A New Synthesis of some Indolecarboxylic Acids

Leandro Baiocchi* and Marilena Giannangeli

Research Institute Angelini Francesco, Viale Amelia 70,
00181 Rome, Italy

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1-Substituted isatins are transformed into indole derivatives by means of ethyl chloroacetate. In fact, under the conditions of the Darzens reaction they give two glycidic ester isomers **4** and **5** which, by hydrolysis in alkaline medium, undergo a transposition to indole-2,3-dicarboxylic acids **2** together with minor amounts of indole-3-carboxylic acids **3**. From isatin itself, 2,3-dicarboxyindole-1-acetic acid (**6**) was obtained.

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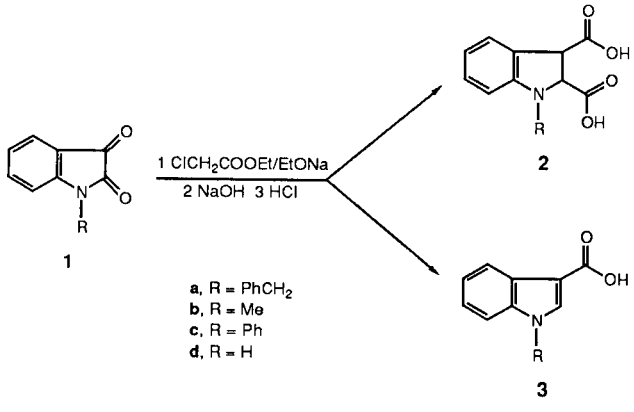
Among the great number of known syntheses of indoles [1], the reduction of the easily available isatins [2,3] very often leads to mixtures of disproportionation and autocondensation products [4]. Actually we found that the reduction of isatins, both *N*-substituted and unsubstituted, to indoles can be brought about by means of ethyl chloroacetate.

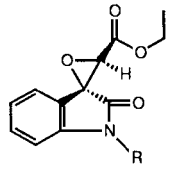
As a matter of fact 1-benzylisatin (**1a**) was treated with ethyl chloroacetate in toluene in the presence of sodium ethylate, and the oily crude material obtained was hydrolysed in aqueous alkaline medium. By acidification of the hydrolysis solution, a mixture of 1-benzylindole-2,3-dicarboxylic acid (**2a**) and 1-benzylindole-3-carboxylic acid (**3a**) (6:1 ratio) was obtained (68% yield of the sum of the two recrystallized products).



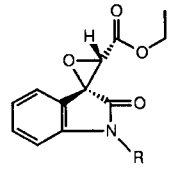
1 2 3

Since it is known that indolecarboxylic acids decarboxylate on heating more or less easily to the corresponding indoles [5,6], a practical and clean reduction from isatins to indoles was achieved.

The composition of the oily matter obtained from the reaction between ethyl chloroacetate and 1-benzylisatin, before hydrolysis, was investigated. Two isomeric substances (mp 100-102° and 120-122°, 5:1 ratio), were separated. On the basis of their elemental analysis and spectroscopic data, their nature of glycidic esters was recognized (as a matter of fact this reaction is a Darzens reaction). As regards their configuration, the upfield solvent shift between chloroform and benzene of the oxirane proton in the nmr spectrum of the higher melting product (Table I), suggests for it the structure **4a** (*E*) [7]. On the other hand, the structure **5a** (*Z*) for the lower melting product is not in contrast with its nmr behaviour. Furthermore we did not think it right, even though rather tempting, to make a final assignment of the two structures only on the grounds of the spectroscopic data without any chemical proof.



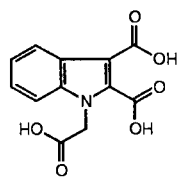
4 (*E*)



5 (*Z*)

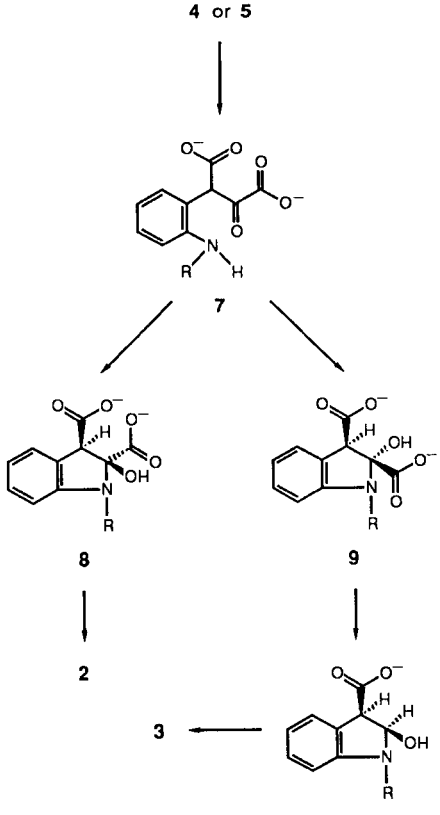
We submitted the two glycidic esters to alkaline hydrolysis separately. From both substances, **2a** and **3a** were obtained in about the same good yields and in a similar ratio (6:1).

The reaction applies well also to *N*-methylisatin (**1b**) from which both 1-methylindole-2,3-dicarboxylic acid (**2b**) and 1-methylindole-3-carboxylic acid (**3b**) were obtained, also if in lower yields due to the water solubility of the two acids (no attempt was made for a better workup). The more abundant of the two glycidic esters, **5b**, was also separated and characterized. From 1-phenylisatin (**1c**) the still unknown 1-phenylindole-2,3-dicarboxylic acid (**2c**) was obtained in fairly good yields. In this case the monocarboxylic acid was detected by gas/mass analysis of the crude reaction mixture, but not separated. With isatin itself (**1d**), the reaction gave a more complex mixture. A small amount of one glycidic ester, **5d**, was obtained from the raw intermediate, whereas the tricarboxylic acid **6** was separated as the main product after alkaline hydrolysis.

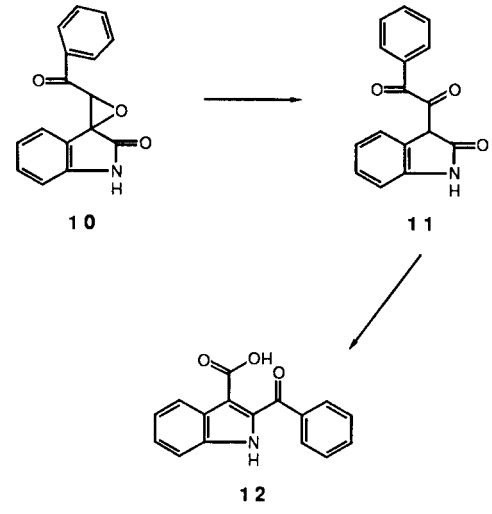


6

The fact that the acids **2** and **3** were obtained in the same ratio from the two glycidic esters suggests a common intermediate in their formation. Such an intermediate seems to be the dianon **7**. It is in fact well known that the glycidic esters are easily transformed, in alkaline medium, into the corresponding α-ketoacids [8], and that the isatins, together with many of their derivatives, easily undergo hydrolysis of the amidic bond [9]. The dianon **7** may be in equilibrium with two different internal addition products, **8** and **9**, of NH on the carboxylic double bond. In the isomer **8** the hydroxy group is in the *trans* position to the proton and the dehydration turns out to be extremely easy, whereas in the isomer **9** the dehydration can take place only after inversion of the chiral center, through decarboxylation, in position 2 of the indole ring.



Oddly, it has not been reported that the Darzens reaction - at least in its classical form - has ever been applied to isatins. Actually some oxirane derivatives were obtained making a benzyl or phenacyl halide react with isatin [10]. Ainley and Robinson [11] who described, in the first half of the current century, the reaction product between isatin itself and phenacyl bromide, assigned to it the structure **10**, and noticed that this oxirane isomerized, by alkaline hydrolysis, first to the α-diketone **11** and then to a substance for which the structure of 2-benzoylindole-3-carboxylic acid (**12**) was hypothesized.



There is evidently a certain analogy between the formation of **12** and that of **2**. It is noteworthy that the abovementioned work has been undervalued to the extent that Black and Wong [12], who have recently obtained the same acid **12** by a different route, have completely ignored the observation of Ainley and Robinson whose paper they cite, however in a different context. It is therefore impossible, on the basis of our present knowledge, to confirm the correctness of the structure **12** proposed by Ainley and Robinson. In fact neither Black and Wong nor, more recently, Grigg and Gunaratne [13], who described another synthesis of **12**, have not even taken the trouble of mentioning the melting point, the structure proofs and the literature references of the product obtained.

The analytical and spectroscopic characteristics of the new products, as well as some hitherto unpublished data of the already known indolecarboxylic acids obtained by this new synthesis, are reported in Table I.

EXPERIMENTAL

The microanalyses were performed with a CHN analyzer Carlo Erba 1104. The ^{1}H nmr spectra were recorded on an AC 100 SC Bruker apparatus with TMS as an internal standard. The ir spectra were recorded on a Perkin Elmer 781 spectrophotometer. The uv spectra were determined on a Perkin Elmer 552 spectrophotometer. The mass spectra were obtained on a Hewlett-Packard 5995 gas chromatograph/mass spectrometer. The acids were always esterified with a few drops of an ethereal solution of diazomethane before gc analysis.

1-Benzylindole-2,3-dicarboxylic Acid (**2a**) and 1-Benzylindole-3-carboxylic Acid (**3a**).

To a cooled solution (0°) of 1-benzylisatin [2] (34.5 g, 0.15 mole) and ethyl chloroacetate (25.5 ml, 0.24 mole) in toluene (300 ml), a solution of sodium ethylate (from 5.45 g, 0.24 mole, of sodium in 90 ml of ethanol) was added dropwise. After stirring at room temperature for 20 hours, the reaction mixture was washed with water and the solvent removed. The resulting oily residue was suspended in a 5*N* sodium hydroxide solution (200 ml) and heated with stirring at 80-90° until complete dissolution (5-10 minutes). The mixture was then cooled and diluted with 500 ml of

Table I

Compound	Mp °C (lit)	Analyses % Calcd./Found C H N Molecular formula	UV, λ max nm (log ε)	IR, cm^{-1}	MS, M/e* (%I)	^1H NMR (solvent, δ)	
2a	194-196 dec (EtOH) (198) [6]	$C_{17}H_{13}NO_4 \cdot H_2O$	303 (4.15) 236 (4.33) 215 (4.52)	3470 2500 1690	323 (M^+) (58) 292 (20) 291 (29) 259 (100) 91 (62)	(DMSO): 5.55 (s, 2H, CH_2-Ar) 6.87-7.72 (m, 8H, ArH) 7.92-8.25 (m, 1H, ArH) 8.75 (s, 2H, COOH)	
2b	208-209 dec (*i*-PrOH) (218) [5]	$C_{11}H_9NO_4$	303 (4.15) 236 (4.36) 217 (4.46)	3000 1695	247 (M^+) (77) 216 (100) 186 (20) 157 (24) 129 (17)	(DMSO): 3.91 (s, 3H, CH_3-N) 7.27-7.77 (m, 3H, ArH) 8.07-8.16 (m, 1H, ArH) 13.05 (s, 2H, COOH)	
2c	207-210 dec (MeOH)	68.32 3.94 4.98 68.06 3.97 4.78 $C_{16}H_{11}NO_4$	302 (4.19) 235 (4.35)	3050 2500 1730	309 (M^+) (100) 278 (99)	(DMSO): 7.20-7.60 (m, 8H, ArH) 8.06-8.26 (m, 1H, ArH) 9.85 (s, 2H, COOH)	
3a	194-196 dec (Hex-AcOEt) (198-201) [14]	$C_{16}H_{13}NO_2$	288 (4.11) 214 (4.54)	3000 2500 1655	265 (M^+) (100) 234 (25) 91 (30)	(DMSO): 5.46 (s, 2H, CH_2-Ar) 6.74-7.72 (m, 8H, ArH) 7.81-8.22 (m, 1H, ArH) 8.16 (superimposed s, 1H, CH=) 12.18 (s, 1H, COOH)	
3b	200-201 dec (*i*-PrOH) (212) [15]	$C_{10}H_9NO_2$	288 (3.98) 223 (4.49)	3100 2600 1680 1630	189 (M^+) (55) 158 (100) 130 (16) 103 (11) 77 (14)	(DMSO): 3.85 (s, 3H, CH_3-N) 7.19-7.57 (m, 3H, ArH) 8.01-8.10 (m, 1H, ArH) 8.06 (superimposed, s, 1H, CH=) 11.95 (s, 1H, COOH)	
4a	120-122 (Hex-AcOEt)	70.57 5.30 4.33 70.83 5.35 4.28 $C_{19}H_{17}NO_4$	311 (3.04) 222 (4.40)	1755 1725 1220	323 (M^+) (38) 238 (13) 208 (29) 91 (100)	($CDCl_3$): 1.31 (t, J = 7 Hz, 3H, CH_2CH_3) 4.21 (s, 1H, oxirane proton) 4.36 (q, J = 7 Hz, 2H, CH_2CH_3) 4.96 (s, 2H, CH_2Ar) 6.75-7.30 (m, 9H, ArH)	(C_6D_6): 1.12 (t, J = 7 Hz, 3H, CH_2CH_3) 3.84 (s, 1H, oxirane proton) 4.29 (q, J = 7 Hz, 2H, CH_2CH_3) 4.41 (s, 2H, CH_2Ar) 6.20-6.98 (m, 9H, ArH)
5a	100-102 (Hex-AcOEt)	70.57 5.30 4.33 70.29 5.23 4.22 $C_{19}H_{17}NO_4$	311 (3.10) 222 (4.40)	1755 1735 1200	323 (M^+) (46) 307 (10) 238 (19) 208 (46) 91 (100)	($CDCl_3$): 1.30 (t, J = 7 Hz, 3H, CH_2CH_3) 4.31 (q, J = 7 Hz, 2H, CH_2CH_3 4.29 (superimposed s, 1H, oxirane proton) 4.95 (s, 2H, CH_2Ar) 6.65-7.43 (m, 9H, ArH)	(C_6D_6): 0.72 (t, J = 7 Hz, 3H, CH_2CH_3) 3.77 (q, J = 7 Hz, 2H, CH_2CH_3) 4.37 (s, 1H, oxirane proton) 4.46 (s, 2H, CH_2Ar) 6.26-6.35 (m, 1H, ArH) 6.62-7.15 (m, 7H, ArH) 7.74-7.84 (m, 1H, ArH)
5b	102-103 (Hex-AcOEt	63.15 5.30 5.67 62.99 5.06 5.48 $C_{13}H_{13}NO_4$	311 (3.11) 223 (4.36)	1750 1725 1210	247 (M^+) (25) 190 (16) 162 (99) 146 (16) 117 (10)	($CDCl_3$): 1.29 (t, J = 7 Hz, 3H, CH_2CH_3) 3.26 (s, 3H, CH_3N) 4.20 (superimposed s, 1H, oxirane proton) 4.28 (q, J = 7 Hz, 2H, CH_2CH_3) 6.67-7.05 (m, 2H, ArH) 7.34-7.48 (m, 2H, ArH)	(C_6D_6): 1.76 (t, J = 7 Hz, 3H, CH_2CH_3) 2.46 (s, 3H, CH_3N) 3.81 (q, J = 7 Hz, 2H, CH_2CH_3) 4.30 (s, 1H, oxirane proton) 6.07-6.15 (m, 1H, ArH) 6.75-7.06 (m, 2H, ArH) 7.70-7.79 (m, 1H, ArH)

Table I (continued)

Compound	Mp °C (lit)	Analyses % Calcd./Found C	H	N	Molecular formula	UV, λ max nm (log ε)	IR, cm^{-1}	MS, M/e* (%I)	^1H NMR (solvent, δ)
5d	136-137 (Hex-AcOEt)	61.80 61.53	4.75 4.57	6.01 5.79	$C_{12}H_{11}NO_4$	310 (3.31) 223 (4.33)	3240 1750 1695 1200	233 (M^+) (56) 217 (68) 176 (34) 148 (100) 132 (18)	($CDCl_3$): 1.31 (t, J = 7 Hz, 3H, CH_2CH_3) 4.21 (superimposed s, 1H, oxirane proton) 4.30 (q, J = 7 Hz, 2H, CH_2CH_3) 6.94-7.49 (m, 4H, ArH) 8.72 (s, 1H, NH)
6	213-215 dec (Water)	52.94 52.68	3.68 3.95	5.15 5.24	$C_{12}H_9NO_6 \cdot ½H_2O$	290 (4.05) 222 (4.47)	3000 2500 1720	305 (M^+) (100) 273 (93) 246 (83) 216 (70) 202 (17)	(DMSO): 5.31 (s, 2H, CH_2COOH) 7.31-8.19 (m, 4H, ArH) 11.20 (s, 3H, COOH)
13	197-199 dec (Hex-AcOEt) (195) [16]				$C_{16}H_{13}NO_2$	292 (4.25) 208 (4.43)	3100 2500 1670	265 (M^+) (85) 233 (21) 206 (12) 91 (100)	(DMSO): 5.85 (s, 2H, CH_2Ar) 6.82-7.75 (m, 10H, ArH and 12.95 (s, 1H, COOH)

water as to keep it in solution the precipitating sodium salts and then acidified with 6*N* hydrochloric acid solution. The precipitate was taken up with ethyl acetate (300 ml). This solution was extracted with a saturated sodium bicarbonate solution (2 x 100 ml). By acidification of the aqueous separated phase, a solid precipitated (22.2 g, yield 58%) which, when recrystallized from ethanol-water (8:2), showed mp 194-196° dec, and an elemental analysis in accordance with the formula $C_{17}H_{13}NO_4 \cdot H_2O$.

The spectrophotometric characteristics of the product and the mass spectrum of its dimethyl ester were consistent with the structure of 1-benzylindole-2,3-dicarboxylic acid (**2a**). Such a structure was confirmed by decarboxylation to the known 1-benzylindole-2-carboxylic acid (**13**) (mixed mp).

The ethyl acetate solution was evaporated and the solid residue (3.7 g, yield 10%) was identified as 1-benzylindole-3-carboxylic acid (**3a**), by its spectrophotometric characteristics, by the mass spectrum of its methyl ester, as well as by the fact that, by heating, it decarboxylated to 1-benzylindole [16] (mass spectrum, positive Elrich reaction).

1-Benzyl-2,3-dihydro-2-oxospiro(1*H*-indole-3,2′-oxirane)-3′-carboxylic Acid Ethyl Esters (**4a, 5a**).

In a run as above starting from 1.15 g (5 mmoles) of 1-benzylisatin, the crude oily mixture obtained before alkaline hydrolysis was chromatographed on a silica gel column (eluent hexane-ethyl acetate 7:3) to give a compound with a shorter r. v. (0.55 g, mp 100-102°) and a minor component with a longer r. v. (0.1 g, mp 120-122°). The spectrometric characteristics of the two compounds were reported in Table I. These characteristics suggest the structure **4a** (*E*) for the higher melting product and **5a** (*Z*) for the lower melting product.

Both **4a** and **5a** were separately treated at 80° with a 5*N* sodium hydroxide solution for 5 minutes. The gas chromatographic analysis of the reaction raw mixtures showed in both cases the formation of **2a** as the main product together with a smaller amount of **3a** (7:1 ratio). Traces of **13** were also detected.

2,3-Dicarboxy-1*H*-indole-1-acetic Acid (**6**).

Using the same procedure and the same molar ratio as for 1-benzylisatin, starting from isatin (22 g, 0.15 mole), an oily residue (20 g) was obtained. This matter was then suspended in a 5*N* sodium hydroxide solution (100 ml) and heated up to complete dissolution. After cooling and acidification, the precipitate was taken up with ethyl acetate (100 ml) and the organic solution extracted with a sodium bicarbonate solution (2 x 50 ml). By acidification, extraction with ethyl acetate and evaporation of the solvent, a residue was obtained, which was crystallized from acetic acid and then recrystallized from water (mp 213-215°). The product obtained (1 g) showed spectrophotometric characteristics and an elemental analysis consistent with the structure **6**.

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