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1:2:4-Fluorodinitrobenzene

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During the war we carried out extensive investigations on the synthesis and physiological properties of organic compounds containing fluorine (McCombie & Saunders, 1941, 1946 *a*, *b*, *c*). In connexion with this work we had occasion to prepare 1:2:4-fluorodinitrobenzene, and as several workers have recently used this compound for other purposes (e.g. Sanger, 1945), its preparation is now given in detail.

1:2:4-Fluorodinitrobenzene was first prepared by Holleman & Beekmann (1904) by nitrating *p*-fluoronitrobenzene which in turn was prepared from *p*-nitroaniline. Later, Gottlieb (1936) obtained it by the action of potassium fluoride on 1:2:4-chlorodinitrobenzene. Neither method is entirely satisfactory. The second method is obviously more direct, but as described by Gottlieb is laborious. It consists in heating 1:2:4-chlorodinitrobenzene dissolved in nitrobenzene with potassium fluoride (2/3 equiv.), cooling, adding more potassium fluoride, reheating, cooling, filtering, and then repeating the whole procedure twice more, thus using 4 equiv. of potassium fluoride. Gottlieb maintains that this procedure is essential, otherwise the potassium fluoride becomes coated with potassium chloride and the reaction stops. We have found, however, that the method can be greatly improved as described in the experimental part. Only 2 equiv. of potassium fluoride are required, and in particular the intermittent additions and filtrations are unnecessary.

Pure 1:2:4-fluorodinitrobenzene is a colourless liquid which darkens slowly on standing, and solidifies when cooled in ice water. In aliphatic compounds containing the C–F link, the fluorine atom is usually less reactive than the chlorine atom in the corresponding chloro compound. In 1:2:4-fluorodinitrobenzene, however, the fluorine atom is more reactive than the chlorine atom in 1:2:4-chlorodinitrobenzene towards many reagents.

Whereas methyl fluoroacetate is a powerful convulsant poison (McCombie & Saunders, 1946*c*), 1:2:4-fluorodinitrobenzene is found to be relatively non-toxic, and does not exhibit any fluoroacetate-like activity. 1:2:4-Fluorodinitrobenzene, however, shows slight vesicant action on human skin, and in this respect it resembles 1:2:4-chlorodinitrobenzene. This vesicant action, though slight, persists with some individuals for a considerable time, therefore the compound should be handled with care.

EXPERIMENTAL

Preparation of 1:2:4-*Fluorodinitrobenzene*

1:2:4-Chlorodinitrobenzene (101 g., 0·5 mol.) was dissolved in dry nitrobenzene (101 g.) and to this solution was added dry, finely powdered KF (60 g., 1 mol.) and the mixture heated to 190–195° for 5 hr., under reflux, with vigorous stirring. The product was then cooled and filtered from inorganic salts, which were washed with hot toluene. The combined toluene filtrates were dried overnight over anhyd. Na_2SO_4. After filtering off the Na_2SO_4, the toluene was distilled off on the water pump and the residue fractionally distilled. The fraction of b.p. 136–138°/2 mm. was collected (yield 66 g., 71%). This sample was sufficiently pure for most purposes. A second fractionation gave a product which was entirely chlorine free and solidified readily on being cooled in ice water.

The fluorine was estimated by the method of Chapman, Heap & Saunders (1947). Found: F, 10·03; 10·38. Calc. for $C_6H_3O_4N_2F$: F, 10·2%.

No appreciable reaction took place when NaF, in place of KF, was heated with 1:2:4-chlorodinitrobenzene employing the conditions given above.

Physiological examination

(1) A batch of 23 rabbits, rats, guinea-pigs and mice were exposed to a Ct* of 5000 mg. min./m.^{3} in a 1·87m.^{3} static chamber. The material was sprayed in ether (25 ml.). During exposure the animals suffered from irritant action, but recovered after being removed from the chamber. At the end of a week there were no deaths. The batch was then re-exposed to the same Ct. The irritation seemed more intense and all four guinea-pigs died in 48 hr. The post-mortem examination showed changes typical of those caused by a lung irritant.

(2) Subcutaneous injection into mice, using propylene glycol as solvent: 100 mg./kg. killed 1/6.

(3) *Vesicancy on human skin.* Benzene solutions of 1:2:4-fluorodinitrobenzene (*F*) were dropped on to the right arms of two subjects, and similar solutions of 1:2:4-chlorodinitrobenzene (*Cl*) were dropped on to the left arm. There was free evaporation.

5 mg. drops of 1% solution (i.e. 50 μg.) had no effect within 4 days. 5 mg. drops of 10% solutions (i.e. 500 μg.) produced considerable irritation as follows:

Subject 1. *F patch.* Smarting and swelling in 7 hr., blister without surrounding erythema in 36 hr. No change when blister was pricked on 3rd day. Scar almost healed by 9th day. *Cl patch.* During the first 9 days there was no more than a red weal. By the 12th day there was irritation and swelling which subsided on the 15th day.

Subject 2. *F patch.* Immediate smarting and swelling which persisted for 1 day, and subsided the next day without a blister. After 3 days the skin broke down with formation of pus and scabs. After 8 days only a scar remained. *Cl patch.* Slight redness during first 8 days. Swelling on 9th day and weal rash of vesicles on 10th day. The spots oozed freely on the 14th day. Recovery on 20th day.

* Ct is the dose expressed as concentration mg./m.^{3} × time of exposure (min.).

SUMMARY

1. A convenient method of preparing 1:2:4-fluorodinitrobenzene is described.

2. The compound is relatively non-toxic in comparison with the highly toxic fluoroacetates. It produces, however, a slight vesication on human skin.

Our thanks are due to the Director General of Scientific Research (Defence) for permission to publish the above and to Mr K. J. Carpenter who carried out the physiological examination of the action of the compound on animals.

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The Utilization of Nicotinamide Derivatives and Related Compounds by Mammals, Insects and Bacteria

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This investigation was prompted by the desire to find an antipellagra drug of the efficiency of nicotinamide, but of a greater lasting effect similar to that of nicotindiethylamide (nikethamide) (Ellinger & Coulson, 1944). For this purpose a number of nicotinamide derivatives in which one or both hydrogen atoms of the amide were replaced by alkyl, cyclohexyl, or aryl groups were tested for their ability to form nicotinamide and to exhibit antipellagra activity. This aim was not reached, but the investigation gave results which are of interest, since they give some information about the relation of chemical constitution to pharmacological action and about the ability of widely different species to transform