974. *The Amides of 4-Hydroxy- and 4-Alkoxy-*iso*phthalic Acids.*

By J. M. Z. GLADYCH, A. S. LINDSEY, and E. P. TAYLOR.

Some mono- and di-amides of 4-hydroxy- and 4-alkoxy-*iso*phthalic acids are prepared.

THE reported analgesic and antipyretic properties of 4-hydroxy*iso*phthalic acid[1] suggest that the mono- and di-amides of this and the related 4-alkoxy-acids might be of interest. Some of our preliminary work has already been reported.[2]

Jacobsen[3] claimed to prepare 4-hydroxy*iso*phthalamide by treating the dimethyl or diethyl ester with alcoholic ammonia. We found the major product to be the alkyl 3-carbamoyl-4-hydroxybenzoate, only a small amount of the diamide being isolated. However, treatment of the dimethyl ester with liquid ammonia for 30 hr. at 100—110° gave the diamide in good yield, although 15 hours' heating gave the ester-amide.

4-Alkoxy*iso*phthalic acids, on treatment with thionyl chloride followed by ammonium hydroxide or carbonate, were smoothly converted into the diamides; in one experiment with 4-methoxy*iso*phthalic acid in which ammonium carbonate was added before complete removal of thionyl chloride, the product contained considerable quantities of a methoxy-cyanobenzamide which must have arisen by dehydration. By the general method 4-hydroxy*iso*phthalic acid gave apparently a mixture of the isomeric 1- and 3-monoamide (independent preparation of the latter will be described elsewhere). We have confirmed the orientation of the latter by isolating it, although in small yield, from a Kolbe–Schmitt carboxylation of the potassium derivative of salicylamide.

EXPERIMENTAL

*4-Hydroxy*iso*phthalamide.*—Dimethyl 4-hydroxy*iso*phthalate (21 g.) and liquid ammonia (approx. 50 ml.) were heated in a rotating bomb at 100—110° for 30 hr. After cooling, the residue was dissolved in water and filtered from a trace of insoluble matter, and the filtrate acidified with 2N-hydrochloric acid. The precipitate was filtered off, washed with water, made into a slurry with an excess of 5% aqueous sodium hydrogen carbonate, filtered, washed with water, and dried. The crude solid [16 g.; m. p. 258—259 (decomp.)] was recrystallised once from ethanol and twice from aqueous dimethylformamide, to give 4-hydroxy*iso*phthalamide (10 g.), prisms, m. p. 264—264·5° (decomp.) (Found: C, 53·6; H, 4·7; N, 15·2. Calc. for $C_8H_8O_3N_2$: C, 53·3; H, 4·5; N, 15·6%). Jacobsen[3] records m. p. 250°.

When this experiment was repeated but with the addition of ethanol (50 ml.) the crude product (17·7 g.), obtained by evaporation of the mixture, had m. p. 216—228° (decomp.). Repeated fractional crystallisation from ethanol and aqueous dimethylformamide gave the diamide (1 g.) [m. p. and mixed m. p. 264—264·5° (decomp.)] and methyl 3-carbamoyl-4-hydroxybenzoate (4·2 g.), m. p. 256—257°.

Methyl 3-Carbamoyl-4-hydroxybenzoate.—Dimethyl 4-hydroxy*iso*phthalate (21 g.) and liquid ammonia (approx. 40 ml.) were heated in a rotating bomb at 90—100° for 15 hr., then dissolved in water and acidified as before, yielding 16·5 g. of material, m. p. 249—250° (decomp.). After

---

[1] Chesher, Collier, Robinson, Taylor, Hunt, Jones, and Lindsey, *Nature*, 1955, **175**, 206; Collier and Chesher, *Brit. J. Pharmacol.*, 1956, **11**, 20.

[2] Hunt, Jones, and Lindsey, *Chem. and Ind.*, 1955, 417; Gladych and Taylor, *J.*, 1956, 4678.

[3] Jacobsen, *Ber.*, 1878, **11**, 380.

three recrystallisations from ethanol, the *ester-amide* was obtained as rosettes, m. p. 256—257° (Found: C, 55·4; H, 4·6; N, 6·8. $C_9H_9O_4N$ requires C, 55·4; H, 4·65; N, 7·2%).

The solid (2·0 g.) was kept in N-sodium hydroxide (30 ml.) at 20° for 5 hr., then acidified with 2N-hydrochloric acid. The precipitate was washed with water and dried *in vacuo*. The crude product had m. p. 296—297° (decomp.) alone or mixed with the 3-monoamide of 4-hydroxy*iso*phthalic acid. This and the following experiment confirmed the structure of the ester-amide.

The 3-monoamide (3·6 g.), methanol (50 ml.), benzene (30 ml.), and toluene-*p*-sulphonic acid (1·0 g.) were heated together for 15 hr. under a Dean and Stark apparatus. After cooling, the solid was filtered off, washed with a little benzene, and dried. The crude ester-amide (2·6 g., m. p. 254—255°) crystallised from absolute ethanol in rosettes, m. p. 256—257°.

Methyl 3-carbamoyl-4-hydroxybenzoate (0·5 g.) was also obtained when dimethyl 4-hydroxy*iso*phthalate (2·0 g.) was heated for 2 hr. in boiling aqueous ammonia (25 g., *d* 0·88).

Ethyl 3-Carbamoyl-4-hydroxybenzoate.—Diethyl 4-hydroxy*iso*phthalate (4·0 g.), ethanol (60 ml.), and liquid ammonia (approx. 30 ml.) were heated in a rotating bomb at 100° for 9 hr. After evaporation the residual *ester-amide* (3·5 g.; m. p. 216—218°) recrystallised from ethanol (after charcoal) as needles, m. p. 225—226° (Found: C, 57·3; H, 5·1; N, 6·5. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3; N, 6·7%). Hydrolysis gave the 3-monoamide, m. p. and mixed m. p. 295—296° (decomp.), in excellent yield.

*Treatment of 4-Hydroxy*iso*phthalic Acid with Thionyl Chloride and Ammonia.*—4-Hydroxy*iso*phthalic acid (10 g.) and thionyl chloride (35 ml.) were heated under reflux for 6 hr. The excess of thionyl chloride was then distilled off as azeotrope with benzene, the solvent completely removed, and the oil poured into stirred aqueous ammonia (*d* 0·88) at 0°. The mixture was diluted with water, acidified with 2N-hydrochloric acid, and filtered, and the precipitate washed with water and dried. The resulting yellow solid [5·3 g.; m. p. 249—250° (decomp.)] was dissolved in 2N-sodium hydroxide, reprecipitated with 2N-hydrochloric acid, filtered off, washed with water, and dried. The faintly yellow product had m. p. 247—249° (decomp.) which was raised on admixture with the 1-monoamide [mixed m. p. 253—254° (decomp.)] or the 3-monoamide of 4-hydroxy*iso*phthalic acid [mixed m. p. 251—252° (decomp.)]. Recrystallisation from aqueous dimethylformamide gave needles, m. p. 259—260° (decomp.) [mixed m. p. with the 1-amide, 258—259° (decomp.); with the 3-amide, 263—264° (decomp.)] (Found: C, 53·2; H, 3·8; N, 7·8. Calc. for $C_8H_7O_4N$: C, 53·0; H, 3·9; N, 7·7%). The product therefore seems to be a mixture of monoamides. [A 1 : 1 mixture of the monoamides has m. p. 266—267° (decomp.), and a 2 : 1 mixture of 1- and 3-amide has a m. p. of 257—257·5° (decomp.).]

*4-Alkoxy*iso*phthalic Acids.*—Dimethyl 4-hydroxy*iso*phthalate (1 mol.), alkyl bromide (or iodide) (2 mols.), and anhydrous potassium carbonate (1 mol.) in ethanol were refluxed for 35—40 hr., then cooled and filtered. The filtrate was concentrated to small bulk, diluted with water, and extracted with benzene. The benzene extract was washed with 2N-sodium hydroxide and water, shaken with magnesium sulphate, filtered, and evaporated. The crude ester was then hydrolysed for 15 hr. at room temperature with 2N-sodium hydroxide (4 mols.), enough alcohol being added to effect dissolution. The solution was then acidified with 2N-hydrochloric acid and cooled. The crude alkoxy-acid was filtered off, washed with water, dried, and recrystallised.

The following 4-alkoxy*iso*phthalic *acids* are new: *Benzyloxy*, prisms [from acetone–light petroleum (b. p. 40—60°)], m. p. 194—195° (crude yield 71%) (Found: C, 66·5; H, 4·7. $C_{15}H_{12}O_5$ requires C, 66·2; H, 4·45%); *allyloxy*, needles (from aqueous methanol) (62%), m. p. 222—223° (decomp.) (Found: C, 59·4; H, 4·4. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%); iso-*butoxy*, needles (from aqueous ethanol) (5%), m. p. 211—212° (Found: C, 60·3; H, 5·8. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%); sec.-*butoxy*, needles (from aqueous ethanol) (5%), m. p. 177—178° (Found: C, 61·0; H, 5·9%).

We also prepared the following known 4-alkoxy*iso*phthalic acids:

Methoxy, m. p. 276° (decomp.) (as recorded [4]), ethoxy, m. p. 261—262° (lit.,[5] 259—260°), *n*-propoxy, m. p. 231—232° (lit.,[5] 214—215°) (Found: C, 58·9; H, 5·9. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4%), *iso*propoxy, m. p. 224—225° (lit.,[5] 230—231°) (Found: C, 59·3; H, 5·4%), and *n*-butoxy, m. p. 195—196° (lit.,[5] 193—195°).

---

[4] Hunt, Jones, and Lindsey, *J.*, 1956, 3099.

[5] Mndzhoyan and Aroyan, *Izvest. Akad. Nauk. Armyan. S.S.R., Ser. Fiz.-Mat., Estestven i Tekh Nauk*, 1955, **8**, (6), 29 (*Chem. Abs.*, 1956, **50**, 11,982).

On treatment of the 4-alkoxy*iso*phthalic acids with thionyl chloride and aqueous ammonia (or in some cases powdered ammonium carbonate), as described above for 4-hydroxy*iso*phthalic acid, the corresponding diamides were obtained in good yield, namely: *methoxy*, needles (from ethanol), m. p. 246—247° (crude yield 30%) (Found: C, 55·7; H, 5·4; N, 14·4. $C_9H_{10}O_3N_2$ requires C, 55·7; H, 5·2; N, 14·4%), *ethoxy*, needles (from aqueous alcohol) (79%), m. p. 275—276° (decomp.) (Found: C, 58·2; H, 5·7; N, 13·3. $C_{10}H_{12}O_3N_2$ requires C, 57·7; H, 5·8; N, 13·5%), n-*propoxy*, needles (from aqueous dimethylformamide) (78%), m. p. 243—244° (decomp.) (Found: C, 59·7; H, 6·1; N, 12·7. $C_{11}H_{14}O_3N_2$ requires C, 59·5; H, 6·4; N, 12·6%), iso*propoxy*, needles (from ethanol) (62%), m. p. 197—198° (Found: C, 59·4; H, 6·6; N, 12·7. $C_{11}H_{14}O_3N_2$ requires C, 59·5; H, 6·4; N, 12·6%), *allyloxy*, cream-coloured needles (from aqueous dimethylformamide) (100%), m. p. 220—221° (decomp.) (Found: C, 59·5; H, 5·5; N, 12·7. $C_{11}H_{12}O_3N_2$ requires C, 60·0; H, 5·5; N, 12·7%), n-*butoxy*, needles (from aqueous dimethylformamide) (90%), m. p. 261—262° (Found: C, 61·5; H, 7·0; N, 11·8. $C_{12}H_{16}O_3N_2$ requires C, 61·0; H, 6·8; N, 11·9%), and *benzyloxy*, needles (from ethanol) (100%), m. p. 227—228° (Found: C, 66·7; H, 5·4; N, 10·5. $C_{15}H_{14}O_3N_2$ requires C, 66·7; H, 5·2; N, 10·4%).

With 4-methoxy*iso*phthalic acid, when ammonium carbonate was added before complete removal of the thionyl chloride, the product contained appreciable quantities of a *methoxycyanobenzamide*, which crystallised from ethanol as needles, m. p. 256—257° (Found: C, 61·5; H, 4·7; N, 15·9. $C_9H_8O_2N_2$ requires C, 61·4; H, 4·6; N, 15·9%. The infrared spectrum revealed a band of medium strength at 2232 cm.$^{-1}$ (C≡N). Hydrolysis with hot 50% (v/v) sulphuric acid gave 4-methoxy*iso*phthalic acid (mixed m. p.).

4-*n*-Butoxy*iso*phthalamide was also prepared in good yield by heating 4-hydroxy*iso*phthalamide (1·8 g.) with *n*-butyl bromide (3·0 g.), anhydrous potassium carbonate (1·4 g.), and ethanol (50 ml.) under reflux for 40 hr.

*Structure of the 3-Monoamide of 4-Hydroxy*iso*phthalic Acid.*—The potassium derivative of salicylamide (3·6 g.) and solid carbon dioxide (20 g.) were heated in a bomb at 165—172° for 3 hr. at a maximum pressure of 22 atm. After cooling, the residue was extracted with cold water, leaving 0·7 g. of insoluble salicylamide (m. p. and mixed m. p. 140—141°). The aqueous extract was acidified with 2N-hydrochloric acid. The precipitate was filtered off, washed with water, dried [0·5 g., m. p. 240—241° (decomp.)], and recrystallised twice from aqueous dimethylformamide, giving light brown needles, m. p. 244·5—245° (decomp.) [Wohl [6] gives m. p. 245° (decomp.) for the 3-amide of 2-hydroxy*iso*phthalic acid]. The acid filtrate obtained as above deposited a second crop (0·04 g.) of crystals. After two recrystallisations from aqueous dimethylformamide these had m. p. 294—295° (decomp.), mixed m. p. with the 3-monoamide of 4-hydroxy*iso*phthalic acid (prepared by ammonolysis of the 3-methyl ester) 297° (decomp.).

Some of the microanalyses were carried out by Miss M. Corner and the staff of the microanalytical section of the Chemical Research Laboratory, Teddington. One of us (A. S. L.) thanks Dr. Idris Jones for his interest; the others thank Mr. I. J. Gibson for technical assistance. We are indebted to the Directors of Allen and Hanburys Ltd. and the Director of the Chemical Research Laboratory, Teddington, for permission to publish this work.

RESEARCH DIVISION, ALLEN & HANBURYS LTD.,
WARE, HERTS (J. M. Z. G. and E. P. T.).
CHEMICAL RESEARCH LABORATORY,
D.S.I.R., TEDDINGTON, MIDDLESEX (A. S. L.).

[*Received, August 13th*, 1957.]

---

[6] Wohl, *Ber.*, 1910, **43**, 3483.