543. *Some Further Derivatives of 4-Hydroxyisophthalic Acid.*

By J. M. Z. Gladych and E. P. Taylor.

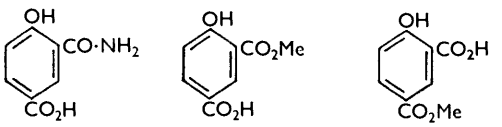
Numerous derivatives of 4-hydroxyisophthalic acid have been prepared and tested as potential analgesics, diuretics, fungicides, local anæsthetics, and neuromuscular blocking agents. A novel concurrent transesterification and transetherification is reported.

Comparatively little work appears to have been done on the pharmacological activity of 4-hydroxyisophthalic acid and its derivatives. The analgesic and antipyretic properties of the parent acid have been described by Chesher *et al.*,[1,2] and its absorption and excretion in rats and human subjects have also been investigated.[3] Fosdick and Fancher[4] found some alkyl and aminoalkyl esters of 4-methoxyisophthalic acid to possess an anæsthetic efficiency approximately equal to that of procaine. Antitubercular activity has been claimed[5] for 6-amino-4-hydroxyisophthalic acid (a by-product in the manufacture of 4-aminosalicylic acid), but other workers[6,7] have reported lower activity. Diethyl 5-amino-4-hydroxyisophthalate[8] has no antibacterial activity.[9] Salts[10] and acyl derivatives[11] of 4,6-dihydroxyisophthalic acid, and salts of 5-halogeno-4,6-dihydroxyisophthalic acid[12] have been claimed to possess analgesic and antiarthritic activity.

[1] Chesher, Collier, Robinson, Taylor, Hunt, Jones, and Lindsey, *Nature*, 1955, **175**, 206
[2] Collier and Chesher, *Brit. J. Pharmacol.*, 1956, **11**, 20.
[3] Robinson, Fehr, and Fitzgerald, *Biochem. J.*, 1956, **63**, 362.
[4] Fosdick and Fancher, *J. Amer. Chem. Soc.*, 1941, **63**, 1277.
[5] Bavin, Drain, Seiler, and Seymour, *J. Pharm. Pharmacol.*, 1952, **4**, 844.
[6] Beyerman and Alberda, *Rec. Trav. chim.*, 1950, **69**, 1021.
[7] Checcacci, Logemann, Pistoia, and Lauria, *Nature*, 1954, **173**, 588.
[8] Hunt, Jones, and Lindsey, *J.*, 1956, 3099.
[9] Collier, unpublished results quoted in ref. 8.
[10] G.P. 1,044,106.
[11] G.P. 1,024,092.
[12] G.P. 1,047.790.

In view of these results and since salicylamide [13] and certain of its derivatives [14] possess analgesic, antipyretic, or antifungal activity, it was initially decided to examine a series of amides of 4-hydroxy- and 4-alkoxy-isophthalic acids, some of which we have already reported.[15] The most active analgesic of the compounds tested was the 3-monoamide (I), which was more active and less toxic than the parent acid in rats. Although still significant, the activity when administered orally was less than by intraperitoneal injection. Other derivatives, *e.g.*, the corresponding ethylamide and 4-n-propoxyisophthalamide, showed good analgesic activity when administered intraperitoneally but were ineffective orally. (After our work had been completed, Erlenmeyer [16] reported that monoamides of 4-hydroxyisophthalic acid possessed marked analgesic activity and low toxicity; they were well tolerated in humans, and caused fewer undesirable secondary effects than the usual salicylic acid preparations.) None of the compounds of this series tested by us was found to have encouraging antifungal activity.

Since most of the 3-monoamides have been prepared by aminolysis of the 3-monomethyl ester (II), it is desirable to clear up certain misconceptions in the literature. Hunt, Jones, and Lindsey [8] obtained the isomeric 1-monomethyl ester (III) by partial hydrolysis of the dimethyl ester with boiling aqueous-methanolic potassium hydroxide. We have



(I) (II) (III)

confirmed this but in addition have shown that hydrolysis of the dimethyl ester with aqueous sodium hydroxide at room temperature gives the 3-monomethyl ester (II).[17] It is stressed, however, that our results do not contradict those of Hunt, Jones, and Lindsey, despite a recent statement to this effect by Dansi *et al.*[18]

We esterified 4-hydroxyisophthalic acid with methanol and sulphuric acid, but were unable to confirm the finding of Dansi *et al.* that the 3-monomethyl ester was formed; when the experimental conditions were suitably controlled, the crude 1-monomethyl ester was isolated in 54% yield. Similarly we failed to isolate any 3-monomethyl ester on hydrolysis of the dimethyl ester with 8% sodium carbonate at 37° under the conditions of Dansi *et al.*, obtaining only small yields of the 1-monomethyl ester and 4-hydroxyisophthalic acid, together with unchanged dimethyl ester.

Attempts to confirm the results of Dansi *et al.* concerning the preparation of the 3-*N*-n-butylamide and its 1-methyl ester, and of the di-n-butylamide also failed. By refluxing an alcoholic solution of dimethyl 4-hydroxyisophthalate and n-butylamine we obtained, not the di-n-butylamide, but the n-butylamine salt (IV) of the 1-monoester 3-amide; the same compound was also obtained by carrying out the reaction at room temperature. The identity of this product was proved by cold basification, followed by immediate acidification, which gave the 1-monoester 3-n-butylamide, and by alkaline hydrolysis at room temperature, which gave the acid 3-n-butylamide. The m. p.s of our ester amide and 3-n-butylamide do not agree with those reported by Dansi *et al.*; we have prepared these two compounds by various methods and obtained consistent physical constants.

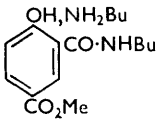
Dansi *et al.* report that they have repeated Jacobsen's claim [19] that 4-hydroxyisophthalamide is readily obtained by ammonolysis of the dimethyl ester, but, as we have

[13] Ross and Hart, *J. Pharmacol.*, 1947, **89**, 205.
[14] Coates, Drain, Kerridge, Macrae, and Tattersall, *J. Pharm. Pharmacol.*, 1957, **9**, 855; Jules, Faust, and Sahyun, *J. Amer. Pharm. Assoc., Sci. Ed.*, 1956, **45**, 514; Hok, Hamilton, Pilcher, and Nieman, *Antibiotics and Chemotherapy*, 1956, **6**, 456; Pilcher and Hamilton, *ibid.*, p. 573.
[15] Gladych, Lindsey, and Taylor, *J.*, 1957, 4834.
[16] Erlenmeyer, B.P. 802,841.
[17] Gladych and Taylor, *J.*, 1956, 4678.
[18] Dansi, Garzia, Grasso, and Semeria, *Boll. Chim. Farm.*, 1957, **96**, 388.
[19] Jacobsen, *Ber.*, 1878, **11**, 380.

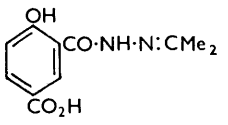
previously indicated,[15] it is necessary to use very vigorous conditions in order to carry out this reaction and to avoid formation of the ester amide.

The 3-monohydrazide of 4-hydroxyisophthalic acid, obtained by the action of hydrazine hydrate on the 3-monomethyl ester,[18] when condensed with acetone yielded the hydrazone (V), which was readily hydrolysed back to the hydrazide by boiling 95% ethanol.

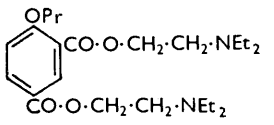
Following the lead of Fosdick and Fancher,[4] we prepared a series of dialkylaminoalkyl esters of 4-alkoxyisophthalic acids for test as potential local anæsthetics. Some of these have considerable activity, in particular, the dihydrochloride of bis(diethylaminoethyl) 4-n-propoxyisophthalate (VI). This compound, although approximately 3·5 times as toxic as procaine hydrochloride in mice, has approximately 4·5 times the local anæsthetic activity of procaine hydrochloride in guinea pigs.



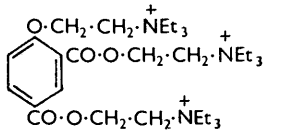
(IV)



(V)



2HCl (VI)



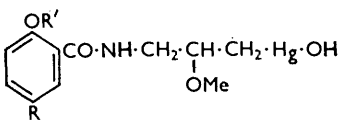
3I⁻ (VII)

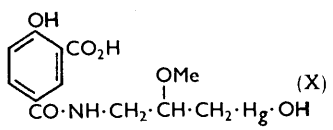
In view of their structural resemblance to Gallamine, some trisquaternary salts of dialkylaminoalkyl 4-dialkylaminoalkoxyisophthalates have been synthesised as possible neuromuscular blocking agents. The most active member of this series was the tris-ethiodide (VII) of bis(diethylaminoethyl) 4-2′-diethylaminoethoxyisophthalate which had a curare-like action of comparatively short duration. This compound has been independently prepared and its pharmacology described by Carissimi *et al.*[20]

Our method of preparation of these compounds, which consisted of treating dimethyl 4-methoxyisophthalate with an excess of a dialkylaminoalkanol in the presence of metallic sodium, and subsequent quaternisation of the product, involved a concurrent transetherification and transesterification which has apparently not been realised hitherto.

During the preparation of dimethyl 4-methoxyisophthalate, the desired product was obtained when dimethyl 4-hydroxyisophthalate was heated with methyl iodide in methanol in the presence of anhydrous potassium carbonate, but diethyl 4-methoxyisophthalate resulted when ethanol was used as solvent.

	R	R′
(VIII)	H	$CH_2 \cdot CO_2H$
(IX)	CO_2H	H





(X)

Two analogues of Mersalyl (VIII) were prepared as potential diuretic agents, but both were less active than Mersalyl when administered intraperitoneally to rats. The synthesis of these two compounds, (IX) and (X), involved the treatment of the appropriate monomethyl ester of 4-hydroxyisophthalic acid with allylamine, and subsequent mercuration with mercuric acetate.

The pharmacological properties of all these compounds will be described in full elsewhere.

Experimental

Light petroleum had b. p. 40—60°.

Esters of 4-Hydroxyisophthalic Acid.—The 1-monomethyl ester was prepared according to Hunt, Jones, and Lindsey's directions,[8] and also by the following method: 4-Hydroxyisophthalic acid (21·6 g.), methanol (216 ml.), and concentrated sulphuric acid (6·0 ml.) were

[20] Carissimi, Ravenna, Milla, Grumelli, and Grasso, *Farmaco, Edn. Sci.*, 1958, **13**, 231.

boiled under reflux for 3 hr. The mixture was then cooled and poured into ice-water (450 ml.). Sufficient solid sodium hydrogen carbonate was added to bring the pH to 8, and the mixture was filtered; the crude insoluble dimethyl 4-hydroxyisophthalate, after being washed with water and dried, had m. p. 95—96° (lit.,[8] 97·5°) (9·3 g., 37%). The aqueous-methanolic filtrate was acidified with hydrochloric acid to Congo Red, and the crude 1-methyl hydrogen 4-hydroxyisophthalate filtered off, washed with water, and dried (12·6 g., 54%). This crystallised from aqueous methanol in plates, m. p. 199—199·5° (lit.,[8] 200°), undepressed on admixture with a sample prepared by partial hydrolysis of the dimethyl ester with aqueous-methanolic potassium hydroxide.[8] Hydrolysis of the dimethyl ester with 8% aqueous sodium carbonate at 37° by the method of Dansi *et al.*[18] gave unchanged dimethyl ester (32%), 1-monomethyl ester, m. p. 199—199·5° (14%), and crude 4-hydroxyisophthalic acid, m. p. 290—300° (decomp.) (12%). No 3-monomethyl ester could be isolated.

The 3-monomethyl and 3-monoethyl esters were prepared by partial hydrolysis of the corresponding dialkyl ester with excess of aqueous sodium hydroxide at room temperature.[17]

The following mixed dialkyl esters were prepared by Fischer–Speier esterification of the appropriate 3-monoalkyl esters: *3-ethyl 1-methyl 4-hydroxyisophthalate*, rosettes, m. p. 45—46·5°, from aqueous acetone (Found: C, 58·6; H, 5·25. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%); *1-ethyl 3-methyl 4-hydroxyisophthalate*, needles, m. p. 92—92·5°, from absolute ethanol (Found: C, 59·0; H, 5·4%).

Transesterification of Dimethyl 4-Hydroxyisophthalate.—Dimethyl 4-hydroxyisophthalate (10·5 g., 0·05 mole), anhydrous potassium carbonate (6·9 g., 0·05 mole), and absolute ethanol (250 ml.) were heated under reflux for 48 hr. with the exclusion of moisture, then evaporated to dryness *in vacuo*, the solid residue (14·3 g.) was dissolved in water (100 ml.), and 2N-hydrochloric acid was added to pH 8·4—8·7. The crude diethyl 4-hydroxyisophthalate (3·34 g., 28%) was filtered off, dried, and recrystallised from light petroleum as rosettes, m. p. and mixed m. p. 52—53° (lit.,[8] 54·5°) (Found: C, 60·25; H, 5·9. Calc. for $C_{12}H_{14}O_5$: C, 60·5; H, 5·9%). The aqueous filtrate was acidified to pH 3·6 and the precipitated crude 1-ethyl hydrogen 4-hydroxyisophthalate (5·01 g., 47·7%) was filtered off and dried at 90°. It recrystallised from aqueous ethanol as rosettes, m. p. and mixed m. p. 194—195° (lit.,[8] 195·6°) (Found: C, 57·1; H, 4·6. Calc. for $C_{10}H_{10}O_5$: C, 57·1; H, 4·8%).

Esters of 5-Substituted 4-Hydroxyisophthalic Acids.—Dimethyl 5-bromo-4-hydroxyisophthalate was prepared according to instructions of Hunt *et al.*[8]

3-Methyl hydrogen 5-bromo-4-hydroxyisophthalate was prepared from the dimethyl ester by partial hydrolysis,[17] and crystallised from absolute ethanol in needles, m. p. 249—250° (Found: C, 39·2; H, 2·8; Br, 29·1. $C_9H_7BrO_5$ requires C, 39·3; H, 2·6; Br, 29·1%).

Dimethyl 4-hydroxy-5-iodoisophthalate was prepared as follows: Iodine monochloride (4·9 g.) in acetic acid (10 ml.) was added slowly, with stirring, to dimethyl 4-hydroxyisophthalate (2·1 g.) in acetic acid (30 ml.); the mixture was heated on a steam-bath for 30 min. and cooled. Water (125 ml.) was added, and the precipitate filtered off, washed with water, sodium thiosulphate solution, and again water, and dried. The product (3·0 g., 89%) crystallised from acetone in needles, m. p. 145—145·5° (Found: C, 36·0; H, 2·5; I, 37·8. $C_{10}H_9IO_5$ requires C, 35·7; H, 2·7; I, 37·8%). A very small quantity of the same compound was obtained when the sodio-derivative of dimethyl 4-hydroxyisophthalate was treated with potassium tri-iodide solution at room temperature (cf. general method of Papa *et al.*[21]), the major product, other than unchanged dimethyl ester, being 3-methyl hydrogen 4-hydroxyisophthalate, m. p. 253—254° as recorded.[17] Iodination of 4-hydroxyisophthalic acid in alkaline solution with potassium tri-iodide gave only 4-hydroxy-3,5-di-iodobenzoic acid and 2,4,6-tri-iodophenol (cf. Hunt *et al.*[8] who found that 4-hydroxyisophthalic acid was converted into 2,4,6-tribromophenol by aqueous bromine).

Esters of 4-Alkoxy- and 4-Dialkylaminoalkoxy-isophthalic Acids.—The following esters were prepared by Fischer–Speier esterification of the appropriate alkoxy-acids:[15] *dimethyl 4-ethoxyisophthalate*, needles, m. p. 65·5—66·5°, from light petroleum (Found: C, 60·6; H, 5·8. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%); diethyl 4-methoxyisophthalate, prisms, m. p. 53·5—54° (lit.,[4] 57°), from light petroleum (Found: C, 61·6; H, 5·9. Calc. for $C_{13}H_{16}O_5$: C, 61·9; H, 6·4%); *dimethyl 4-n-butoxyisophthalate*, needles, m. p. 44—45°, from light petroleum (Found: C, 63·4; H, 6·5. $C_{14}H_{18}O_5$ requires C, 63·15; H, 6·8%); *diethyl 4-benzyloxyisophthalate*, prisms, m. p. 64·5—65·5°, from light petroleum (Found: C, 69·4; H, 6·2. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·15%).

[21] Papa, Breiger, Schwenk, and Peterson, *J. Amer. Chem. Soc.*, 1950, **72**, 4906.

The following esters were prepared by *O*-alkylation of dialkyl 4-hydroxyisophthalates in a suitable solvent with the appropriate alkyl bromide or iodide in the presence of anhydrous potassium carbonate (cf. Gladych *et al.*[15]): dimethyl 4-methoxyisophthalate (solvent methanol), needles, m. p. 98—99° (lit.,[8] 95°) from light petroleum (Found: C, 58·8; H, 5·3. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4%) [when ethanol was used as solvent, diethyl 4-methoxyisophthalate was obtained as prisms, m. p. and mixed m. p. 53—54° (from light petroleum) (Found: C, 61·9; H, 6·1%)]; *1-ethyl 3-methyl* (solvent acetone), needles, m. p. 59—59·5°, from light petroleum (Found: C, 60·25; H, 5·5. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%), and *1-methyl 3-ethyl 4-methoxyisophthalate* (solvent acetone), needles, m. p. 58—58·5°, from light petroleum (Found: C, 60·2; H, 5·9. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%) (mixed m. p. of these two 42·5—47·5°); *dimethyl 4-2′-dimethylaminoethoxyisophthalate hydrochloride* (this reaction was unsuccessful with methanol or acetone as solvent, but use of ethanol gave a 2% yield), needles, m. p. 131—132°, from ethanol–ether (Found: C, 52·8; H, 7·0; N, 4·3; Cl, 11·2. $C_{14}H_{20}ClNO_5$ requires C, 52·9; H, 6·35; N, 4·4; Cl, 11·2%).

The following *bisdiethylaminoethyl esters* were prepared from 4-alkoxyisophthalic acids by treatment with thionyl chloride followed by 2-diethylaminoethanol (cf. general method of Fosdick and Fancher [4]): *4-ethoxyisophthalate dihydrochloride*, needles, m. p. 178—179°, from absolute ethanol (Found: N, 6·2; Cl, 15·25. $C_{22}H_{38}Cl_2N_2O_5$ requires N, 5·8; Cl, 14·8%), *4-n-propoxyisophthalate dihydrochloride* (VI), needles, m. p. 146—147°, from absolute ethanol (Found: C, 55·5; H, 8·1; N, 5·6; Cl, 14·4. $C_{23}H_{40}Cl_2N_2O_5$ requires C, 55·75; H, 8·1; N, 5·7; Cl, 14·3%) [*dimethiodide*, rosettes, m. p. 200—200·5° (decomp.), from methanol–ether (Found: C, 42·9; H, 5·85; N, 3·6; I, 35·2. $C_{25}H_{44}I_2N_2O_5$ requires C, 42·5; H, 6·3; N, 4·0; I, 36·0%); *diethiodide*, rosettes, m. p. 181—182°, from methanol–ether (Found: C, 44·0; H, 6·6; N, 3·95; I, 34·0. $C_{27}H_{48}I_2N_2O_5$ requires C, 44·1; H, 6·6; N, 3·8; I, 34·6%), *4-allyloxyisophthalate dihydrochloride*, needles, m. p. 153—154°, from absolute ethanol–ether (Found: C, 55·55; H, 7·75; N, 5·5; Cl, 14·3. $C_{23}H_{38}Cl_2N_2O_5$ requires C, 56·0; H, 7·8; N, 5·7; Cl, 14·4%) [*dimethiodide*, rosettes, m. p. 191—192° (decomp.), from methanol–ether (Found: C, 42·9; H, 5·7; N, 3·8; I, 35·5. $C_{25}H_{42}I_2N_2O_5$ requires C, 42·6; H, 6·0; N, 4·0; I, 36·1%)]; *4-isopropoxyisophthalate dihydrochloride*, needles, m. p. 129—131°, from absolute ethanol–ether (Found: N, 5·9; Cl, 14·3. $C_{23}H_{40}Cl_2N_2O_5$ requires N, 5·7; Cl, 14·3%); *4-n-butoxyisophthalate dihydrochloride*, rosettes, m. p. 133—134°, from absolute ethanol–ether (Found: C, 55·8; H, 8·35; N, 5·5; Cl, 13·8. $C_{24}H_{42}Cl_2N_2O_5$ requires C, 56·6; H, 8·3; N, 5·5; Cl, 13·95%).

The last-mentioned hydrochloride was also prepared by transesterification as follows: Dimethyl 4-n-butoxyisophthalate (13·3 g., 0·05 mole), 2-diethylaminoethanol (23·4 g., 0·2 mole), anhydrous potassium carbonate (6·9 g., 0·05 mole), and dry toluene (100 ml.) were heated together for 40 hr. at such a rate that only material of b. p. up to 65° distilled through a Vigreux column. After cooling, sufficient water was added to dissolve the solid, and the toluene layer was separated, washed with water, and dried ($MgSO_4$). The solvent was then removed *in vacuo*, and the residual pale yellow oil (13·5 g.) dissolved in a small quantity of absolute ethanol and treated with a slight excess of alcoholic hydrogen chloride. Anhydrous ether was then added to turbidity, a seed of the hydrochloride added, and the mixture left for some days. After filtration and recrystallisation from absolute ethanol–ether, the dihydrochloride of bis(diethylaminoethyl) 4-n-butoxyisophthalate was obtained as rosettes, m. p. and mixed m. p. 133—134° (1·09 g.); it gave a *diethiodide*, rosettes, m. p. 195—196° (decomp.) (from absolute ethanol–ether) (Found: C, 45·4; H, 6·7; N, 3·4; I, 33·4. $C_{28}H_{50}I_2N_2O_5$ requires C, 44·9; H, 6·7; N, 3·7; I, 34·0%).

Certain esters were prepared by concurrent transetherification and transesterification of dimethyl 4-methoxyisophthalate, for example, bisdimethylaminoethyl 4-dimethylaminoethoxyisophthalate trimethiodide. Dimethyl 4-methoxyisophthalate (5·62 g., 1 mol.), dimethylaminoethanol (11·17 g., 5 mol.), and toluene (100 ml.) were dried by distillation until the temperature of the vapour reached 110°. The solution was then cooled, sodium (0·1 g.) added, and methanol distilled off slowly (2 hr.) through a Vigreux column with exclusion of moisture. The residual liquid was then refluxed for 40 hr., cooled, and extracted with 2N-hydrochloric acid; the acid extract was washed with benzene and made alkaline with 13% ammonia solution to pH 9—9·6. The resulting oil was extracted with benzene, and the combined extracts were washed with water and dried ($MgSO_4$). The solvent was recovered *in vacuo*, and the oily residue refluxed with methyl iodide (10 g.) in dry benzene (50 ml.) for 16 hr., cooled, and treated with excess of anhydrous ether. The precipitate was filtered off, washed

with ether, and dried (7·3 g.); after two recrystallisations from methanol–ether, the required *trimethiodide* was obtained as pale yellow rosettes, m. p. 217—218° (decomp.) (Found: C, 34·0; H, 5·1; N, 4·8; I, 45·5. $C_{23}H_{42}I_3N_3O_5$ requires C, 33·6; H, 5·2; N, 5·1; I, 46·4%). The corresponding *trisethiodide* formed pale yellow rosettes, m. p. 197·5—198·5° (Found: C, 36·1; H, 5·8; N, 4·9; I, 43·4. $C_{26}H_{48}I_3N_3O_5$ requires C, 36·15; H, 5·6; N, 4·9; I, 44·15%).

Similarly, dimethyl 4-methoxyisophthalate (44·8 g., 1 mol.), 2-diethylaminoethanol (117 g., 5 mol.), and toluene (1000 ml.), dried as before, were treated with sodium (2·0 g.) and distilled through a Vigreux column for 18·5 hr. at such a rate that the vapour temperature did not exceed 65°. The cooled residue was extracted with 2N-hydrochloric acid, the extract basified with solid potassium carbonate, and the resulting oil extracted with benzene and dried (Na_2SO_4). After removal of solvent, the oil (69·5 g.) was mixed with ethyl iodide (102 g., 10% excess) in ethyl methyl ketone and left at room temperature for 100 hr. The supernatant liquid was then decanted from the gum which had separated; the latter, when triturated with ether, solidified; it was dried (100 g.) and recrystallised from methanol–ether; bisdiethylaminoethyl 4-diethylaminoethoxyisophthalate triethiodide was obtained as almost colourless needles, m. p. 205—206° (decomp.) (Found: C, 40·5; H, 6·2; N, 4·5; I, 39·7. Calc. for $C_{32}H_{60}I_3N_3O_5$: C, 40·55; H, 6·4; N, 4·4; I, 40·2%). Carissimi *et al.*[20] record m. p. 78° (decomp.) for material made differently, but have apparently not recrystallised their product; repeating their work, we found the crude product to melt with frothing between 70° and 80°, but after several recrystallisations from methanol–ethanol–ether, it had m. p. 205—206°.

Amides.—*3-Monoamides.* A mixture of the 3-monoamide of 4-hydroxyisophthalic acid (4·4 g., 1 mol.), propyl iodide (12·4 g., 3 mol.), anhydrous potassium carbonate (6·7 g., 2 mol.), and ethanol (150 ml.) was heated under reflux for 39 hr., cooled, filtered, concentrated to small bulk, and treated with excess of water. The product (4 g.) that separated was recrystallised twice from ethanol, giving needles of *propyl 3-carbamoyl-4-propoxybenzoate*, m. p. 142—143° (Found: C, 63·0; H, 7·2; N, 5·2. $C_{14}H_{19}NO_4$ requires C, 63·4; H, 7·2; N, 5·3%). With 2N-sodium hydroxide at room temperature for 5 hr., this yielded *3-carbamoyl-4-propoxybenzoic acid*, needles (from dimethylformamide), m. p. 263—264° (decomp.) (Found: C, 58·8; H, 6·3; N, 6·3. $C_{11}H_{13}NO_4$ requires C, 59·2; H, 5·9; N, 6·3%); *allyl 4-allyloxy-3-carbamoylbenzoate*, prisms, m. p. 108—110°, from absolute ethanol (Found: C, 63·8; H, 5·8; N, 4·7. $C_{14}H_{15}NO_4$ requires C, 64·4; H, 5·8; N, 5·4%), and the corresponding *acid*, needles, m. p. 230—231° (decomp.) (from dimethylformamide) (Found: C, 59·9; H, 4·9; N, 6·25. $C_{11}H_{11}NO_4$ requires C, 59·7; H, 5·0; N, 6·3%), were obtained similarly.

5-Bromo-3-carbamoyl-4-hydroxybenzoic acid, prepared by ammonolysis [15] of the corresponding methyl ester, crystallised from aqueous ethanol as needles, m. p. 277—278° (decomp.) (Found: C, 37·5; H, 2·6; N, 5·2. $C_8H_6BrNO_4$ requires C, 36·9; H, 2·3; N, 5·4%).

The following were prepared from the 3-monomethyl ester by aminolysis with the appropriate alkylamines in sealed tubes at 100—110° for 4—5 hr.: 3-N-*methyl-*, m. p. 280—281° (decomp.) (Found: C, 55·5; H, 4·8; N, 6·7. $C_9H_9NO_4$ requires C, 55·4; H, 4·65; N, 7·2%), 3-NN-*dimethyl-*, m. p. 224—225° (decomp.) (Found: C, 57·2; H, 5·4; N, 6·9. $C_{10}H_{11}NO_4$ requires C, 57·4; H, 5·3; N, 6·7%), 3-N-*ethyl-*, m. p. 242—243° (decomp.) (Found: C, 57·5; H, 5·3; N, 6·65. $C_{10}H_{11}NO_4$ requires C, 57·4; H, 5·3; N, 6·7%) (in attempts to prepare the *NN*-diethylamides dealkylation or failure to react was observed), 3-N-*propyl-*, m. p. 243—244° (decomp.) (Found: C, 59·3; H, 5·9; N, 6·05. $C_{11}H_{13}NO_4$ requires C, 59·2; H, 5·9; N, 6·3%), all needles from aqueous dimethylformamide, and 3-*N*-butyl-carbamoyl-4-hydroxybenzoic acid, plates, m. p. 241—242°, from aqueous dimethylformamide (Found: C, 60·8; H, 6·3; N, 5·75. Calc. for $C_{12}H_{15}NO_4$: C, 60·8; H, 6·4; N, 5·9%) (Dansi *et al.*[18] record m. p. 260°).

The butylamide with methanol and toluene-*p*-sulphonic acid in benzene (cf. Gladych *et al.*[15]) gave methyl 3-*N*-butylcarbamoyl-4-hydroxybenzoate as rosettes, m. p. 58·5—59° (lit.,[18] 200°) (from light petroleum) (Found: C, 62·3; H, 6·6; N, 5·6. Calc. for $C_{13}H_{17}NO_4$: C, 62·15; H, 6·8; N, 5·6%). This was also obtained as follows: Butylamine (25 ml.), dimethyl 4-hydroxyisophthalate (5·0 g.), and 95% ethanol (50 ml.) were heated under reflux for 2 hr., then evaporated to dryness *in vacuo*. The residue recrystallised from absolute ethanol to give the *butylamine salt* (IV) (3·7 g.) of methyl 3-*N*-butylcarbamoyl-4-hydroxybenzoate as plates, m. p. 129·5—130° (Found: C, 63·0; H, 9·0; N, 8·6. $C_{17}H_{28}N_2O_4$ requires C, 63·0; H, 8·7; N, 8·6%). This (2 g.) was dissolved in cold 2N-sodium hydroxide (25 ml.) and immediately made acid to Congo Red with hydrochloric acid. The oil which separated was extracted with ether, washed with water, dried (Na_2SO_4), and recovered, as an oil (1·2 g.) which crystallised *in vacuo* and on

crystallisation once from acetone–light petroleum and twice from light petroleum gave rosettes, m. p. and mixed m. p. 58·5—59°. On hydrolysis of the butylamine salt (IV) (2·0 g.) with N-sodium hydroxide (30 ml.) at room temperature for 5 hr., the 3-*N*-butylcarbamoyl-4-hydroxybenzoic acid, m. p. and mixed m. p. 241—242°, was obtained (1·46 g.).

The 3-hydrazide of 4-hydroxyisophthalic acid was prepared by treatment of the 3-monomethyl ester with hydrazine as described by Dansi *et al.*[18] After concentration, the mixture was acidified to Congo Red with dilute hydrochloric acid, and the precipitate recrystallised twice from aqueous ethanol. The resulting cream rosettes had m. p. 275—276° (lit.,[18] 274°) (Found: C, 49·3; H, 4·4; N, 14·3. Calc. for $C_8H_8N_2O_4$: C, 49·0; H, 4·1; N, 14·3%). This hydrazide (1 g.) was heated with acetone (10 ml.) and water (10 ml.) on a steam-bath for 20 min. After cooling, *5-carboxy-2-hydroxy-N′-isopropylidenebenzhydrazide* (V) was filtered off, washed with acetone, and dried. The microcrystalline crude product (1·06 g.) had m. p. 300—302° (decomp) (Found: C, 55·6; H, 5·1; N, 12·2. $C_{11}H_{12}N_2O_4$ requires C, 55·9; H, 5·1; N, 11·9%). Attempts to recrystallise it from boiling 95% ethanol resulted in hydrolysis to the original hydrazide, m. p. and mixed m. p. 275—276° (decomp.).

Mersalyl Analogues (IX) *and* (X).—*5-Carboxy-N-(3-hydroxymercuri-2-methoxypropyl)-salicylamide* (IX). 3-Methyl hydrogen 4-hydroxyisophthalate (1·9 g.) and allylamine (2·3 g.) were heated in a sealed tube at 106—117° for 4·5 hr.,[22] diluted with water, and acidified to Congo Red. The precipitate (2·3 g.) was filtered off, washed with water, dried, and recrystallised from acetone, giving needles of *N-allyl-5-carboxysalicylamide*, m. p. 234—235° (decomp.) (Found: C, 59·7; H, 5·35; N, 6·2. $C_{11}H_{11}NO_4$ requires C, 59·7; H, 5·0; N, 6·3%). Mercuric acetate (1·44 g.) in methanol (40 ml.) was added dropwise to a refluxing solution of this amide (1·06 g.) in methanol (60 ml.); a fine white solid separated. After being boiled for 8 hr., the mixture was set aside overnight; the *mercurial*, when filtered off, washed with methanol, and dried *in vacuo*, had m. p. 225—226° (decomp.) (2·0 g.) (Found: C, 30·9; H, 3·1; N, 3·2. $C_{12}H_{15}HgNO_6$ requires C, 30·7; H, 3·2; N, 3·0%).

3-Carboxy-4-hydroxy-N-(3-hydroxymercuri-2-methoxypropyl)benzamide (X). 1-Methyl hydrogen 4-hydroxyisophthalate (2·0 g.) was heated with allylamine (2·3 g.) in a sealed tube at 134—146° for 10 hr., and the reaction mixture worked up as before. The product (2·0 g.), recrystallised from acetone–light petroleum, gave needles of *N-allyl-3-carboxy-4-hydroxybenzamide*, m. p. 190—191° (Found: C, 59·9; H, 5·1; N, 6·1. $C_{11}H_{11}NO_4$ requires C, 59·7; H, 5·0; N, 6·3%). This, as in the previous experiment, gave the *mercurial* as a powder, m. p. 203—204° (decomp.) after sintering at 195° (Found: C, 31·1; H, 3·2; N, 3·2. $C_{12}H_{15}HgNO_6$ requires C, 30·7; H, 3·2; N, 3·0%).

Miscellaneous Salts.—4-Hydroxyisophthalic acid (5·4 g., 1 mol.) was added to a warm solution of diethanolamine (6·3 g., 2 mol.) in absolute ethanol (25 ml.), and the solution evaporated to dryness *in vacuo*. The resulting viscous yellow oil (13 g.) solidified when kept over calcium chloride in a vacuum for 5 weeks. After several recrystallisations from methanol–ether, *bis*-[NN-*di*-(*2-hydroxyethyl*)*ammonium*] *4-hydroxyisophthalate* was obtained as prisms, m. p. 76—77° (Found: C, 49·0; H, 7·2; N, 6·9. $C_{16}H_{28}N_2O_9$ requires C, 49·0; H, 7·2; N, 7·1%). The corresponding *bis*(*2-hydroxyethylammonium*) *salt*, prepared similarly, crystallised from ethanol as faintly pink needles, m. p. 137—138° (Found: C, 47·45; H, 6·6; N, 8·95. $C_{12}H_{20}N_2O_7$ requires C, 47·4; H, 6·6; N, 9·2%).

We thank Dr. H. O. J. Collier and Dr. P. F. D'Arcy for the pharmacological results and Mr. I. J. Gibson for technical assistance.

RESEARCH DIVISION, ALLEN AND HANBURYS LTD.,
WARE, HERTS.

[*Received, February 2nd,* 1960.]

[22] Tsofin, Magidson, and Chkhikvadze, Russian Patent, 44,932/1935; *Chem. Abs.*, 1938, **32**, 2956; Phillips, *Chem. and Ind.*, 1952, 782.