Reaction of *N*-(4-Chlorobutyryl)isatin with Potassium Hydroxide

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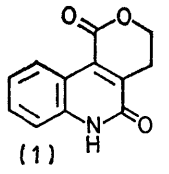
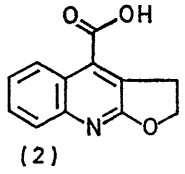
The reaction of *N*-(4-chlorobutyryl)isatin (4) with potassium hydroxide is shown to be solvent dependent. In protic solvents (water or ethanol) it gives rise to 2-(2-oxopyrrolidin-1-yl)phenylglyoxylic acid (5) and in aprotic solvents (benzene or dimethylformamide) to *N*-(3-carboxypropyl)isatin (8). The conversion (5) ⟶ (8) is brought about in aprotic medium.

RECENTLY we outlined the synthesis of 2,3-dihydrofuro-[2,3-*b*]quinoline-4-carboxylic acid (2) [1] by a route which involved the δ-lactone (1), obtained from 1,2-dihydro-2-oxo-3-vinylquinoline-4-carboxylic acid by ring closure, as a key intermediate. With a view to evolving an



(1)



(2)

$ClCO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2Cl$

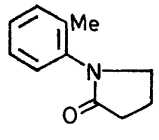
(3)

alternative method for the synthesis of the lactone (1) and the furoquinoline acid (2), we studied the reaction of *N*-(4-chlorobutyryl)isation (4) [obtained from 4-chlorobutyryl chloride (3) and sodioisatin] with potassium hydroxide in protic and aprotic solvents. The reaction did not give either compound (1) or (2), and the products in fact obtained depended on the nature of the solvent (protic or aprotic).

Treatment of compound (4) with an excess of potassium hydroxide in water or ethanol at room temperature, followed by acidification, furnished the pyrrolidone acid (5), identified from spectral and analytical data. Cleavage of the product with alkaline hydrogen peroxide gave the known 2-(2-oxopyrrolidin-1-yl)benzoic acid (6). The m.p. (198—199·5°) of this material differed considerably from that reported (147°) for material prepared [2] by the oxidation of *N*-(*o*-tolyl)pyrrolidin-2-one (10) obtained by the condensation of *o*-toluidine with butyrolactone. We obtained compound (10) from *o*-toluidine by treatment with compound (3) in the presence of pyridine followed by ethanolic potassium hydroxide, but our attempts to convert it into (6) by Reppe's procedure [2] were not fruitful. We therefore synthesised compound (6) as shown in Scheme 2 from methyl anthranilate; the product was identical with that obtained from compound (5).

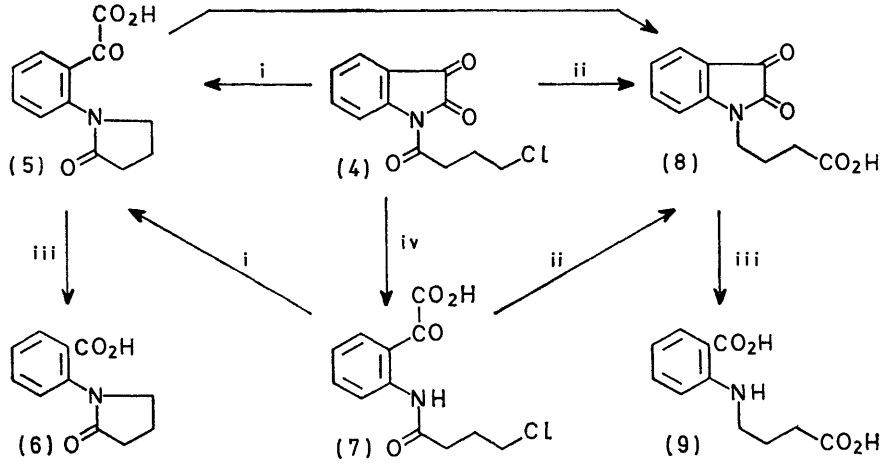
On treatment with a stoicheiometric amount of potassium hydroxide, compound (4) yielded the open-chain acid (7), which could also be converted into (5) by reaction with an excess of ethanolic or aqueous potassium hydroxide.

When compound (4) was stirred with powdered potassium hydroxide in benzene or dimethylformamide, and



(10)

the mixture was then acidified, the acid (8) was readily obtained. The product was cleaved by alkaline hydrogen peroxide to give the known 4-(2-carboxyanilino)-



SCHEME 1

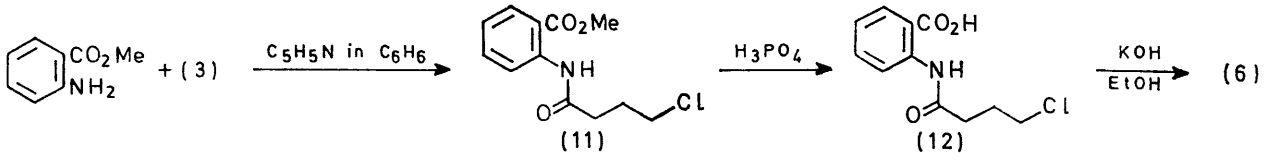
Reagents: i, OH^- (EtOH or H_2O) then H^+; ii, OH^- (C_6H_6 or $Me_2N{\cdot}CHO$) then H^+; iii, OH^-, then H_2O_2; iv, OH^- (1 equiv.).

[1] P. Lakshminarayana, P. Shanmugam, and K. K. Balasubramanian, *Tetrahedron Letters*, 1970, 4947.

[2] *Annalen*, 1955, **596B**, 205.

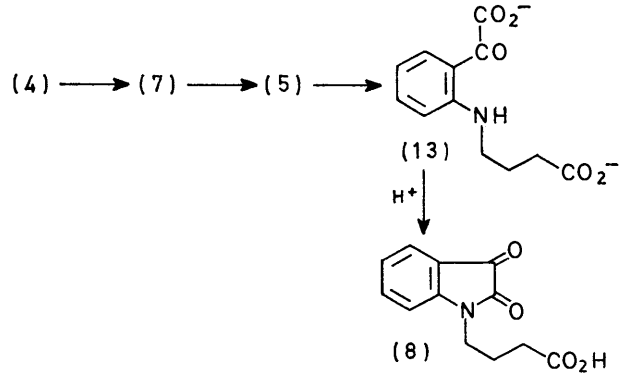
butyric acid[3] (9). Structures (8) and (9) were fully corroborated by their n.m.r. spectra. Compound (8) was also formed from compound (5) or (7) in aprotic solvents.

It would be of interest to know why compound (5) is

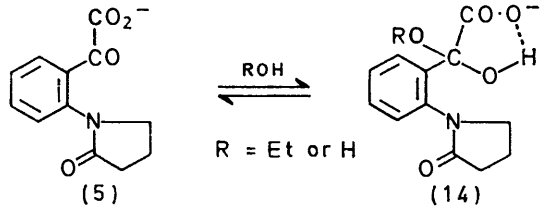


SCHEME 2

stable in protic media, yet is readily hydrolysed in aprotic solvents. In protic solvents the ketonic carbonyl group may well be masked in the form of the



hemiacetal (14), which is stabilised by intramolecular hydrogen bonding with the carboxylate anion. Such



hemiacetal formation is precluded in aprotic solvents, and the amide system in (5) is perhaps rendered more labile towards nucleophilic attack by mesomeric electron withdrawal due to the ketonic carbonyl group. Hydrolysis would then give the intermediate (13) which when acidified would furnish (8). The amide (6), which lacks the ketonic carbonyl group, was stable in aprotic solvents.

Bass has recently reported[4] that the reactivity of isatin towards electrophilic attack is enhanced in methanol compared to other solvents. He attributes the enhanced reactivity in methanol to acetalisation of the ketonic carbonyl group.

[3] I. McCall, G. R. Proctor, and L. Purdie, *J. Chem. Soc.* (*C*), 1970, 1126.
[4] R. J. Bass, *Tetrahedron Letters*, 1971, 1087.

EXPERIMENTAL

A Perkin-Elmer 221 spectrometer was used to obtain i.r. spectra. N.m.r. spectra were obtained with a Varian A60 spectrometer for solutions in $CDCl_3$. U.v. spectra were obtained with a Beckman DU-R spectrophotometer.

N-(4-*Chlorobutyryl*)*isatin* (4).—To a stirred suspension of sodioisatin (14·5 g) in dry benzene (150 ml), cooled in ice–water, 4-chlorobutyryl chloride (3) (12·5 g) in dry benzene (20 ml) was added dropwise. Stirring was continued for an additional hour and then the mixture was filtered. Evaporation of the filtrate furnished a solid (7·5) which on recrystallisation from benzene–petroleum yielded golden-yellow *needles* (4), m.p. 128·5—129·5°, $\nu_{max.}$ ($CHCl_3$) 1779, 1745, and 1724 cm^{-1}; $\lambda_{max.}$ (EtOH) 237, 264, and 335 nm (log ε 4·36, 3·94, and 3·58); δ ($CDCl_3$) 2·25 (2H, m, $CH_2{\cdot}CH_2Cl$), 3·30 (2H, t, *J* 7 Hz, $CO{\cdot}CH_2$), 3·7 (2H, t, *J* 7 Hz, CH_2Cl), and 7·2—8·4 (4H, m, aromatic) (Found: C, 57·4; H, 4·3. $C_{12}H_{10}ClNO_3$ requires C, 57·35; H, 4·0%).

Reaction of N-(4-*Chlorobutyryl*)*isatin* (4) *with Potassium Hydroxide in Water or Ethanol.*—(*a*) Compound (4) (500 mg) was shaken with 2N-potassium hydroxide (10 ml) in water or ethanol for 3 h, or warmed on a steam-bath for 10 min. The mixture was acidified with conc. hydrochloric acid. The solid that separated crystallised from aqueous ethanol to give 2-(2-oxopyrrolidin-1-yl)phenylglyoxylic acid as *prisms*, m.p. 200—201° (420 mg), $\nu_{max.}$ (KBr) 1730, 1690, and 1640 cm^{-1}, $\lambda_{max.}$ (EtOH) 233 and 293 nm (log ε 4·07 and 3·18), δ ($CDCl_3$) 2·28 (4H, m, $CO{\cdot}CH_2{\cdot}CH_2{\cdot}$), 3·83 (2H, t, $N{\cdot}CH_2$), 7·2—7·85 (4H, m, ArH), and 9·66 (1H, s, CO_2H) (Found: C, 62·0; H, 4·8; N, 6·3. $C_{12}H_{11}NO_4$ requires C, 61·8; H, 4·75; N, 6·0%).

(*b*) *Stoicheiometric amount.* Compound (4) (1·25 g) was stirred with potassium hydroxide (0·3 g) in water (15 ml). When most of the starting compound had dissolved the solution was filtered and acidified. The white solid that separated was washed with water and dried (yield 1·1 g). Recrystallisation from benzene–petroleum furnished 2-(4-chlorobutyrylamino)phenylglyoxylic acid as dull white *flakes*, m.p. 115—116·8°, $\lambda_{max.}$ (EtOH) 230, 263, 270, and 327 nm (log ε 4·38, 4·03, 3·99, and 3·64), δ ($CDCl_3$) 2·25 (2H, m, $CH_2{\cdot}CH_2Cl$), 2·67 (2H, m, $CO{\cdot}CH_2$), 3·68 (2H, t, CH_2Cl), 7—8·8 (4H, m, ArH), and 11·66 (1H, s, OH) (Found: C, 53·6; H, 4·7; N, 5·3. $C_{12}H_{12}ClNO_4$ requires C, 53·45; H, 4·45; N, 5·2%).

Degradation of the Acid (5) *with Alkaline Hydrogen Peroxide.*—To a solution of the acid (5) (500 mg) in aqueous 2N-potassium hydroxide (20 ml) was added hydrogen peroxide (20%; 5 ml). The solution was stirred at room temperature for 3 h, then acidified and the white solid that separated was washed with water. Recrystallisation from ethanol furnished 2-(2-oxopyrrolidin-1-yl)benzoic acid (6) as needles, m.p. 198—199·5° (lit.,[4] 147°) (340 mg), $\nu_{max.}$ (KBr) 1695 and 1629 cm^{-1}, δ ($CDCl_3$) 2—2·6 (4H, m,

CH_2·CH_2·CO), 3·78 (2H, t, N·CH_2), 7·15—8 (4H, m, ArH), and 9·01 (1H, s, CO_2H) (Found: C, 64·3; H, 5·2; N, 6·7. Calc. for $C_{11}H_{11}NO_3$: C, 64·4; H, 5·4; N, 6·85%).

Synthesis of 2-(2-*Oxopyrrolidin*-1-*yl*)*benzoic Acid* (6).—(*a*) A solution of the acid chloride (3) (7·1 g) in benzene was added dropwise with shaking to an ice-cold mixture of methyl anthranilate (7·55 g) and dry pyridine (7 ml) in benzene. The usual work-up afforded the anilide as viscous solid (11 g). A mixture of the crude anilide (2 g) with phosphoric acid was heated on a steam-bath for 4 h, cooled, and poured into ice–water. The white solid that separated (1·1 g) was recrystallised from petroleum to furnish *N*-(4-chlorobutyryl)anthranilic acid (12) as *needles*, m.p. 115·5—117°, $\nu_{max.}$ (KBr) 1686, 1634, and 1600 cm^{-1}, δ ($CDCl_3$) 2·31 (2H, m, CH_2·CH_2Cl), 2·71 (2H, t, *J* 6·5 Hz, CO·CH_2), 3·68 (2H, t, *J* 6·5 Hz, CH_2Cl), 7—8·8 (4H, m, ArH), and 11·25 (2H, d, OH, NH) (Found: C, 54·4; H, 5·0; N, 5·9. $C_{11}H_{12}ClNO_3$ requires C, 54·75; H, 5·0; N, 5·8%).

(*b*) A solution of the acid (12) (1 g) in ethanolic potassium hydroxide (5 g in 30 ml) was kept under reflux for 1 h, cooled, and acidified. The precipitated acid (620 g) crystallised from aqueous ethanol to yield the acid (6) as crystals, m.p. 198—199·5°, identical with that derived from compound (5) (m.p., mixed m.p., i.r. and n.m.r. spectra).

Reaction of N-(4-*Chlorobutyryl*)*isatin* (4) *with Potassium Hydroxide in Aprotic Media.*—A solution of compound (4) (250 mg) in anhydrous dimethylformamide or benzene (20 ml) was stirred with powdered potassium hydroxide (400 mg) for 6 h with the exclusion of moisture. The solvent was decanted and the residue was dissolved in water (10 ml) and acidified. The precipitate (190 mg) crystallised from aqueous ethanol to furnish 1-(3-carboxypropyl)isatin as orange-red *crystals*, m.p. 158—160° (190 mg), $\nu_{max.}$ (KBr) 1745, 1715, and 1602 cm^{-1}, $\lambda_{max.}$ (EtOH) 210, 246, and 301 nm (log ε 4·24, 4·36, and 3·41), δ ($CDCl_3$) 2·05 (2H, m, CH_2·CH_2·CO_2H), 2·35 (2H, m, N·CH_2), 3·78 (2H, t, CH_2·CO_2H), 6·95—7·85 (4H, m, ArH), and 8·96 (1H, s, CO_2H) (Found: C, 61·5; H, 4·6; N, 6·0. $C_{12}H_{11}NO_4$ requires C, 61·8; H, 4·75; N, 6·0%).

Reactions of the Acids (5) *and* (7) *with Potassium Hydroxide in Aprotic Media.*—Compound (5) (230 mg) was treated with potassium hydroxide in dimethylformamide or dry benzene (15 ml). Work-up as in the previous case furnished the acid (8) (180 mg). Similarly the acid (7) (70 mg) gave the acid (8) (41 mg).

Degradation of 1-(3-*Carboxypropyl*)*isatin* (8).—A solution of the acid (8) (1·5 g) in 2N-potassium hydroxide (30 ml) was stirred with hydrogen peroxide (30%; 10 ml) in the cold. After 2 h the mixture was acidified. The solid that separated was recrystallised from benzene–methanol to furnish 4-(2-carboxyanilino)butyric acid (9) as dull white crystals, m.p. 192—193° (650 mg) (lit.,[2] m.p. 192°), $\nu_{max.}$ (KBr) 3367, 1695, and 1653 cm^{-1}, δ ($CDCl_4$) 1·97 (2H, m, CH_2·CH_2·CO_2H), 2·32 (2H, m, CH_2·CO_2H), 3·24 (2H, t, N·CH_2), 6·34—7·98 (4H, m, ArH), and 9·5 (3H, m, 2OH and NH).

Reaction of the Acid (5) *with Aqueous or Ethanolic Potassium Hydroxide under Reflux.*—A solution of compound (5) (500 mg) in aqueous or alcoholic 2N-potassium hydroxide (10 ml) was kept under reflux for 16 h, cooled and acidified. The acid (5) separated unchanged (480 mg).

Treatment of the Acid (6) *with Potassium Hydroxide in Dimethylformamide or Benzene.*—A mixture of compound (6) (100 mg) and powdered potassium hydroxide (200 mg) was mixed in anhydrous benzene or dimethylformamide and stirred at room temperature for 8 h. The starting material was recovered unchanged (90 mg) after the usual work-up.

N-(o-*Tolyl*)*pyrrolidin*-2-*one* (10).—To an ice-cold solution in benzene (100 ml) of *o*-toluidine (10·7 g) and pyridine (10 ml), a solution of compound (3) (14 g) in benzene was added dropwise with shaking. The usual work-up afforded *N*-(4-chlorobutyryl)-*o*-toluidine, m.p. 75—76° (17 g). The crude product (3·5 g) was briefly (10 min) treated with ethanolic potassium hydroxide (1·6 g in 70 ml). The mixture was cooled, and acidified after dilution with water. The usual work-up furnished a viscous solid (10), which crystallised from petroleum (b.p. 60—80°) as white flakes (12 g), m.p. 41—42°, $\nu_{max.}$ (KBr) 1646 cm^{-1}, δ ($CDCl_3$) 2·2 (3H, s, Me), 1·8—2·6 (4H, m, CO·CH_2·CH_2), 3·6 (2H, t, N·CH_2), and 7·12 (4H, m, ArH), identical with an authentic sample prepared by Reppe's procedure [2] (m.p., t.l.c., and i.r. spectra).

Permanganate oxidation of compound (10) under the conditions reported [2] could not be successfully carried out.

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