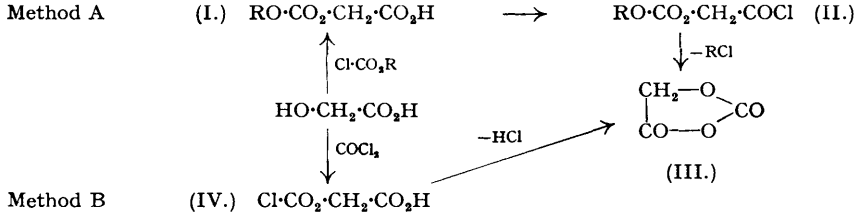
302. *Anhydrocarboxy-derivatives of Hydroxy- and Mercapto-acids.*

By W. H. Davies.

Anhydrocarboxy-derivatives have been prepared from glycollic, α-mercaptoacetic, lactic, mandelic, and salicylic acids by reaction with carbonyl chloride. These compounds react vigorously with water and carbon dioxide is eliminated. The first four react with aniline with evolution of carbon dioxide to give anilides: anhydro-*O*-carboxysalicylic acid with aniline gives *o*-carboxyphenyl phenylcarbamate. The anhydrocarboxy-compounds react with aromatic hydrocarbons under Friedel–Crafts conditions to give ketones.

Although anhydro-*N*-carboxyamino-acids (oxazolid-2 : 5-diones) and anhydro-*O*-carboxysalicylic acid (benzo-1 : 3-dioxen-2 : 4-dione) have been known for many years, the corresponding derivatives from α-hydroxy-acids [1 : 3-dioxolan-2 : 4-diones (III)] and α-mercapto-acids (1 : 3-oxathiolan-2 : 5-diones) have not been reported. These have now been obtained by reaction of the appropriate acids with carbonyl chloride.*

Attempts were made to prepare anhydro-*O*-carboxyglycollic acid (III) from the carbonate (I) by method A, analogous to Bergmann's preparation of anhydro-*N*-carboxyamino-acids (*Ber.*, 1932, **65**, 1194). Carbonato-esters (I) were prepared by reaction of glycollic acid with chloroformates. The benzyl ester, which was obtained only in poor yield, was rather unstable, and the ethyl ester was therefore prepared. This was converted into the ester chloride (II; R = Et) which could not be cyclised: it was recovered unchanged after being heated to 180°, and heating in the presence of a trace of pyridine caused decomposition to carbon dioxide and a black solid. This method of approach was therefore discontinued, and Method B, analogous to the patented preparation of anhydro-*N*-carboxyamino-acids (B.P. 646,033), was examined.



Preliminary work showed that dioxan was a very suitable solvent for the interaction of glycollic acid with carbonyl chloride. From a series of experiments with glycollic acid in this solvent, it was found that a large excess of carbonyl chloride and a long reaction time at room temperature minimised the formation of the carbonate $CO(O{\cdot}CH_2{\cdot}CO_2H)_2$ and helped conversion into the chloroformate (IV). The cyclisation of (IV) to (III) was effected by removing the solvent at low temperature and heating the residual oil at 60°/20 mm. for two hours. Longer heating under these conditions, though not improving the yield of (III), reduced the ionisable halogen in the crude product: this probably indicates slow removal of some diacid chloride, $Cl{\cdot}CO_2{\cdot}CH_2{\cdot}COCl$. By a similar method, lactic, mandelic, and α-mercaptoacetic acids were converted into their anhydrocarboxy-derivatives. In all these cases, poorer yields were obtained when salts of the acids were used in place of the free acids, though anhydro-*O*-carboxysalicylic acid was best prepared by Dupont's method of reaction of the disodium salt of salicylic acid in toluene with carbonyl chloride (B.P. 426,243).

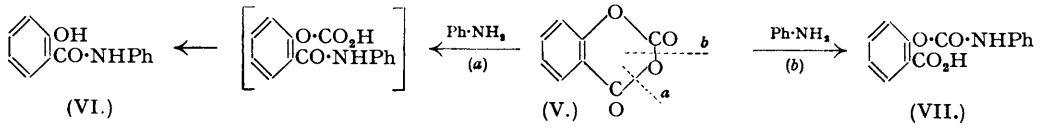
The purity of the crude anhydrocarboxy-acids was found approximately by treating samples with water and observing the loss in weight due to evolution of carbon dioxide. Although this method was not accurate—even pure anhydro-*O*-carboxyglycollic acid gave low results, and by-products such as carbonates might also give carbon dioxide on treatment with water—the results were reasonably consistent and tallied with the yield of anilide obtained by treatment with aniline.

The anhydrocarboxy-derivatives were easily purified by crystallisation from dry, low-boiling solvents. The stability of the products varied with the particular acid used. When heated at 100° for 18 hours, anhydro-*O*-carboxyglycollic acid lost carbon dioxide to give the polymer

* Patent protection pending.

$H\cdot[O\cdot CH_2\cdot CO]_n\cdot X$, whereas the lactic acid derivative after such treatment was recovered largely unchanged. (The HX in such polymers is presumably provided by adventitious traces of water or acid.) The anhydrocarboxy-derivatives of α-substituted acids also decomposed with evolution of carbon dioxide upon reaction with water or amines : with limited amounts of the reagent, polymeric material was formed but with excess of water or aniline the products were mainly monomeric, HO(or HS)·CHR·COX.

Anhydro-*O*-carboxysalicylic acid (V), with its six-membered heterocyclic ring, liberated carbon dioxide on heating or on treatment with water but not on treatment with excess of aniline. The product formed was the aniline salt of *o*-carboxyphenyl phenylcarbamate (VII), indicating that fission occurred at (*b*) in (V) and not at (*a*), which would have yielded salicylanilide (VI).



(VI.) (V.) (VII.)

Statham (*J.*, 1951, 213) has shown that anhydro-*N*-carboxyamino-acids react with, *e.g.*, benzene under Friedel–Crafts conditions to give α-amino-ketones. It has now been found that in the same way anhydro-*O*-carboxyglycollic acid reacts with benzene or acenaphthene to give an α-hydroxyacetyl derivative, and anhydro-*O*-carboxysalicylic acid reacts with benzene to give *o*-hydroxybenzophenone.

Experimental.

Preparation of Carbonato-glycollic Acid Derivatives.—(a) O-*Carbethoxyglycollic acid* (I; R = Et). This was prepared by Fischer and Fischer's method (*Ber.*, 1914, **47**, 771) for the corresponding methyl ester, ethyl chloroformate being used in place of methyl chloroformate. The *acid*, b. p. 99—100°/0·12 mm., m. p. 46—48°, was hygroscopic (Found : C, 40·1; H, 5·65%; equiv., 152. $C_5H_8O_5$ requires C, 40·5; H, 5·4%; equiv., 148).

(b) O-*Carbethoxyglycollyl chloride* (II; R = Et). The acid (18·3 g.) in ether (10 c.c.) was treated with thionyl chloride (18·3 c.c.) at 35° and then kept at 50° for 1½ hours. The product was fractionated to give the *acid chloride*, b. p. 88—90°/18 mm. (Found : Cl′, 21·4%; equiv., 83. $C_5H_7O_4Cl$ requires Cl′, 21·3%; equiv., 83·2).

Preparation of Anhydrocarboxy-acids.—(a) 1 : 3-*Dioxolan*-2 : 4-*dione* (*anhydro*-O-*carboxyglycollic acid*). A solution of glycollic acid (228 g., 3 mols.) in dioxan (840 c.c.) was run into a solution of carbonyl chloride (900 g., 9 mols.) in dioxan (720 c.c.) during 1 hour at 5°. The solution was kept at room temperature for 4 days and then heated at 30° under reduced pressure for 4 hours to remove part of the hydrogen chloride and excess of carbonyl chloride. The solvent was removed at 40°/20 mm. during 5 hours, and the residual fuming yellow oil heated at 60°/15 mm. for 5½ hours, giving crude *anhydro*-O-*carboxyglycollic acid* as a brown oil (337 g.). Analysis indicated that it was about 67% pure (by CO_2-loss in water) and contained Cl′, 3·2%. (The halogen probably indicates the presence of $Cl\cdot CO\cdot CH_2\cdot COCl$.) Crystallisation from an equal bulk of ether with good cooling gave the pure anhydro-acid, m. p. 18° (Found : C, 35·45; H, 2·35. $C_3H_2O_4$ requires C, 35·3; H, 2·0%). It was distilled in small amounts though with considerable decomposition, b. p. 49°/0·1 mm.

(b) 1 : 3-*Oxathiolan*-2 : 5-*dione* [*anhydro*(*carboxythio*)*acetic acid*]. This was prepared as in (a) from α-mercaptoacetic acid (13·8 g., 0·15 mol.) and carbonyl chloride (30 g., 0·3 mol.), the final cyclisation being effected during 3 hours at 60°/15 mm. A solution of the crude oil in ethyl acetate (15 c.c.) cooled below 0° gave *anhydro*(*carboxythio*)*acetic acid*, m. p. 68—70° (decomp.) (Found : C, 30·45; H, 2·0. $C_3H_2O_3S$ requires C, 30·5; H, 1·7%).

(c) 5-*Methyl*-1 : 3-*dioxolan*-2 : 4-*dione* (*anhydro*-O-*carboxylactic acid*). This was prepared from freshly distilled lactic acid (45 g., 0·52 mol.) and carbonyl chloride (155 g., 1·53 mols.) in dioxan as in the previous preparations. The final cyclisation was not completed during 2 hours at 60°/15 mm. and continued heating for a further hour at 65°/15 mm. was necessary. The crude oil (69% material, containing Cl′, 1·9%) was twice crystallised from ether (70 c.c.) with good cooling to give *anhydro*-O-*carboxylactic acid* (23·5 g., 40·5%), m. p. 27—28° (Found : C, 41·25; H, 3·4; CO_2-loss in water, 37·4. $C_4H_4O_4$ requires C, 41·4; H, 3·45; CO_2-loss, 37·8%). It distilled, without appreciable decomposition, at 93°/15 mm.

(d) 5-*Phenyl*-1 : 3-*dioxolan*-2 : 4-*dione* (*anhydro*-O-*carboxymandelic acid*). A solution of mandelic acid (10·1 g., 0·065 mol.) was treated with carbonyl chloride (10 g., 0·1 mol.) in dioxan as in the previous preparation. After 4 days, the solvent was removed at 35°/20 mm., and the residue treated with more carbonyl chloride (10 g., 0·1 mol.) in dioxan. After 8 days, the solution was worked up as in the previous experiments. The crude oil was crystallised from ether (1 vol.) with good cooling to give *anhydro*-O-*carboxymandelic acid*, m. p. 55—57° (Found : C, 60·25; H, 3·6. $C_9H_6O_4$ requres C, 60·6; H, 3·4%).

(e) *Benzo*-1 : 3-*dioxen*-2 : 4-*dione* (*anhydro*-O-*carboxysalicylic acid*). This was prepared by a slight modification of Dupont's method (*loc. cit.*). Dry disodium salicylate (44 g.), suspended in dry toluene (150 c.c.), was treated at 20° with carbonyl chloride (50 g.) in toluene (100 c.c.). After being stirred for 18 hours at 20°, the mixture was filtered, and the insoluble material repeatedly extracted with toluene at 40° until a sample extract gave no precipitate with light petroleum. The combined toluene liquors

were concentrated at 40°/20 mm. to give a white crystalline solid (35·5 g., 89%), m. p. 113—121° (decomp.). A sample of this was crystallised from boiling benzene, and anhydro-*O*-carboxysalicylic acid separated on cooling; it had m. p. *ca.* 118—120° (decomp.), the m. p. being affected by the rate of heating (Found: C, 58·8; H, 3·0. Calc. for $C_8H_4O_4$: C, 58·5; H, 2·5%).

Stability of Anhydrocarboxy-acids.—(a) *To water.* All the derivatives were rapidly decomposed by water with evolution of carbon dioxide. They should therefore be handled and stored in a dry atmosphere.

(b) *On storage.* Purified anhydro-*O*-carboxyglycollic acid was kept for 3 weeks at room temperature protected from moisture by a magnesium perchlorate tube. The loss in weight was 3·9%, corresponding to 10% decomposition with loss of carbon dioxide. Crude material (68% pure) lost about 3·0% by weight under similar storage conditions.

(c) *To heat.* (i) Anhydro-*O*-carboxyglycollic acid. Purified material was heated for 18 hours at 80°. Carbon dioxide was evolved at 60° but the evolution of gas was still slow at 80°. A white solid (polyglycollide) was obtained, m. p. 207—211°. The loss in weight was 37·6% [Calc. for formation of $(O{\cdot}CH_2{\cdot}CO)_n$: 43·2%]. (ii) Anhydro-*O*-carboxylactic acid. Purified material was heated at 100° for 18 hours. There was a loss in weight of 5·4% but the residual oil readily solidified on cooling (m. p. 26·5—27·5°). Analysed by the method of CO_2-loss in water, this was 95% pure, so the compound was but little affected by the heat treatment. (iii) Anhydro-*O*-carboxymandelic acid. This was heated for 16 hours at 120° to give a viscous gum. The loss in weight was 10% [Calc. for $(O{\cdot}CHPh{\cdot}CO)_n$: 24·6%]. (iv) Anhydrocarboxy-*O*-salicylic acid. This was heated at 120° for 2½ hours and then at 170° for 4½ hours. The loss in weight was 26·0% [Calc. for $(C_7H_4O_2)_n$: 26·8%].

Reactions of Anhydrocarboxy-acids.—(a) *With aniline.* The anhydrocarboxy-acid (1 mol.) in dioxan was treated with a solution of aniline (2 mols.) in dioxan, the temperature being kept at 10°. An exothermic reaction occurred. In the case of the anhydrocarboxy-α-substituted acids, carbon dioxide was evolved. When this was complete, the solvent was removed at 40°/15 mm., and the residue dissolved in ether. The ethereal extract was washed successively with dilute sodium hydroxide, dilute hydrochloric acid, and water. The ethereal solution was dried, and the solvent removed. The resulting anilides were: glycollic, m. p. 90—92° (lit., m. p.s 92° and 96°); α-mercaptoacetic, m. p. 107—110° (lit., m. p.s 106° and 111°); lactic, m. p. 56—58° (after crystallisation from *cyclo*hexane) (lit., m. p. 58°); mandelic, m. p. 150—152° (after crystallisation from ethanol) (lit., m. p. 151—152°).

With anhydro-*O*-carboxysalicylic acid, no carbon dioxide was evolved on adding the dioxan solution of aniline, and a solid slowly separated. After 18 hours, the solid was collected: this melted at 126—130° but resolidified and then melted with decomposition at 185—189°. Crystallisation from ethyl acetate gave prisms, m. p. 186—189° (decomp.), but if put in a bath at 140°, the crystals melted and rapidly resolidified. This was apparently the aniline salt of *o*-carboxyphenyl phenylcarbamate. The salt was triturated with water containing sufficient hydrochloric acid to keep the solution just acid to Congo-red. The solid was collected and washed, and the acid filtrate was shown by the Runge test to contain aniline. The solid was crystallised from chloroform to give *o-carboxyphenyl phenylcarbamate*, m. p. 148—150° (decomp.) (Found: C, 65·4; H, 4·3; N, 5·7. $C_{14}H_{11}O_4N$ requires C, 65·4; H, 4·3; N, 5·45%).

(b) *With benzene.* (i) Anhydro-*O*-carboxyglycollic acid. The anhydrocarboxy-compound (5·8 g.) was added slowly to a stirred suspension of aluminium chloride (16 g.) in benzene (60 c.c.), the temperature being kept at 10°. The reaction was exothermic, and a thick gum formed which prevented stirring. After a few minutes, hydrogen chloride began to be evolved, and the gum hardened and broke up so that stirring could be re-started. The mixture was stirred for 2½ hours at 10° and then for 16 hours at room temperature: evolution of hydrogen chloride ceased after the first hour. The mixture was poured into ice-water containing hydrochloric acid, and more benzene added to dissolve the precipitate. The benzene layer was washed with dilute hydrochloric acid, dried and clarified with charcoal. The solvent was removed, leaving phenacyl alcohol (6·5 g., 84·5%), m. p. 84·5—86° (lit., m. p. 86—87°). (ii) Anhydro-*O*-carboxysalicylic acid. A well-stirred suspension of aluminium chloride (58·6 g.) in benzene (350 c.c.) was treated with powdered anhydrocarboxy-acid (32·8 g.) at 20°. The mixture was stirred for 1 hour, then warmed to 80° during ½ hour, and kept at 80° for 2 hours. The product was poured into ice-water containing more than an equivalent of hydrochloric acid to break down the stable complex. The benzene layer was clarified with kieselguhr and washed with aqueous sodium carbonate and with water. The benzene solution was dried, the solvent removed, and the crude *o*-hydroxybenzophenone (28·9 g., 73%) was distilled, b. p. 103°/0·15 mm., m. p. 37—38° (lit., m. p. 39°); oxime, m. p. 143—144° (lit., m. p. 142—143°).

(c) *With acenaphthene.* A suspension of aluminium chloride (50 g.) in carbon disulphide (250 c.c.) was treated with technical 95% acenaphthene (28 g.) followed by anhydro-*O*-carboxyglycollic acid (18·5 g.) at 20°. The viscous gum became stirrable after 1 hour. The mixture was stirred for 16 hours at 20°, refluxed for 4 hours, cooled, and poured into acidified ice-water. The insoluble material was collected and repeatedly extracted with warm carbon disulphide. The combined carbon disulphide liquors were concentrated to yield a yellow solid (11·0 g., 29%), m. p. 133—135°. This was crystallised from benzene and from ethanol to give 5(?)-α-*hydroxyacetylacenaphthene*, m. p. 135—137°, as yellow prisms (Found: C, 79·4; H, 5·2. $C_{14}H_{12}O_2$ requires C, 79·25; H, 5·6%). Treatment with acetic anhydride in pyridine gave 5(?)-α-*acetoxyacetylacenaphthene* as white needles, m. p. 111—112° (Found: C, 75·35; H, 5·5. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%).

IMPERIAL CHEMICAL INDUSTRIES LIMITED,
RESEARCH LABORATORIES, HEXAGON HOUSE,
MANCHESTER, 9.

[*Received, January 24th.* 1951.]