180. *Reactions of Alkyl*iso*formanilides. Part I. With Carboxylic Acids, Sulphonic Acids, and Sulphonamides.*

By Edward B. Knott.

Alkyl*iso*formanilides react with carboxylic acids in alcoholic solution giving *diphenylformamidine salts* and alkyl orthoformate. Fusion of the reactants at 160° or above results in the formation of an anilide together with an alkyl ester of the acid, ethyl formate, aniline and carbon monoxide. An anilide and carbon monoxide result from fusion of the diphenylformamidine salt at high temperature. Arylsulphonic acids react in alcoholic or aqueous solution to give *diphenylformamidine arylsulphonates* whilst arylsulphonamides give N-*arylsulphonyl*-N′-*phenylformamidines*.

The alkyl*iso*formanilides (alkoxymethyleneanilines or *N*-phenylformiminoethers) have received scant attention since their preparation by Comstock and Kleeberg (*Ber.*, 1890, **23**, 2274; *Amer. Chem. J.*, 1890, **12**, 497) and by Claisen (*Annalen*, 1895, **287**, 362). The ease with which the alkoxy-group is eliminated by interaction with primary or secondary amines yielding derivatives of *N*-phenylformamidine was reported by Comstock *et al.* (*loc. cit.*). Monier-Williams (*J.*, 1906, **89**, 274) condensed them with arylmagnesium bromides to give anils

whilst Wheeler and Walden (*Amer. Chem. J.*, 1897, **19**, 130) showed that they reacted with acid chlorides yielding *N*-acylformanilides with the elimination of alkyl chloride. It is known (Comstock *et al.*, *loc. cit.*) that these ethers are decomposed slowly by moisture and rapidly by aqueous mineral acids to give diphenylformamidine or its salts. It was thought to be of interest to determine the activity of organic acids towards them.

For the initial experiments, absolute alcohol was used as solvent, and in most cases the reaction took place rapidly on warming the solution. In the majority of cases the chief reaction products were *diphenylformamidine salts*, the only exceptions being the mono-carboxylic fatty acids from *iso*butyric acid upwards which did not react under these conditions. For the most part di-acid salts were obtained. Hydroxybenzoic and furoic acids as well as benzene- and the toluene-sulphonic acids, however, all gave mono-acid salts. Since naphthalene-2-sulphonic acid gave a *di-acid salt* in absolute alcohol and a *mono-acid salt* in aqueous alcohol the formation of mono-acid salts from benzene- and the toluene-sulphonic acids may be explained on the basis of hydrolysis by water, present either as solvent in the case of benzenesulphonic acid or as water of crystallisation in the cases of the toluenesulphonic acids. The formation of mono-acid salts from the hydroxybenzoic and furoic acids cannot be due to hydrolysis since no water was present. Moreover, even in aqueous alcohol such acids as benzoic or oxalic gave only di-acid salts. Since acids giving di-acid salts such as benzoic, succinic, β-benzoylpropionic or β-phenylpropionic are all much weaker acids than either furoic or salicylic acids, mono-acid salt formation does not appear to be a function of acid dissociation constants. This is further exemplified by the fact that *p*-hydroxybenzoic acid, which has a strength similar to β-benzoyl- or β-phenyl-propionic acid, gives only the mono-acid salt.

By recrystallisation of *diphenylformamidine* p-*toluenesulphonate* from an anhydrous solvent the *di*-p-*toluenesulphonate* was obtained. The identity of the salts was checked by their formation from diphenylformamidine and the appropriate acid. Those acids which gave di-acid salts in the above reaction gave the same salts with diphenylformamidine even when mixed in molar proportions. These salts, apart from those derived from the lower fatty acids, are stable and have well defined m. p.s which may be used in characterising the acid. The acetate decomposes on keeping to a brown oil. In all cases the reaction liquor, on boiling, had a strong odour similar to that of ethyl orthoformate. This by-product was isolated in one case in which malonic acid reacted with ethyl*iso*formanilide in ethyl alcohol. It was ethyl orthoformate.

The mechanism of this reaction has not been examined, but in the presence of ethyl alcohol the gross reaction appears to follow equation (I) :

$$2PhN{:}CHOEt + 2R{\cdot}CO_2H + EtOH \longrightarrow PhN{:}CH{\cdot}NHPh,2R{\cdot}CO_2H + CH(OEt)_3 \quad (I.)$$

In an attempt to isolate intermediate reaction products, benzoic acid and ethyl*iso*formanilide were heated in anhydrous benzene but, apart from a little diphenylformamidine salt, much of the *iso*formanilide was recovered together with a little phenyl *iso*cyanide.

Although the majority of fatty acids did not react in alcohol, on fusion with methyl*iso*formanilide at 160° there was a vigorous evolution of volatile substances leaving a residue which solidified in most cases. This consisted chiefly of the anilide. By this method anilides of all normal fatty acids from acetic to lauric acids and of *iso*butyric, *iso*valeric, and *iso*caproic acids were prepared. In a similar way, the anilides of phenylacetic and β-phenylpropionic acid were produced at 160°. The conversion of benzoic acid to its anilide required a temperature of over 200°. This reaction was studied more carefully employing phenylacetic acid and ethyl-*iso*formanilide; all the products of decomposition were fractionated and found to consist of carbon monoxide and ethyl formate in the primary distillate and aniline, ethyl phenylacetate and phenylacetanilide in the secondary distillate. The latter two products were formed in roughly equivalent amounts accounting for nearly all the phenylacetic acid employed. The gross reaction is thus represented by (II) :

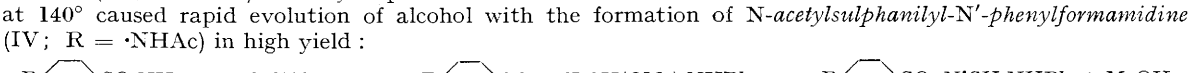
$$2PhN{:}CHOEt + 2R{\cdot}CO_2H \longrightarrow PhNH{\cdot}CO{\cdot}R + R{\cdot}CO_2Et + H{\cdot}CO_2Et + PhNH_2 + CO \quad (II.)$$

From the nature of the reaction products, anilide formation was not a simple decomposition of the diphenylformamidine salts. This was also indicated by fusion of the pure salts at 160°. The acetate gave pure diphenylformamidine whilst other salts remained unchanged. On fusion at 200°, however, the di-phenylacetate and di-β-phenylpropionate readily lost carbon monoxide and gave high yields of anilides. Similarly, the dibenzoate gave benzanilide at 250°. In this case anilide formation may be represented by (III) :

$$PhN{:}CH{\cdot}NHPh,2R{\cdot}CO_2H \longrightarrow 2PhNH{\cdot}CO{\cdot}R + CO + H_2O \quad (III.)$$

Arylsulphonic acids reacted more vigorously than analogous carboxylic acids, and in alcohol or water no application of heat was necessary. Fusion of *p*-toluenesulphonic acid and methyl*iso*formanilide at 250° gave an insoluble powder which was not investigated further.

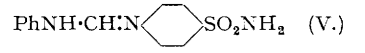
In view of the reactivity of amines towards alkyl*iso*formanilides, the condensation of the reactive sulphonamides seemed to be of interest. Toluene-*p*-sulphonamide reacted readily in boiling alcohol, and as in the case of condensation with aniline, elimination of alcohol occurred giving N-*toluene*-p-*sulphonyl*-N′-*phenylformamidine* (IV; R = Me). Acetylsulphanilamide did not react under these conditions; fusion of the reactants at 140° caused rapid evolution of alcohol with the formation of N-*acetylsulphanilyl*-N′-*phenylformamidine* (IV; R = ·NHAc) in high yield :



(IV.)

This condensation proceeds presumably through the addition compound shown. Hydrolysis of (IV; R =

NHAc) with alkali under mild conditions gave only acetylsulphanilamide whilst acid hydrolysis yielded sulphanilamide. The method of Kwartler and Lucas (*J. Amer. Chem. Soc.*, 1943, **65**, 355) for the hydrolysis of analogous sulphanilylamidines was applied but only sulphanilamide could be isolated. Sulphanilamide also condensed with the reagent but the product consisted chiefly of N-p-*sulphonamidophenyl*-N'-*phenylformamidine*:



(V.)

The formation of (IV; R = NH_2) from *p*-nitrobenzenesulphonamide and an alkyl*iso*formanilide followed by catalytic reduction has not been attempted.

Experimental.

(Microanalyses are by Drs. Weiler and Strauss, Oxford. M. p.s uncorrected.)

Methyl*iso*formanilide was prepared by the method of Lander (*J.*, 1903, **83**, 417). It can also be prepared according to Comstock and Kleeberg (*loc. cit.*; cf. Monier-Williams, *loc. cit.*). Ethyl*iso*formanilide which can be used instead of the methyl ether is best prepared by the method of Claisen (*Annalen*, 1895, **287**, 362).

Condensation Reactions.—(a) *In alcohol*: Molar quantities of the reagents in a minimum of ethanol were refluxed for 30 minutes. Arylcarboxylic acids and sulphonic acids usually gave a precipitate during the refluxing so that it was advisable to dissolve the acid in the alcohol before adding the methyl*iso*formanilide. When crystallisation did not occur on cooling a little ligroin was added. (b) *Fusion*: For these experiments the reactants were immersed in the oil bath at 140—160° with a piece of porous porcelain, the cessation of bubble formation indicating the end of the reaction. This usually occurred within 30 minutes.

*The Fusion of Phenylacetic Acid and Ethyl*iso*formanilide* (II).—Ethyl*iso*formanilide (29·8 g.; 0·2 mol.) and phenylacetic acid (27·2 g.; 0·2 mol.) were fused at 160° for 60 minutes, provision being made to collect the distillate. Ethyl formate, b. p. 54° (5 g.; 68%), was collected (Found: C, 48·5; H, 8·0. Calc. for $C_3H_6O_2$: C, 48·65; H, 8·1%). The residue was distilled until the vapour temperature was 230°. The distillate, consisting of a mixture of ethyl phenylacetate and aniline, was shaken with dilute hydrochloric acid, the insoluble oil taken up in ether, dried and distilled giving ethyl phenylacetate, b. p. 227—228° (15·1 g., 92%) (Found: C, 73·2; H, 7·2. Calc. for $C_{10}H_{12}O_2$: C, 73·15; H, 7·3%). The acid extract was basified, extracted with ether and distilled. Aniline, b. p. 184—188° (6·4 g.; 69%) (Found: N, 15·1. Calc. for C_6H_7N: N, 15·05%), was obtained. The residue from the secondary distillation was recrystallised from alcohol giving phenylacetanilide, m. p. 117° (19·3 g., 91·5%). Mixed m. p. with authentic specimen, 117° (Found: N, 6·85. Calc. for $C_{14}H_{13}ON$: N, 6·65%).

N-*Toluene*-p-*sulphonyl*-N'-*phenylformamidine*.—Toluene-*p*-sulphonamide (1·71 g.; 0·01 mol.) and methyl*iso*formanilide (1·35 g.; 0·01 mol.) in ethanol (2 c.c.) were refluxed for 15 minutes. During this time the liquor set to a mass of white crystals. They were collected and crystallised from alcohol forming fine white needles, m. p. 202—207° (1·7 g., 62%). The *amidine* is insoluble in cold aqueous sodium hydroxide but dissolves on warming (Found: N, 10·25. $C_{14}H_{14}O_2N_2S$ requires N, 9·95%).

N-*Acetylsulphanilyl*-N'-*phenylformamidine*.—Acetylsulphanilamide (6·42 g.; 0·03 mol.) was finely ground and covered by methyl*iso*formanilide (4·05 g.; 0·03 mol.) in a wide-necked flask. The mixture was immersed in an oil bath at 140° and stirred. After a short while there was a vigorous evolution of methanol, and the whole solidified. The continued stirring allowed the formation of grains instead of a solid mass. The flask was cooled, the solid washed with ether and collected (8·7 g., 92%). It crystallised slowly from alcohol in tiny rosettes of needles, m. p. 248—249°, fluorescing blue in ultraviolet light and insoluble in cold aqueous sodium hydroxide (Found: N, 13·0; S, 9·95. $C_{15}H_{15}O_3N_3S$ requires N, 13·25; S, 10·1%).

Hydrolysis.—(a) *Sodium hydroxide*: On dissolving the above in 2½ mols. warm 10% sodium hydroxide and neutralising the cooled solution acetylsulphanilamide was recovered. A strong smell of phenyl*iso*cyanide was noted. (b) *Hydrochloric acid*: On refluxing for 30 minutes with 2N hydrochloric acid followed by neutralisation, sulphanilamide separated. A shorter reaction time and lower temperatures gave only sulphanilamide or acetylsulphanilamide. Shaking for 24 hours in 20% alcoholic hydrochloric acid at room temperature gave sulphanilamide.

	Reaction temperature.		M. p. of diphenylformamidine			Analyses (% N).	
Acid.	78°.	140—160°.	salt.	Crystal form.	Formula.	Found.	Required.
Acetic–Lauric	—	Anilide	—	—	—	—	—
Oxalic	Di-acid salt	?	166°	Cubes §	$C_{15}H_{14}O_4N_2$	10·15	9·8
Malonic	,,	,,	170	Needles §	$C_{16}H_{16}O_4N_2$	9·0	9·35
Succinic	,,	,,	160	Irregular §	$C_{17}H_{18}O_4N_2$	8·8	8·95
Glutaric	,,	,,	135	Needles §	$C_{18}H_{20}O_4N_2$	8·45	8·55
Phenylacetic	,,	Anilide	99—100	Lustrous needles †	—	—	—
β-Phenylpropionic	,,	,,	79	Needles †	$C_{31}H_{32}O_4N_2$	5·75	5·65
						5·05	5·1
β-Benzoylpropionic	,,	?	139	Glistening plates needles §	$C_{33}H_{32}O_6N_2$	C, 71·75	71·8
						H, 5·85	5·8
Cinnamic	,,	Di-acid salt	119	Prisms §	$C_{31}H_{28}O_5N_2$	5·8	5·7
Benzoic	,,	,, (Anilide at 250°)	178—179	Needles §	$C_{27}H_{24}O_4N_2$	6·45	6·25
Salicylic	Mono-acid salt	?	164	Needles §	$C_{20}H_{18}O_3N_2$	8·6	8·4
p-Hydroxybenzoic	,,	,,	195	Needles §	$C_{20}H_{18}O_3N_2$	8·75	8·4
Furoic	,,	,,	144	Cream needles ‡ (alcohol cryst.)	$C_{18}H_{16}O_3N_2$	9·25	9·1
Benzenesulphonic ‖	,,	,,	166—167	Needles ‡	$C_{19}H_{18}O_3N_2S$	S, 8·95	9·0
o-Toluenesulphonic	,,	,,	194	Plates ‡	$C_{20}H_{20}O_3N_2S$	S, 9·0	8·7
p-Toluenesulphonic	,,	,,	215	Needles ‡	$C_{20}H_{20}O_3N_2S$	S, 9·05	8·7
2-Naphthalenesulphonic	Di-acid salt	,,	267	Pearly plates §	$C_{33}H_{28}O_6N_2S_2$	N, 4·95	4·6
						S, 10·3	10·45

* Heller, Kühn (*Ber.*, 1904, **37**, 3116) gave m. p. 177—178°. † From *iso*propyl ether. ‡ From methyl alcohol.
§ From ethyl alcohol. ‖ A 30% aqueous solution of benzenesulphonic acid was used.

*Sulphanilamide and Methyl*iso*formanilide.*—Sulphanilamide (1·72 g.; 0·01 mol.) and methyl*iso*formanilide (1·35 g.; 0·01 mol.) were fused at 130° for 5 minutes by which time the whole had solidified. It was washed out with ether, dissolved in hot spirit, filtered and hot water added until the filtrate was opalescent. On cooling, microscopic needles separated in clusters, m. p. 192—195°. Only a small amount of the substance was obtained; it did not contain a free amino-group and was, probably, N-p-*sulphonamidophenyl*-N′-*phenylformamidine* (Found : S, 11·41. $C_{13}H_{13}O_2N_3S$ requires S, 11·66%).

A summary of the general results is given in the foregoing table.

Diphenylformamidine 2-*naphthalenesulphonate*, obtained by mixing molar amounts of base and acid in alcohol, or by allowing the acid and alkyl*iso*formanilide to react in aqueous alcohol, had m. p. 205° (Found : S, 7·8. $C_{23}H_{20}O_3N_2S$ requires S, 7·95%).

Diphenylformamidine di-p-*toluenesulphonate* obtained from the base and acid formed colourless needles from alcohol–ether, m. p. 240° (Found : S, 11·95. $C_{27}H_{28}O_6N_2S_2$ requires S, 11·85%). It is also obtained on recrystallizing the mono-acid salt from absolute alcohol–ether.

KODAK RESEARCH LABORATORIES, WEALDSTONE, HARROW, MIDDX. [*Received, June 14th,* 1945.]