PREPARATION OF SOME FLUORINE-CONTAINING TRISUBSTITUTED AROMATIC HYDROXYLAMINES[1]

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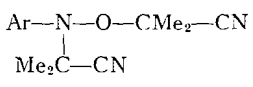
ABSTRACT

The preparation and properties of aryl dialkyl hydroxylamines in which the aryl group is a fluorobenzene derivative, and the two alkyl substituents are 2-cyano-2-propyl groups, are described.

Fluorine and its inorganic derivatives have been known for some time to be toxic to many live species (1) and, more recently, the high toxicity of fluoroacetic acid and many of its derivatives has been demonstrated (2). Although aromatic fluorine compounds have been prepared in good yields since 1927 (3), it was not until 1949 that the first systematic investigation of their fungistatic properties was undertaken (4). It was found that a number of monofluorinated quinones and nitrophenols showed good activity against the organisms *A. niger*, *A. terreus*, *M. verrucaria*, and *C. globosum*, the last two being cellulolytic. Addition of a second fluorine atom resulted in a decrease in potency and, for the fluoronitrophenols, a loss of activity was obtained by addition of another nitro group. However, in the aromatic hydrocarbon series, addition of a second nitro group markedly increased the potency, the most powerful compound being 2,4-dinitro-5-fluorotoluene (5). There are some indications that with multiple halogen dissimilar halogens give higher potencies, the most effective of all the compounds studied being 1-fluoro-3-bromo-4,6-dinitrobenzene, which, in concentration of 0.8 p.p.m., prevented growth of *A. niger* (6).

Most aromatic fluorinated nitro compounds have a yellow color and impart this to materials to which they are applied. This may be an objectionable feature, especially in the treatment of textile fibers for the suppression of microbiological attack. In the search for new antifungal compounds for this latter type of application, a series of colorless derivatives of fluoronitrobenzene have been prepared. These are O,N,N-trisubstituted hydroxylamines (I), similar to those reported by Gingras and Waters (7).

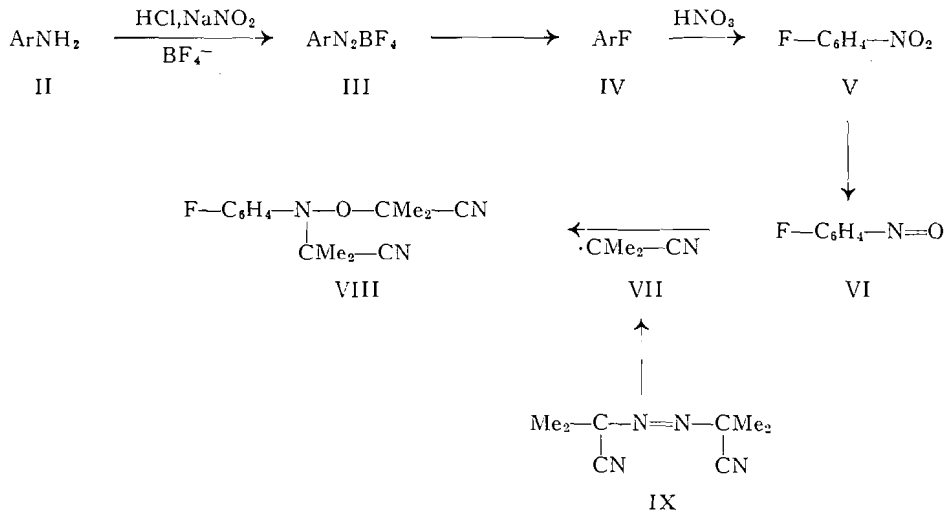


I

They are prepared through a free radical reaction from aromatic *C*-nitroso compounds and 2-cyano-2-propyl free radicals as follows. An aromatic amine (II) is first diazotized and then transformed into the fluorine derivative (IV) through a Schiemann reaction (3, 8). Nitration, followed by mild reduction gives the nitroso compound (VI), which is in turn reduced to the tertiary hydroxylamine (VIII) with two 2-cyano-2-propyl radicals (VII), the latter being produced by thermal dissociation of 2,2′-azo-bis-isobutyronitrile (IX) in solution (9).

In some instances, especially when the resulting mixture from nitration was difficult to separate into pure products, a nitroamine was used as starting material. In these

[1]*Manuscript received February 5, 1959.*
Contribution from the Division of Applied Chemistry, National Research Council, Ottawa, Canada.
Issued as N.R.C. No. 5148.



cases, special precautions had to be taken as thermal decomposition of benzene diazonium fluoborates (III) containing a nitro group is difficult to control with resultant possibility of poor yields (8).

The tertiary hydroxylamines together with the intermediate nitro compounds are listed in the table. Except for 2,4-dimethyl-6-nitrofluorobenzene, all the nitro compounds had been previously described.

TABLE

	Fluoronitro compounds: Ar—NO_2			Fluoro tertiary hydroxylamines: Ar—N(CMe_2CN)—O—CMe_2CN		
Starting material	Ar- groups	M.p. or b.p., °C at mm Hg	Lit. m.p. or b.p., °C at mm Hg	M.p., °C	Found, %	Required, %
p-Nitroaniline	4-FC_6H_4—	95/22	95–97.5/22 (11)	121	C, 64.3 H, 6.4 N, 16.0	64.4 6.1 16.0
o-Nitroaniline	2-FC_6H_4—	110/21	110–112/22 (11)	117.5	C, 64.7 H, 6.3 N, 16.2	64.4 6.1 16.0
2-Methyl-5-nitroaniline	3,4-F(Me)C_6H_3—	m.p. 34	m.p. 34 (12)	79	C, 65.2 H, 6.5 N, 15.0	65.5 6.5 15.3
2,4-Dimethyl-6-nitroaniline	2,3,5-F(Me_2)C_6H_2—	m.p. 70	—	88	N, 14.4	14.5
o-Fluorotoluene*	3,4-Me(F)C_6H_3—	m.p. 42 120/25	m.p. 41.5 99.4/13 (13)	86.5	C, 65.9 H, 7.0 N, 15.4	65.5 6.5 15.3
m-Toluidine	2,4-Me(F)C_6H_3—	111/21 †	78.5/3 216/775 (14)	100	C, 65.2 H, 6.5 N, 15.3	65.5 6.5 15.3
p-Fluoroanisole*	2,5-OMe(F)C_6H_3—	m.p. 62	m.p. 61.5 (15)	97.5	C, 61.9 H, 6.3 N, 14.8	61.8 6.2 14.4

*Eastman organic chemical used without further purification.
†Boiling point arrived at by extrapolation.

The fluorohydroxylamines are white solids, easily purified by chromatography and crystallization. They are practically insoluble in water, but dissolve in most organic solvents. Infrared spectra are of requisite character and, as expected, they are very similar to those obtained for the corresponding chlorine analogs (7). They all show the typical nitrile band at 4.5 μ, a band at 6.25 μ due to vibrations of the aromatic ring, and among others, a medium or strong band in the 9 μ region. Although the latter is indicative of $\rangle C\!\!/\!\!-F$ grouping (10), no conclusion can be drawn here, as this region is also characteristic of the C—O and N—O stretching frequencies. Furthermore, the chlorine analogs also show a strong band in this region (7) and hence, it is probable that this is due to some covalencies of the system $\begin{matrix} C \\ \diagdown \\ \diagup \\ C \end{matrix}\!\!>N—O—C$ of the hydroxylamines.

Preliminary examination shows that reduction of the nitro compounds to the substituted hydroxylamines resulted in a decrease of potency. Other types of fluorine compounds are being examined simultaneously and it is hoped that a full discussion of the biological results will be published elsewhere.

EXPERIMENTAL

2,2′-Azo-bis-isobutyronitrile was the commercial product Porophor N, (Westville laboratories) and was recrystallized before use, from ethyl acetate, to m.p. 104° C; lit. m.p. 103–104° (16). Diazonium fluoborates were prepared and decomposed by the method of Balz and Schiemann (3, 8). Nitro compounds were reduced to the corresponding nitroso compounds by the method of Lutz and Lytton (17). All melting points were taken on a Fisher–Johns apparatus and are corrected.

p-Fluoronitro- and p-Fluoronitroso-benzene

p-Nitroaniline (34.6 g, 0.25 mole) was converted into *p*-fluoronitrobenzene (15.2 g, 45%) by the Schiemann reaction (8). The preparation of *p*-fluoronitrosobenzene is typical and is described in detail. *p*-Fluoronitrobenzene (14.1 g, 0.1 mole) was dissolved in a mixture of alcohol (42 ml) and water (24 ml) and powdered calcium chloride (1.5 g) was added. The mixture was heated to boiling and zinc dust (20 g) was added in small portions. At the end, the solid residue was removed by filtration and the filtrate was poured into an ice-cold solution of ferric chloride (37 g) in water (600 ml). The dark green precipitate of nitroso compound that formed was separated by filtration, and washed with ice-cold water. The product was purified by steam distillation; yield: 6.5 g (52%).

Reaction between p-Nitrosofluorobenzene and 2,2′-Azo-bis-isobutyronitrile

p-Nitrosofluorobenzene (6.5 g, 0.05 mole) and 2,2′-azo-bis-isobutyronitrile (16.4 g, 0.1 mole) were dissolved in toluene (150 ml) and the solution was heated to 80° C. The azo compound was decomposed and the green color of the nitroso compound soon disappeared. Heating was continued under reflux for 2 hours to assure complete decomposition of the azobutyronitrile. The toluene and radical dimer (tetramethylsuccinonitrile formed by combination of two free radicals VII) (9) were distilled with steam and the residue taken up in ether and dried. After evaporation of the ether, the residue was chromatographed through a column of silica gel. A mixture of benzene and ethyl ether 9:1 eluted ON-di-(2-cyano-2-propyl)-N-(*p*-fluorophenyl) hydroxylamine (5.31 g, 40% from the nitroso compound; 8% over-all yield from original amine; m.p. 121°). The product was recrystallized from aqueous alcohol 80%.

o-Fluoronitro- and o-Fluoronitroso-benzene

o-Nitroaniline (34.6 g, 0.25 mole) gave 4.4 g (14%) of *o*-fluoronitrobenzene. This gave, by the method previously described, 1.8 g (46%) *o*-fluoronitrosobenzene.

Reaction between o-Fluoronitrosobenzene and 2,2′-Azo-bis-isobutyronitrile

This reaction was carried out as above using 1.8 g (0.15 mole) *o*-fluoronitrosobenzene, 5 g (0.03 mole) azobutyronitrile, and 50 ml toluene. The solution was heated during $2\frac{1}{2}$ hours under reflux and then steam-distilled. The residue from the steam distillation weighed 1.2 g. Chromatographic separation of this residue yielded ON-di-(2-cyano-2-propyl)-N-(*o*-fluorophenyl) hydroxylamine (0.75 g, 20% from the nitroso compound). After recrystallization from aqueous alcohol it had m.p. 117.5°.

3-Fluoro-4-methylnitro- and 3-Fluoro-4-methylnitroso-benzene

2-Methyl-5-nitroaniline (38 g, 0.25 mole) gave 2-methyl-5-nitrobenzenediazonium fluoborate (58 g, 93%) which when decomposed yielded 2-methyl-5-nitrofluorobenzene (25.5 g, 70%). The corresponding 2-methyl-5-nitrosofluorobenzene was obtained in 50% yield (*ca.* 7 g) from 15.5 g (0.1 mole) of nitro compound.

Reaction between 2-Methyl-5-nitrosofluorobenzene and 2,2′-Azo-bis-isobutyronitrile

The nitroso compound (7 g, 0.05 mole) and the azonitrile (16.4 g, 0.1 mole) were dissolved in toluene (100 ml). After the usual $2\frac{1}{2}$ hours' reflux and steam distillation, the residue (4.8 g) was chromatographed. There was obtained from mixtures of benzene: ethyl ether, 4:1 and 2:1, ON-di-(2-cyano-2-propyl)-N-(3-fluoro-4-methylphenyl) hydroxylamine (3.8 g, 28%) which was recrystallized from *n*-hexane to constant m.p. 79°.

2-Fluoro-3,5-dimethylnitro- and 2-Fluoro-3,5-dimethylnitroso-benzene

2,4-Dimethyl-6-nitroaniline (41.5 g, 0.25 mole) gave the corresponding diazonium fluoborate (36.5 g, 55%). The latter decomposed at 220° C to give 2-fluoro-3,5-dimethylnitrobenzene (7.8 g, 25%; m.p. 70°). Calc. for $C_8H_8FNO_2$, mol. wt. 169: C, 56.8; H, 4.8; N, 8.3. Found: C, 57.8; H, 5.2; N, 8.3. Reduction of 5.6 g (0.03 mole) of the nitro compound gave 2-fluoro-3,5-dimethylnitrosobenzene (*ca.* 5 g).

ON-*Di-(2-cyano-2-propyl)*-N-*(2-fluoro-3,5-dimethylphenyl) Hydroxylamine*

Reaction of 2-fluoro-3,5-dimethylnitrosobenzene (*ca.* 5 g, 0.03 mole) and 2,2′-azo-bis-isobutyronitrile (11.5 g, 0.07 mole) in toluene (125 ml) gave 1 g (12%) of the tertiary hydroxylamine. The product was recrystallized from aqueous alcohol; m.p. 88°.

3-Methyl-4-fluoronitro- and 3-Methyl-4-fluoronitroso-benzene

Nitration of *o*-fluorotoluene (60 g, 0.54 mole) with fuming nitric acid (66 ml, sp. gr. 1.5) by the method of Schiemann (11) afforded 3-methyl-4-fluoronitrobenzene (57 g, 67%, b.p. 120° at 25 mm Hg). Reduction of the nitro compound (15.5 g, 0.1 mole) gave the corresponding nitroso compound (*ca.* 7 g, 50%).

ON-*Di-(2-cyano-2-propyl)*-N-*(3-methyl-4-fluorophenyl) Hydroxylamine*

This reaction was carried out as above using 3-methyl-4-fluoronitrosobenzene (*ca.* 7 g, 0.05 mole) and 2,2′-azo-bis-isobutyronitrile (16.4 g, 0.1 mole) in toluene (150 ml). After usual heating, steam distillation, and chromatography, there was obtained the tertiary hydroxylamine (4.8 g, 35%) which was recrystallized from absolute ethyl alcohol to constant m.p. 86.5°.

2-Methyl-4-fluoronitro- and 2-Methyl-4-fluoronitroso-benzene

m-Fluorotoluene (13.4 g) was nitrated with nitric acid (15 g, sp. gr. 1.42) and concen-

trated sulphuric acid (45 g) to give 2-methyl-4-fluoronitrobenzene (12 g, 70%, b.p. 111° at 21 mm). This was reduced to the corresponding nitroso compound by the usual method.

Reaction between 2-Methyl-4-fluoronitrosobenzene and 2,2′-Azo-bis-isobutyronitrile

This reaction was carried out as before and gave the expected ON-di-(2-cyano-2-propyl)-N-(2-methyl-4-fluorophenyl) hydroxylamine (2.9 g, 25%) which was best recrystallized from ethyl alcohol; m.p. 100°.

2-Methoxy-5-fluoronitro- and 2-Methoxy-5-fluoronitroso-benzene

p-Fluoroanisole (20 g, 0.15 mole) was nitrated by the method of Swarts (15) to give 2-methoxy-5-fluoronitrobenzene (15.7 g, 60%, m.p. 62°). Reduction of the latter (15.7 g, 0.09 mole) gave 2-methoxy-5-fluoronitrosobenzene (7.7 g, 54%).

ON-*Di-(2-cyano-2-propyl)*-N-*(2-methoxy-5-fluorophenyl) Hydroxylamine*

Reaction of 2-methoxy-5-fluoronitrosobenzene (7.7 g, 0.05 mole) with 2,2′-azo-bis-isobutyronitrile (16.4 g, 0.1 mole) gave the expected tertiary hydroxylamine (5 g, 33%), which was recrystallized from *n*-hexane; m.p. 97.5°.

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