Synthesis of Heterocyclic Compounds. A Cyclisation involving a Lactam Nitrogen in a Derivative of Isoquinolin-3-one

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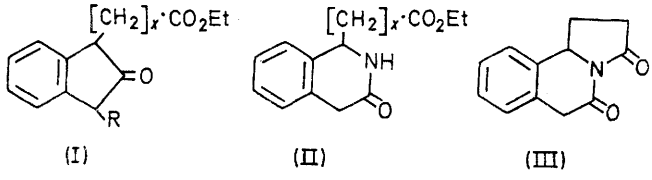
1-Ethoxycarbonylalkyl derivatives of indan-2-one were prepared and converted, by the Schmidt reaction, into the corresponding 1-substituted 1,2-dihydroisoquinolin-3(4*H*)-ones. 1-Ethoxycarbonylethyl-1,2-dihydroisoquinolin-3(4*H*)-one gave 1,10b-dihydropyrrolo[2,1-*a*]isoquinoline-3(2*H*),5(6*H*)-dione by a cyclisation at the lactam nitrogen.

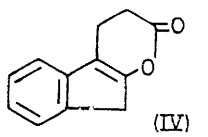
THE indanones (Ia—c) were made by treatment of the morpholine enamine of indan-2-one with the appropriate ethyl bromoalkanoates. Dimethylformamide was found to be a more satisfactory solvent in these reactions than the mixture of dioxan and tetrahydrofuran used by Blomquist and Moriconi [1] in alkylations of enamines of indan-2-one with reactive halides. In dimethylformamide the reaction became possible not only with the reactive ethyl bromoacetate but, in decreasing yields, with the less reactive ethyl 2-bromopropionate and 3-bromobutyrate. Use of an excess of ethyl bromoacetate and an extended reaction time gave 1,3-bis(ethoxycarbonylmethyl)indan-2-one (Id).



(I) (II) (III)

a; $x = 1$, R = H
b; $x = 2$, R = H
c; $x = 3$, R = H
d; $x = 1$; R = $CH_2 \cdot CO_2Et$

a; $x = 1$
b; $x = 2$
c; $x = 3$



(IV)

Indan-2-one was recovered almost quantitatively after attempted reactions of the enamine with ethyl acrylate or acrylonitrile; *N*-alkylation presumably occurs. In one preparation of the indanone (Ib) excess of acid was used in the work-up and the main product was the lactone (IV). No other chemical or spectral evidence indicating that enolisation of the indanone derivatives had occurred was obtained.

Schmidt reactions of the indanones (Ia—c) gave the corresponding derivatives of 1,2-dihydroisoquinolin-3(4*H*)-one (IIa—c). The heterocyclic ring of these compounds contains a methylene group between a benzene ring and a carbonyl group. In this environment, the methylene group of indan-2-one and that of oxindole give n.m.r. singlets at τ 6·5. The alternative structure, arising in the Schmidt reaction by migration of the 2,3-bond of the indanone, has a methylene group in the environment $PhCH_2 \cdot NH \cdot CO$; in reference compounds this gives a singlet near τ 5·4.[2,3] 1,2-Dihydroisoquinolin-3-(4*H*)-one, having methylene groups in both environments gives singlets at τ 5·5 and 6·46. The 1-substituted derivatives (IIa—c) all gave singlets near τ 6·5 and were assigned the structures shown.

The esters (IIa and c) were partially hydrolysed to the corresponding acids during the Schmidt reactions but attempts to hydrolyse the ester (IIb) were not successful. This ester, when heated with polyphosphoric acid, alone or in acetic acid, gave a new compound having an empirical formula consistent with loss of ethanol. In comparison with the parent compound its n.m.r. spectrum again showed a singlet at τ 6·5 and there was no change in the number of aromatic protons. An i.r. peak at 3200 cm^{-1} (NH) was no longer present. Structure (III) was assigned to this compound, 1,10b-dihydropyrrolo[2,1-*a*]isoquinoline-3(2*H*),5(6*H*)-dione

This cyclisation, by substitution at the lactam nitrogen, shows the side chain of the ester (IIb) to be attached to the carbon atom adjacent to nitrogen and confirms the assigned structure. Although reactions involving such a substitution at an amide nitrogen are not unknown (refs. 4 and 5 and refs. therein) we did not expect that this cyclisation would occur in preference to a *peri*-cyclisation into the aromatic ring.

EXPERIMENTAL

Microanalyses were conducted by Mr. G. S. Crouch, School of Pharmacy, London, and by Dr. F. B. Strauss, Oxford. U.v. spectra were run on solutions in spectroscopically pure ethanol with a Unicam SP 800 spectrophotometer; i.r. spectra were recorded on a Perkin-Elmer spectrometer, model 237, and n.m.r. spectra on a Varian A60A spectrometer by courtesy of Professor W. B. Whalley, School of Pharmacy, London.

Indan-2-one.—Indene (B.D.H.) was oxidised by peroxyformic acid [6] to give indan-2-one, m.p. 55—57° (lit.,[6] 57—58°).

2-*Morpholinoindene.*—This was prepared by Blomquist and Moriconis' method; [1] an atmosphere of nitrogen was found not to be essential.

Alkylation of 2-Morpholinoindene.—The appropriate ethyl bromoalkanoate (1·1 mol), diluted with an approximately equal volume of dimethylformamide, was added to a refluxing solution of 2-morpholinoindene (1 mol) in dimethylformamide (*ca.* 600 ml); the solution was then

[1] A. J. Blomquist and E. J. Moriconi, *J. Org. Chem.*, 1961, **26**, 3761.
[2] P. L. Southwick and J. A. Vida, *J. Org. Chem.*, 1962, **27**, 3075.
[3] R. H. L. Deeks, Ph.D. Thesis, University of Wales, 1968, B. Jaques, personal communication.
[4] R. Lukes and N. Janda, *Coll. Czech. Chem. Comm.*, 1959, **24**, 2717.
[5] L. Birkhofer and C-D. Barnikel, *Chem. Ber.*, 1958, **91**, 1996; 1959, **92**, 2990.
[6] J. E. Horan and R. W. Schiesler, *Org. Synth.*, 1961, **41**, 53.

heated under reflux for a further 1—3 h. The solution was cooled, 5N-hydrochloric acid (1·1 mol) was added, and the mixture was heated under reflux for a further 1 h. *Dilute hydrochloric* acid was added, if necessary, to the cooled solution to bring the pH to 4 and the solution was diluted with water and extracted with ether. The ether layer was washed with dilute hydrochloric acid (2 × 10 ml) and with water, dried (Na_2SO_4), and evaporated. The residual oil was distilled to give indan-2-one, followed by the mono-substituted indanones, and then by higher-boiling fractions which, in the reaction with ethyl bromoacetate, contained the 1,3-disubstituted indanone.

1-(*Ethoxycarbonylmethyl*)-*indan*-2-*one*. This compound was obtained as a *wax* (35·6%), m.p. 39—41°, b.p. 120—122° at 0·25 mmHg, $\lambda_{max.}$ 269·5 and 276·3 nm (log ε 3·06 and 3·05), $\nu_{max.}$ (Nujol) 1760 (ketone C=O) and 1735 (ester C=O) cm^{-1}, τ ($CDCl_3$) 2·71 (4H, s, aromatic), 5·92 (2H, q, *J* 7·4 Hz, ester CH_2), 6·21 (1H, t, *J* 6 Hz, CH), 6·46 (2H, s, CH_2), 7·03 (2H, d, *J* 6 Hz, CH_2), and 8·88 (3H, t, *J* 7·4 Hz, Me) (Found: C, 70·9; H, 6·5. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·4%). The *oxime* formed needles (from aqueous ethanol), m.p. 97·5° (Found: C, 67·1; H, 6·65; N, 5·7. $C_{13}H_{15}NO_3$ requires C, 66·95; H, 6·5; N, 6·0%). The *semicarbazone* formed needles (from aqueous ethanol), m.p. 160—161° (Found: C, 66·3; H, 6·3; N, 15·15. $C_{14}H_{17}N_3O_3$ requires C, 66·1; H, 6·2; N, 15·2%). The higher boiling fraction yielded 1,3-bis-(ethoxycarbonylmethyl)indan-2-one as a viscous pale yellow *oil* (15·4%), b.p. 154—156° at 0·25 mmHg, $\lambda_{max.}$ 269 and 276 nm (log ε 3·02 and 3·02), $\nu_{max.}$ (film) 1764 (ketone C=O) and 1740 (ester C=O) cm^{-1}, τ ($CDCl_3$) 2·70 (4H, s, aromatic), 5·89 (6H, m, 2 × CH and 2 × ester CH_2), 6·99 (4H, m, 2 × CH_2), and 8·83 (6H, m, 2 × Me) (Found: C, 66·65; H, 6·3. $C_{17}H_{20}O_5$ requires C, 67·1; H, 6·55%). Alkaline hydrolysis gave 1,3-bis(carboxymethyl)indan-2-one as *needles* (50%) (from water), m.p. 197—198°, $\lambda_{max.}$ 269 and 276·5 nm (log ε 2·87 and 2·88), $\nu_{max.}$ 1758 (ketone C=O) and 1705 (carboxylic acid C=O) cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 2·64 (4H, s, aromatic), 5·81 (2H, m, 2 × CH), and 6·72 (4H, m, 2 × CH_2) (Found: C, 62·6; H, 5·05%; Equiv., 129. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·85%; Equiv., 129).

1-(2-*Ethoxycarbonylethyl*)*indan*-2-*one*.—This compound was obtained as a *wax* (28%), m.p. 31—33°, b.p. 108—110° at 0·2 mmHg, $\lambda_{max.}$ 270 and 276·5 nm (log ε 3·12 and 3·13), $\nu_{max.}$ (Nujol) 1760 (ketone C=O) and 1744 (ester C=O) cm^{-1}, τ ($CDCl_3$) 2·68 (4H, s, aromatic), 5·90 (2H, q, *J* 7 Hz, ester CH_2), 6·46 (3H, s, CH and CH_2), 7·68 (4H, m, C_2H_4), and 8·79 (3H, t, *J* 7 Hz, ester Me) (Found: C, 71·8; H, 6·8. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·95%). The *semicarbazone* formed needles (from aqueous ethanol), m.p. 114—116° (Found: C, 62·5; H, 6·5; N, 14·45. $C_{15}H_{19}N_3O_3$ requires C, 62·3; H, 6·6; N, 14·5%). Use of excess of aqueous hydrochloric acid during hydrolysis of this enamine gave 3-(2-hydroxyinden-3-yl)propionic acid lactone as an oil which crystallised as *needles* when rubbed with ethanol, m.p. 104—106°, $\nu_{max.}$ (Nujol) 1772 (dihydro-2-pyrone C=O) [7] and 1670 (C=C) [7] cm^{-1}, τ ($CDCl_3$) 2·73 (4H, m, aromatic), 6·56 (2H, s, CH_2), and 7·22 (4H, m, C_2H_4) (Found: C, 77·25; H, 5·35. $C_{12}H_{10}O_2$ requires C, 77·4; H, 5·4%).

1-(3-*Ethoxycarbonylpropyl*)*indan*-2-*one*. This compound was obtained as a pale yellow *oil* (27%), b.p. 146—149° at 0·5 mmHg, $\nu_{max.}$ (film) 1750 (ketone C=O) and 1737 (ester C=O) cm^{-1} (Found: C, 73·25; H, 7·4. $C_{15}H_{18}O_3$ requires C, 73·15; H, 7·4%). The *semicarbazone* formed needles (from aqueous ethanol), m.p. 116—118° (Found: C, 63·6; H, 6·9; N, 13·85. $C_{16}H_{21}N_3O_3$ requires C, 63·5; H, 7·0; N, 13·85%).

1-(2-*Carboxyethyl*)*indan*-2-*one*. This compound was obtained as an almost colourless, viscous *oil* (17·5%), b.p. 160—162° at 0·2 mmHg, $\lambda_{max.}$ 269·5 and 276 nm (log ε 3·50 and 3·50), $\nu_{max.}$ (film) 1750 (ketone C=O) and 1715 (carboxylic acid C=O) cm^{-1} (Found: C, 70·3; H, 5·9. $C_{12}H_{12}O_3$ requires C, 70·5; H, 5·9%).

Schmidt Reaction with 1-*Substituted Indan*-2-*ones*.—Concentrated sulphuric acid (25 ml) was added dropwise to a stirred solution of hydrazoic acid [from sodium azide (5 g)] and the 1-substituted indan-2-one (10 g) in chloroform (80 ml) cooled externally to prevent the temperature of the mixture exceeding 10°. The mixture was stirred for 0·5 h, and then cautiously added to water. The aqueous layer was extracted with chloroform and the combined chloroform solutions were washed with sodium hydrogen carbonate solution and with water, dried (Na_2SO_4), and evaporated to leave a residual oil which was worked up as indicated.

1-(*Ethoxycarbonylmethyl*)-1,2-*dihydroisoquinoline*-3(4H)-*one*.—This compound was obtained as a brown oil (77·8%), b.p. 221—223° (bath) at 0·2 mmHg which, when stirred with xylene, gave a white crystalline solid. Recrystallisation from xylene–light petroleum (b.p. 60—80°) gave feathery *needles*, m.p. 94—95°, $\nu_{max.}$ (Nujol) 3180 (lactam NH), 1730 (ester C=O), and 1675 (amide C=O) cm^{-1}, τ ($CDCl_3$) 2·78 (4H, s, aromatic), 3·16 (1H, s, NH), 5·0 (1H, t, *J* 5 Hz, CH), 5·8 (2H, q, *J* 6 Hz, ester CH_2), 6·39 (2H, s, CH_2), 7·24 (2H, d, *J* 5 Hz, CH_2), 8·73 (3H, t, *J* 6 Hz, ester Me) (Found: C, 66·8; H, 6·5; N, 6·2. $C_{13}H_{15}NO_3$ requires C, 66·9; H, 6·5; N, 6·0%).

1-(*Carboxymethyl*)-1,2-*dihydroisoquinolin*-3(4H)-*one*.— A solution of 1-(ethoxycarbonylmethyl)1,2-dihydroisoquinolin-3(4*H*)-one (1·4 g) in excess of ammonia (*d* 0·880) was heated strongly. The oily residue was rubbed with methanol to afford a white solid (0·4 g) which was dissolved in water and treated with dilute hydrochloric acid to give a white solid. Crystallisation from water (charcoal) gave *needles* (0·4 g, 34%), m.p. 210—212·5°, $\lambda_{max.}$ 269 and 271·5 nm (log ε 2·47 and 2·39), $\nu_{max.}$ (Nujol) 3170 (lactam NH), 1713 (carboxylic acid C=O), and 1658 (amide C=O) cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 0·77br (1H. NH), 2·77 (4H, m, aromatic), 4·65br (1H, CH), 5·97 (2H, s, CH_2), and 6·87 (2H, d, *J* 7 Hz, CH_2) (Found: C, 64·15; H, 5·45; N, 6·8%; Equiv., 208. $C_{11}H_{11}NO_3$ requires C, 64·35; H, 5·4; N, 6·8%; Equiv., 205).

1-(3-*Carboxypropyl*)-1,2-*dihydroisoquinolin*-3(4H)-*one*.— The brown oil recovered from the Schmidt reaction (91%), b.p. 205° at 0·5 mmHg, showed the characteristics expected of 1-(3-ethoxycarbonylpropyl)-1,2-dihydroisoquinolin-3(4*H*)-one, $\nu_{max.}$ (film) 3200 (lactam NH), 1737 (ester C=O), and 1670 (amide C=O) cm^{-1}. Hydrolysis with cold sulphuric acid gave the corresponding acid as yellow *needles* (from water), m.p. 167—169°, $\nu_{max.}$ (Nujol) 3260 and 3180 (lactam NH), 1695 (carboxylic C=O), and 1630 (amide C=O) cm^{-1}, τ (CF_3CO_2D) 2·42 (1H, s, NH), 2·57 (4H, m, aromatic), 5·0br (1H, m, CH), 5·93 (2H, s, CH_2), 7·4 (2H, t, *J* 7 Hz, CH_2), and 7·98 (4H, m, C_2H_4) (Found: C, 66·9; H, 6·45; N, 5·95. $C_{13}H_{15}NO_3$ requires C, 66·9; H, 6·5; N, 6·0%).

1-(2-*Ethoxycarbonylethyl*)-1,2-*dihydrosoisoquinolin*-3(4H)-

[7] K. Nakaniski, 'Infra-Red Absorption Spectroscopy,' Holden-Day, San Francisco, 1962, p. 44.

one.—The residual oil (87·6%), b.p. 200—205° at 1 mmHg had $\lambda_{max.}$ 223 and 272·5 nm, $\nu_{max.}$ 3200 (lactam NH), 1740 (ester C=O), and 1685 (amide C=O) cm^{-1}, τ ($CDCl_3$) 2·21br (1H, NH), 2·61 (1H, aromatic), 2·81 (3H, m, aromatic), 4·68br (1H, CH), 5·91 (2H, q, *J* 6·5 Hz, ester CH_2), 6·42 (2H, s, CH_2), 7·7 (4H, m, C_2H_4), and 8·81 (3H, t, *J* 6·5 Hz, ester Me). This substance gave an unsatisfactory analysis and was used directly in the following preparation.

1,2,6,10b-*Tetrahydropyrrolo*[2,1-a]*isoquinoline*-3,5-*dione*.—The crude ester from the previous preparation (35 g) was added to a mixture of polyphosphoric acid (155 g) and glacial acetic acid (155 g); the mixture was then gradually heated to 120° during 10 min. The mixture was heated for a further 15 min, poured into water (500 ml), and extracted with chloroform; the extract was washed with saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated. The residual oil was rubbed with ethanol and filtered, and the solid was washed with ether. Crystallisation from water (charcoal) gave *needles* (10·0 g, 38%), m.p. 196—198°, $\nu_{max.}$ (Nujol) 1773 and 1683 (imide C=O) cm^{-1}, τ ($CDCl_3$) 2·73 (4H, s, aromatic), 4·92 (1H, m, CH), 6·32 (2H, s, CH_2), and 7·4 (4H, m, C_2H_4) (Found: C, 71·75; H, 5·75; N, 7·2. $C_{12}H_{11}NO_2$ requires C, 71·6; H, 5·6; N, 7·0%).

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