Reports

Reactions of Hexafluorobenzene

The preparation of hexafluorobenzene has been described by several investigators (*1–3*). Of the methods used, the one of Desirant (*2*), pyrolysis of tribromofluoromethane, is the simplest and most direct procedure for preparing sizable quantities of hexafluorobenzene. When the procedure is carried out under pressure and with a platinum furnace, this method has produced yields of better than 60 percent (*4, 5*). Yields of between 20 and 50 percent have been obtained with Pyrex, graphite, and nickel furnaces (*4, 5*). In addition, other valuable materials—for example, bromopentafluorobenzene and dibromotetrafluorobenzene—are obtained as by-products (*4*).

Recently, Tatlow *et al.* (*3*) have shown that hexafluorobenzene reacts with methanolic sodium methoxide at reflux temperature to yield pentafluoroanisole. We have found that pyridine is an excellent solvent in which to perform these nucleophilic replacement reactions. For example, with methanolic sodium methoxide, by use of the inverse procedure—that is, by addition of the base to the hexafluorobenzene-pyridine solution—a 70 percent yield of pentafluoroanisole is realized in a short period of time. Similarly, by use of solid potassium hydroxide pellets in this medium, a 52 percent yield of pentafluorophenol is obtained. However, when alcoholic potassium hydroxide was used as the base to prepare pentafluorophenol, four products were identified by mass spectrometer analysis: pentafluorophenol, 40 percent; tetrafluorodihydroxybenzene, 40 percent; pentafluorophenetole, 4 percent; and tetrafluorodiethoxybenzene, 4 percent. The appearance of the latter two products can be accounted for by postulating the formation of small amounts of potassium ethoxide in the equilibrium mixture of 95 percent ethanol and potassium hydroxide and subsequent reaction with hexafluorobenzene.

The infrared spectrum of pentafluorophenol exhibits a strong hydroxyl band at 2.75 μ and also a band at 2.90 μ, the hydrogen-bonding frequency. The low boiling point (144° to 146°C) of the pentafluorophenol suggests that hydrogen bonding occurs intramolecularly with the ortho fluorine atoms adjacent to the hydroxyl group rather than intermolecularly. The phenomenon is also apparent from the boiling points of *p*-fluorophenol (189°C) and *o*-fluorophenol (152°C) (*6*). In the former case there is no opportunity for intramolecular hydrogen bonding, only intermolecular, and as a result the boiling point approaches that of ordinary phenol (182°C).

Sodium hydride failed to react with hexafluorobenzene even at its boiling point, when only trace amounts of pyridine were used. This reaction has not been investigated further.

However, when sodium and hexafluorobenzene were sealed in a thick-walled Pyrex tube and heated for ½ hour at 125°C, the tube exploded with severe violence. Apparently, once the reaction has been initiated, it proceeds exothermally at an uncontrollable rate. No reaction occurred at room temperature or at 100°C for 1 hour.

An attempt to couple hexafluorobenzene and methylmagnesium iodide in ether resulted in a 3 percent yield of pentafluorotoluene. It seems likely that a higher-boiling solvent would improve this low yield, and this type of reaction is being actively pursued.

Pentafluoroanisole. Into a three-necked flask were placed 25 g (0.134*M*) of hexafluorobenzene and 25 ml of dry pyridine. The solution was stirred and heated to 80°C, at which time a solution of 3.45 g of sodium in 40 ml of methanol was added dropwise over a ½-hour period and refluxed for an additional ½ hour. The reaction mixture was cooled and poured into 100 ml of cold 10 percent hydrochloric acid. The bottom organic layer was separated, dried (Na_2SO_4), and distilled. There was obtained 18.66 g (70 percent) of pentafluoroanisole (boiling point 154° to 156°C), reported boiling point 155° to 157°C (*3*), and 1.04 g (5 percent) of unreacted hexafluorobenzene.

Pentafluorophenol. To 160 g (0.82*M*) of hexafluorobenzene and 75 ml of dry pyridine, stirred and heated to reflux temperature, was added slowly 90 g (1.62*M*) of solid potassium hydroxide pellets over a 1.5-hour period. The mixture was refluxed for 1 hour more, cooled, diluted with 100 ml of water, and poured into 200 ml of 10 percent hydrochloric acid. The aqueous solution was extracted with five 100-ml portions of ether. The combined ether extracts were dried (Na_2SO_4) and distilled. There was obtained 50.7 g of unreacted hexafluorobenzene and 56.3 g (52.2 percent based on reacted C_6F_6) of pentafluorophenol, boiling point 72° to 73°/48 mm, 144° to 146°C (micro cap.), N_D^{26} 1.4263. The infrared spectrum showed two bands at 2.75 μ and 2.90 μ.

Pentafluorophenol was also obtained in 20 percent yield by refluxing 5 g of pentafluoroanisole and 25 ml of 47 percent hydriodic acid solution for 48 hours.

Pentafluorophenol reacts readily with benzoyl chloride in pyridine to form pentafluorophenylbenzoate, melting point 76.5° to 78.2°C. Analysis: calculated for $C_{13}F_5H_5O_2$: C, 54.18; H, 1.74; F, 32.9. Found: C, 54.0; H, 2.1; F, 33.2.

Alcoholic potassium hydroxide and hexafluorobenzene. The procedure was the same as that stated above for the pentafluoroanisole, except the following quantities were used: 10 g (0.054*M*) hexafluorobenzene, 25 ml pyridine, and 6.16 g (0.11*M*) of potassium hydroxide in 40 ml of 95 percent ethanol. The usual workup gave 9.21 g of a colorless liquid having the following mass spectrometer analysis: 40 percent pentafluorophenol, 40 percent tetrafluorodihydroxybenzene, 4 percent pentafluorophenetole, and 4 percent tetrafluorodiethoxybenzene.

Sodium hydride and hexafluorobenzene. Twenty grams (0.107*M*) of hexafluorobenzene, 2.64 g (0.106*M*) of sodium hydride, and 0.56 g of pyridine were refluxed for 5 hours. The reaction mixture was cooled, and water was slowly added until the sodium hydride was destroyed. The organic layer was separated and distilled to give 16 g of unchanged hexafluorobenzene. No other product was evident from the mass spectrometer analysis.

Sodium and hexafluorobenzene. Ten grams (0.054*M*) of hexafluorobenzene and 2.3 g (0.10 g-atoms) of sodium metal were sealed in an evacuated, 8-inch-long, heavy-walled, Pyrex tube and allowed to stand at room temperature for 72 hours. There was no apparent reaction. The tube was inserted in an oil bath at 50°C, slowly raised to 100°C, and held at this temperature for 1 hour. The sodium blackened slightly, and some solid ma-

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terial was visible, probably sodium fluoride. The temperature was then raised to 125°C, and after ½ hour the tube exploded with extreme violence. Nothing was recoverable.

Pentafluorotoluene. To the Grignard reagent prepared from 1.31 g (0.054 g-atoms) of magnesium turnings and 13.07 g (0.054M) of methyl iodide in 15 ml of anhydrous ether, was added 10 g (0.054M) of hexafluorobenzene. Slight refluxing of the ether was observed during the addition. The mixture was refluxed for 2 hours more, cooled in ice, and decomposed by the addition of 50 ml of cold 10 percent hydrochloric acid. The organic layer was separated, dried (Na_2SO_4), and the ether was removed. The residual liquid, 7.1 g, was analyzed by mass spectrometer and found to contain 65 percent unreacted hexafluorobenzene, 3 percent pentafluorotoluene, and 20 percent of a nonvolatile residue which has not been characterized (*7*).

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14 November 1957

Homing in Nonmigratory Bats

Homing at high speeds (*1*) and over long distances (*2*) has been observed in species of bats which normally migrate and which may have some familiarity with the territory covered. Although the means by which a bat navigates in returning to its roost are not known, it is known that visual and auditory clues are important factors in the homing of birds (*3*). In order to test the importance of these factors in bat movements, experiments are being conducted with the big brown bats, *Eptesicus fuscus fuscus,* which seems to be nonmigratory in the Cincinnati, Ohio, area. Bats collected from roosts in Cincinnati were carried north or south and released in locations with which they were not familiar.

The 155 bats taken north were captured, weighed, and banded on 20 July 1957. These bats were divided into five groups according to the amount of wear on their teeth—the higher the number of the group, the older the bats in the group (*4*). This criterion indicates only the relative age and not years (*5*). However, the season's young, born during the last week in May and the first week in June, were distinguishable. Of the 155 bats, all of the 57 males and 47 of the 98 females were juveniles. Among the other females, 16 were from group 2, 21 were from group 3, 7 were from group 4, and 7 were from group 5. All of these females had borne young, and the mammary glands had regressed. On 21 July they were transported in the trunk of an automobile in cages surrounded with crushed ice, since the temperature was in the middle 90's. The bats seemed torpid.

The bats were reweighed and released in the late evening at Pilgrim, Mich., north of Frankfort, 450 miles north of their home roosts. The temperature was below 70°, and many of the bats had to be exercised individually before they would fly voluntarily.

The roosts were rechecked on 24 August. Three bats were recaptured, all adult females. Two of these—one from group 2 and one from group 5—had been banded for the first time on 20 July; the third, from group 4, had been recaptured from the same roost nine times in eight different calendar months over a period of 2 years. Two other bats were observed after release. One juvenile male was killed 3 days after release, two miles north of the point of release; another juvenile male was observed about a mile south on the day following release. On 26 Oct., four more females were recaptured after they had returned from Michigan, two from group 3 and one each from groups 4 and 5.

For the southern trip, only 18 bats (nine males and nine females) could be captured on 31 July in Cincinnati. Eight of the males and six of the females were juveniles; one male and one female were from group 2; one female was from group 3, and one was from group 4. These were released at Reelfoot Lake, Tenn., 340 miles to the southwest, on 2 Aug. 1957. The temperature was 95°F, and all the bats flew immediately upon release. On 17 Aug., two of these bats were recaptured at the original roost in Cincinnati. One was a female from group 4 which had previously been captured nine times in seven different calendar months, from April through December, over a period of 2 years. The other was a juvenile male about 2 months old. Another of the juvenile males released at Reelfoot Lake was killed in Charleston, Ill., on 10 Sept. This bat was already north of the latitude of Cincinnati and 200 miles to the west.

The big brown bats seem to be nonmigratory in the Cincinnati area, since individual banded specimens have been collected in ten different calendar months. Two of the bats that returned during these experiments had been recaptured nine times in the previous 2 years. The juvenile male about 2 months old was certainly not familiar with the territory covered. Both of the bats that returned from Tennessee gained weight on the trip, whereas five of the seven bats that returned from Michigan lost weight. Two of 18 (11 percent) bats returned from Tennessee; seven of 155 (4.6 percent) returned from Michigan. However, the difficulties encountered in collecting bats in large attics and barns make our recapture figures minimal, and no significance can be attached to the difference in percentage of bats returned.

In our experiments, bats returned 450 miles south within a month or less, and 340 miles northeast within 2 weeks or less, to their original roosts, over unfamiliar territory (*6*).

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6 December 1957

6-Aminonicotinamide and Acute Degenerative Changes in the Central Nervous System

Two analogs of nicotinic acid and nicotinamide, 3-acetylpyridine (3-AP) and 6-aminonicotinamide (6-AN), cause toxic effects in mammals which are prevented by the administration of the metabolite and some of which resemble nicotinic acid deficiency (*1, 2*). Neurological changes appear to be a prominent feature of the intoxication. As examples, mice given 3-AP lose control of the hind legs and eventually become almost completely paralyzed (*1*); in nicotinic acid deficient dogs a toxic dose of 3-AP causes limb paralysis (*3*); and 6-AN in oral doses of 15 to 30 mg/kg produces in rats and rabbits loss of motor control and paralysis (*4, 5*). We undertook a toxicological study of 6-AN in preparation for its possible clinical use as an anticancer