Steric Effects in the Base-catalysed Conversion of 2-Cyanophenyl 2,4,6-Tri-t-butylbenzoate into 2,4,6-Tri-t-butylbenzonitrile in Aqueous Alcohol

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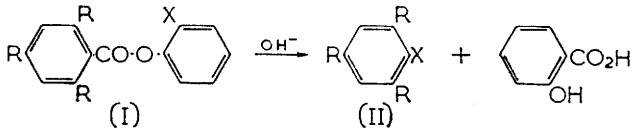
That conditions appropriate for the hydration of a nitrile to an amide are also appropriate for the reverse dehydration of an amide to a nitrile is demonstrated in the base-catalysed conversion of 2-cyanophenyl 2,4,6-tri-t-butylbenzoate into 2,4,6-tri-t-butylbenzonitrile and salicylic acid *via* amide intermediates, the equilibria between amide and nitrile being determined in part by the steric environment of the groups concerned.

We have recently described a series of reactions (Scheme 1) which result in the formation of a highly hindered amide (IIa) *via* the intramolecular rearrangement of a less hindered amide (Ia).[1]



(I) (II)

a; R = Me, X = CO·NH$_2$ a; R = Me, X = CO·NH$_2$
b; R = Bu^t, X = CN b; R = Bu^t, X = CN
c; R = Bu^t, X = CO·NH$_2$ c; R = Bu^t, X = CO·NH$_2$

SCHEME 1

We now report a formally analogous process in which the group X transposed is a cyano-group.

RESULTS

In connection with other work an attempt was made to prepare the very highly hindered ester 2-carbamoylphenyl 2,4,6-tri-t-butylbenzoate (Ic). The reactions of 2,4,6-tri-t-butylbenzoyl chloride with salicylamide in the presence of pyridine and of 2,4,6-tri-t-butylbenzoic acid with salicylamide with trifluoroacetic anhydride as dehydrating agent did not yield the desired product. Under sufficiently forcing conditions (140° for 7 hr. in pyridine) it was possible however to detect (i.r. spectra) the formation of the highly hindered ester linkage at the expense of the amide group which was dehydrated to the nitrile (Ib). Guided by the assumption that the amide to nitrile dehydration had occurred prior to the difficult ester-coupling step, which was then facilitated by the lesser spatial requirements of the nitrile compared with the amide group, it was possible to prepare the ester-nitrile (Ib) in relatively high yield (84%) by the reaction of 2,4,6-tri-t-butylbenzoyl chloride with *o*-cyanophenol in pyridine at 175° for 4 hr.

The ester-nitrile (Ib) proved to be relatively inert to treatment with alkali unless very vigorous conditions were applied. Under such conditions (0·1M-sodium hydroxide in 95% aqueous ethanol contained in a steel bomb and heated at 230° for 10 days) the ester-nitrile (Ib) was converted (30% yield) into 2,4,6-tri-t-butylbenzonitrile (IIb) and salicylic acid. An identical result was observed when the ester-amide (Ic) [prepared by treatment of the ester-nitrile (Ib) with alkaline hydrogen peroxide] was similarly treated with aqueous ethanolic alkali (240—250° for 12 days yielded 49·5% of 2,4,6-tri-t-butylbenzonitrile). Under less vigorous conditions (100° for 10 hr. in 50% aqueous ethanol) it was possible to isolate the amide (IIc) and to verify its structure by comparison with a sample prepared by the reaction of 2,4,6-tri-t-butylbenzoyl chloride with ammonia.

DISCUSSION

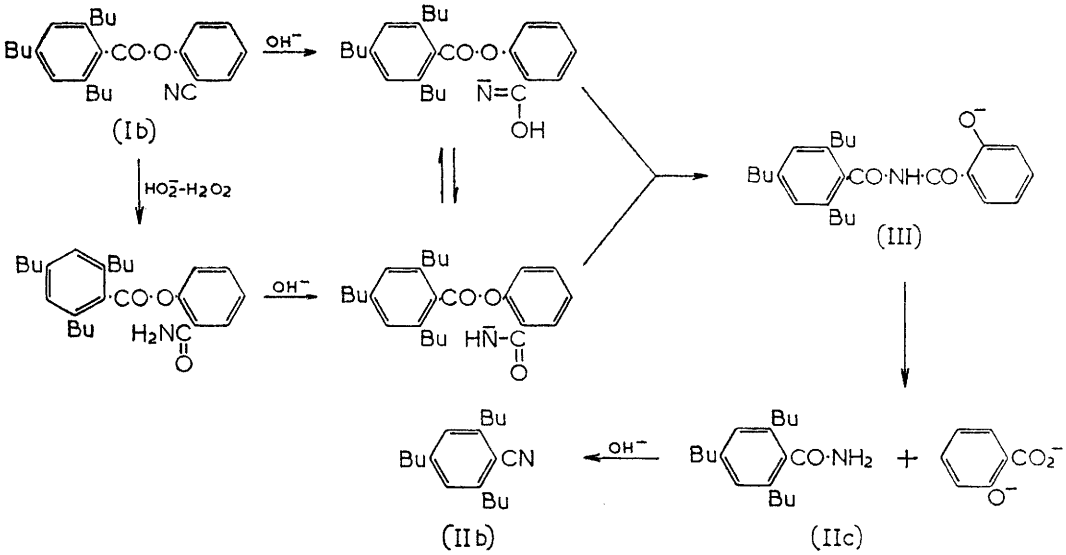
Treatment of either the 2-cyanophenyl ester (Ib) or the 2-carbamoylphenyl ester (Ic) of 2,4,6-tri-t-butylbenzoic acid with 0·1M-sodium hydroxide in 95% aqueous ethanol contained in a steel bomb heated to 200—250° for several days resulted in the formation of 2,4,6-tri-t-butylbenzonitrile and salicylic acid. These results may be rationalised in terms of Scheme 2.

2,4,6-Tri-t-butylbenzoic acid, the ultimate product anticipated from intermolecular attack by hydroxide ion on the ester carbonyl group was never observed in more than trace quantity (<5%). Even under the most vigorous conditions, therefore, the steric shield afforded by the t-butyl groups effectively blocked intermolecular attack at the ester carbonyl groups. Instead intramolecular attack led to the imide (III) which, being subject to base attack at only one of its carbonyl groups, was selectively hydrolysed to salicylic acid and 2,4,6-tri-t-butylbenzamide (IIc). In the final step 2,4,6-tri-t-butylbenzonitrile was formed by base-catalysed dehydration of the amide (IIc).

A rearrangement analogous to that of ester-nitrile (Ib) to amide (IIc) was first reported for the aliphatic nitrile

[1] R. M. Topping and D. E. Tutt, *J. Chem. Soc.* (*B*), 1967, 1346; *Chem. Comm.*, 1966, 698; *J. Chem. Soc.* (*B*), 1969, 104.

α-cyanoisopropyl mesitoate.[2] The final step of the sequence of Scheme 2, the dehydration of 2,4,6-tri-t-butylbenzamide (IIc) to give 2,4,6-tri-t-butylbenzonitrile (IIb) also has precedent in the formation of (*a*) benzonitrile (by fusion of benzamide with calcium hydroxide) [3], (*b*) mesitonitrile (by heating an intimate mixture of mesitamide and powdered sodium hydroxide at 290—310°/20 mm. for ½ hr.),[4] and (*c*) 2,4,6-tri-isopropylbenzonitrile (by co-distillation with ethylene glycol during the course of its formation from a solution of 2,4,6-tri-isopropylbenzamide in an ethylene glycol–alkali mixture heated to 195—197° at atmospheric pressure.) [4] The mechanism of the dehydration has been suggested to involve a base-catalysed elimination from the enol tautomer of the amide.[4]



SCHEME 2 Bu = Bu^t throughout

In the system under discussion in order to avoid any possibility of the driving force for formation of the nitrile being derived from loss of water from the reaction mixture (with the resultant shift in equilibrium from amide to nitrile), all reactions were carried out in the presence of aqueous solvents and contained in sealed vessels. Under such conditions (*e.g.* M-potassium hydroxide in 50% aqueous ethanol heated at 240° for 3 days) 2,4,6-tri-t-butylbenzamide (IIc) was converted into 2,4,6-tri-t-butylbenzonitrile (IIb) in 41% yield. This result suggests that for the sequence of reactions described by Scheme 2, the steric-relief associated with the conversion of the sp^2 carbon of (IIc) into the *sp* carbon of (IIb) was sufficient to cause the dehydration of the amide to the nitrile under the same prevailing conditions which had resulted in the hydration of the less hindered nitrile group of (Ib) to amide.

EXPERIMENTAL

Preparation of 2,4,6-Tri-t-butylbenzoyl Chloride.—A mixture of 2,4,6-tri-t-butylbenzoic acid [5] (5·8 g., 0·02 mole) and thionyl chloride (6 ml., 0·083 mole) was set aside for 5 days before removal of excess of thionyl chloride under reduced pressure to yield a white solid (5·1 g., 83%). The i.r. spectrum showed characteristic absorptions at 1800 and 1690 cm.$^{-1}$. The crude *acid chloride* was used in subsequent preparations without further purification.

Preparation of 2,4,6-Tri-t-butylbenzamide (IIc).—A solution of crude 2,4,6-tri-t-butylbenzoyl chloride (3·0 g., 0·01 mole) in dry benzene (100 ml.) was added dropwise to dry benzene (200 ml.) at reflux temperature through which was passed dry ammonia for a period of 5½ hr. The mixture was set aside overnight after which the white crystalline *amide* was recrystallised from aqueous methanol (yield 1·4 g., 50%), sublimes below m.p. (Found: C, 78·6; H, 11·05; N, 4·95. $C_{19}H_{31}NO$ requires C, 78·8; H, 10·8; N, 4·8%). The i.r. spectrum showed characteristic absorptions at 3410, 3190, and 1635 cm.$^{-1}$; mass spectrum parent peak, *m/e* 289. The n.m.r. spectrum (in $CDCl_3$) showed bands at τ 2·57 (s), 3·5—4·5br (amide H), 8·51 (s) and 8·7 (s), the singlets in the ratio 2·2 : 18 : 8·1 (anticipated ratio 2 : 18 : 9).

Preparation of 2-Cyanophenyl 2,4,6-Tri-t-butylbenzoate (Ib).—A solution of 2,4,6-tri-t-butylbenzoyl chloride (3·6 g., 0·012 mole) in anhydrous pyridine (15 ml.) was added to a solution of 2-cyanophenol (2 g., 0·017 mole) (prepared from salicylaldoxime) [6] in anhydrous pyridine (10 ml.). The reaction mixture was heated (oil-bath at 170°) for 4 hr. set aside at room temperature overnight, made just acid with concentrated hydrochloric acid; the crude *ester* was filtered off and washed with cold 2N-sodium hydroxide (50 ml.) and water (50 ml.). The resultant solid was recrystallised from aqueous alcohol after being decolourised

[2] J. P. Freeman and G. B. Lucas, *J. Amer. Chem. Soc.*, 1955, **77**, 2334.
[3] (*a*) F. Wohler, *Annalen*, 1878, **192**, 362; (*b*) R. Anschütz and G. Schultz, *Annalen*, 1879, **196**, 48.
[4] L. Tsai, T. Miwa, and M. S. Newman, *J. Amer. Chem. Soc.*, 1957, **79**, 2530.
[5] E. E. Betts and L. R. C. Barclay, *Canad. J. Chem.*, 1955, **33**, 1768.
[6] V. Meyer, *Chem. Ber.*, 1893, **26**, 1254.

with charcoal (yield 3·8 g., 83%). Recrystallisation of the pale yellow solid from light petroleum (b.p. 80—100°) afforded white needles, m.p. 160—162° (Found: C, 80·1; H, 8·8; N, 3·6. $C_{26}H_{33}NO_2$ requires C, 79·8; H, 8·5; N, 3·6%). The i.r. spectrum showed characteristic absorptions at 2250 and 1755 cm.$^{-1}$; mass spectrum parent peak *m/e* 392. The n.m.r. spectrum (CCl_4) showed bands at τ 1·7—3·1 (m), 2·55 (s), 8·55 (s), and 8·65 (s) in the ratio 4 : 2·2 : 18 : 9. (Anticipated ratio 4 : 2 : 18 : 9).

Preparation of 2-Carbamoylphenyl 2,4,6-Tri-t-butylbenzoate (Ic).—A mixture of 2-cyanophenyl 2,4,6-tri-t-butylbenzoate (2 g., 0·005 mole), acetone (350 ml.), water (50 ml.), 2N-sodium hydroxide (20 ml.) and 30% hydrogen peroxide (70 ml.) [7] was set aside at room temperature for 14 days. Water (400 ml.) was then added and the acetone was removed on a steam-bath to yield a white solid which was filtered off, dissolved in ether (100 ml.), washed with 2N-sodium hydroxide (100 ml.) and water (2 × 50 ml.), dried ($MgSO_4$), and the ether removed. The resultant white solid *ester* was crystallised from light petroleum (b.p. 80—100°) (yield 1·8 g., 87%), m.p. 172—173° (Found: C, 76·3; H, 8·7; N, 3·45. $C_{26}H_{35}NO_3$ requires C, 76·3; H, 8·6; N, 3·4%). The i.r. spectrum showed absorptions at 3500 (sharp), 3350, 3290, 3160, 1755 and 1680 cm.$^{-1}$; mass spectrum parent peak *m/e* 409. The n.m.r. spectrum (in CCl_4; after a second recrystallisation from acetone and being dried at 100° for 1 hr.) showed bands at τ 1·8—3·0 (m), 2·6 (s), 3·15br, 3·45br, 8·05 (s), 8·63 (s), and 8·72 (s). The band at τ 8·05 was assigned to acetone of crystallisation. The ratio of bands at τ 2·6, 8·63, and 8·72 was 2·3 : 19·7 : 8·6 (anticipated ratio 2 : 18 : 9).

Conversion of the Amide-ester (Ic) *into the Amide* (IIc).—A solution of the amide-ester (Ic) (0·5 g., 0·00122 mole) in 95% aqueous ethanol (100 ml.) and 2M-potassium hydroxide (90 ml.) was heated at 130° for 24 hr. and then set aside overnight at room temperature. A white crystalline solid was filtered off and identified (i.r. and t.l.c.) as the amide (IIc) (81% yield) by comparison with authentic samples of salicylic acid, salicylamide, salicylonitrile, ethyl salicylate, 2,4,6-tri-t-butylbenzoic acid, 2,4,6-tri-t-butylbenzonitrile, 2,4,6-tri-t-butylbenzamide and ethyl 2,4,6-tri-t-butylbenzoate. By the same means salicylic acid was shown to be a major product and 2,4,6-tri-t-butylbenzoic acid and salicylamide to be present in trace amounts (<5%).

Conversion of the Amide-ester (Ic) *into the Nitrile* (IIb).—A solution of the amide-ester (Ic) (0·03 g., $7·4 \times 10^{-5}$ mole) in 95% aqueous ethanol (40 ml.), 10M-sodium hydroxide (0·4 ml.), and water (0·2 ml.) was sealed in 3 ml. stainless-steel ampoules and heated in a silicone-oil-bath at 240° for 13 days. The contents of the ampoules (7/12) were combined, water (10 ml.) was added, ethanol was distilled off, the aqueous phase (pH 8) was extracted with ether and the ether was removed to give an oil. I.r. analysis (in CCl_4) of this oil at 2230 cm.$^{-1}$ by using a previously prepared calibration curve of absorbance *vs.* concentration of the nitrile (IIb) indicated a 49·5% recovery of the nitrile (IIb).

Conversion of the Cyano-ester (Ib) *into the Nitrile* (IIb).—By a similar procedure to that outlined above (ampoules heated at 230° for 10 days) the cyano-ester (Ib) afforded a 30% yield of the nitrile (IIb).

Conversion of the Amide (IIc) *into the Nitrile* (IIb).—A solution of the amide (IIc) (0·3 g., 0·001 mole) in 95% aqueous alcohol (6 ml.) and 2M-potassium hydroxide (6 ml.) was sealed in 6 stainless-steel ampoules and heated at 270° for 3 days. Ether extraction of the combined contents gave a white crystalline solid (0·115 g., 41%), m.p. 147—148° (from aqueous alcohol) (Found: C, 84·0; H, 10·9; N, 5·3. $C_{19}H_{29}N$ requires C, 84·1; H, 10·8; N, 5·2%). The i.r. spectrum showed a characteristic absorption at 2230 cm.$^{-1}$ (CCl_4); mass spectrum parent peak *m/e* 271.

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[7] J. V. Murray and J. B. Cloke, *J. Amer. Chem. Soc.*, 1934, **56**, 2749.