417. 6-*Aminosalicylic Acid: The Hydrolysis of 2-Carboxytrinitrodiphenyl Ethers.*

By A. A. Goldberg and H. A. Walker.

Hydrolysis of 2-chloro-6-nitrobenzoic acid with aqueous potassium carbonate at 175° gave 6-nitrosalicylic acid in unsatisfactory yield. Condensation of 2-chloro-6-nitrobenzoic acid with phenol and nitration of the product yielded 2-carboxy-3 : 2′ : 4′-trinitrodiphenyl ether; this was hydrolysed by dilute alkali to 6-nitrosalicylic acid and 2 : 4-dinitrophenol. Yields were high at all stages.

The hydrolytic scission of 2-carboxydiphenyl ethers bearing 2′- and 4′-nitro-groups appears to be general.

Much has been published on the use of 4-aminosalicylic acid against human tuberculosis. Since its introduction by Lehman (*Lancet*, **1946**, **250**, 15). The activities of 3- and 5-aminosalicylic acids against *M. tuberculosis in vitro* are far lower than that of the 4-isomer (Hurt and Hurni, *Helv. Chim. Acta*, 1949, **32**, 378) but there is no record of the activity of 6-aminosalicylic acid. Justoni (*Farm. sci. e tec., Pavia*, 1950, **5**, 165; *Chem. Abs.*, 1950, 7807) prepared the compound but did not report experimental details or the synthetical route.

The necessary intermediate, 6-nitrosalicylic acid, was isolated in unspecified yield by Mehta and Ayyar (*J. Univ. Bombay*, 1939, **8**, Part 3, 176) as an oxidation product of 5-nitrobenzo-1 : 3-dioxen (cf. Buehler, Deeble, and Evans, *J. Org. Chem.*, 1941, **6**, 216). This

method was found to have little preparative value and attention was turned to the easily accessible 2-chloro-6-nitrobenzoic acid. Attempted hydrolysis of this by aqueous potassium carbonate at 150° in the presence of a copper catalyst was unsuccessful. At 175°, however, 6-nitrosalicylic acid was obtained in *ca.* 10% yield together with considerable quantities of *m*-chloronitrobenzene and unchanged 2-chloro-6-nitrobenzoic acid. The stability of the halogen in 2-chloro-6-nitrobenzoic acid towards potassium carbonate is remarkable in view of the rapid hydrolysis of the 3-, 4-, and 5-nitro-isomers by this reagent (Goldberg, *J.*, 1952, 4368).

Fission of a diphenyl ether group in nitroxanthones by alkali (Meisenheimer, *J. pr. Chem.*, 1928, **119**, 315) or piperidine (Le Fèvre, *J.*, 1928, 3249) and in polynitrodiphenyl ethers by nucleophilic reagents (G.P. 620,761; Borrows *et al.*, *J.*, 1949, 5190) suggested that polynitrated 2-carboxy-diphenyl ethers would be amenable to hydrolytic cleavage to nitrosalicylic acids and nitrophenols: 2′- and 4′-nitro-groups should create a sufficiently strong electron defect at $C_{(1')}$. Condensation of 2-chloro-6-nitrobenzoic acid with phenol and treatment of the 2-carboxy-3-nitrodiphenyl ether thus produced with nitric acid gave 2-carboxy-3 : 2′ : 4′-trinitrodiphenyl ether, which with aqueous alkali at 100° disrupted into 6-nitrosalicylic acid and 2 : 4-dinitrophenol, which were easily separated; yields at all stages were high.

Similarly, nitration of 2-carboxy-5- and -6-nitrodiphenyl ether gave the 5 : 2′ : 4′- and 6 : 2′ : 4′-trinitro-ethers, which were hydrolysed by alkali to 4- and 3-nitrosalicylic acid respectively. Treatment of 2-carboxydiphenyl ether with nitric acid under the same conditions afforded the 4 : 2′ : 4′-trinitro-ether and thence 5-nitrosalicylic acid and 2 : 4-dinitrophenol.

Hydrogenation of 6-nitrosalicylic acid over palladium–charcoal gave 6-aminosalicylic acid.

The annexed Table shows the minimum concentration (mg./l.) of the compounds which completely inhibit growth of *M. tuberculosis* H37 during an incubation period of 3 weeks.

Acid	Veal broth (*a*)	Veal broth 5% Serum	D'Arcy Hart (*b*)	D'Arcy Hart 5% Serum
3-Aminosalicylic	125	250	125	250
4-Aminosalicylic	0·5	0·5	0·5	0·5
5-Aminosalicylic	>250	>250	>250	>250
6-Aminosalicylic	125	125	250	250

(*a*) Floating pellicle growth (Goldberg, Jefferies, Turner, and Besly, *J. Pharm. Pharmacol.*, 1946, **19**, 483). (*b*) Dispersed growth; inoculum 1 million organisms per c.c. of medium (Dubos and Davies, *J. Exp. Med.*, 1946, **83**, 409; D'Arcy Hart, *Nature*, 1947, **160**, 94).

Experimental

Equivalent weights of the 2-carboxytrinitrodiphenyl ethers were determined by titration with aqueous potassium hydroxide at 0° in order to avoid hydrolysis.

2-Carboxy-3-nitrodiphenyl Ether.—2-Chloro-6-nitrobenzoic acid (50 g.) and copper bronze (1 g.) were added to a solution of potassium hydroxide (30 g.) in phenol (250 g.) and the mixture stirred at 150° (internal) for 6 hr. The phenol was distilled off in a current of steam, and the residual aqueous solution filtered (charcoal) and acidified to pH 3 with 10N-hydrochloric acid. The precipitate was dissolved in boiling water (600 c.c.) containing potassium carbonate (30 g.), and the solution evaporated to small volume and chilled. The potassium salt, on collection and conversion into the free acid, gave *2-carboxy-3-nitrodiphenyl ether* (30 g.; m. p. 158°) as a light brown powder. A sample crystallised from 90% alcohol in colourless needles, m. p. 162° (Found: equiv., 257; N, 5·5%. $C_{13}H_9O_5N$ requires equiv., 259; N, 5·4%). The acid is appreciably soluble in hot water.

2-Carboxy-3 : 2′ : 4′-trinitrodiphenyl Ether.—2-Carboxy-3-nitrodiphenyl ether (21 g.) was added during ½ hr. to nitric acid (200 c.c.; *d* 1·5) stirred at 0°. After a further 2 hr. at 0—5° the solution was poured on ice (500 g.); the precipitate (27 g.), crystallised from alcohol, gave *2-carboxy-3 : 2′ : 4′-trinitrodiphenyl ether* (18 g.) in fine pale yellow needles, m. p. 194° (Found: equiv., 346; N, 12·1%. $C_{13}H_7O_9N_3$ requires equiv., 349; N, 12·0%).

6-Nitrosalicylic Acid.—A solution of the foregoing acid (35 g.) in 2·5N-sodium hydroxide (250 c.c.) was heated on the steam-bath for 1 hr., cooled, and acidified to pH 4·5 with hydro-

chloric acid. The precipitate of 2 : 4-dinitrophenol, m. p. and mixed m. p. 114° (Found : N, 14·8. Calc. for $C_6H_4O_5N_2$: N, 15·2%), was removed and the filtrate acidified to pH 2 with 10N-hydrochloric acid and extracted with ether (4 × 250 c.c.). Removal of the ether gave 6-nitrosalicylic acid (10 g.), pale yellow needles, m. p. 172° (from toluene) [Found : equiv., 183; *M* (Rast), 180; C, 45·8; H, 2·8; N, 7·7%. Calc. for $C_7H_5O_5N$: equiv. = *M*, 183; C, 45·8; H, 2·7; N, 7·7%). In contrast to 4- and 5-nitrosalicylic acids, the 6-isomer is very soluble in cold water and in ether.

6-*Aminosalicylic Acid*.—The foregoing acid (10 g.), water (120 c.c.) and 5N-hydrochloric acid (10 c.c.) were shaken with palladium chloride (0·6 g.) and charcoal (3 g.) in hydrogen at 15°/760 mm. (uptake, 3800 c.c. at N.T.P.; $3H_2$, 3680 c.c.). The filtered solution was evaporated at reduced pressure to *ca.* 70 c.c. and chilled. The colourless crystalline precipitate of 6-*aminosalicylic acid hydrochloride* (6·6 g.), m. p. 216° (decomp.), was collected (Found : N, 8·2; Cl, 18·8. $C_7H_8O_3NCl$ requires N, 7·4; Cl, 18·7%); evaporation of the filtrate to dryness yielded a residue (5 g.), m. p. 178°. This, together with the first precipitate, was dissolved in 5% aqueous sodium hydrogen carbonate (120 c.c.), and the filtered solution acidified to pH 4 with acetic acid; plates of 6-aminosalicylic acid (4·2 g.), m. p. 148°, separated which were collected and dried at 20°/2 mm. (Found : equiv., 154; N, 9·2%. Calc. for $C_7H_7O_3N$: equiv., 153; N, 9·2%).

2-*Carboxy*-5 : 2′ : 4′-*trinitrodiphenyl Ether*.—2-Carboxy-5-nitrodiphenyl ether (11 g.; Goldberg and Walker, *J.*, 1953, 1348) was added during ¼ hr. to nitric acid (100 c.c.; *d* 1·5) stirred at 5—10°. The solution was kept for a further 2¼ hr. at 10° and then poured on ice (600 g.). The precipitate (15 g.) was collected, washed with water, dried *in vacuo*, and dissolved in 150 c.c. of toluene–dioxan (3 : 1), and the hot filtered solution diluted with 90 c.c. of ligroin (b. p. 80—100°). 2-*Carboxy*-5 : 2′ : 4′-*trinitrodiphenyl ether* separated in colourless hydrated tablets; these (12·7 g.), on drying at 90°, gave the anhydrous acid (11·5 g.), m. p. 188—190° (Found : equiv., 348; N, 12·1%. $C_{13}H_7O_9N_3$ requires equiv., 349; N, 12·0%).

4-*Nitrosalicylic Acid*.—A solution of the foregoing crude acid (10·0 g.) and potassium carbonate (250 g.) in water (150 c.c.) was heated on the water-bath for 6 hr. A precipitate obtained at pH 5 consisted of 2 : 4-dinitrophenol and its potassium salt, giving on recrystallisation from acidic aqueous alcohol, 2 : 4-dinitrophenol (4·0 g.), m. p. and mixed m. p. 116—118°. Adjustment to pH 2 gave 4-nitrosalicylic acid (4·9 g.), lemon-yellow needles (from aqueous alcohol), m. p. and mixed m. p. 236° (Found : equiv., 183; N, 7·8%).

2-*Carboxy*-6 : 2′ : 4′-*trinitrodiphenyl Ether*.—Nitration of 2-carboxy-6-nitrodiphenyl ether (20 g.; Goldberg and Walker, *loc. cit.*) as for the 3-nitro-isomer, gave the 6 : 2′ : 4′-*trinitro-ether* (21 g.) in pale yellow plates (from ethanol), m. p. 176° (Found : equiv., 340; N, 12·1%).

3-*Nitrosalicylic Acid*.—A solution of the foregoing acid (10 g.) in 5% aqueous potassium carbonate (500 c.c.) was evaporated on the water-bath to incipient crystallisation. Treatment as previously described gave 2 : 4-dinitrophenol (4·0 g.; m. p. 111°) and 3-nitrosalicylic acid (4·0 g.), needles (from water), m. p. and mixed m. p. 145° (Found : equiv., 184; N, 7·5%).

2-*Carboxy*-4 : 2′ : 4′-*trinitrodiphenyl Ether*.—2-Carboxydiphenyl ether (21·4 g.) was added during 1 hr. to nitric acid (200 c.c.; *d* 1·5) stirred at 0°. After a further 2 hr. at 5—10° the solution was poured on ice (1000 g.) and the 4 : 2′ : 4′-*trinitro-ether* (28 g.; m. p. 155°) collected, washed and, dried at 60°. A sample crystallised from dilute alcohol in pale yellow needles with the same m. p. (Found : equiv., 346; N, 12·1%).

5-*Nitrosalicylic Acid*.—A solution of the foregoing acid (20 g.) in N-sodium hydroxide (500 c.c.), heated on the water-bath for 2 hr., gave 2 : 4-dinitrophenol (9 g.; m. p. 110°) at pH 5 and, at pH 2, 5-nitrosalicylic acid (7·5 g.), needles, m. p. and mixed m. p. 232° (Found : equiv., 186; N, 7·8%).

Hydrolysis of 2-*Chloro*-6-*nitrobenzoic Acid*.—A solution of 2-chloro-6-nitrobenzoic acid (20·2 g.) in water (500 c.c.) and potassium carbonate (20·2 g.) was heated with copper bronze (1 g.) and cuprous iodide (1 g.) in an autoclave for 7 hr. at 175° (internal); the pressure was 110 lb./sq. in. After chilling, the catalyst and impure *m*-chloronitrobenzene (*ca.* 6 g.) were filtered off and the solution extracted with ether. The aqueous layer was evaporated to *ca.* 300 c.c., strongly acidified with 5N-sulphuric acid, and set aside overnight. The precipitate of unchanged 2-chloro-6-nitrobenzoic acid (5·5 g.; m. p. and mixed m. p. 160—162°) was removed and the filtrate extracted with ether. Evaporation of the ethereal solution gave 6·5 g. of very impure 6-nitrosalicylic acid; this was dissolved in dilute potassium carbonate, the solution evaporated to very small volume and chilled and the precipitated potassium salt collected (filtrate F). The precipitate was dissolved in a small amount of water, the solution acidified, and the precipitate (3 g.; m. p. 160°) of 2-chloro-6-nitrobenzoic acid removed. The filtrate was combined with filtrate F, acidified, and extracted with ether; evaporation of the

ether yielded 1·6 g. of 6-nitrosalicylic acid, m. p. and mixed m. p. 166—168° (Found: equiv., 186).

When the above experiment was carried out at 150—155° for 6½ hr. 2-chloro-6-nitrobenzoic acid (15 g.) was recovered.

RESEARCH DEPARTMENT, WARD, BLENKINSOP & CO., LTD.,
SHEPTON MALLET, SOMERSET.

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