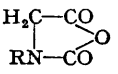
44. *Anhydro*-N-*carboxyamino-acids. A Friedel–Crafts Type Reaction.*

By F. S. Statham.

Anhydro-*N*-carboxy-derivatives of glycine and sarcosine react with benzene in the presence of anhydrous aluminium chloride to give ω-amino- and ω-methylamino-acetophenone, respectively. Similarly isatoic anhydride with benzene yields *o*-aminobenzophenone. Anhydro-*N*-carboxy-DL-β-phenylalanine is cyclised to 2-aminoindanone by anhydrous aluminium chloride.

Although the reaction of internal acid anhydrides of the type of succinic and phthalic anhydrides with benzene in the presence of anhydrous aluminium chloride is well known, there is no information of a corresponding reaction between anhydro-*N*-carboxyamino-acids and benzene under similar conditions. It has now been found that three types of anhydro-*N*-carboxyamino-acids will react under Friedel–Crafts conditions with loss of carbon dioxide.

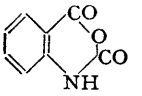
The five-membered anhydro-*N*-carboxy-derivatives of glycine (I; R = H) and sarcosine (I; R = Me) react with benzene in the presence of anhydrous aluminium chloride to give ω-aminoacetophenones (II; R = H and R = Me, respectively) in fair yield.



(I.)

$$PhCO{\cdot}CH_2{\cdot}NHR$$

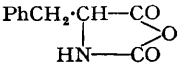
(II.)

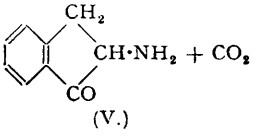


(III.)

Similarly, isatoic anhydride (III) reacts with benzene to give *o*-aminobenzophenone in 30—40% yield.

The effect of aluminium chloride on an anhydro-*N*-carboxy-α-amino-acid containing a phenyl radical, and capable of self-condensation, was also examined. When anhydro-*N*-carboxy-DL-β-phenylalanine (IV) was treated with aluminium chloride in the absence of benzene, cyclisation with loss of carbon dioxide occurred, giving 2-aminoindanone (V) (isolated as picrate) in 54% yield.

(IV.) 

$\xrightarrow{AlCl_3}$ 

(V.)

Experimental.

When the free amino-ketone was known to be unstable, the yield was estimated from the amount of derivative actually isolated. These figures appear in parentheses after the names of the derivatives prepared.

ω-Aminoacetophenone.—Anhydro-*N*-carboxyglycine (2 g., 0·02 mol.), suspended in methylene dichloride (10 c.c.), was cooled to −10° and powdered aluminium chloride (6 g., 0·045 mol.) was gradually added with stirring. There was no sign of decomposition even on allowing the mixture to warm to 0°; most of the solid material was out of solution. Dry benzene (4 g., 0·5 mol.) was added and the mixture allowed to warm. At 20° vigorous gas evolution began; the temperature was maintained at 10—20° by slight cooling until gas was no longer evolved (2 hours). The reaction mixture was poured on crushed ice (80 g.) containing hydrochloric acid (*d* 1·18; 5 c.c.), filtered, and the methylene dichloride layer separated and discarded. The aqueous layer was extracted three times with ether and divided into portions from which the following derivatives were prepared: Picrate (79%), yellow needles, m. p. (placed in bath at 165°) 174—176° (decomp.), from ethyl alcohol [Goedeckemeyer, *Ber.*, 1888, **21**, 2687, gives m. p. 175° (decomp.)] (Found: N, 15·4. Calc. for $C_8H_9ON,C_6H_3O_7N_3$: N, 15·4%). Platinichloride (67%), m. p. 210—213° (decomp.) with darkening at 200° [Goedeckemeyer, *loc. cit.*, gives m. p. "about 210°" (decomp.)] (Found: N, 3·8; Cl, 31·5; Pt, 28·3. Calc. for $2C_8H_9ON,H_2PtCl_6$: N, 4·1; Cl, 31·2; Pt, 28·5%). Hydrochloride, isolated by saturation of the aqueous layer with gaseous hydrogen chloride at 0° to precipitate inorganic material, filtration of the mixture, and evaporation of the filtrate to dryness; crystallisation of the residue from ethyl alcohol–acetone, gave white needles (56%), m. p. (alone or mixed with an authentic specimen of ω-aminoacetophenone hydrochloride) 185·5° (decomp.), brown at 178°. Benzoyl derivative, m. p. (alone or mixed with an authentic specimen of ω-benzamidoacetophenone) 118—120°.

ω-Methylaminoacetophenone.—Anhydro-*N*-carboxysarcosine (4·6 g.) was mixed with methylene dichloride (20 c.c.), cooled to −10° and, with stirring, powdered aluminium chloride (12 g.) was added. Benzene (8 c.c.) was run in, and the mixture was allowed to warm to room temperature and then stirred overnight. The reaction mass was poured on crushed ice (200 g.), containing concentrated hydrochloric acid (10 c.c.), and extracted with ether. Derivatives of ω-methylaminoacetophenone were prepared from aliquot portions of the aqueous layer as follows: *Picrate* (57%), m. p. (placed in bath at 130°), 143—144° (decomp.) (Found: N, 14·2. $C_9H_{11}ON,C_6H_3O_7N_3$ requires N, 14·3%); recrystallisation from water caused slight decomposition [Gabriel, *Ber.*, 1914, **47**, 1336, gives m. p. 136° (brown at 100°), but no analysis]. Hydrochloride, m. p. 215—217° (decomp.) (Gabriel, *loc. cit.*, gives m. p. 219°) (Found: Cl, 19·1. Calc. for $C_9H_{11}ON,HCl$: Cl, 19·1%). Toluene-*p*-sulphonyl derivative (prepared by using toluene-*p*-sulphonyl chloride and sodium hydrogen carbonate), m. p. 116—118°; repeated crystallisation failed to raise the m. p. (Gabriel, *loc. cit.*, gives m. p. 122°) (Found: N, 4·2. Calc. for $C_{16}H_{17}O_3NS$: N, 4·6%).

2-*Aminoindanone.*—A suspension of anhydro-*N*-carboxy-DL-β-phenyl-α-alanine (3·8 g.) in methylene dichloride (50 c.c.) was cooled to −10°, and powdered aluminium chloride (6 g.) was added all at once with stirring. The temperature was then allowed to rise to 20° during about 1 hour; at 12°, carbon dioxide was evolved. Stirring was continued at room temperature overnight and then at 40° for a further 5 hours. The reaction mixture was poured on to ice (140 g.)–concentrated hydrochloric acid (10 c.c.), and the majority of the methylene dichloride was separated and discarded. The aqueous layer was filtered to remove a yellow, amorphous solid (1 g.), the filtrate was extracted with ether, and the aqueous layer divided into portions from which the following derivatives of 2-aminoindanone were prepared: Hydrochloride (in poor yield, after removal of inorganic material by precipitation with

gaseous hydrogen chloride), pinkish-white needles from ethyl alcohol–ether; it darkens at 220°, shrinks at 230°, but is not completely molten at 250° (Gabriel and Stelzner, *Ber.*, 1896, **29**, 2606, give decomp. at 230—240°, brown at 200°); it stains filter-paper and the skin a bright bluish-red. Picrate (54%), yellow crystals from chloroform–acetone; it darkens at 140°, is black at 148°, m. p. (placed in bath at 140°) 152° (decomp.) [Gabriel and Stelzner, *loc. cit.*, give m. p. 152° (decomp.)] (Found: N, 14·5. Calc. for $C_9H_9ON,C_6H_3O_7N_3$: N, 14·9%).

o-*Aminobenzophenone.*—An intimate mixture of isatoic anhydride (5·5 g.) and anhydrous aluminium chloride (20 g.) in benzene (30 c.c.) was stirred for 17 hours at laboratory temperature and then at reflux for a further 4·5 hours. Most of the benzene was removed below 60° under reduced pressure, and the residue was poured on ice–hydrochloric acid. The solution was kept overnight, filtered to remove insoluble matter (not further investigated), and the filtrate was made alkaline (Clayton-yellow) with aqueous sodium hydroxide. The precipitated *o*-aminobenzophenone was extracted into ether, and the extract dried and treated with excess of dry hydrogen chloride to precipitate *o*-aminobenzophenone hydrochloride, m. p. 178—183° (decomp.) (yield 30% based on isatoic anhydride). When the time of heating under reflux was increased to 8 hours, the yield was increased (43%), but the product was rather less pure, m. p. 172—174° (decomp.). Recrystallisation from acetone raised the m. p. to 186° (decomp.) [Graebe and Ullmann, *Annalen*, 1896, **291**, 14, give m. p. 179—180° (decomp.)] (Found: Cl, 15·2. Calc. for $C_{13}H_{11}ON,HCl$: Cl, 15·2%). The free base crystallised from light petroleum in flat, pale-yellow needles, m. p. 107—108° (Geigy and Königs, *Ber.*, 1885, **18**, 2403, give m. p. 105—106°; Carré, *Bull. Soc. chim.*, 1909, (4), **5**, 280, gives m. p. 110—111°) (Found: N, 7·4. Calc. for $C_{13}H_{11}ON$: N, 7·1%). The acetyl derivative had m. p. 88° (Auwers, *Ber.*, 1896, **29**, 1263, gives m. p. 88·5—89°).

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