Nitrogen Heterocycles. Part 9.[1,2] Some Reactions of Phthalimidin-2-ylacetic Acid Derivatives, and a New Route to Isoindolobenzazepines

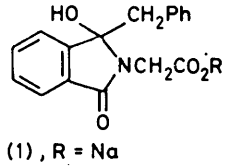
By **Valerio Scartoni,* Rita Fiaschi, Serena Catalano, Ivano Morelli,** and **Antonio Marsili,** Istituti di Chimica Organica e di Chimica Farmaceutica, Facoltà di Farmacia dell'Università di Pisa, Via Bonanno 6, 56100 Pisa, Italy

3-Benzyl-3-hydroxyphthalimidin-2-ylacetic acid (2) can be converted to (*E*)- and (*Z*)-3-benzylidenephthalimidin-2-ylacetic acids (3) and (4). These two compounds give (*Z*)-3-(α-bromobenzylidene)phthalimidin-2-ylacetic acid (9) on bromination. Whilst reaction of bromine with the sodium salt of the (*Z*)-isomer (8) affords (9), the same reaction with the (*E*)-isomer (7) leads to 10b-bromo-1-phenyl-4,10b-dihydroisoindolo[1,2-*c*][1,4]oxazine-3,6(1*H*)-dione (10), and 9b-(α-bromobenzyl)-3,10b-dihydroisoindolo[1,2-*b*][1,3]oxazole-2,5-dione (11). Cyclisation of (4) with polyphosphoric acid gives isoindolo[2,3-*a*][3]benzazepine-5,8(7*H*)-dione (12). A series of products were obtained from this compound, including both 7,8,13,13a-tetrahydro-5*H*-isoindolo[2,3-*a*][3]-benzazepine (26) and its methiodide (27), related to Schöpf's base VI.

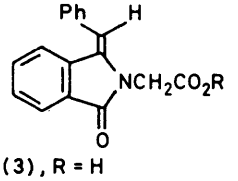
PREVIOUS work has shown that suitably substituted phthalimidines can be converted to isoquinoline,[3,4] pyrrole and benzazepine,[4] and indole [5] derivatives. We wish to report in this paper some transformations of 3-benzylidenephthalimidin-2-ylacetic acids, and the conversion of the (*Z*)-isomer to a tetracyclic isoindolobenzazepine related to Schöpf's base VI.[6] A similar compound has been recently converted to α-allocryptopine.[7]

RESULTS AND DISCUSSION

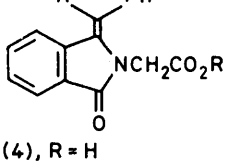
By heating an alcoholic solution containing 3-benzylidenephthalide and sodium glycinate, sodium 3-benzyl-3-hydroxyphthalimidin-2-ylacetate (1) was obtained in good yield. Treatment of (1) with mineral acids in the cold gave acid (2). When (2) was heated with hydrochloric acid in acetic acid, a 4 : 1 mixture of (*E*)- and (*Z*)-3-benzylidenephthalimidin-2-ylacetic acids (3) and (4) was obtained. This reaction of (2) is thus analogous to that already observed for similar compounds.[8] The stereochemistry of (3) and (4) was determined by n.m.r.



(1), R = Na
(2), R = H

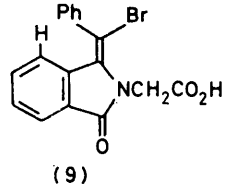


(3), R = H
(5), R = Me
(7), R = Na



(4), R = H
(6), R = Me
(8), R = Na

spectroscopy; the vinylic proton of (3) resonates at higher, and the methylene protons at lower field, than the corresponding protons of (4) (see Experimental section); moreover, the aromatic resonance is more complex in the spectrum of (4), thus indicating increased conjugation, due to the presence of a *trans*-stilbene system in its molecule.



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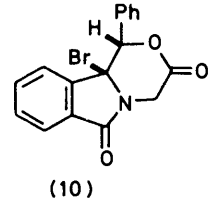

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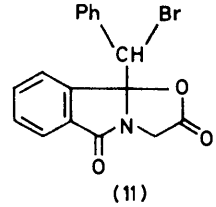


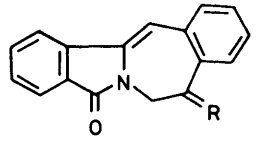
(11)

A good conversion of the (*E*)- to the (*Z*)-isomer was achieved by photochemical isomerisation, either by irradiating the (*E*)-acid in ethanol, or its sodium salt in ethanol–water. A chemical proof of the stereochemistry of (4) was obtained by reaction of (*Z*)-3-benzylidenephthalimidine [8] with methyl bromoacetate in the presence of potassium t-butoxide: the methyl ester (6) thus formed was identical with the product obtained by treatment of (4) with diazomethane [and different from (5), prepared by analogous treatment of (3)].

Both acids (3) and (4) gave on bromination a single product, which was given structure (9) on the basis of n.m.r. spectra: thus a doublet at δ 6.07 p.p.m. due to an aromatic proton, was attributed to H-4, by analogy with results obtained from similar compounds.[4,8] This proton is shielded by the benzylidene phenyl group, which should lie in a plane almost perpendicular to the plane of the phthalimidine ring.

Bromination of the sodium salt (8) also gave (9). However, when (7) was treated with bromine, two isomeric neutral bromides were unexpectedly formed, in the ratio 3 : 2. The i.r. spectra of these bromides showed, in addition to the band attributable to the phthalimidine carbonyl, another band, at 1 795 cm^{-1} for the minor component, and at 1 770 cm^{-1} for the major one. These

could arise from carbonyl groups in a five- and a six-membered lactone ring respectively. Therefore, structures (10) and (11) were assigned to the two neutral bromides, on the basis of elemental analysis and spectral data. In fact, the lactone rings in both compounds are strained because of their fusion with the five-membered lactam ring and, moreover, they contain nitrogen and electronegative substituents: these factors could well influence their carbonyl frequencies.[9] In addition, in the n.m.r. spectra of both compounds the ring-CH_2 protons give rise to AB quartets because of their differing magnetic environments, due to the rigid structures of the lactone rings.

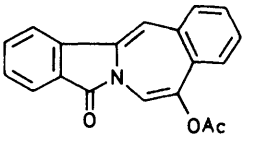


(12), R = O

(14) a; R = $(OMe)_2$ b; R = $(OEt)_2$

(15), R = NOH

(18), R = H_2



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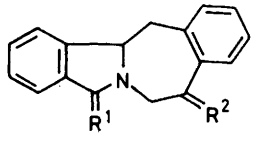
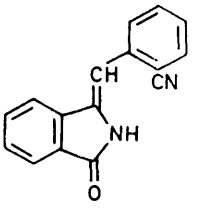


(19), R^1 = O; R^2 = H, OH

(20), R^1 = R^2 = O

(25), R^1 = O; R^2 = H_2

(26), R^1 = R^2 = H_2



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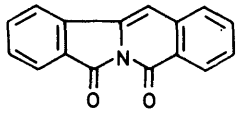

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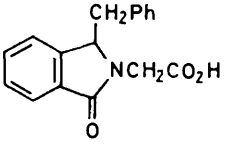

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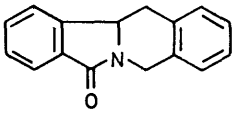

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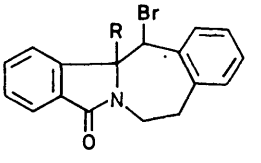
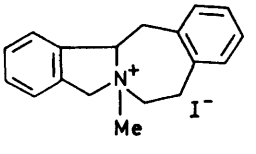


(23), R = OMe

(24), R = OH

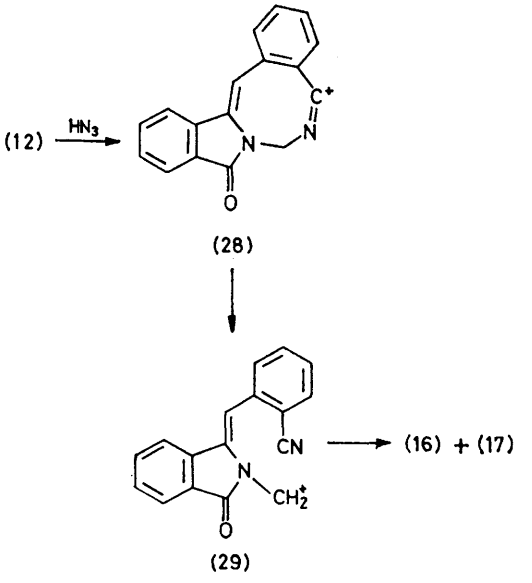


(27)

The different behaviour of the salts (7) and (8) toward bromination deserves some comment. If a bromonium ion intermediate is to be assumed as the electrophilic step of the process, a subsequent intramolecular attack by the nucleophilic carboxylate anion may be possible only if there can be neither steric nor electronic repulsions between the negatively charged attacking group and the benzene ring in the transition state, which must have a stereochemistry very similar to that of the starting product. This appears to be the case for (7), where the $CH_2CO_2^-$ group is located on the opposite side of the double bond, with respect to the benzylidene group. For (8), on the other hand, the repulsions between these groups may well make proton elimination an easier process, thus leading to (9). Since the addition to the double bond is an *anti*-process,[10] (10) and (11) should have the indicated stereochemistry.

When the (*Z*)-acid (4) was heated with polyphosphoric acid, cyclisation to the isoindolobenzazepine derivative (12) took place; this compound could easily be transformed into the enol acetate (13), the acetals (14a,b), and the oxime (15). By reaction with hydrazoic acid compound (12) afforded two products, which were assigned structures (16) and (17), respectively, on the basis of elemental analysis, i.r. spectra, and mechanistic considerations. It appears very likely that both products may originate from the same precursor (29), formed by ring-opening of the reaction intermediate [11] (28). A (*Z*)-configuration could therefore be tentatively assigned to (16) on the basis of the probable mechanism of its formation, and also because it bears no substituent at nitrogen.[8] N.m.r. spectroscopy was not helpful in confirming assignment.

Wolff–Kishner reduction of (12) gave (18), whereas catalytic hydrogenation over platinum led to alcohol (19), which was oxidised by chromium trioxide to (20). This latter compound could be prepared also from 3-benzyl-



(28)

(29)

phthalimidin-2-ylacetic acid (21) and polyphosphoric acid. In this cyclisation large amounts of the iso-

indoloisoquinoline derivative (22) were obtained also, due to the loss, before cyclisation, of carbon monoxide from the acyl cation intermediate, as already observed in similar cases.[12] Bromination of (18) in methanol gave methoxy-bromide (23), whereas bromination in aqueous acetic acid gave hydroxy-bromide (24). The regiochemistry of these reactions was deduced on the basis of the fact that (23) was recovered unchanged after prolonged reflux with ethanolic potassium hydroxide, and (24) was not oxidised by Jones' reagent. Compounds (18), (23), and (24) were converted to the tetrahydroisoindolobenzazepinone (25) by catalytic hydrogenation over palladium. Lithium aluminium hydride reduction of (25) gave the unstable tetrahydroisoindolobenzazepine (26),* which was transformed into the corresponding methiodide (27).

Work is in progress to test whether the series of reactions described above can be applied to similar products, bearing appropriate substituents in the benzene rings, in the hope of finding a new route to alkaloids of the protopine, and possibly of the rhoeadine series.

EXPERIMENTAL

M.p.s were determined with a Kofler apparatus; i.r. spectra were recorded for Nujol mulls with a Perkin-Elmer 197 spectrophotometer; n.m.r. spectra were recorded with a JEOL C-60 HL spectrometer ($SiMe_4$ as internal standard).

Sodium 3-Benzyl-3-hydroxyphthalimidin-2-ylacetate (1).—A mixture of 3-benzylidenephthalide (40 g), glycine (15.5 g), 10N sodium hydroxide (20 ml), and ethanol (180 ml) was heated on a steam bath for 30 min, then cooled and set aside at 0 °C for 12 h. The precipitate (55 g) crystallised from methanol as *needles*, m.p. 179—182 °C. An analytical sample was dried over phosphorus pentaoxide at 105 °C (Found: C, 64.0; H, 4.65; N, 4.2. $C_{17}H_{14}NNaO_4$ requires C, 64.0; H, 4.4; N, 4.4%); $\nu_{max.}$ 1 580 and 1 640 cm^{-1} (CO_2^- and CO).

3-Benzyl-3-hydroxyphthalimidin-2-ylacetic Acid (2).—The above sodium salt (10 g) was dissolved in water (100 ml) and the solution was acidified with 2N hydrochloric acid at 5 °C. The precipitate (8.5 g) crystallised from methanol as *needles*, m.p. 99—101 °C (Found: C, 68.4; H, 5.35; N, 4.4. $C_{17}H_{15}NO_4$ requires C, 68.7; H, 5.1; N, 4.7%); $\nu_{max.}$ 1 668 and 1 700 cm^{-1}; δ[$(CD_3)_2SO$–$CDCl_3$] 2.98, 3.20, 3.35, 3.57 (2 H, AB q, benzyl-CH_2), 3.92, 4.20, 4.27, and 4.55 (2 H, AB q, N-CH_2).

(E)- *and* (Z)-*3-Benzylidenephthalimidin-2-ylacetic Acids* [(3) *and* (4)].—A suspension of (2) (10 g) in acetic acid (100 ml) and 6N hydrochloric acid (10 ml) was heated on a steam bath for 30 min, then diluted with water (200 ml) and set aside at 0 °C for 12 h. The precipitate (8.2 g) was shown by n.m.r. to contain (3) and (4) in the ratio 4 : 1. Fractional crystallisation from acetic acid and from acetic acid–water gave (3) as the less soluble, and (4) as the more soluble material. The former (*E*)-product (*needles*) had m.p. 207—209 °C (Found: C, 73.1; H, 4.9; N, 5.0. $C_{17}H_{13}NO_3$ requires C, 73.1; H, 4.7; N, 5.0%); $\nu_{max.}$ 1 655 and 1 735 cm^{-1} (CO); $\delta(CDCl_3)$ 4.72 (2 H, s, CH_2), and 6.45 (1 H, s, olefinic H). The latter (*Z*)-product (*prisms*) had m.p. 188—190 °C (Found: C, 73.20 H, 4.7; N, 5.0. $C_{17}H_{13}NO_3$ requires C, 73.1; H, 4.7; N, 5.0%); $\nu_{max.}$ 1 635 and 1 690 cm^{-1} (CO); $\delta(CDCl_3)$ 4.35 (2 H, s, CH_2), 6.81 (1 H, s, olefinic-H).

Methyl Esters (5) *and* (6).—A stirred ethereal suspension of either (3) or (4) was treated with a slight excess of diazomethane; a clear solution was obtained. The residue formed on evaporation was crystallised from chloroform–hexane. Ester (5), *prisms*, had m.p. 98—101 °C (Found: C, 73.6; H, 5.25; N, 4.6. $C_{18}H_{15}NO_3$ requires C, 73.7; H, 5.15; N, 4.8%); $\nu_{max.}$ 1 695 and 1 740 cm^{-1} (CO); $\delta(CDCl_3)$ 3.85 (3 H, s, Me), 4.76 (2 H, s, CH_2), and 6.47 (1 H, s, olefinic-H). Ester (6), *prisms*, had m.p. 151—153 °C (Found: C, 73.65; H, 5.3; N, 4.6. $C_{18}H_{15}NO_3$ requires C, 73.7; H, 5.15; N, 4.8%); $\nu_{max.}$ 1 710 and 1 750 cm^{-1} (CO); $\delta(CDCl_3)$ 3.57 (3 H, s, Me), 4.42 (2 H, s, CH_2), and 6.94 (1 H, s, olefinic-H). Alternatively, ester (6) was obtained as follows: a solution of (*Z*)-3-benzylidenephthalimidine (2.2 g) in t-butanol (30 ml) containing potassium t-butoxide (2.8 g) was treated with methyl bromoacetate (2 ml) and refluxed for 7 h. The residue obtained after evaporation was taken up in chloroform, and the inorganic material was filtered off. Addition of increasing amounts of hexane caused separation of three fractions (0.6, 0.7, and 0.3 g respectively). The first and second contained 3-benzylidenephthalimidine and (6) in the ratio 1 : 1, and the third contained pure (6).

Sodium Salts (7) *and* (8).—A solution of either (3) or (4) (2.9 g) in ethanol (50 ml) containing sodium hydroxide (0.4 g) was evaporated on a steam bath almost to dryness. Benzene (30 ml) was added to the residue and evaporation was continued until formation of a solid took place. Salt (7) had m.p. >320 °C (Found: C, 67.55; H, 4.1; N, 4.6. $C_{17}H_{12}NNaO_3$ requires C, 67.8; H, 4.0; N, 4.65%); $\nu_{max.}$ 1 580 and 1 690 cm^{-1} (CO_2^- and CO), δ[$(CD_3)_2SO$–D_2O] 4.48 (2 H, s, CH_2) and 5.90 (1 H, s, olefinic-H). Salt (8) had m.p. >320 °C (Found: C, 67.5; H, 4.2; N, 4.7. $C_{17}H_{12}NNaO_3$ requires C 67.8; H, 4.0; N, 4.65%); $\nu_{max.}$ 1 593 and 1 680 cm^{-1} (CO_2^- and CO), δ[$(CD_3)_2SO$–D_2O] 4.06 (2 H, s, CN_2) and 6.04 (1 H, s, olefinic H).

Photochemical Isomerisations.—(*a*) *Isomerisation of* (3) *to* (4). A stirred suspension of the 4 : 1 mixture of (3) and (4) (60 g) in ethanol (1.2 l) was irradiated at room temperature with a 70 W high-pressure mercury lamp (Hanau TQ 81) equipped with an immersion-well system (Pyrex glass). The solid dissolved slowly. After 20 h the ratio of (3) : (4) was 2 : 3, after 30 h 1 : 3, and after 60 h 1 : 4.

(*b*) *Isomerisation of* (7) *to* (8). By irradiating as described above a suspension of salts (7) and (8) (30 g, 4 : 1 mixture) in 1 : 1 ethanol–water (300 ml) for 15 h, a 3 : 7 mixture of (7) and (8) was obtained.

(Z)-3-(α-Bromobenzylidene)phthalimidin-2-ylacetic Acid (9).—(*a*) *From* (3) *and* (4). A stirred suspension of either (3) or (4) (1.4 g) in chloroform (12 ml) was treated with bromine (0.3 ml) and the mixture was heated on a steam bath until a clear solution was obtained. Evaporation of the solvent left a residue which solidified on trituration with hexane. The product (1.5 g) crystallised from ethanol or acetic acid as *prisms*, m.p. 189—192 °C (Found: C, 56.9; H, 3.6; N, 3.7. $C_{17}H_{12}BrNO_3$ requires C, 57.0; H, 3.35; N, 3.9%); $\nu_{max.}$ 1 665 and 1 740 cm^{-1} (CO), δ[$(CD_3)_2SO$–$CDCl_3$] 5.11 (2 H, s, CH_2) and 6.07 (1 H, d, *J* 7.5 Hz, H-4).

(b) *From* (8). A stirred suspension of (8) (1.6 g) in chloroform (60 ml) was treated with bromine (0.3 ml). The precipitated sodium bromide was filtered off and the

* A compound having the same skeleton as (26), but with oxygenated substituents in the aryl rings, has been prepared by another route (H. O. Bernhard and V. Snieckus, *Tetrahedron Letters*, 1971, 4867).

residue obtained on evaporation (1.7 g) was identical with the product from (*a*).

10b-*Bromo*-1-*phenyl*-4,10b-*dihydroisoindolo*[1,2-c][1,4]-*oxazine*-3,6(1H)-*dione* (10) *and* 9b-(α-*Bromobenzyl*)-3,10b-*dihydroisoindolo*[1,2-b][1,3]*oxazole*-2,5-*dione* (11).—Compound (7) (9 g) in chloroform (150 ml) was treated with bromine (1.8 ml). Addition of hexane (50 ml) caused separation of sodium bromide which was filtered off. The filtrate was evaporated to about 30 ml, and diluted with hexane (200 ml). The oil which precipitated solidified on trituration with ethanol to give a 3 : 2 mixture of compounds (10) and (11) (7.4 g). Fractional crystallisation from ethanol gave (10) as the more insoluble material, as *prisms*, m.p. 147—149 °C (Found: C, 56.8; H, 3.3; N, 3.8. $C_{17}H_{12}BrNO_3$ requires C, 57.0; H, 3.35; N, 3.9%); $\nu_{max.}$ 1 705, 1 720, and 1 770 cm^{-1} (CO); δ[$(CD_3)_2SO$–$CDCl_3$] 4.04, 4.34, 4.46, 4.76 (2 H, AB q, CH_2), and 6.25 (1 H, s, CH). Compound (11), obtained by concentration of the mother liquor from (10), crystallised from benzene as *prisms*, m.p. 128—130 °C (Found: C, 56.8; H, 3.3; N, 3.8. $C_{17}H_{12}BrNO_3$ requires C, 57.0; H, 3.35; N, 3.9%); $\nu_{max.}$ 1 705 and 1 795 cm^{-1} (CO); δ[$(CD_3)_2SO$–$CDCl_3$] 3.63, 3.92, 4.18, 4.47 (2 H, AB q, CH_2), and 5.74 (1 H, s, CH).

Isoindolo[2,3-a][3]*benzazepine*-5,8(7H)-*dione* (12).—A 3 : 7 mixture of (3) and (4) (5 g) was stirred with polyphosphoric acid [prepared from phosphorus pentaoxide (25 g) and 85% phosphoric acid (10 ml)] and heated on a steam bath for 2 h. Dilution with water caused separation of a solid, which was dissolved in dichloromethane, washed with 2N sodium carbonate, and filtered over neutral alumina. The residue obtained by evaporation of the combined eluates (1.5 g) crystallised from ethanol as yellow *needles*, m.p. 181—183 °C (Found: C, 77.9; H, 4.3; N, 5.3. $C_{17}H_{11}NO_2$ requires C, 78.15; H, 4.2; N, 5.4%); $\nu_{max.}$ 1 665 and 1 700 cm^{-1} (CO); δ($CDCl_3$) 4.75 (2 H, s, CH_2) and 6.57 (1 H, s, H-13).

Enol Acetate (13).—A mixture of (12) (0.5 g), pyridine (3 ml) and acetic anhydride (2 ml) was refluxed for 20 min. The precipitate obtained on cooling (0.3 g) crystallised from acetic acid as red *plates*, m.p. 161—163 °C (Found: C, 75.35; H, 4.3; N, 4.8. $C_{19}H_{13}NO_3$ requires C, 75.2; H, 4.3; N, 4.6%); $\nu_{max.}$ 1 675 and 1 730 cm^{-1} (CO); δ($CDCl_3$) 2.29 (3 H, s, Me), 6.16 (1 H, s, H-13), and 6.76 (1 H, s, H-7).

Acetals (14a) *and* (14b).—A mixture of (12) (1.0 g), methyl orthoformate (15 ml), methanol (30 ml), and toluene-*p*-sulphonic acid (0.2 g) was refluxed for 6 h. After cooling, the mixture was diluted with 1N sodium carbonate (70 ml). The precipitate (0.5 g) crystallised from aqueous methanol as orange *prisms*, m.p. 183—185 °C (Found: C, 74.5; H, 5.5; N, 4.7. $C_{19}H_{17}NO_3$ requires C, 74.25; H, 5.6; N, 4.6%); $\nu_{max.}$ 1 680 (CO). Compound (14b) was prepared by the same method. The product [0.7 g from 1.0 g of (12)] crystallised from ethanol as orange *prisms*, m.p. 146—148 °C (Found: C, 75.1; H, 6.3; N, 4.1. $C_{21}H_{21}NO_3$ requires: C, 75.2; H, 6.3; N, 4.2%); $\nu_{max.}$ 1 675 cm^{-1} (CO).

Oxime (15).—A mixture of (12) (0.5 g), hydroxylamine hydrochloride (0.5 g), pyridine (2 ml), and ethanol (20 ml) was refluxed for 30 min. Dilution with water caused separation of a solid which crystallised from aqueous methanol as yellow *prisms*, m.p. 215—220 °C (Found: C, 73.8; H, 4.5; N, 10.3. $C_{17}H_{12}N_2O_2$ requires C, 73.9; H, 4.4; N, 10.1%).

Schmidt Reaction with (12).—A stirred solution of (12) (0.5 g) in acetic acid (50 ml) and sulphuric acid (10 ml) was treated with sodium azide (0.5 g) at 40—70 °C. After 30 min, dilution with water (10 ml) caused separation of *isoindolo*[2,3-b]*isoquinoline*-5,7-*dione* (17) (0.15 g) as yellow prisms, m.p. >320 °C (Found: C, 78.0; H, 3.6; N, 5.4. $C_{16}H_9NO_2$ requires C, 77.7; H, 3.7; N, 5.7%); $\nu_{max.}$ 1 650 and 1 690 cm^{-1} (CO). From the mother liquor, by further dilution with water, 3-(*o*-*cyanobenzylidene*)*phthalimidine* (16) (0.3 g) was obtained, which crystallised from acetic acid as light yellow *needles*, m.p. 245—248 °C (decomp.) (Found: C, 78.2; H, 4.0; N, 11.3. $C_{16}H_{10}N_2O$ requires C, 78.0; H, 4.1; N, 11.4%); $\nu_{max.}$ 1 698 (CO) and 2 220 cm^{-1} (CN); δ(CF_3CO_2H) 7.52 (1 H, s, olefinic-H), 7.8—8.6 (8 H, m, aromatic-H), and 10.65 (1 H, m, NH).

7,8-*Dihydroisoindolo*[2,3-a][3]*benzazepin*-5-*one* (18).— A mixture of compound (12) (8.0 g), 80% hydrazine hydrate (20 ml), ethanol (80 ml), and diethylene glycol (0.5 l) was refluxed for 2 h. After addition of potassium hydroxide (8.0 g) the solvent was distilled until the internal temperature reached 200 °C. Heating was continued for 1 h. The cooled mixture was diluted with 2N hydrochloric acid (1.5 l) and extracted with chloroform. Filtration of the organic layer over neutral alumina and evaporation afforded a residue (5.3 g) which crystallised from methanol as light yellow *prisms*, m.p. 128—130 °C (Found: C, 82.5; H, 5.4; N, 5.6. $C_{17}H_{13}NO$ requires C, 82.6; H, 5.3; N, 5.7%); $\nu_{max.}$ 1 695 (CO); δ($CDCl_3$) 3,15 (2 H, m, C-CH_2), 4.20 (2 H, m, N-CH_2), and 6.70 (1 H, s, H-13).

8-*Hydroxy*-7,8,13,13a-*tetrahydroisoindolo*[2,3-a][3]*benzazepin*-5-*one* (19).—Compound (12) (0.2 g) in acetic acid (50 ml) was hydrogenated at room temperature and pressure in the presence of platinum dioxide (0.1 g). The usual work-up gave (19) (0.1 g) which crystallised from acetic acid–water as *needles*, m.p. 193—195 °C (Found: C, 76.8; H, 5.8; N, 5.35. $C_{17}H_{15}NO_2$ requires C, 77.0; H, 5.8; N, 5.3%); $\nu_{max.}$ 1 630 (CO) and 3 270 cm^{-1} (OH).

13,13a-*Dihydroisoindolo*[2,3-a][3]*benzazepine*-5,8(7H)-*dione* (20).—Compound (19) (0.2 g) in acetone (10 ml) was treated with Jones' reagent (0.1 ml). After 30 min dilution with water caused separation of a solid (0.15 g) which crystallised from acetone–water as *prisms*, m.p. 170—173 °C (Found: C, 77.5; H, 5.1; N, 5.2. $C_{17}H_{13}NO_2$ requires C, 77.55; H, 5.0; N, 5.3%); $\nu_{max.}$ 1 678 cm^{-1} (CO); δ($CDCl_3$) 4.00, 4.31, 5.00, 5.31 (2 H, AB q, N–CH_2), 3.22—3.92 (2 H, m, C–CH_2), and 5.10 (1 H, m, CH).

3-*Benzylphthalimidin*-2-*ylacetic acid* (21).—The mixture of (3) and (4) (10 g) was hydrogenated at room temperature and pressure in ethanol (200 ml) in the presence of Pd–C (10%, 0.3 g). The usual work-up gave (21) (8.5 g), which crystallised from ethanol–water as *needles*, m.p. 171—173 °C (Found: C, 72.4; H, 5.1; N, 4.7. $C_{17}H_{15}NO_3$ requires C, 72.6; H, 5.4; N, 5.0%); $\nu_{max.}$ 1 625 and 1 710 cm^{-1} (CO); δ($CDCl_3$) 3.75, 4.05, 4.62, 4.92 (2 H, AB q, N–CH_2), 2.77, 2.90, 3.01, 3.13, 3.20, 3.30, 3.43, 3.53, and 5.00, 5.10, 5.12, and 5.22 (2 H, and 1 H, N–CH–CH_2).

Cyclisation of (21) *with Polyphosphoric Acid.*—Compound (21) (2.5 g) was heated with polyphosphoric acid (35 g) as described above for the preparation of (12). Usual work-up and crystallisation of the neutral material from dichloromethane–hexane gave compound (20) (0.3 g) in the first fractions, and 12,12a-*dihydroisoindolo*[2,3-b]*isoquinolin*-5(7H)-*one* (22) (0.6 g) in the last ones, as *needles*, m.p. 126—128 °C (Found: C, 81.55; H, 5.75; N, 6.1. $C_{16}H_{13}NO$ requires C, 81.7; H, 5.6; N, 5.95%); $\nu_{max.}$ 1 655 cm^{-1} (CO); δ($CDCl_3$) 4.32, 4.62, 5.15, 5.45 (2 H, AB q, N–CH_2), 2.27, 2.47, 2.53, 2.73, 3.20, 3.27, 3.45, 3.52 and 4.42, 4.50, and 4.67 (2 H and 1 H, N–CH–CH_2).

13-*Bromo*-13a-*methoxy*-7,8,13,13a-*tetrahydroisoindolo*-[2,3-a][3]*benzazepin*-5-*one* (23).—A stirred suspension of (18) (3.5 g) in methanol (70 ml) was treated with bromine (0.9 ml). After 10 min the mixture was treated with 10% sodium bisulphite (5 ml) and diluted with water (200 ml). The precipitate (3 g) crystallised from chloroform–hexane as *prisms*, m.p. 138—140 °C (Found: C, 60.4; H, 4.6; N, 3.9. $C_{18}H_{16}BrNO_2$ requires C, 60.35; H, 4.5; N, 3.9%); $\nu_{max.}$ 1 670 cm^{-1} (CO), δ($CDCl_3$) 2.85 (3 H, s, Me), 5.54 (1 H, s, H-13), and 4.75 and 2.95—3.92 (1 H, m and 3 H, m, ring-CH_2–CH_2).

13-*Bromo*-13a-*hydroxy*-7,8,13,13a-*tetrahydroisoindolo*-[2,3-a][3]*benzazepin*-5-*one* (24).—Compound (18) (3 g) in acetic acid (60 ml) and water (3 ml) was treated with bromine (0.8 ml) with stirring. Dilution with water caused separation of a solid (2.5 g) which crystallised from chloroform–hexane as *prisms*, m.p. 141—143 °C (Found: C, 59.05; H, 4.0; N, 4.0. $C_{17}H_{14}BrNO_2$ requires C, 59.3; H, 4.1; N, 4.1%); $\nu_{max.}$ 1 650 (CO) and 3 220 cm^{-1} (OH); δ($CDCl_3$) 2.70—4.60 (4 H, m, ring-CH_2–CH_2), 5.06 (1 H, s, OH), and 5.55 (1 H, s, H 13).

7,8,13,13a-*Tetrahydroisoindolo*[2,3-a][3]*benzazepin*-5-*one* (25).—Compound (18) (0.5 g) in ethanol (20 ml) was hydrogenated at room temperature and pressure in the presence of Pd–C (10%, 0.1 g). The usual work-up gave (25) (0.4 g) which crystallised from ethanol–water as *needles*, m.p. 193—195 °C (Found: C, 81.8; H, 6.15; N, 5.7. $C_{17}H_{15}NO$ requires C, 81.9; H, 6.1; N, 5.6%); $\nu_{max.}$ 1 660 cm^{-1} (CO), δ($CDCl_3$) 2.70—3.50 and 4.35—5.00 (5 H, m and 2 H, m, aliphatic H). Analogous results were obtained by hydrogenation of either (23) or (24).

7,8,13,13a-*Tetrahydro*-5H-*idoindolo*[2,3-a][3]*benzazepine* (26) *and its Methiodide* (27).—A mixture of compound (25) (0.5 g) and lithium aluminium hydride (0.4 g) in tetrahydrofuran (50 ml) was refluxed for 5 h. Addition of a little ethanol and water caused separation of aluminium hydroxide which was filtered off. The residue obtained on evaporation (26) (0.4 g) crystallised from hexane as *needles*, m.p. 46—50 °C, which rapidly turned dark brown on standing (Found: C, 86.4; H, 7.3; N, 5.7. $C_{17}H_{17}N$ requires C, 86.8; H, 7.3; N, 5.95%); $\nu_{max.}$ 2 980, 2 900, 2 760, 1 440, 1 360, 1 345, 1 300, 1 140, 965, 950, 745, and 730 cm^{-1} (main absorption bands); δ ($CDCl_3$) 2.63—2.65 (9 H, m, aliphatic-H). The product was dissolved in acetone (20 ml), treated with methyl iodide (1 ml) and the solution refluxed for 1 h. Concentration and addition of ether caused separation of (27) (0.5 g) as *prisms*, m.p. 225—230 °C (decomp., and sintering at 213 °C) (Found: C, 57.2; H, 5.3; N, 3.5. $C_{18}H_{20}IN$ requires C, 57.3; H, 5.3; N, 3.7%), δ[$(CD_3)_2SO$] 2.70—4.20, 5.00 and 5.38 (3 H, m, 2 H, s, and 1 H, m, aliphatic H), 3.60 (3 H, s, Me).*

* In ref. 7 the description of the n.m.r. spectrum of a product similar to (27) is reported, and a singlet at δ 2.07 is assigned to the *N*-methyl group. We believe this signal is very probably due to acetone.

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