Synthesis of 1,2,3,9b-Tetrahydro-9b-hydroxy-1-phenylpyrrolo-[2,1-*a*]isoindol-5-one *via* the Hydrazinolysis of 2-Phenyl-2-(2-phthalimidoethyl)indan-1,3-dione

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Hydrazinolysis of 2-phenyl-2-(2-phthalimidoethyl)indan-1,3-dione gave 1,2,3,9b-tetrahydro-9b-hydroxy-1-phenylpyrrolo[2,1-*a*]isoindol-5-one *via* the conversion of 2-(2-aminoethyl)-2-phenylindan-1,3-dione into the carbinolamine which underwent ring expansion followed by a transannular cyclisation.

The hydrazinolysis of 2-phenyl-2-(2-phthalimidoethyl)indan-1,3-dione (1) has been reported [1] to give 8b-hydroxy-3a-phenyl-1,3,3a,8b-tetrahydroindeno[1,2-*b*]pyrrol-4(2*H*)-one (2). In addition it has been claimed [1] that treatment of (2) with acid gives the imine (3).

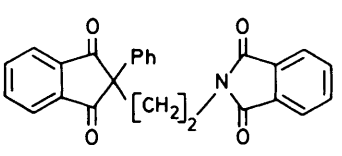
On reinvestigation of these transformations it was found that treatment of the hydrazinolysis product with acid gave a compound which was non-basic and therefore could not be the imine (3). In addition, the ^{1}H n.m.r. spectrum of the product showed two two-proton multiplets at δ 3.5 and 4.1, and the i.r. spectrum a strong band at 1 680 cm^{-1} attributed to a tertiary amide group. Thus the evidence supports the 2,3-dihydro-1-phenylpyrrolo[2,1-*a*]isoindol-5-one structure (4) and eliminates the previously proposed structure (3). As shown in the Scheme, (4) must originate *via* the carbinolamine (2) by ring opening to give the 3,4-dihydro-6-hydroxy-5-phenylbenz[3,4]azocin-1(2*H*)-one (5) which on acid treatment gives rise to (4).

The hydrazinolysis product itself was characterised as 1,2,3,9b-tetrahydro-9b-hydroxy-1-phenylpyrrolo[2,1-*a*]isoindol-5-one (6) rather than as (2) [1] largely on the basis of 270 MHz ^{1}H n.m.r. spectroscopic data. The spectrum showed a set of five one-proton multiplets for the protons of the pyrrolidine ring and decoupling experiments permitted assignments as follows: δ 2.5 (2-H), 2.8 (1-H), 2.95 (2′-H), 3.48 (3-H), and 3.62 (3′-H). A one-proton singlet at δ 6.6, removed on addition of deuterium oxide, indicated the presence of only one exchangeable proton in the molecule. The i.r. spectrum showed absorption at 3 250 and 1 680 cm^{-1} consistent with structure (6).

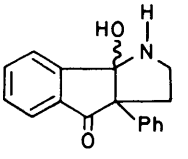
Additional evidence supporting structure (4) for the product obtained by acid treatment of 1,2,3,9b-tetrahydro-9b-hydroxy-1-phenylpyrrolo[2,1-*a*]isoindol-5-one (6) was provided by the catalytic hydrogenation of (4) over Raney nickel. The acid-treatment product assigned structure (3) by Vanag *et al.*[1] would be expected to afford the secondary amine derivative (7) on catalytic reduction, whereas the lactam (4) would afford the pyrrolizidine derivative (8).

The product isolated on catalytic hydrogenation was a crystalline solid, m.p. 112 °C. The i.r. spectrum of this showed a sharp band at 1 680 cm^{-1}. No bands were observed in the secondary amine N–H stretching vibration frequency region. The ^{1}H n.m.r. spectrum showed a one-proton doublet at δ 5.1 (*J* 7.5 Hz) clearly assignable to 9b-H in (8) [*cf.* δ 3.5 for 8a-H in the indolizidin-6-one (9) [2] which does not carry the aromatic ring as in (8) which will result in additional deshielding of the angular proton]. In addition, the spectrum showed the absence of NH protons.

The doublet of triplets at δ 4.15 ($J_{3,3'}$ −12 Hz, $J_{3,2}$ 9 Hz, $J_{3,2}$ 9 Hz) was assigned to one of the 3-protons. The other 3-proton absorbed at δ 3.53 ($J_{3,3'}$ −12 Hz, $J_{3',2}$ 9 Hz, $J_{3',2}$ 4 Hz). Decoupling of the 9b-H signal at δ 5.1 simplified the signals at δ 3.70 permitting assignment of these to the 1-proton ($J_{1,9}$ 7 Hz, $J_{1,2}$ 7 Hz, $J_{1,2}$ 3 Hz).



(1)



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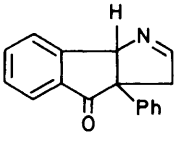

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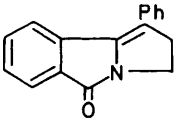


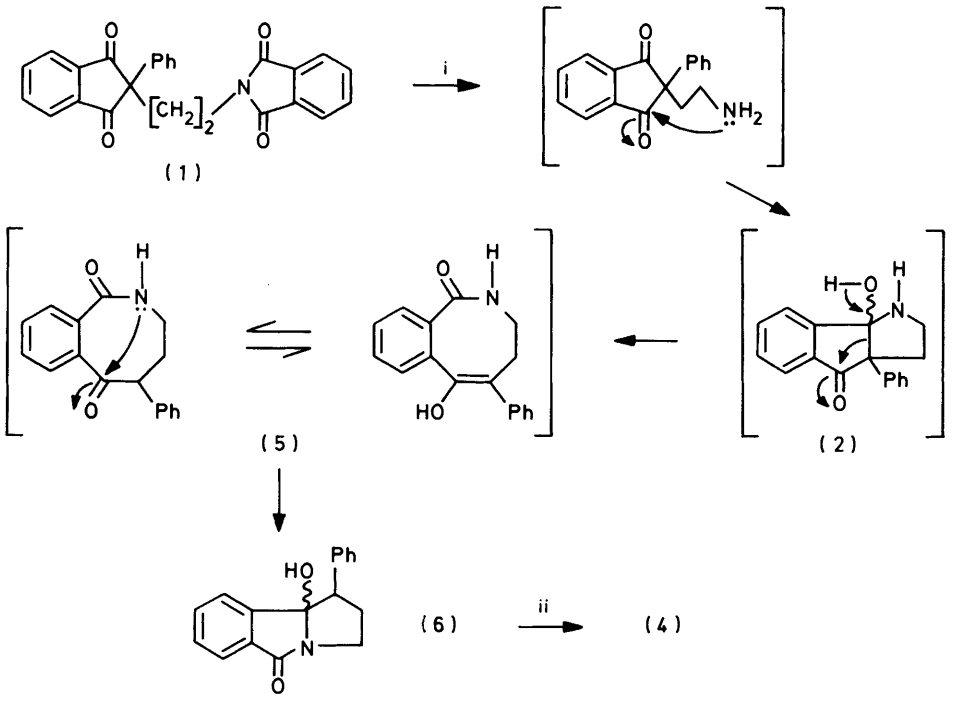
(4)

Catalytic reduction of compound (4) over Adams platinum oxide catalyst gave a white crystalline solid, $C_{17}H_{27}NO$, m.p. 101 °C. The i.r. spectrum showed a band at 1 685 cm^{-1} attributed to the amide group, thus giving additional support for the proposed structure (4) for the starting material, since the previously proposed structure (3) [1] would, on catalytic reduction, be expected to afford the fully saturated amino-ketone (10), which would show a carbonyl absorption band in the i.r. spectrum around 1 740—1 750 cm^{-1}, and secondary amine absorption bands at *ca.* 1 500 and 3 300—3 500 cm^{-1}. The n.m.r. spectrum of the hydrogenation product showed no aromatic ring protons indicating that the product was fully saturated, and no exchangeable proton signal was observed, which eliminated structure (10). All the data were therefore in accord with the 1-cyclohexylperhydropyrrolo[2,1-*a*]isoindol-5-one structure (11).

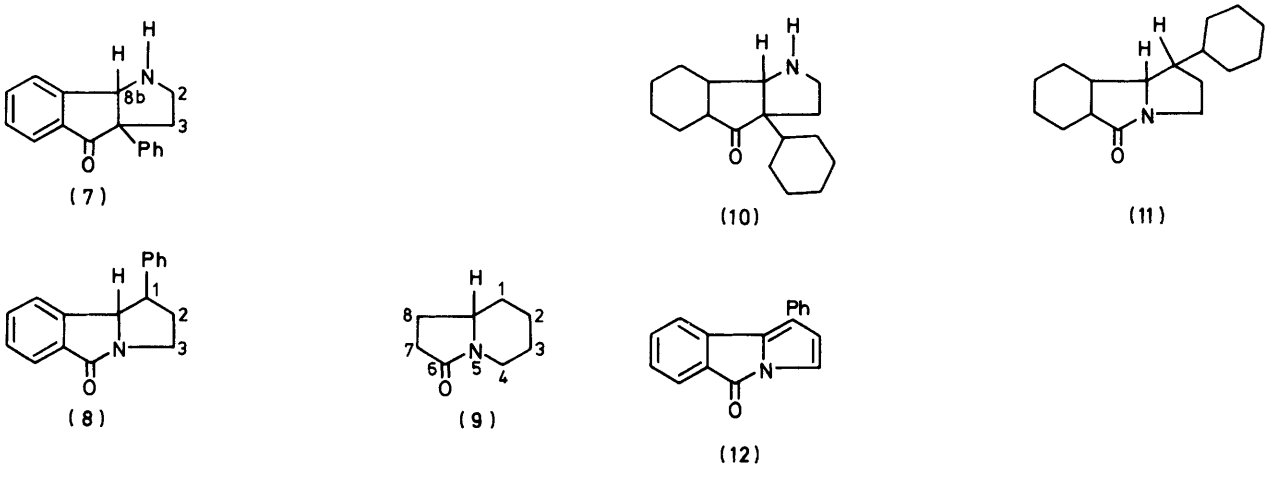
Further support for the assignment of structure (4) was provided by the treatment of (4) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in dioxan, which afforded an orange crystalline solid, $C_{17}H_{11}NO$, m.p. 101 °C. The n.m.r. spectrum of this showed two one-proton doublets at δ 6.35 (*J* 4 Hz) and δ 7.15 (*J* 4 Hz) attributed to the 2- and 3-protons in 1-phenylpyrrolo[2,1-*a*]isoindol-5-one (12).

Experimental

Elemental analyses were carried out at the Butterworth Microanalytical Laboratory, Teddington, Middlesex, Glaxo Group Research Ltd., Analytical Research Department, and



Scheme. *Reagents*: i, Hydrazine hydrate, ethanol; ii, HCl



Portsmouth Polytechnic Analytical service. I.r. spectra were recorded on a Perkin-Elmer (SP 197) spectrometer in either deuteriochloroform or chloroform, unless otherwise stated. ^{1}H N.m.r. spectra were determined at 60 MHz with a Varian T60 spectrometer and/or at 90 MHz with an EM 390 spectrometer, and/or at 270 MHz with a Brüker Spectrospin WH-270 spectrometer. The solutions employed for recording the spectra at 60 MHz and/or 90 MHz and/or 270 MHz were in deuteriochloroform, deuteriobenzene, deuteriodimethyl sulphoxide unless otherwise stated, with tetramethylsilane as internal standard; assignment of hydroxy-protons were checked by deuterium exchange. U.v. spectra were recorded on a Pye-Unicam spectrometer (SP 800A) in solutions of absolute alcohol or methanol.

Column chromatography was carried out with Woelm neutral alumina. Woelm neutral alumina of Brockmann activity 1 was deactivated as required by addition of the appropriate amount of distilled water, the alumina being allowed to stand for 2 h.

Melting points were determined in sealed tubes and are uncorrected.

3-*Benzylidenephthalide*.—A mixture of phenylacetic acid (100 g), phthalic anhydride (110 g), and anhydrous sodium acetate (3 g) was heated at 210 °C (6 h) during which time water (8 ml) was collected. The cooled mass was leached with boiling water, filtered, dried, and recrystallised from methanol to afford 3-benzylidenephthalide as a crystalline yellow solid (77 g, 48%), m.p. 96—98 °C (lit.,[3] 96—98 °C), $\nu_{max.}$ ($CHCl_3$) 1 580, 1 600, and 1 700 cm^{-1}; $\lambda_{max.}$ (EtOH) 215, 295.5, 303, and 337 nm; δ ($CDCl_3$) 6.4 [1 H, s, C(Ph)-*H*], 7.35 (5 H, s, Ar), and 7.6—8.1 (4 H, m, Ar).

2-*Phenylindan*-1,3-*dione*.—3-Benzylidenephthalide (76.8 g) was added to a solution of sodium (6.5 g) in methanol (850 ml) and the resulting dark red solution stirred and boiled under reflux for 15 min. The cooled reaction was poured into water,

and dilute HCl was added until the red colour was discharged. The resulting yellow solid was filtered off, washed with water, and recrystallised from ethanol to give 2-phenylindan-1,3-dione as shiny yellow flakes (69 g, 69%), m.p. 149—150 °C (lit.,[3] 145 °C), $\nu_{max.}$ ($CHCl_3$) 1 720, 1 700, and 1 600 cm^{-1} $\lambda_{max.}$ (EtOH) 213, 287, and 335 nm; δ ($CDCl_3$) 7.6—8.4 (4 H, m, aromatic), 7.0—7.3 (5 H, s, aromatic), and 4.34 [1 H, s, C(Ph)-*H*].

2-(2-*Hydroxyethyl*)-2-*phenylindan*-1,3-*dione*.—2-Phenylindan-1,3-dione (15 g), 2-chloroethanol (5.5 g), and sodium iodide (10 g) were added to a solution of sodium (4.6 g) in n-propanol (80 ml) at room temperature. The resulting solution was stirred and boiled under reflux for 7 h. The dark red solution formed was cooled and poured into water, and the resulting precipitate formed was filtered off, washed with water, dried, and recrystallised from ethanol to give 2-(2-hydroxyethyl)-2-phenylindan-1,3-dione as a shiny crystalline solid (10.7 g, 58%), m.p. 161 °C, $\nu_{max.}$ ($CHCl_3$) 3 400, 1 750, 1 710, and 1 600 cm^{-1}; δ ($CDCl_3$) 7.7—8.1 (4 H, m, Ar), 7.0—7.65 (5 H, m, Ar), 3.55 (2 H, t, $^{-}CH_2OH$), 2.5 (2 H, t, $^{-}CH_2$-CH_2OH), and 1.9 (1 H, s, OH) (Found: C, 76.5; H, 5.4. $C_{17}H_{14}O_3$ requires C, 76.7; H, 5.3%).

2-(2-p-*Tolylsulphonyloxyethyl*)-2-*phenylindan*-1,3-*dione*.—Toluene-*p*-sulphonyl chloride (7.5 g) was added portionwise to an ice-cooled solution of 2-(2-hydroxyethyl)-2-phenylindan-1,3-dione (8 g) in dry pyridine (53 ml). The mixture was left at room temperature overnight, and then poured into water. The solid which separated out was filtered off, washed with dilute HCl, dried, and recrystallised from ethanol to give 2-(2-*p*-tolylsulphonyloxyethyl)-2-phenylindan-1,3-dione as a white solid (6.1 g, 44%), m.p. 96—97 °C, $\nu_{max.}$ ($CHCl_3$), 1 740, 1 710, and 1 600 cm^{-1}; δ ($CDCl_3$) 7.2—8.1 (8 H, m, Ar), 7.36 (5 H, s, Ar), 4.2 (2 H, t, $^{-}CH_2OTs$), 2.65 (2 H, t, CH_2CH_2-OTs), and 2.45 (3 H, s, p-$C_6H_4CH_3$) (Found: C, 74.2; H, 5.1. $C_{24}H_{20}O_3S$ requires C, 74.2; H, 5.2%).

2-*Phenyl*-2-(2-*phthalimidoethyl*)*indan*-1,3-*dione*.—2-(2-*p*-Tolylsulphonyloxyethyl)-2-phenylidan-1,3-dione (7.6 g) was heated on a water-bath with potassium phthalimide (7.6 g) in dimethylformamide (52 ml) for 4 h. The solution was then poured into water and the solid which separated out was filtered off, washed with water, dried, and recrystallised from ethanol to afford 2-phenyl-2-(2-phthalimidoethyl)indan-1,3-dione as a white solid (3.6 g), m.p. 174—175 °C (lit.,[1] 173 °C), $\nu_{max.}$ ($CHCl_3$) 1 780, 1 740, 1 710, and 1 600 cm^{-1}; $\lambda_{max.}$ (EtOH) 225 and 240 nm; δ ($CDCl_3$) 7.77 (5 H, s, Ar), 7.2—8.2 (8 H, m, Ar), 3.7 (2 H, t, CH_2N), and 2.65 (2 H, t, CH_2-CH_2N).

1,2,3,9*b*-*Tetrahydro*-9*b*-*hydroxy*-1-*phenylpyrrolo*[2,1-a]*isoindol*-5-*one*.—2-Phenyl-2-(2-phthalimidoethyl)indan-1,3-dione (8.6 g) was stirred and heated under reflux with hydrazine hydrate (2.1 ml) in ethanol (300 ml) for 1½ h. The phthalhydrazide formed on cooling was filtered off and the filtrate evaporated to dryness, to give a white solid. Chromatographic separation over Woelm neutral alumina (grade III) with ether as eluant gave 1,2,3,9b-tetrahydro-9b-hydroxy-1-phenylpyrrolo[2,1-*a*] isoindol-5-one as a white crystalline solid (4.4 g, 76%), m.p. 214 °C, $\nu_{max.}$ (Nujol) 3 250, 1 680, and 1 600 cm^{-1}; $\lambda_{max.}$ (MeOH) 205 and 226infl.; δ $(CD_3)_2SO$ 6.9—8.0 (9 H, m, Ar), 6.6 (1 H, s, OH), 3.62 (1 H, q, NCH_{eq}), 3.48 (1 H, m, $N^{-}CH_{ax.}$), 2.95 (1 H, m, 2′-H), 2.80 (1 H, m, 1-H), and 2.50 (1 H, m, 2-H) (Found: C, 76.9; H, 5.6; N 5.2. $C_{17}H_{15}NO_2$ requires C, 77.0; H, 5.7; N, 5.3%).

2,3-*Dihydro*-1-*phenylpyrrolo*[2,1-a]*isoindol*-5-*one*.—1,2,3,-9b-Tetrahydro-9b-hydroxy-1-phenylpyrrolo[2,1-*a*]isoindol-5-one (6 g) was suspended in concentrated HCl (140 ml) and warmed on a water-bath for 1 h. The yellow solid formed on cooling was filtered off, washed with water, dried, and recrystallised from ethanol and ethyl acetate to afford 2,3-dihydro-1-phenylpyrrolo[2,1-*a*]isoindol-5-one as a shiny yellow crystalline solid (3 g, 54%), m.p. 196—197 °C, $\nu_{max.}$ (Nujol) 1 680 cm^{-1}; $\lambda_{max.}$ (EtOH) 220, 248, 273, and 350 nm; δ ($CDCl_3$) 7.7—8.0 (2 H, m, Ar), 7.3—7.7 (7 H, m, Ar), 4.1 (2 H, m, CH_2N), and 3.55 (2 H, m, CH_2CH_2N) (Found: C, 82.3; H, 5.3; N, 5.7. $C_{17}H_{13}NO$ requires C, 82.6; H, 5.3; N, 5.7%).

1,2,3,9*b*-*Tetrahydro*-1-*phenylpyrrolo*[2,1-a]*isoindol*-5-*one*.—2,3-Dihydro-1-phenylpyrrolo[2,1*a*]isoindol-5-one (1.5 g) was dissolved in ethanol (500 ml) and hydrogenated at 1 atm over Raney nickel (0.25 g, W2) as catalyst. When the uptake of hydrogen had ceased, the catalyst was filtered off and the solvent evaporated to afford a white solid. Recrystallisation from ethyl acetate gave 1,2,3,9*b*-*tetrahydro*-1-*phenylpyrrolo*-[2,1-*a*]*isoindol*-5-*one* as a white crystalline solid (0.7 g, 49%), m.p. 110—112 °C, $\nu_{max.}$ ($CHBr_3$) 1 680 cm^{-1}; $\lambda_{max.}$ (EtOH) 207, 231, 248, and 282 nm; δ ($CDCl_3$) 7.6 (1 H, m, Ar), 6.7—7.4 (8 H, m, Ar), 5.1 (1 H, d, HCN), 4.15 (1 H, dt, CH_2-$CH_{eq}N$), 3.70 (1 H, dt, C(Ph)*H*), 3.53 (1 H, oct, $CH_2CH_{ax}N$), and 2.3—3.0 (2 H, m, CH_2CH_2N) (Found: C, 81.8; H, 6.1; N, 5.6. $C_{17}H_{15}NO$ requires C, 81.9; H, 6.1; N, 5.6%).

1-*Phenylpyrrolo*[2,1-a]*isoindol*-5-*one*.—2,3-Dihydro-1-phenylpyrrolo[2,1-*a*]isoindol-5-one (0.2 g) was dissolved in dioxan (15 ml) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.0 g) added gradually. The reaction mixture was stirred at room temperature for 1 h, after which it was gently heated on a water-bath for 15 min. The cooled reaction mixture was diluted with dichloromethane (40 ml) and filtered through a short column of Woelm neutral alumina. Solvent evaporation afforded a yellow solid. Recrystallisation from ether afforded 1-*phenylpyrrolo*[2,1-a]isoindol-5-one as a yellow crystalline solid (0.1 g, 50%), m.p. 100—101 °C, $\nu_{max.}$ ($CDCl_3$) 1 650 and 1 600 cm^{-1}; $\lambda_{max.}$ (EtOH) 210, 233, 265, and 300 nm; δ ($CDCl_3$) 7.2—7.8 (9 H, m, Ar), 7.15 (1 H, d, =CHN), and 6.35 (1 H, d, C*H*=CHN) (Found: C, 83.3; H, 4.7; N, 5.8. $C_{17}H_{11}NO$ requires C, 83.2; H, 4.5; N, 5.7%).

1-*Cyclohexylperhydropyrrolo*[2,1-a]*isoindol*-5-*one*.—2,3-Dihydro-1-phenylpyrrolo[2,1-*a*]isoindol-5-one (2.0 g) was dissolved in methanol (200 ml) and concentrated HCl (10 ml) and hydrogenated at 1 atm over Adams platinum oxide catalyst. When the uptake of hydrogen had ceased, the catalyst was filtered off, and the solvent distilled off under reduced pressure. The acidic solution was made alkaline with dilute NaOH, extracted with ethyl acetate, and dried (Na_2SO_4). Solvent evaporation gave a viscous oil chromatographic separation of which over Woelm neutral alumina (grade III) with ether as eluant afforded 1-cyclohexylperhydropyrrolo-[2,1-*a*]isoindol-5-one as a white crystalline solid (1.3 g), m.p. 101 °C, $\nu_{max.}$ ($CDCl_3$) 2 250 and 1 685 cm^{-1}; $\lambda_{max.}$ (EtOH) 215 nm; δ ($CDCl_3$) 3.8—4.2 (2 H, m, CH_2N), and 1.0—3.0 (25 H, m, complex aliphatic) (Found: C, 78.3; H, 10.6; N, 5.4. $C_{17}H_{27}NO$ requires C, 78.2; H, 10.4; N, 5.4%).

Acknowledgements

We thank the S.R.C. for a C.A.S.E. award (to A. P.).

References

1 G. Vanag and J. Dregaris, *Latvijas. P.S.R. Zinatnu. Akad. Vestis. Khim. Ser.*, 1964, **5**, 559.
2 R. Cahill and T. A. Crabb, *Org. Magn. Reson.*, 1973, **5**, 295.
3 A. M. Khaletskii, M. B. Kolesova, and K. M. Metrikina, *Zhur. obschei Khim.*, 1956, **26**, 871.

Received 17*th May* 1982; *Paper* 2/805