ethylidene}-5-nitroindolin-3-one have been unsuccessful. On the other hand 9-aminoellipticine has been prepared by ring closure of 5-acetamido-2-{1-[3-(1-methoxyethyl)-4-pyridyl]ethyl}indole. The mechanism of the reduction of alkylideneindolinones by sodium borohydride is discussed and an anomalous nitration reaction of indoles in concentrated sulphuric acid is reported.

THERE is continuing interest in the antineoplastic activity of the 6*H*-pyrido[4,3-*b*]carbazole system,[1,2] and human clinical trials with the alkaloid ellipticine (1; R = H) are being conducted.[3]



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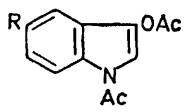

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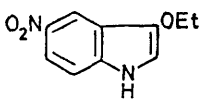

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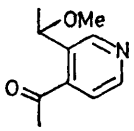

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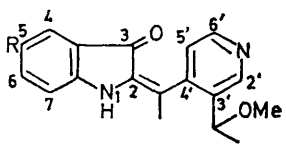

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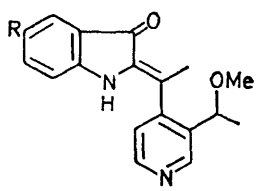

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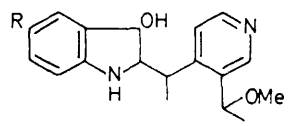
Hansch has commented recently [4] upon the difficulties surrounding the selection of those derivatives of a pharmacologically interesting molecule most likely to reveal trends in structure–activity relationships, but, taking as his examples 9-substituted ellipticines, this author indicated how by the use of substituent constants and regression analyses it is possible to make a judicious choice of targets for synthesis and bioassay.

Thus, in view of the ease by which a nitro-group can be transformed into other functions, we decided to prepare 9-nitroellipticine (1; R = NO_2) as the starting material for a series of experiments designed to evaluate some of the Hansch proposals. The first step of the synthesis required the combination of 1,3-diacetyl-5-nitroindoxyl (2; R = NO_2) with the 4-acetylpyridine (3). However, no such reaction was observed under a variety of basic and acidic conditions, although in our preliminary studies [5] the corresponding reaction between compounds (2, R = H) and (3) gave a good yield of the *E*- and *Z*-isomers (5) and (6) (R = H).

A small yield of the required isomers † was obtained when the nitroindoxyl (2; R = NO_2) was converted into the ether (4) and this was treated with the ketone (3) in aqueous hydrogen bromide. Owing to the inefficiency of this approach, however, direct nitration of a mixture of the unsubstituted isomers (5) and (6) (R = H) was attempted next. This reaction proceeded smoothly to give the corresponding nitro-derivatives in moderate yield. From our previous experience [5] we anticipated that the mixture of isomers, on reduction with sodium borohydride in boiling ethanol, would form the indoline alcohol (7; R = NO_2) and that this would be readily dehydrated to the 5-nitroindole (8; R = NO_2). In fact only the 5-aminoindole (8; R = NH_2) was isolated from the reaction product, in trace amounts together with much resinous material. Under less severe conditions the major product was



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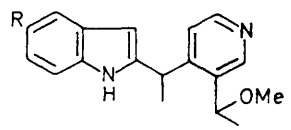

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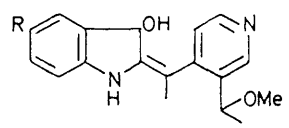

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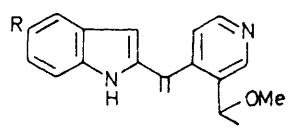

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the unstable alcohol (9; R = NO_2) which upon attempted recrystallization, or on heating in benzene solution, gradually formed the vinyl derivative (10;

† Each of the isomers exists as a pair of diastereoisomers owing to the presence of the chiral centre joined to C-3 of the pyridine ring and to restricted rotation about the bond joining the enone and pyridine units of structure;[6] because of the temperature dependence of their n.m.r. spectra, it is possible to calculate potential energy barriers to rotation (see Experimental).

[1] G. Mathé, M. Hayat, F. de Vassal, L. Schwarzenberg, M. Schneider, J. R. Schlumberger, C. Jasmin, and C. Rosenveld, *Rev. Europ. Études Clin. et Biol.*, 1970, **15**, 541.

[2] J. B. Le Pecq, C. Gosse, N. Dat-Xuong, and C. Paoletti, *Compt. rend.*, 1973, **277D**, 2289.

[3] Ellipticine: N.S.C.-71,795; personal communication from R. B. Engle, National Cancer Institute, N.I.H., Bethesda, Maryland, U.S.A.

[4] C. Hansch, *Cancer Chemother. Rep.*, 1972, **56** (1), 433.

[5] K. N. Kilminster and M. Sainsbury, *J.C.S. Perkin I*, 1972, 2264.

[6] K. N. Kilminster and M. Sainsbury, *J.C.S. Perkin I*, 1972, 2415.

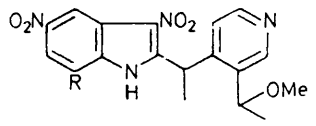
R = NO_2). We were unable to define conditions necessary to give either (7; R = NO_2) or (8; R = NO_2).

Hooper and Pitkethly [7] have shown that normally the reduction of the αβ-unsaturated system of alkylideneindolinones with sodium borohydride involves 1,4-addition of hydrogen as the first step. Therefore the formation of the alcohol (9; R = NO_2) is interesting since, unless tautomeric phenomena are involved, it suggests that this reaction involves an initial 1,2-addition of hydrogen. Certainly the selection of conditions for the reduction of alkylideneindolinones is critical and we have indications that the reduction of the isomeric mixtures (5) and (6) (R = H or NHAc) with sodium borohydride at room temperature also gives compounds (9; R = H or NHAc), whereas at higher temperatures the indoline alcohols (7; R = H or NHAc) are formed normally.

Although compound (10; R = NO_2) is at the correct oxidation level to form 9-nitroellipticine on cyclisation, attempts to bring about such a reaction with the small amount of material available failed.

Nitration of 2-substituted indoles in concentrated sulphuric acid solution affords the corresponding 5-nitroindoles,[8] and it is generally assumed [9] that initial protonation at C-3 prevents the introduction of the nitro-group at this site. When, however, the indole (8; R = H) was treated with sulphuric acid and potassium nitrate at 0°, a dinitroindole and a trinitroindole were isolated. In the n.m.r. spectra of both these products the signal anticipated for the C-3 proton [δ *ca.* 6·5 in $(CD_3)_2SO$] is absent. Each must therefore contain a nitro-substituent at this position, despite the fact that the spectrum of the parent indole (8; R = H) in 90% sulphuric acid solution shows that it is extensively protonated at C-3. Thus either there is sufficient unprotonated compound present to allow direct 3-nitration or, more probably, initial attack by the nitronium ion occurs in the benzenoid ring, resulting in a decrease in the overall basicity of the indolic system with a subsequent shift in the equilibrium between protonated and unprotonated species in favour of the latter. It is this mononitro-intermediate which then undergoes further nitration.

The precise location of the nitro-group(s) in the benzene ring of the indole system is uncertain; chemical shift data do not allow an unequivocal decision between 3,6- or 3,5- and 3,4,6- or 3,5,7-substitution patterns for the dinitro- and trinitro-derivatives, respectively. However, the u.v. spectrum of 2-methyl-3,6-dinitroindole shows maxima at 225 (ε 10,230), 291 (13,800), 306 (14,130) and 341 (14,790) nm, whereas 2-methyl-3,5-dinitroindole exhibits maxima at 251 (23,440), 314 (10,960), and 347 (10,960) nm.[10] Our dinitro-compound shows $\lambda_{max.}$ 255 (ε 22,300), 320 (10,600), 345sh (9600), and 412 (6860) nm, and on this basis we formulate, tentatively, this product as (11; R = H). Unfortunately the u.v. spectra of 2-methyl-3,4,6-trinitroindole [$\lambda_{max.}$ 294 (ε 15,850) and 347 (12,020) nm] and 2-methyl-3,5,7-trinitroindole [$\lambda_{max.}$ 284 (17,780) and 350 (9550) nm] [10] are similar, but the positions of the maxima for our trinitro-derivative [272 (17,500), 345sh (9600), and 411 (10,200) nm] are more in accord with those of 2-methyl-3,5,7-trinitroindole and thus we allocate structure (11; R = NO_2) to this product.



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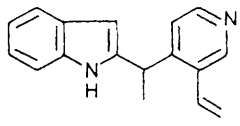

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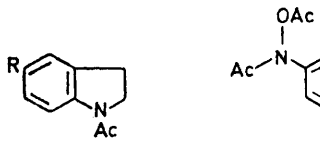
The parent indole (8; R = H) was regenerated unchanged from concentrated sulphuric acid solution at temperatures ranging from 0 to 90°, but after heating at 100° in sulphuric acid progressively less of the indole was liberated upon basification as the duration of the experiment was extended, and after 30 min the only product isolated was the 3-vinylpyridine derivative (12). No ellipticine derivatives were obtained.

At this point we abandoned the projected synthesis of 9-nitroellipticine in favour of that of the 9-amino-analogue (1; R = NH_2). Initially we attempted to hydrogenate the nitroindoxyl (2; R = NO_2) at atmospheric pressure in acetic acid–acetic anhydride over Adams catalyst, but the product was the indoline (13; R = NHAc) or, if the acetic anhydride was omitted, (13; R = NH_2). Under milder conditions, for example in dimethylformamide solution containing acetic anhydride and with 5% palladium–carbon as catalyst, the phenylhydroxylamine derivative (14) was formed. Finally, however, repetition of the latter experiment, but in the absence of acetic anhydride and with a longer reaction time, gave the indoxyl (2; R = NH_2) in the crude state, acetylation of which with acetic anhydride gave the amide (2; R = NHAc) together with small amounts of compounds (15) and (16).



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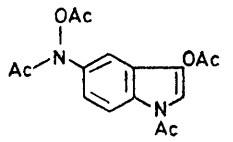

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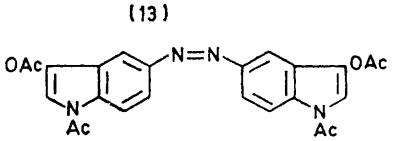

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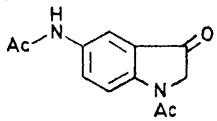

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Condensation of the amide (2; R = NHAc) with the ketone (3) afforded a mixture of isomers (5) and (6)

[7] M. Hooper and W. N. Pitkethly, *J.C.S. Perkin I*, 1972, 1607.
[8] W. E. Noland, L. R. Smith, and D. C. Johnson, *J. Org. Chem.*, 1963, **28**, 2262.
[9] W. A. Remers in 'The Chemistry of Heterocyclic Compounds,' vol. 25 (1), ed. W. J. Houlihan, Wiley-Interscience, London, 1972, p. 78.
[10] W. E. Noland, L. R. Smith, and K. R. Rush, *J. Org. Chem.*, 1965, **30**, 3463; 1966, **31**, 65.

(R = NHAc) in 35% yield and this, on reduction with sodium borohydride in boiling ethanol, gave the indoline alcohol (7; R = NHAc). Treatment of the alcohol with methanolic hydrogen chloride gave the indole (8; R = NHAc), which with hot aqueous 60% hydrogen bromide underwent cyclisation, dehydrogenation, and hydrolysis to yield 9-aminoellipticine, as the bis-hydrobromide, in one step. The free base was obtained on basification of the salt and from the filtrate, after removal of 9-aminoellipticine, a small quantity of ellipticine (1; R = H) was isolated. 9-Aminoellipticine and some of the derivatives described in this paper are undergoing biological examination.

EXPERIMENTAL

U.v. spectra were recorded for solutions in 95% aqueous ethanol unless otherwise stated; i.r. spectral data refer to Nujol mulls; ^{1}H n.m.r. spectra were recorded at either 60 or 100 MHz with tetramethylsilane as internal standard.

1-Acetyl-5-nitroindol-3-yl Acetate (2; R = NO_2).—This compound was prepared from 2-chloro-5-nitrobenzoic acid by the published method.[11]

5-Acetamido-1-acetylindol-3-yl Acetate (2; R = NHAc).—(*a*) 1-Acetyl-5-nitroindol-3-yl acetate (200 mg) in acetic acid (70 ml) and acetic anhydride (10 ml) was hydrogenated at room temperature and atmospheric pressure, over Adams catalyst, for 2 h. Filtration and evaporation gave *1-acetyl-5-acetamidoindoline* (13; R = NHAc) as a pale yellow solid (81 mg, 48·7%), m.p. 213—215° (from ethanol), *m/e* 218, 176, and 133 (base), $\nu_{max.}$ 1690 (NAc), 1640 (NHAc), 1600, 1537, and 3300 cm^{-1} (NH), $\lambda_{max.}$ 275 (ε 25,500), 278 (25,300), 297sh (12,300), and 310sh (7840) nm, δ ($CDCl_3$) 2·1 (3H, s, NHAc), 2·2 (3H, s, NAc), 3·1 (2H, t, $J_{3.2}$ 8 Hz, 3-H_2), 4·0 (2H, t, $J_{2,3}$ 8 Hz, 2-H_2), 7·0 (1H, d, $J_{5.6}$ 8 Hz, 5-H), 7·4 (1H, s, NH), 7·7 (1H, d, $J_{4.6}$ 2 Hz, 4-H), and 8·1 (1H, 2× d, $J_{6.5}$ 8, $J_{6.4}$ 2 Hz, 6-H) (Found: C, 66·1; H, 6·4; N, 12·8. $C_{12}H_{14}N_2O_2$ requires C, 66·0; H, 6·5; N, 12·8%).

(*b*) Repetition of experiment (*a*) but without acetic anhydride gave colourless prisms of *1-acetyl-5-aminoindoline* (13; R = NH_2) (35%), m.p. 165—167° (from benzene), *m/e* 176, 134, and 133 (base), $\nu_{max.}$ 1625 (CO) and 1590 cm^{-1}, $\lambda_{max.}$ 272 (ε 15,800) and 310sh (3870) nm, δ ($CDCl_3$) 2·1 (3H, s, NAc), 3·05 (2H, t, $J_{3.2}$ 8 Hz, 3-H_2), 3·3br (2H, s, NH_2), 3·95 (2H, t, $J_{2,3}$ 8 Hz, 2-H_2), 6·45 (1H, 2× d, $J_{6.7}$ 8, $J_{6.4}$ 2 Hz, 6-H), 6·50 (1H, d, $J_{4.6}$ 2 Hz, 4-H), and 8·0 (1H, d, $J_{7.6}$ 8 Hz, 7-H) (Found: C, 68·0; H, 6·9; N, 15·9. $C_{10}H_{12}N_2O$ requires C, 68·2; H, 6·9; N, 15·9%).

(*c*) Hydrogenation of (2; R = NO_2) (130 mg) in dimethylformamide (30 ml) and acetic anhydride (15 ml) over 5% palladium–carbon during 3 h gave, after work-up, a dark coloured solid. This was extracted with hot ethanol; the extract was filtered and evaporated to give *5-N-acetoxyacetamido-1-acetylindol-3-yl acetate* (14) (40 mg, 24·4%), m.p. 141—142° (from ethanol), *m/e* 332, 290, 274, 232, 230, 190, and 148 (base), $\nu_{max.}$ 1785 (NOAc), 1760, 1686 (CO), and 1195 cm^{-1} (CO) [PhNAc(OAc) shows $\nu_{max.}$ 1795, 1684, and 1186 cm^{-1}], $\lambda_{max.}$ 246 (ε 25,000), 301 (4330), and 308sh (4220) nm, δ ($CDCl_3$) 2·05 (3H, s, NAc), 2·2 (3H, s, NAc), 2·35 (3H, s, OAc), 2·60 (3H, s, OAc) 7·5 (1H, 2 × d, *J* 9 and 2 Hz, 6-H) 7·7 (1H, d, *J* 2 Hz, 4-H), 7·8 (1H, s, 2-H), and 8·55 (1H, d, *J* 9 Hz, 7-H) (Found: C, 57·8; H, 5·1; N, 8·3. $C_{16}H_{16}N_2O_6$ requires C, 57·8; H, 4·85; N, 8·4%).

(*d*) Reduction of (2; R = NO_2) as in (*c*), but in dimethylformamide alone and for 12 h, gave, on work-up, a gum. This was treated with acetic anhydride; removal of the reagent left a solid which partly dissolved in hot ethanol. The red residue was characterized as *1,1′-diacetyl-5,5′-azoindole-3,3′-diyl diacetate* (15) (100 mg, 5·7%), microcrystals, m.p. 268—270° (from chloroform), *m/e* 460, 418, 376, 174, and 132 (base), $\nu_{max.}$ 1760 (OAc), 1700 (NAc), and 1200 cm^{-1} (CO), $\lambda_{max.}$ 245sh (ε 22,800),255 (23,700), 288 (2560), and 298sh (18,700) nm, δ (CF_3·-CO_2H) 2·60 (6H, s, 2 × NAc), 2·90 (6H, s, 2 × OAc), 8·20 (2H, s, 2- and 2′-H), 8·4 (2H, 2 × d, *J* 10 and 2 Hz, 6- and 6′-H), 8·60 (2H, d, *J* 2 Hz, 4- and 4′-H), and 8·9 (2H, d, *J* 10 Hz, 7- and 7′-H) (Found: C, 62·5; H, 4·4;N, 12·1. $C_{24}H_{20}N_4O_6$ requires C, 62·6; H, 4·4; N, 12·2%).

On concentration of the ethanolic extract the *acetamido-derivative* (2, R = NHAc) crystallised, giving needles (1·4 g, 67%), m.p. 221—223, *m/e* 274, 232, and 190 (base), $\nu_{max.}$ 3300 (NH), 1750 (OAc), 1710 (NAc), 1660 (NHAc), and 1210 cm^{-1} (CO), $\lambda_{max.}$ 247 (ε 20,900), 300 (4120), and 305 (4000) nm, δ ($CDCl_3$) 2·1 (3H, s, NHAc), 2·35 (3H, s, NAc), 2·55 (3H, s, OAc), 7·4 (1H, 2 × d, *J* 8 and 2 Hz, 6-H), 7·75 (1H, s, 2-H), 8·1 (1H, d, *J* 2 Hz, 4-H), and 8·45 (1H, d, $J_{7.6}$ 8 Hz, 7-H) (Found: C, 61·3; H, 5·3; N, 10·0. $C_{14}H_{14}N_2O_4$ requires C, 61·3; H, 5·1; N, 10·2%).

Further concentration of the mother liquor from which the amide (2; R = NHAc) separated gave *5-acetamido-1-acetylindoxyl* (16) (255 mg, 14·4%), m.p. 246—247° (from ethanol), $\nu_{max.}$ 1725 (NAc), 1690 (CO), and 1645 cm^{-1} (NHAc), $\lambda_{max.}$ 249 (ε 27,500), 269sh (17,700), 278 (21,500), 286sh (16,800), and 368 (3840) nm, δ [$(CD_3)_2SO$] 2·05 (3H, s, NHAc), 2·2 (3H, s, NAc), 2·5 (2H, s, 2-H_2), 7·7 (1H, 2 × d, *J* 8 and 2 Hz, 6-H), 8·0 (1H, d, *J* 2 Hz, 4-H), 8·3 (1H, d, $J_{7.6}$ 8 Hz, 7-H), and 10·1br (1H, s, NH) (Found: C, 61·95; H, 5·2; N, 12·1. $C_{12}H_{12}N_2O_3$ requires C, 62·1; H, 5·2; N, 12·1%).

3-Ethoxy-5-nitroindole (4).—The nitroindole (2; R = NO_2) (4·2 g) in ethanol (50 ml) was heated under reflux with aqueous 20% sulphuric acid (10 ml) under nitrogen for 1 h. On dilution and extraction with ether, compound (4) was obtained as a gum which slowly crystallized and was recrystallized from aqueous ethanol to give pale yellow *prisms* (30 g), m.p. 112°, *m/e* 206, 178 (base), 132, and 131, $\nu_{max.}$ 3400 (NH), 1620 (C=C), 1510 (N=O), and 1330 cm^{-1} (NO), $\lambda_{max.}$ 268sh (ε 7250), 288 (13,000), and 337 (5230) nm, δ ($CDCl_3$) 0·95 (3H, t, *J* 7 Hz, CH_2·CH_3), 3·65 (2H, q, *J* 7 Hz, CH_2·CH_3), 6·6 (1H, s, 2-H), 7·0 (1H, d, *J* 9 Hz, 7-H), 7·55 (1H, 2 × d, *J* 9 and 2·5 Hz, 6-H), and 8·05 (1H, d, *J* 2·5 Hz, 4-H) (Found: C, 58·0; H, 5·0; N, 13·5. $C_{10}H_{10}N_2O_3$ requires C, 58·25; H, 4·9; N, 13·6%).

(E)- *and* (Z)-2-{1-[3-(1-*methoxyethyl*)-4-*pyridyl*]*ethylidene*}-*5-nitroindolin-3-one* [(5) *and* (6) (R = NO_2)].—(*a*) A mixture of 3-ethoxy-5-nitroindole (4·8 g) and 4-acetyl-3-(1-methoxyethyl)pyridine (4·3 g) [5] in aqueous 10% hydrogen bromide (125 ml) was refluxed for 10 min under nitrogen atmosphere and then kept at room temperature for 72 h. Basification and extraction with chloroform furnished a red oil, together with a considerable amount of a deep purple insoluble solid which could not be purified. Trituration of the oil with ethanol afforded the *E*-isomer (5; R = NO_2), m.p. 250° (decomp.) (from ethanol), and evaporation of the ethanolic filtrate gave the *Z*-isomer (6; R = NO_2), m.p. 225—230°; total yield 4%; *m/e* 339, 307 (base), 292, and 280.

The (E)-*isomer* showed $\nu_{max.}$ 1688 (CO), 1630 (C=C),

[11] S. J. Holt and V. Petrow, *J. Chem. Soc.*, 1947, 607.

1505, and 1325 cm^{-1}, $\lambda_{max.}$ 256 (ε 12,500), 266 (12,900), 287sh (14,000), 297 (15,100), 372 (10,100), 420sh (5900), and 444 (5150) nm, δ ([$^2H_5$]pyridine; 30°) 1·45 and 1·51 (3H, 2 × d, *J* 6 Hz, CH·C*H*$_3$), 2·32 and 2·38 (3H, 2 × s, C·C*H*$_3$), 3·19 and 3·28 (3H, 2 × s, OMe), *ca.* 4·6 (1H, 2 × interleaving q, C*H*·CH$_3$), 7·02 (1H, d, *J* 8·5 Hz, 7-H), 7·20 (1H, d, *J* 5 Hz, 5′-H), 8·32 (1H, 2 × d, *J* 8·5 and 2·0 Hz, 6-H), 8·56 (1H, d, *J* 2·0 Hz, 4-H), 8·6 (1H, d, *J* 5 Hz, 6′-H), and 9·12 (1H, s, 2′-H). From the temperature dependence of this spectrum, E_a, the potential energy barrier to rotation, is calculated to be 71 kJ mol^{-1}.

The (Z)-*isomer* showed $\nu_{max.}$ 1695 (CO), 1635 (C=C), 1605, 1515, and 1325 cm^{-1} (the electronic spectra of *E* and *Z*-isomers are identical), [(CD$_3$)$_2$SO; 30°] 1·35 (3H, d, *J* 6 Hz, CH·C*H*$_3$), 3·1 (3H, s, C·CH$_3$), 3·3 (3H, s, OMe), *ca.* 4·3 (1H, q, C*H*·CH$_3$), 7·0 (1H, d, *J* 9 Hz, 7-H), 7·3 (1H, d, *J* 5 Hz, 5′-H), 8·2 (1H, 2 × d, *J* 9 and 2 Hz, 6-H), 8·25 (1H, d, *J* 2 Hz, 4-H), 8·6 (1H, d, *J* 5 Hz, 6′-H), 8·7 (1H, s, 2′-H), and 9·7 (1H, s, NH). In the case of this isomer the n.m.r. spectrum obtained was that of the enantiomeric mixture, the coalescence temperature being below 30° (Found: C, 63·5; H, 5·0; N, 12·5. $C_{18}H_{17}N_3O_4$ requires C, 63·7; H, 5·05; N, 12·4%).

(*b*) The indolinone (6; R = H) (2 g) in concentrated sulphuric acid (6 ml) at 0° was treated dropwise with potassium nitrate (1·2 mol. equiv.) in concentrated sulphuric acid during 10 min. The mixture was then poured on ice (30 g), basified with sodium hydrogen carbonate, and extracted with chloroform to give, after removal of solvent, a red gum which was worked up to give a mixture of (5) and (6) (R = NO$_2$) (750 mg).

2-{1-[3-(1-*Methoxyethyl*)-4-*pyridyl*]*ethylidene*}-5-*nitroindolin*-3-*ol* (9; R = NO$_2$).—The indolinones (5) and (6) (R = NO$_2$) (500 mg) in 95% ethanol (50 ml) were treated with sodium borohydride in portions at room temperature. After 15 min the solvent was evaporated off and the residue partitioned between chloroform and water. Concentration of the chloroform layer afforded a red gum which when triturated with ether gave an orange solid. This when recrystallized from ethanol provided deep red crystals (76 mg), m.p. 194—195° (subsequent crops from the mother-liquor were yellow and melted in the range 145—155°), *m/e* 341 (v. weak), 323, 307, 292 (base), and 278, $\nu_{max.}$ *ca.* 3320, 1620, 1510, 1320, and 1180 cm^{-1}, $\lambda_{max.}$ 254 (ε 8950) and 410 (15,400) nm, δ [(CD$_3$)$_2$SO] 1·40 (3H, d, *J* 6 Hz, CH·C*H*$_3$), 2·0 (3H, s, CH$_3$), 3·2 (3H, s, OMe), 4·5 (1H, q, *J* 6 Hz, C*H*·CH$_3$), 5·6 [1H, s, C(OH)*H*], 6·8 (1H, d, *J* 7 Hz, 5′-H), 7·25 (1H, d, *J* 8 Hz, 7-H), 8·0 (1H, d, *J* 2 Hz, 4-H), 8·15 (1H, 2 × d, *J* 7 and 2 Hz, 6-H), 8·45 (1H, d, *J* 7 Hz, 6′-H), 8·6 (1H, s, 2′-H), and 9·75 (1H, s, NH) (an additional peak, probably due to OH plus water, is observed at δ 3·1). This material could not be dried (see later) and consistent analytical figures were not obtained.

2-{1-[3-(1-*Methoxyethyl*)-4-*pyridyl*]*vinyl*-5-*nitroindole* (10; R = NO$_2$).—A solution of the alcohol (9; R = NO$_2$) (50 mg) in dry benzene was heated in a Dean–Stark apparatus for 12 h. Removal of the solvent and crystallization of the residue from aqueous ethanol gave (10; R = NO$_2$) as yellow *prisms* (22 mg, 46·5%), m.p. 239°, *m/e* 323, 291 (base), and 276, $\nu_{max.}$ 1620sh, 1610, 1592, 1515, 1330, and 1110 cm^{-1}, $\lambda_{max.}$ 288sh (ε 36,800), 293 (37,800), 310sh (13,070), and 341 (9950) nm, δ (CDCl$_3$) 1·3 (3H, d, *J* 6 Hz, CH·C*H*$_3$), 3·0 (3H, s, OMe), 4·35 (1H, q, *J* 6 Hz, CH·CH$_3$), 5·3 and 6·2 (2H 2 × s, C=CH$_2$), 6·21 (1H s, 3-H), 7·25 (1H, d, *J* 5 Hz, 5′-H), 7·5 (1H, d, *J* 9 Hz, 7-H), 8·0 (1H, 2 × d, *J* 9 and 2 Hz, 6-H), 8·45 (1H, d, *J* 2 Hz, 4-H), 8·55 (1H, d, *J* 5 Hz, 6′-H), and 8·7 (1H, s, 2′H) (Found: C, 67·2; H, 5·3; N, 12·7. $C_{18}H_{17}N_3O_3$ requires C, 66·9; H, 5·3; N, 13·0%).

5-*Amino*-2-{1-[3-(1-*methoxyethyl*)-4-*pyridyl*]*ethyl*}*indole* (8; R = NH$_2$).—Reduction of the indolinones (5) and (6) (R = NO$_2$) with sodium borohydride in boiling ethanol gave, on work-up, a small amount of an almost colourless solid [*m/e* 295, 248 (base), and 233], which on acetylation afforded (8; R = NHAc) (see later).

2-{1-[3-(1-*Methoxylethyl*)-4-*pyridyl*]*ethyl*}-3,5-*dinitroindole* (11; R = H).—The indole (8; R = H) (1·2 g) in concentrated sulphuric acid (10 ml) * was treated dropwise with a solution of potassium nitrate (1·2 mol. equiv.) in sulphuric acid at 0°. After the addition (*ca.* 30 min), the mixture was poured on ice, basified, and extracted with ethyl acetate. Evaporation of the extract and trituration of the residue with ether afforded a yellow solid which crystallized from acetone as *prisms* (486 mg), m.p. 140° (decomp.), *m/e* 370 (weak), 323, and 292 (base), $\nu_{max.}$ 1600, 1540, 1520, 1350, and 1105 cm^{-1}, $\lambda_{max.}$ 255 (ε 22,300), 320br (10,600), and 412 (6860) nm, δ (CDCl$_3$) 1·45 [3H, d, *J* 7 Hz, CH(OMe)·C*H*$_3$], 1·74 and 1·70 (3H, 2 × d, *J* 7 Hz, CH·C*H*$_3$) (diastereoisomerism; see ref. 6), 3·1 and 3·2 (3H, 2 × s, OMe), 4·85br [1H, q, *J* 7 Hz, C*H*(OMe)·CH$_3$], 5·5br (1H, q, *J* 7 Hz, C*H*·CH$_3$), 7·05 (1H, m, 5′-H), 7·8 (1H, d, *J* 9 Hz, 7-H), 8·25 (1H, 2 × d, *J* 9 and 2 Hz, 6-H), 8·45br (1H, d, *J* 5 Hz, 6′-H), 8·6 (1H, s, 2′-H), and 8·9 (1H, d, *J* 2 Hz, 4-H) (Found: C, 58·2; H, 4·9; N, 15·1. $C_{18}H_{18}N_4O_5$ requires C, 58·4; H, 4·9; N, 15·1%).

2-{1-[3-(1-*Methoxyethyl*)-4-*pyridyl*]*ethyl*}-3,5,7-*trinitroindole* (11; R = NO$_2$).—The foregoing reaction was repeated with 4 mol. equiv. of potassium nitrate. After purification, the product (11; R = NO$_2$) was obtained as yellow *prisms* (60%), m.p. 235° (decomp.) (from ethanol) *m/e* 415, 368, 337 (base), and 321, $\nu_{max.}$ *ca.* 3400 (EtOH, NH), 1600, 1540, and 1105 cm^{-1}, $\lambda_{max.}$ 272 (ε 17,800), 330 (11,500), and 411 (10,200) nm, δ [(CD$_3$)$_2$SO] 1·0 (3H, t, *J* 7 Hz, C*H*$_3$·CH$_2$·OH), 1·4 (3H, d, *J* 6·5 Hz, C*H*$_3$·CH(OMe)], 1·17 (3H, d, *J* 6·5 Hz, C*H*$_3$C), 3·1 (3H, s, OMe), 3·5 (2H, q, *J* 7 Hz, CH$_3$·C*H*$_2$·OH), 4·8 [1H, q, *J* 6·5 Hz, C*H*(OMe)Me], 5·5 (1H, q, *J* 6 Hz, C*H*·CH$_3$), 7·0 (1H, d, *J* 5 Hz, 5′-H), 8·35 (1H, s, 4-H), 8·5 (1H, d, *J* 5 Hz, 6′-H), and 8·7 (2H, s, 6- and 2′-H) (Found: C, 52·3; H, 4·9; N, 15·1. $C_{18}H_{17}N_5O_7$,C_2H_5OH requires C, 52·1; H, 5·0; N, 15·2%).

2-[1-(3-*Vinyl*-4-*pyridyl*)*ethyl*]*indole* (12).—The indole (8; R = H) (200 mg) in concentrated sulphuric acid (10 ml) was heated for 30 min at 100°, cooled, and poured on ice. Basification and extraction with ether yielded (12) as *prisms* (152 mg, 86%), m.p. 140—141°, *m/e* 248 and 233 (base), $\nu_{max.}$ 3110, 1625, 1610, and 1540 cm^{-1}, $\lambda_{max.}$ 260 (ε 11,900), 280sh (10,500), and 293 (8100) nm, δ (CDCl$_3$) 1·6 (3H, d, *J* 7 Hz, CH·C*H*$_3$), 4·4 (1H, q, *J* 7 Hz, C*H*·CH$_3$), 5·25, 5·4, and 5·7 (2H, 3 × d, *J* 1·5 Hz, CH=C*H*$_2$), 6·4br (1H, s, 3-H), 6·7—7·2 (5H, m, 4-, 5-, 6-, and 5′-H, and C*H*=CH$_2$), 7·5 (1H, m, 7-H), 8·25 (1H, d, *J* 5 Hz, 6′-H), 8·5 (1H, s, 2′-H), and 8·7br (1H, s, NH) (Found: C, 82·4; H, 6·7; N, 11·3. $C_{17}H_{16}N_2$ requires C, 82·2; H, 6·7; N, 11·3%).

(E)-5-*Acetamido*-2-{1-[3-(1-*methoxyethyl*)-4-*pyridyl*]*ethylidene*}*indolin*-3-*one* (5; R = NHAc).—To a mixture of the

* The n.m.r. spectrum of the indole (8; R = H) in sulphuric acid exhibits a broad two-proton singlet at δ 4·0. This is absent in the spectrum of a solution in deuteriochloroform, where the C-3 proton gives a clearly defined singlet at δ 6·4.

indoxyl (2; R = NHAc) (2 g) and the ketone (3) (1 mol. equiv.) in methanol (60 ml) under nitrogen was added potassium hydroxide (15·6 g) in water (60 ml). The mixture was then sealed up and left for 7 days, and the *product* was then filtered off under nitrogen; yield 0·7 g (27·8%), m.p. 232—234°, *m/e* 351, 304 (base), 292, and 262, $\nu_{max.}$ 1673 (CO), 1630 (NAc), and 1605 cm^{-1} (C=C), $\lambda_{max.}$ 269 (ε 22,100), 290sh (14,500), and 488 (3440) nm, δ [$(CD_3)_2SO$] 1·2 and 1·3 (3H, 2 × d, *J* 7 Hz, CH·CH_3), 2·1 and 2·15 (3H, 2 × s, C·CH_3), 3·0 and 3·1 (3H, 2 × s, OMe), 4·3 (1H, q, *J* 7 Hz, C*H*·CH_3), 7·05 (1H, d, *J* 8 Hz, 7-H), 7·1 (1H, d, *J* 5 Hz, 5′-H), 7·65 (1H, 2 × d, *J* 8 and 2 Hz, 6-H), 7·75 (1H, d, *J* 2 Hz, 4-H), 8·5 (1H, d, *J* 5 Hz, 6′-H), 8·65 (1H, s, 2′-H), 9·4br (1H, s, NH), and 9·9br (1H, s, NHAc) (Found: C, 68·1; H, 5·95; N, 11·9. $C_{20}H_{21}N_3O_3$ requires C, 68·4; H, 6·0; N, 12·0%). In other experiments an extractive work-up, rather than filtration, was employed; in such cases a mixture of *E*- and *Z*-isomers was isolated which were not separated but used directly.

5-Acetamido-2-{1-[3-(1-methoxyethyl)-4-pyridyl]ethyl}indole (8; R = NHAc).—The indolinone mixture [(5) and (6) (R = NHAc)] was reduced with sodium borohydride in boiling ethanol and the product (7; R = NHAc), in ether was treated with hydrogen chloride. Evaporation, and crystallization of the residue from acetone and petroleum (b.p. 60—80°) afforded (8; R = NHAc) as *prisms* (66%), m.p. 222—223°, *m/e* 337, 308, and 291 (base), $\nu_{max.}$ 3220 (NH), 1660 (NAc), 1590, and 1545 cm^{-1}, $\lambda_{max.}$ 243 (ε 31,200), 301 (9000), and 311 (8300) nm, δ [$(CD_3)_2SO$] 1·3 and 1·35 [3H, 2 × d, *J* 7 Hz, CH(OMe)·CH_3], 1·6 (3H, d, *J* 7 Hz, CH·CH_3), 2·0 (3H, s, NHAc), 3·08 and 3·12 (3H, 2 × s, OMe), 4·6 (1H, q, *J* 7 Hz, C*H*·CH_3), 4·8 [1H, q, *J* 7 Hz, C*H*(OMe)·CH_3], 6·15 (1H, s, 3-H), *ca.* 7·2 (3H, m, 6-, 7-, and 5′-H), 7·7 (1H, d, *J* 2 Hz, 4-H), 8·4 (1H, d, *J* 5 Hz, 6′-H), 8·5 (1H, s, 2′-H), 9·65 (1H, s, NH), and 10·7 (1H, s, N*H*Ac) (Found: C, 71·0; H, 6·8; N, 12·4. $C_{20}H_{23}N_3O_2$ requires C, 71·2; H, 6·9; N, 12·45%).

9-Aminoellipticine (*9-Amino-5,11-dimethylpyrido*[4,3-b]*carbazole*) (1; R = NH_2).—The indole (8; R = NHAc) (140 mg) in aqueous 60% hydrobromic acid (4 ml) was heated under reflux for 18 h. The yellow product was then filtered off, dissolved in water, basified with sodium hydrogencarbonate, and extracted with ethyl acetate.* The solvent was removed and the residue was crystallized from benzene to give *9-aminoellipticine benzene solvate* (63 mg) as yellow prisms, m.p. 255—260° (decomp.), *m/e* 261 (base), $\nu_{max.}$ 3125 (NH), 1615, and 1595 cm^{-1}, $\lambda_{max.}$ 253 (ε 12,600), 283 (36,800), 297·5 (42,500), 341 (6370), 358sh (4150), and 420 (3240) nm, δ ($CDCl_3$) 2·7 (3H, s, 5-Me), 3·2 (3H, s, 11-Me), 4·8br (2H, s, NH_2), 6·9 (1H, d, *J* 8 Hz, 8-H), 7·3 (1H, d, *J* 8 Hz, 7-H), 7·65 (1H, s, 10-H), 7·8 (1H, d, *J* 6 Hz, 4-H), 8·35 (1H, d, *J* 6 Hz, 3-H), 9·6 (1H, s, 1-H), and 10·8 (1H, s, NH) [Found (sample dried at 100° for 10 h under high vacuum): C, 78·0; H, 5·7; N, 16·1. $C_{17}H_{15}N_3$ requires C, 78·1; H, 5·8; N, 16·1%].

We thank the Cancer Research Campaign for interest and support and Dr. T. A. Connors, Chester Beatty Research Institute, London, for organizing the pharmacological testing of the compounds described.

[3/2610 *Received, 28th December,* 1973]

* Re-extraction of the aqueous extract from which 9-aminoellipticine was obtained with chloroform gave ellipticine (1; R = H) (21 mg), m.p. 309—312° (lit.,[5] 309—312°).