Derivatives of Indole in an Attempted Cyclisation of *o*-Nitrophenylsuccinic Acid

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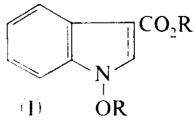
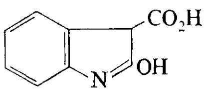
Treatment of *o*-nitrophenylsuccinic anhydride with fluorosulphonic acid at steam-bath temperature gave 1-hydroxyindole-3-carboxylic acid and oxindolic acid.

UNDER Friedel–Crafts conditions *o*-nitrophenylpropionic acid can be cyclised to give 4-nitroindanone.[1] In this singular cyclisation the nitro-group may be sterically prevented from exerting its full deactivating effect by the adjacent side chain. We attempted to cyclise *o*-nitrophenylsuccinic acid and its anhydride, compounds in which this steric effect would be enhanced. No experiments on the acid chloride could be made as all attempts to prepare this led to the anhydride only. *o*-Nitrophenylsuccinic acid was unchanged by the action of anhydrous hydrogen fluoride and gave tarry products when heated with polyphosphoric acid. The anhydride could not be cyclised under Friedel–Crafts conditions using ethylene dichloride or nitrobenzene as solvent, and when heated with polyphosphoric acid gave unchanged anhydride and tarry material only. When *o*-nitrophenylsuccinic anhydride was heated with fluorosulphonic acid no ketone was formed but two heterocyclic acids both having an equivalent weight of 180 could be isolated. The structures (I; R = H) and (II) have been assigned to these compounds; they provide a further example of the reactions of nitro-groups with neighbouring groups which have been reviewed by Loudon and Tennant.[2]



(I)



(II)

Compound (I; R = H) could be acetylated and the i.r. spectrum of the crude product showed a peak at 1800 cm.$^{-1}$ found in *N*-acetoxy-compounds.[3] It was methylated by diazomethane to give a methoxy-ester (I; R = Me) the n.m.r. spectrum of which showed a multiplet for four aromatic protons, centre τ 2·29, a singlet for one proton at τ 3·95 (ethylenic H), two singlets each for three protons at τ 5·91 (=N·OMe) [4] and τ 6·03 (CO_2Me). The product from the action of toluene-*p*-sulphonyl chloride and sodium hydroxide solution was spectroscopically and chromatographically identical with a sample of indigotin, a remarkable transformation which gave supporting evidence that (I) was a derivative of indole. Compound (I; R = H) differed from the known *N*-hydroxyindole-2-carboxylic acid [5] and the 3-isomer remained as the only structure consistent with the evidence. A carbonyl peak at 1654 cm.$^{-1}$ in its i.r. spectrum confirmed that (I; R = H) had a carboxyl group at position 3; this peak occurs in indole-2-carboxylic acids at higher frequencies.[6] Attempts using various reagents to reduce (I; R = H or R = Me) to indole-3-carboxylic acid gave a compound to which the structure *NN*′-bi-indolyl-3,3′-dicarboxylic acid has been assigned. The i.r. spectrum of this compound showed no peak due to NH. The n.m.r. spectrum in trifluoroacetic acid showed no peak due to NH, a multiplet, centre τ 2·04 for four aromatic protons and a singlet

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[1] H. Hoyer, *J. prakt. Chem.*, 1934, **139**, 94; K. Bhave, M.Sc. Thesis, Univ. of London, 1958; C. A. Grob and O. Weissbach, *Helv. Chim. Acta*, 1961, **44**, 1736.

[2] J. D. Loudon and G. Tennant, *Quart. Rev.*, 1964, **18**, 389.

[3] J. D. Loudon and I. Wellings, *J. Chem. Soc.*, 1960, 3462.

[4] H. Morimoto and H. Oshio, *Annalen*, 1965, **682**, 212.

[5] S. Gabriel, W. Gerhardt, and R. Wohlter, *Ber.*, 1923, **56**, 1024.

[6] F. Millich and E. J. Becker, *J. Org. Chem.*, 1958, **23**, 1096.

for one proton at τ 3·32 (ethylenic H). Molecular-weight determination (ebullioscopic) confirmed the bi-indole structure, although at the temperature required for mass spectrometry splitting to single indole units apparently occurred. This compound and compounds (I; R = H and R = Me) showed peaks in u.v. spectra within the ranges 227—232, 269—276, and 277—284 mμ typical of indole derivatives.

A β-keto-acid structure, or its tautomer, was suggested for compound (II) by the fact that it lost carbon dioxide at its melting point. The n.m.r. spectrum showed a singlet for one proton (exchangeable with D in $CDCl_3$ solution) at τ 0·03 (CO_2H), a multiplet, centre τ 2·66 for four aromatic protons, a singlet for one proton at τ 5·72 (OH), and a singlet for one proton at τ 7·19 (H adjacent to CO_2H). The carboxylic acid group in (II) must be in position 3 as both (I) and (II) give *NN'*-bi-indolyl-3,3'-dicarboxylic acid when reduced.

The hitherto unreported *o*-nitrophenylsuccinimide was isolated from the mother liquor remaining after preparations of *o*-nitrophenylsuccinic acid by the method of London and Wellings.[3]

EXPERIMENTAL

M.p.s are uncorrected. U.v. spectra were determined in spectroscopic ethanol on a Unicam S.P. 800 spectrophotometer, and i.r. spectra on KBr discs, unless otherwise stated, using a Perkin-Elmer spectrophotometer, model 237.

o-*Nitrophenylsuccinic Anhydride*.—*o*-Nitrophenylsuccinic acid, prepared by the method of Loudon and Wellings [3] (23·9 g.) was heated under reflux with acetyl chloride (80 ml.) for ½ hr. The acetyl chloride was removed and the residue crystallised from dry benzene–dry ether to give squat needles (19·7 g., 89%), m.p. 128—129° (lit., 128°,[3] 129° [7]). The same product was obtained from a similar procedure using either oxalyl chloride, thionyl chloride, or phosphorus pentachloride in benzene.

Attempted Friedel–Crafts Cyclisation of o-*Nitrophenylsuccinic Anhydride*.—*A*. Anhydrous aluminium chloride (1·7 g., 0·0127 mole) was added to *o*-nitrophenylsuccinic anhydride (1·1 g., 0·005 mole) in dry ethylene dichloride (30 ml.), and the mixture heated gently under reflux (4 hr.). The reaction mixture was decomposed with ice and dilute sulphuric acid, and the mixture extracted with ether. The extract was washed, dried (Na_2SO_4), and the ether distilled to leave a brown oily residue (1·05 g.). Several recrystallisations from water (charcoal) gave a brown solid m.p. 177—179° giving no reaction for ketone with 2,4-dinitrophenylhydrazine. The i.r. spectrum of this product was identical with that of *o*-nitrophenylsuccinic acid. Mixed m.p. with *o*-nitrophenylsuccinic acid 180—181°. When the above experiment was repeated using the anhydride (1·1 g., 0·005 mole) anhydrous aluminium chloride (2·35 g., 0·017 mole), and ethylene dichloride (20 ml.) with 2½ hr. reflux, only tarry matter (1·07 g.) was isolated.

B. *o*-Nitrophenylsuccinic anhydride (2·1 g.) was added to polyphosphoric acid (10 g.) preheated to 70°. The mixture was heated to 100—110° for 4½ hr. and the blue complex which had formed was decomposed by addition of ice and water. Tarry material (0·4 g.) was filtered off. *o*-Nitrophenylsuccinic anhydride, (1·27 g., 63%), m.p. and mixed m.p. 127·5—128·5°, separated from the cooled solution.

C. *o*-Nitrophenylsuccinic acid (1·0 g.) was dissolved in anhydrous hydrogen fluoride (10 ml.) in a screw-cap Polythene bottle and set aside for periods in successive experiments from 18 hr. to 8 weeks. The reaction mixture was allowed to evaporate, the residue dried in air and finally *in vacuo* over potassium hydroxide. The dark solid was recrystallised from water (charcoal) to give *o*-nitrophenylsuccinic acid m.p. and mixed m.p. 188°.

N-*Hydroxyindole-3-carboxylic Acid*.—*o*-Nitrophenylsuccinic anhydride (10·5 g.) and fluorosulphonic acid (50 ml.) were heated together on a steam bath. After ½ hr. the solution was cooled and cautiously added to a mixture of ice and water (600 g.). A red-brown solid was gradually deposited (6·67 g.). Cautious evaporation of the mother-liquors gave a further 0·64 g. solid. Recrystallisation from water (charcoal) gave pale pink *needles*, (4·48 g., 53·4%), m.p. 284° (decomp.), $\lambda_{max.}$ 232, 271, 284, and 320 mμ, (log ε 4·73, 3·78, 3·73, and 3·64). The n.m.r. spectrum (Me_2SO) showed a singlet at τ 4·2 (ethylenic proton) and a multiplet (four aromatic protons) centred at τ 2·3. (Found: C, 60·6; H, 4·1; N, 7·6%; Equiv., 180. $C_9H_7NO_3$ requires: C, 60·6; H, 4·0; N, 8·0%; Equiv., 177).

Oxindolic Acid.—*o*-Nitrophenylsuccinic anhydride (8·45 g.) and fluorosulphonic acid (40 ml.) were heated on a steam bath. After ½ hr. the solution was cooled and cautiously added to a mixture of ice and water (400 g.). A brown solid separated immediately (3·23 g., 48·5%, m.p. 92·5°), and was filtered off. The solid was dissolved in ether and filtered through charcoal. Removal of the ether gave a pale brown solid. Recrystallisations from ether gave almost colourless *needles*, m.p. 95° (decomp.). $\lambda_{max.}$ 204·5 and 315·5 mμ, (log ε 4·20 and 4·12), $\nu_{max.}$ 1718 cm.$^{-1}$ (acid C:O). (Found: C, 61·1; 60·75; H, 4·2, 4·05; N, 7·8, 7·6%; Equiv., 181).

The mother-liquors, on standing, deposited a pale brown solid (1·4 g. 21·0%). Recrystallisation from water (charcoal) gave needles of *N*-hydroxyindole-3-carboxylic acid, m.p. 273°; mixed m.p. 276°.

Indigotin.—*N*-Hydroxyindole-3-carboxylic acid (0·5 g.), toluene-*p*-sulphonyl chloride (0·6 g.), and 10% sodium hydroxide solution (3 ml.) were warmed on a water bath (1 hr.). On cooling, a blue solid was deposited. The solid was filtered and washed with absolute ethanol leaving an amorphous blue solid (0·2 g.), $\lambda_{max.}$, (nitrobenzene) 603 mμ, (synthetic indigotin B.D.H. Ltd., $\lambda_{max.}$ 605 mμ). The i.r. spectra of individual and mixed samples were identical. T.l.c. [Eastman Chromatogram sheet, type K 301 R (silica gel) showed identical R_F values for the two samples eluted with benzene–acetone (2 : 1)].

Methyl N-*Methoxyindole-3-carboxylate*.—*N*-Hydroxyindole-3-carboxylic acid (0·5 g.) was dissolved in purified dioxan (200 ml.) with the aid of gentle heat. Ethereal diazomethane (from 1 g. *N*-nitrosomethylurea) was added to the cooled solution. After standing for 24 hr. at room temperature the excess of diazomethane was allowed to evaporate on a steam-bath and the dioxan was removed under reduced pressure to leave a pale pink residue. Recrystallisation from water gave *needles*, (0·47 g. 83%), m.p. 82—87°. Three further recrystallisations from water raised the melting point to 113—114°, $\lambda_{max.}$ 229, 269,

[7] L. Horner, K. Klupfel, and W. Sahler, *Annalen*, 1955, **591**, 85.

271·5, and 316 mμ, (log ε 4·68, 3·77, 3·74, and 3·64). Found: C, 64·2; H, 5·4; N, 7·0. $C_{11}H_{11}NO_3$ requires: C, 64·4; H, 5·4; N, 6·8%. The *picrate* (yellow needles from water) had m.p. 169—170° (Found: C, 47·2; H, 3·3; N, 13·3. $C_{17}H_{14}N_4O_{10}$ requires: C, 47·0; H, 3·25; N, 12·9%).

NN′-*Bi-indolyl*-3,3′-*dicarboxylic Acid*.—*N*-Hydroxyindole-3-carboxylic acid (0·21 g.) was heated under reflux with constant-boiling hydriodic acid (S.G. 1·7, 10 ml.) for 1 hr. On cooling, long colourless needles separated and were filtered off. The needles were dissolved in warm 5% sodium hydroxide solution and reprecipitated with dilute hydrochloric acid. Recrystallisation from absolute alcohol gave white feathery *needles*, (0·18 g. 95%), m.p. darkens 329°, completely melted at 339°, $\lambda_{max.}$ 227·5, 270·5, 280·5, and 313 mμ (log ε 4·90, 4·12, 4·12, and 4·11). [Found: C, 67·35; H, 4·0; N, 9·0%; Equiv., 162. *M* (ebullioscopic in ethanol) 300. $C_{18}H_{12}N_2O_4$ requires: C, 67·5; H, 3·75; N, 8·75%; Equiv., 160. *M*, 320. Mass spectrometry (temp. 265°) gave a main peak at 161].

The same product was obtained when (a) *N*-hydroxyindole-3-carboxylic acid was reduced in ethanol or acetic acid solution with hydrogen and 5% palladium–charcoal or with zinc, hydrochloric acid, and acetic acid, (b) methyl *N*-methoxyindole-3-carboxylate was reduced with constant-boiling hydriodic acid, and (c) oxindolic acid was reduced in ethanolic solution with hydrogen and 5% palladium–charcoal.

o-*Nitrophenylsuccinimide*.—The residue from the mother-liquors remaining after the recrystallisation of a number of batches of *o*-nitrophenylsuccinic acid were bulked and heated under reflux with acetyl chloride (1 hr.). The insoluble material was filtered off and recrystallised several times from water (charcoal) to give colourless *needles*, m.p. 142—143°, $\lambda_{max.}$ 205·5 and 260 mμ, (log ε 4·18 and 3·75), $\nu_{max.}$ 3390 and 3125 cm.$^{-1}$, (NH); 1770 and 1698 cm.$^{-1}$, (cyclic imide C:O), 1520 and 1337 cm.$^{-1}$, (NO_2) (Found: C, 55·0; H, 3·7; N, 12·6. $C_{10}H_8N_2O_4$ requires: C, 54·55; H, 3·6; N, 12·7%).

The mother-liquors were evaporated and the residue recrystallised from dry benzene–dry ether to give *o*-nitrophenylsuccinic anhydride, m.p. and mixed m.p. 128—129°.

o-*Aminophenylsuccinimide*.— *o*-Nitrophenylsuccinimide (1·0 g.) was dissolved in absolute ethanol (150 ml.) and hydrogenated over 10% palladium on charcoal catalyst (0·1 g.). After 2 hr. the catalyst was filtered off and the solvent evaporated to yield a white solid (0·8 g., 92·5%). Recrystallisation from 95% ethanol gave white *needles*, m.p. 244—245°, $\lambda_{max.}$ 206·5, 252, and 284·7 mμ, (log ε 4·41, 3·998, and 3·298), $\nu_{max.}$ 3400 and 3310 cm.$^{-1}$, (NH_2 and NH) 1695 and 1660 cm.$^{-1}$, (cyclic imide C:O); 1634 cm.$^{-1}$ (NH_2). (Found: C, 63·1; H, 5·45; N, 14·5. $C_{10}H_{10}N_2O_2$ requires: C, 63·2; H, 5·3; N, 14·7%).

N.m.r. and mass spectra were produced at the School of Pharmacy, London, by courtesy of Professor W. B. Whalley and Professor L. Saunders.

Microanalyses were carried out by Mr. G. S. Crouch at the School of Pharmacy, London. One of us (R. H. L. D.) received a research scholarship from the Welsh College of Advanced Technology.

[7/1344 *Received, October* 18*th*, 1967]