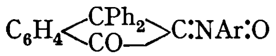
159. N-*Oximino-ethers. Part IV. Formation of Oximino-ethers in the Ehrlich–Sachs Reaction.*

By F. Barrow and F. J. Thorneycroft.

The condensation of phenylacetonitrile with aromatic nitroso-compounds gives rise to *N*-ethers of phenyloximinoacetonitrile, CPh(CN)⁚N(⁚O)R, in addition to the anils, CPh(CN)⁚NR. A similar formation of an oximino-ether has also been observed in the condensation of 2 : 4-dinitrotoluene with *p*-nitrosodimethylaniline.

It was shown by Ehrlich and Sachs (*Ber.*, 1899, **32**, 2341, and subsequent papers) that compounds containing an active methylene group undergo condensation with aromatic nitroso-compounds, yielding azomethines or anils. Although this reaction has since been the subject of numerous investigations, it has only recently been found that the interaction of nitroso- and active methylene compounds may take another course, resulting in the formation of *N*-oximino-ethers or nitrones. For example, Schönberg and Michaelis (J., 1937, 627) have shown that the condensation of 3 : 3-diphenylhydrindone with aromatic nitroso-compounds yields nitrones of the type (I), and Bergmann (*ibid.*, p. 1628) found that fluorene gives rise to *N*-ethers of fluorenone oxime (II). In none of these reactions was there any evidence of the presence of the corresponding anil among the condensation products.



$C_6H_4{<}\genfrac{}{}{0pt}{}{CPh_2}{CO}{>}C{:}NAr{:}O$

(I.)

$(C_6H_4)_2{>}C{:}NAr{:}O$

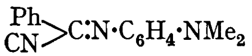
(II.)

$C_6H_4{<}\genfrac{}{}{0pt}{}{C(NAr{:}O)}{CO}{>}C{:}NAr$

(III.)

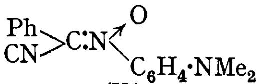
In the case of indan-1-one, the condensation with nitroso-compounds resulted in the formation of a mixed nitrone-anil (III) (Pfeiffer and Milz, *Ber.*, 1938, **71**, 272).

The formation of *N*-oximino-ethers was first observed by one of us (Thorneycroft, Thesis, London, 1927) during the interaction of phenylacetonitrile with nitroso-compounds. In the presence of potassium hydroxide, the nitrile condenses with *p*-nitrosodimethylaniline, yielding the anil (IV), described by Ehrlich and Sachs (*loc. cit.*), together with a small amount of oximinophenylacetonitrile *N*-*p*-dimethylaminophenyl ether (V), which has been previously prepared by the condensation of the nitroso-compound with phenylchloroacetonitrile (Barrow and Thorneycroft, J., 1934, 722). If the action of the alkali is prolonged, the anil undergoes hydrolysis to benzo-*p*-dimethylaminoanilide (VI).



$\genfrac{}{}{0pt}{}{Ph}{CN}{>}C{:}N{\cdot}C_6H_4{\cdot}NMe_2$

(IV.)



$\genfrac{}{}{0pt}{}{Ph}{CN}{>}C{:}N{<}\genfrac{}{}{0pt}{}{\nearrow O}{C_6H_4{\cdot}NMe_2}$

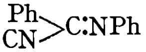
(V.)

$COPh{\cdot}NH{\cdot}C_6H_4{\cdot}NMe_2$

(VI.)

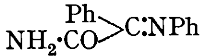
A similar formation of *N*-oximino-ethers has also been observed in the condensation of phenylacetonitrile with the *p*-nitroso-derivatives of diethyl-, monomethyl-, and monoethyl-aniline. The tendency to the formation of *N*-oximino-ethers is more pronounced with the monoalkyl derivatives, but in all cases the anil constitutes the main product of the reaction.

The condensation of phenylacetonitrile with nitrosobenzene is of particular interest, in that Sachs and Bry (*Ber.*, 1901, **34**, 494; cf. Sachs, Goldmann, and Whittaker, *Ber.*, 1902, **35**, 3319), who investigated it, isolated an oximino-ether without being aware of its identity. In addition to the anil (VII) these authors isolated a substance, m. p. 141°, which they regarded as the amide (VIII). It was suggested that the latter compound was produced by the partial hydrolysis of the anil, but all attempts to prepare the amide in this manner or by the condensation of nitrosobenzene with phenylacetamide were unsuccessful.



$\genfrac{}{}{0pt}{}{Ph}{CN}{>}C{:}NPh$

(VII.)



$\genfrac{}{}{0pt}{}{Ph}{NH_2{\cdot}CO}{>}C{:}NPh$

(VIII.)

$\genfrac{}{}{0pt}{}{Ph}{CN}{>}C{:}NPh{:}O$

(IX.)

We have repeated the condensation of phenylacetonitrile with nitrosobenzene, and have isolated from the product (*a*) the anil (VII), (*b*) both the α- and the β-*N*-phenyl ether of oximinophenylacetonitrile (IX) (m. p. 170° and 143° respectively), previously prepared by the condensation of phenylchloroacetonitrile with nitrosobenzene (Barrow and Thorneycroft, *loc. cit.*), (*c*) azoxybenzene, and (*d*) benzanilide. Separate experiments have shown that the last-named is formed by the alkaline hydrolysis of the anil, and the failure of Sachs and Bry to prepare the amide (VIII) in this manner is thus accounted for. The identity of the β-phenyl ether was fully established by its reduction to the anil, and also by its hydrolysis with hydrochloric acid to benzoic acid and *p*-chloroaniline. From these results there can be no doubt that the substance, m. p. 141°, described by Sachs and Bry, is not the amide (VIII) but the *N*-phenyl ether of oximinophenylacetonitrile (IX).

We have also discovered another instance in which an *N*-oximino-ether has been isolated and erroneously described as an anil. By the interaction of 2 : 4-dinitrotoluene with *p*-nitrosodimethylaniline Sachs and Kempf (*Ber.*, 1902, **35**, 1224) obtained a compound,

m. p. 193,° which crystallised from various solvents in either green or reddish-brown needles, and was considered by them to be 2 : 4-dinitrobenzylidene-*p*-dimethylamino-aniline (X), combined with one molecule of water.

(X.) $C_6H_3(NO_2)_2{\cdot}CH{:}N{\cdot}C_6H_4{\cdot}NMe_2$ $C_6H_3(NO_2)_2{\cdot}CH{:}N({:}O){\cdot}C_6H_4{\cdot}NMe_2$ (XI.)

The anil has now been prepared by the condensation of 2 : 4-dinitrobenzaldehyde with *p*-aminodimethylaniline; it forms green needles, m. p. 211°, and is anhydrous. We have also repeated the condensation of 2 : 4-dinitrotoluene with *p*-nitrosodimethylaniline and find that the main product consists of the anil (X), which is accompanied by a small amount of 2 : 4-dinitrobenzaldoxime *N*-*p*-dimethylaminophenyl ether (XI), crystallising in brownish-red needles, m. p. 193°, and identical with the ether prepared by Barrow, Bloom, and Griffiths (J., 1922, **121**, 1713) from 2 : 4-dinitrobenzyl chloride and *p*-nitrosodimethyl-aniline. There can be no doubt that the green compound described by Sachs and Kempf is the anil (X), and the red compound is the oximino-ether (XI).

With regard to the mechanism of the reaction resulting in the formation of oximino-ethers, we agree with Schönberg and Michaelis (*loc. cit.*) that the nitroso- and the active methylene compound condense to form a hydroxylamine derivative, $CHR_1R_2{\cdot}NAr{\cdot}OH$, which then loses water to form the anil, or undergoes oxidation, yielding the oximino-ether. The oxidation is effected by means of the unchanged nitroso-compound, which is thereby reduced to the corresponding amine or azoxy-compound. Evidence in favour of this view has now been furnished by the isolation of azoxybenzene from the products of the condensation of phenylacetonitrile with nitrosobenzene, and of *p*-aminodimethyl-aniline by the interaction of the nitrile with *p*-nitrosodimethylaniline.

The anils, $CPh(CN){:}NAr$, derived from phenylacetonitrile show an interesting difference in their behaviour towards acid and alkaline hydrolysis: in alkaline solution the cyano-group is removed with the formation of an anilide, whereas in acid solution the anil undergoes scission at the double linkage. Thus the anil (IV) is converted by alcoholic potassium hydroxide into the anilide (VI), but, with concentrated hydrochloric acid, it yields benzoyl cyanide and *p*-aminodimethylaniline.

EXPERIMENTAL.

Condensations of Phenylacetonitrile.—(a) *With* p-*nitrosodimethylaniline.* Aqueous potassium hydroxide (4 c.c. of 30%) was added slowly to a mechanically stirred solution of *p*-nitrosodimethylaniline (27 g.) and phenylacetonitrile (17·5 g.) in aqueous alcohol (500 c.c. of 50%), and the mixture kept overnight. The reddish-brown solid (28·5 g.) which separated on the addition of water (500 c.c.) was dried, shaken with cold benzene (150 c.c.), and successively crystallised from acetone and alcohol; it furnished oximinophenylacetonitrile *N*-*p*-dimethyl-aminophenyl ether (3 g.) in red prisms, m. p. 185°, not depressed by an authentic specimen (Found: N, 15·9. Calc. for $C_{16}H_{15}ON_3$: N, 15·8%). The residue obtained on evaporation of the benzene extract was crystallised twice from alcohol and gave α-*p*-dimethylaminophenyl-iminophenylacetonitrile (IV) in red prisms, m. p. 90°, as described by Ehrlich and Sachs (*loc. cit.*) (Found: N, 17·1. Calc. for $C_{16}H_{15}N_3$: N, 16·9%).

The aqueous acetone mother-liquor, from which the above condensation products had been removed, was made alkaline with potassium hydroxide and shaken with *p*-nitrobenzoyl chloride (6 g.) dissolved in benzene (100 c.c.). The solid which separated was washed successively with water and hot alcohol and crystallised from xylene, separating in bronze leaflets (4 g.), identified by m. p. and mixed m. p. 258° as *p*-nitrobenzo-*p*-dimethylaminoanilide (Barrow and Thorneycroft, *loc. cit.*).

In a second experiment, the condensation of the nitroso-compound and phenylacetonitrile was effected with twice the amount of potassium hydroxide, and the mixture kept for 4 days; the residue remaining after the condensation product had been shaken with cold benzene consisted of a mixture of the *N*-ether and benzo-*p*-dimethylaminoanilide (VI). The latter compound was separated by extraction with boiling *cyclo*hexane, in which it was sparingly soluble, and crystallised from alcohol; it had m. p. 229°, not depressed by an authentic specimen prepared by benzoylating *p*-aminodimethylaniline (Börnstein, *Ber.*, 1896, **29**, 1482).

(b) *With* p-*nitrosodiethylaniline.* The condensation was effected by the addition of aqueous potassium hydroxide (10 c.c. of 10%) to a solution of the nitroso-compound (19 g.) and phenylacetonitrile (11·7 g.) in aqueous acetone (300 c.c. of 50%). After the addition of water (500 c.c.) the solid (17 g.) was collected, dried, and extracted with boiling light petroleum (300 c.c.; b. p. 60—80°). The crop which separated from the cooled extract was removed, and the filtrate used again for extracting the undissolved residue. After this process had been repeated several times, the combined crops were crystallised thrice from alcohol and gave α-*p*-diethylaminophenyliminophenylacetonitrile, m. p. 111° (Found: N, 15·3. Calc. for $C_{18}H_{19}N_3$: N, 15·2%). The final residue remaining after extraction with light petroleum was crystallised twice from alcohol; oximinophenylacetonitrile *N*-*p*-diethylaminophenyl ether was then obtained in crimson prisms, m. p. and mixed m. p. 153° (Found: N, 14·3. Calc. for $C_{18}H_{19}ON_3$: N, 14·3%).

(c) *With* p-*nitrosomethylaniline.* The product (6·5 g.) obtained by the condensation of the nitrile (5·9 g.) with the nitroso-compound (7·5 g.), dissolved in acetone (50 c.c.) and water (10 c.c.), in the presence of aqueous potassium hydroxide (1 c.c. of 30%) was crystallised three times from alcohol and gave oximinophenylacetonitrile *N*-*p*-methylaminophenyl ether, m. p. (and mixed m. p.) 193° (Found: N, 16·8. Calc. for $C_{15}H_{13}ON_3$: N, 16·7%). The residue obtained by evaporation of the alcoholic liquors furnished, after several crystallisations from benzene–light petroleum, *p*-methylaminophenyliminophenylacetonitrile, m. p. 128° (Sachs and Bry, *loc. cit.*) (Found: N, 17·8. Calc. for $C_{15}H_{13}N_3$: N, 17·9%).

(d) *With* p-*nitrosoethylaniline.* The interaction of the nitrile (23 g.) and the nitroso-compound (32 g.) was carried out in a similar manner to that described for the diethyl derivative, and the product (33·6 g.), after being dried, was shaken with benzene (400 c.c.). Crystallisation of the residue from acetone yielded oximinophenylacetonitrile *N*-*p*-ethylaminophenyl ether (5·7 g.) in orange-red needles, m. p. 185° (Found: N, 16·0. Calc. for $C_{16}H_{15}ON_3$: N, 15·8%). The benzene extract gave on evaporation *p*-ethylaminophenyliminophenylacetonitrile, which was obtained in a pure condition, m. p. (and mixed m. p.) 111°, by crystallisation from *cyclo*hexane (Found: N, 16·8. Calc. for $C_{16}H_{15}N_3$: N, 16·9%).

(e) *With nitrosobenzene.* Aqueous sodium carbonate (12 c.c. of 20%) was added to a solution of phenylacetonitrile (13·8 g.) and nitrosobenzene (12·9 g.) in boiling alcohol (150 c.c.). After the initial vigorous reaction had subsided, the mixture was heated for 10 minutes and then diluted with water (500 c.c.). A dark oil was precipitated, which, when kept overnight in contact with the aqueous solution, partly solidified. The brown solid (4·5 g.) was separated from the oil, extracted with boiling light petroleum (60 c.c.; b. p. 40—60°), and shaken with benzene (60 c.c.). A small residue remained undissolved, which crystallised from benzene–light petroleum in pale yellow needles (0·1 g.). It showed the characteristic behaviour of the α-*N*-phenyl ether of oximinophenylacetonitrile: when heated slowly, it melted at 143°, but when plunged in a bath at 170°, it required *ca.* 15 seconds for complete fusion. The benzene extract, on evaporation, yielded the β-*N*-phenyl ether, which was obtained in a pure condition (2·5 g.) after two crystallisations from alcohol; m. p. (and mixed m. p.) 143°. The reduction to the anil and hydrolysis to benzoic acid and *p*-chloroaniline (isolated as *p*-chloroacetanilide, m. p. 178°) were carried out as described previously (Barrow and Thorneycroft, *loc. cit.*). The brown oil from which the solid had been separated, together with the original alcoholic solution, was submitted to steam distillation in order to remove unchanged phenylacetonitrile. The residual oil partly solidified overnight to a dark brown mass, which was freed from oil (porous tile) and extracted with light petroleum (60 c.c.; b. p. 60—80°); crystallisation from alcohol furnished colourless leaflets of benzanilide, m. p. and mixed m. p. 164°. The light petroleum extract was decolourised (charcoal) and evaporated; the pale yellow oil obtained readily solidified and, after crystallisation from the same solvent, was identified as azoxybenzene (m. p. and mixed m. p. 35°). In a second experiment, the solid which separated from the crude condensation product was freed from accompanying oil and crystallised from alcohol. After filtration from the β-*N*-phenyl ether of oximinophenylacetonitrile which separated, the alcoholic solution was diluted with water and the solid obtained was fractionally crystallised from aqueous alcohol; the more soluble fractions furnished α-phenyliminophenylacetonitrile (VII) in yellow leaflets, m. p. 71°, not depressed by an authentic specimen (Sachs and Whittaker, *Ber.*, 1901, **34**, 501).

2 : 4-*Dinitrobenzylidene*-p-*dimethylaminoaniline* (X).—2 : 4-Dinitrobenzaldehyde (3 g.) and *p*-aminodimethylaniline (2 g.) were heated for 30 minutes in concentrated alcoholic solution, in the presence of a few drops of acetic acid. The *anil*, which readily separated from the hot solution, crystallised from benzene in dark green, filamentous needles, appearing reddish-brown by transmitted light, m. p. 211° (Found: C, 57·5; H, 4·6. $C_{15}H_{14}O_4N_4$ requires C, 57·3; H, 4·5%).

Condensation of 2 : 4-*Dinitrotoluene with* p-*Nitrosodimethylaniline.*—The condensation was carried out as described by Sachs and Kempf (*loc. cit.*) and the dark green product was repeatedly extracted with warm acetone until the portion remaining undissolved had acquired a reddish-brown colour; crystallisation from pyridine–alcohol then furnished 2 : 4-dinitrobenzaldoxime *N*-*p*-dimethylaminophenyl ether in red needles, m. p. 193°, both alone and when mixed with an authentic specimen (Barrow, Bloom, and Griffiths, *loc. cit.*). The residue obtained by evaporation of the earlier acetone extracts was crystallised several times from benzene and gave 2 : 4-dinitrobenzylidene-*p*-dimethylaminoaniline, m. p. and mixed m. p. 211°.

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