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# The Reaction of Fluoroölefins with Hydrazines. A New Synthesis of *sym*-Tetrazines

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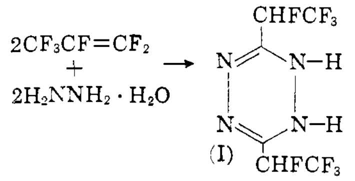
A novel synthesis of 1,2-dihydro-3,6-bis-(fluoroalkyl)-*sym*-tetrazines from fluoroolefins and hydrazine hydrate is described. When hexafluoropropene is treated with hydrazine hydrate in inert solvents, a monomeric $\alpha$-fluorohydrazone is produced which can be converted to the corresponding 1,2-dihydro-*sym*-tetrazine. Some physical properties of these *sym*-tetrazines are described.

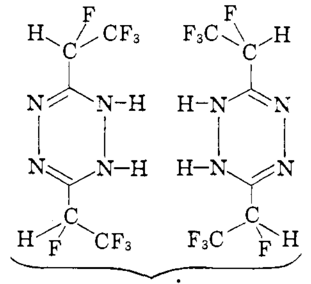
The first *sym*-tetrazine derivative was prepared by the dimerization of ethyl diazoacetate by Curtius and co-workers.[1] Several other routes to *sym*-tetrazine derivatives subsequently have been described including the reactions of hydrazine with nitriles,[2] imido esters,[3] thioamides,[4] dithioamides[5] and aroyl chloride azines.[6] An excellent review of *sym*-tetrazines has appeared recently[7].

We wish to report a new and convenient synthesis of 1,2-dihydro-3,6-bis-(fluoroalkyl)-*sym*-tetrazines from fluoroölefins and hydrazine. For example, reaction of hexafluoropropene with hydrazine hydrate in hydroxylic solvents at temperatures below 100° gave 1,2-dihydro-3,6-bis-(1,2,2,2-tetrafluoroethyl)-*sym*-tetrazine (I) in 40–45% yields.

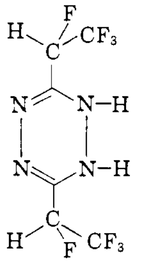


(I)

Two yellow crystalline solids were isolated which melted at 105–106° and 137–138°. The separation of the two components was facilitated by the lower solubility of the higher-melting product in aromatic hydrocarbons. The ultraviolet spectra of both solids exhibited a maximal absorption at 227 $m\mu$ ($\epsilon$ 3690) and a low intensity absorption peak at 328 $m\mu$ ($\epsilon$ 77). Elemental analyses and molecular weight determinations of each form were in accord with the proposed structure I. The infrared spectra of the high- and low-melting products in chloroform were identical except for slight differences in the relative intensities of the 6.2 and 6.3 $\mu$ bands. However, each compound was recovered unchanged on recrystallization from a xylene solution seeded with the other product. It is likely, therefore, that the solids are DL- and *meso*-isomers rather than dimorphic forms. Since internally compensated *meso* compounds are generally higher melting than the corresponding *dl*-diastereoisomers,[8] the product melting at 137–138° is considered to have the *meso* configuration.



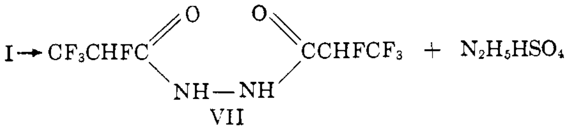
racemic



*meso*

Tetrafluoroethylene and 1,1,4,4-tetrafluoro-1,3-butadiene reacted similarly with hydrazine hydrate to yield 1,2-dihydro-3,6-bis-(difluoromethyl)-*sym*-tetrazine (II), m.p. 98–99°, and 1,2-dihydro-3,6-bis-(3,3-difluoroallyl)-*sym*-tetrazine (III), m.p. 130–132°, respectively.[9] The possibility of stereoisomers in II and III is precluded by the absence of an asymmetric carbon atom. Only one product was isolated in each case.

When the dihydrotetrazine (I) was warmed in the presence of sulfuric acid, it readily hydrolyzed to 1,2-bis-(2,3,3,3-tetrafluoropropionyl)-hydrazine (VII).[10]



VII

Oxidation of the dihydrotetrazines (I and II) with concentrated nitric acid in acetic acid yielded volatile red solids which analyzed for the corresponding tetrazines (IV and V). Furthermore, visible absorption spectra in acetone exhibited maxima at 522 $m\mu$ ($\epsilon$ 395) and 512 $m\mu$ ($\epsilon$ 545), respectively, characteristic of *sym*-tetrazines.[11]

When 1,2-dihydro-3,6-bis-(3,3-difluoroallyl)-*sym*-tetrazine was oxidized in a similar manner, the corresponding tetrazine (VI) was obtained as a magenta liquid which gradually decomposed on long standing. The liquid exhibited a typical *sym*-

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(1) Th. Curtius, *Ber.*, **18**, 1284 (1885); **20**, 1632 (1887); Th. Curtius and J. Lang, *J. prakt. Chem.*, **38**, 532 (1888).

(2) K. A. Hoffmann and O. Ehrhardt, *Ber.*, **45**, 2731 (1912); Th. Curtius and A. Hess, *J. prakt. Chem.*, **125**, 40 (1930).

(3) A. Pinner, *Ann.*, **297**, 221 (1897).

(4) A. Junghahn, *Ber.*, **31**, 312 (1898); A. Junghahn and J. Bruni-mowicz, *ibid.*, **35**, 3932 (1902).

(5) M. H. Wuyts and A. Lacourt, *Bull. soc. chim. Belges*, **45**, 685 (1936).

(6) R. Stollé, *J. prakt. Chem.*, **73**, 277 (1906).

(7) J. G. Erickson, P. F. Wiley and V. P. Wystrach, "The Chemistry of Heterocyclic Compounds, Vol. X. The 1,2,3- and 1,2,4-Triazines Tetrazines, and Pentazines," Interscience Publishers. Inc., New York, N. Y., 1956, Chapter IV.

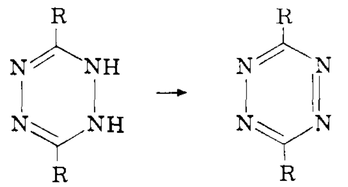
(8) R. Stern, J. English, Jr., and H. G. Cassidy, THIS JOURNAL, **79**, 5797 (1957).

(9) We are indebted to Drs. D. C. England and E. L. Martin, who investigated the reactions with tetrafluoroethylene and 1,1,4,4-tetrafluoro-1,3-butadiene, respectively.

(10) The first examples of 1,2-bis-(1-haloacyl)-hydrazines were reported recently by A. Kreutzberger, *J. Org. Chem.*, **22**, 679 (1957).

(11) (a) E. Müller and L. Herrdegen, *J. prakt. Chem.*, **102**, 113 (1921); (b) C. H. Lin, E. Lieber and J. P. Horwitz, THIS JOURNAL, **76**, 427 (1954).

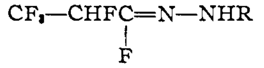
tetrazine absorption maximum at 537 mμ (ε 515). Further, its infrared spectrum showed a strong C═C stretching vibration at 5.65 μ attributed to the $CF_2═CH—$ group in the difluoroallyl side chain (VI).



II, R = $CHF_2$
III, R = $CH_2$-CH═$CF_2$
IV, R = $CHFCF_3$
V, R = $CHF_2$
VI, R = $CH_2$–CH═$CF_2$

The dihydrotetrazine derivatives were easily regenerated by reduction of the corresponding tetrazines with hydrogen sulfide. These reversible transformations with their accompanying color changes had been noted many years ago[12] with other *sym*-tetrazines.

When the reaction of hexafluoropropene with hydrazine hydrate was carried out in relatively nonpolar solvents such as ether or dioxane, none of the expected dihydrotetrazine I was formed. Instead, a good yield of a colorless liquid was obtained. Elemental analyses and molecular weight determinations indicated that the product was monomeric and had the empirical formula $C_3H_3F_5N_2$. The α-fluorohydrazone structure VIII is proposed on the basis of properties and spectroscopic data. The infrared spectrum exhibited bands at 2.95, 3.0, 3.1 and 6.15 μ characteristic of $NH_2$, and a strong band at 5.90 μ attributed to the F—C═N— unsaturation. The nuclear magnetic resonance spectrum was also in agreement with this assignment. When allowed to stand at room temperature for several days, or when heated, the α-fluorohydrazone VIII was converted to the dihydrotetrazine (I) with evolution of hydrogen fluoride. The dihydrotetrazine also formed readily when the α-fluorohydrazone was treated with a trace of mineral acid, or warmed in acetic acid at 90° for 5 minutes. When the latter solution contained nitric acid, the tetrazine (IV) was obtained directly. The above transformations are illustrated in the diagram below. The cyclization may proceed through stages A and B by the reciprocal addition of the amino group from one molecule of VIII to the activated C═N group of a second molecule.



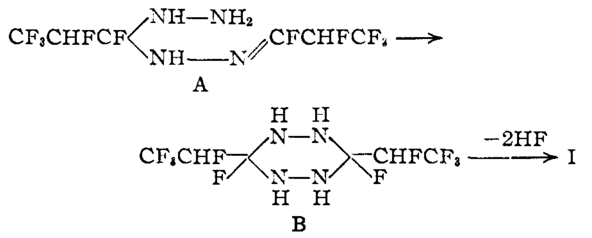
$$CF_3—\underset{F}{CH}C═N—NHR$$

VIII, R = H
IX, R = $C_6H_5$
X, R = $CONH_2$

$$2CF_3CF═CF_2 + 2NH_2NH_2 \longrightarrow$$

$$2CF_3CHFCF═NNH_2 \longrightarrow$$

VIII



When hexafluoropropene was treated with substituted hydrazines such as phenylhydrazine and semicarbazide, the only products isolated were the α-fluorophenylhydrazone (IX) and the α-fluorosemicarbazone (X), respectively, regardless of the solvent employed.

2,3,3,3-Tetrafluoropropionyl fluoride hydrazone (VIII) has shown an interesting property as a hydrazone transfer agent. Thus, when a mixture of VIII and benzophenone was refluxed in ethyl alcohol for 2 hours, benzophenone azine and ethyl tetrafluoropropionate were formed in good yield. This facile formation of the azine is in sharp contrast to the more rigorous conditions required when benzophenone is treated with hydrazine.[13]

$$VIII + (C_6H_5)_2C═O \xrightarrow{C_2H_5OH}$$

$$(C_6H_5)_2C═N—N═C(C_6H_5)_2 + CF_3CHFCOOC_2H_5$$

Some novel reactions of these new fluoroalkyl substituted tetrazines will be reported in a later paper.

**Acknowledgment.**—The authors wish to express their appreciation to Dr. J. C. Kauer for helpful discussions.

## Experimental

**1,2-Dihydro-3,6-bis-(1,2,2,2-tetrafluoroethyl)-*sym*-tetrazine (I).**[14]—A mixture of 75.0 g. (0.50 mole) of hexafluoropropene, 50.0 g. (1.0 mole) of hydrazine hydrate, and 100 ml. of water was shaken in a silver-lined bomb at room temperature for 6 hours, then at 50° for 4 hours. The cooled reaction mixture was filtered and the dark-colored solid extracted with 500 ml. of ether. The ether extract was washed with water, dried over sodium sulfate and evaporated to dryness. The crystalline residue was sublimed at 100° (15 mm.) to obtain bright yellow 1,2-dihydro-3,6-bis-(1,2,2,2-tetrafluoroethyl)-*sym*-tetrazine (29.3 g., 41%), m.p. 110–114°. Recrystallization from toluene gave yellow crystals melting at 112–116°. A second recrystallization raised the melting point to 119–123°, presumably due to changing proportions of the two stereoisomers.

*Anal.* Calcd. for $C_6H_4F_8N_4$: C, 25.36; H, 1.42; F, 53.49; mol. wt., 284. Found: C, 25.65; H, 1.71; F, 53.40; mol. wt., 264.

The less soluble higher melting fraction was obtained by crystallizing the mixed product three times from xylene. The solid separated as yellow rodlets, m.p. 137–139°. The mother liquors were combined, concentrated and allowed to stand. The yellow product that separated melted at 105–106.5°.

**1,2-Dihydro-3,6-bis-(difluoromethyl)-*sym*-tetrazine (II).**—A mixture of 25 g. (0.25 mole) of tetrafluoroethylene, 25 g. (0.50 mole) of hydrazine hydrate and 25 ml. of ethyl alcohol was sealed in a Carius tube and allowed to react at room temperature for 20 hours. After collecting the unreacted tetrafluoroethylene (12 g., 0.12 mole), the residual mixture was poured into 300 ml. of ice-water and extracted with three 100-ml. portions of ether. The combined ether extract was washed with water, dried over anhydrous sodium sulfate and evaporated nearly to dryness. Upon addition of 45 ml. of pentane, the dihydrotetrazine derivative (II) separated as soft, yellow crystals, yield 5.2 g. (44% based on tetrafluoroethylene consumed). Several recrystallizations from an ether–pentane mixture gave yellow needles, m.p. 93–94°. In a similar preparation, a solid was obtained which melted at 98–99°.

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[12] A. Pinner, *Ber.*, **26**, 2133 (1893).

[13] E. R. Blout, THIS JOURNAL, **68**, 1983 (1946). It is reported that benzophenone and hydrazine must be heated in a bomb at 150–160° for the reaction to proceed beyond the hydrazone stage to the azine.

[14] R. A. Carboni, U. S. Patent 2,817,622 (1957).

*Anal.* Calcd. for $C_4H_4F_4N_4$: C, 26.09; H, 2.19; F, 41.28. Found: C, 26.15; H, 2.42; F, 41.01.

**1,2-Dihydro-3,6-bis-(3,3-difluoroallyl)-*sym*-tetrazine (III).**—Into a solution of 10 g. (0.2 mole) of hydrazine hydrate in 30 ml. of dimethylformamide cooled to 0–5° was distilled slowly 12.6 g. (0.1 mole) of 1,1,4,4-tetrafluoro-1,3-butadiene.[15] The mixture was stirred at 0–5° for 0.5 hour during which time a white solid separated. The reaction mixture was brought to room temperature and stirred for an additional hour. The mixture was diluted with 100 ml. of water, warmed to 90°, then cooled to 0°. The pale yellow plates (6.5 g., 55% yield) which separated were collected by filtration and recrystallized from aqueous ethyl alcohol, m.p. 130–132°.

*Anal.* Calcd. for $C_8H_8F_4N_4$: C, 40.66; H, 3.42. Found: C, 40.91; H, 3.69.

**3,6-Bis-(1,2,2,2-tetrafluoroethyl)-*sym*-tetrazine (IV).**—To a stirred solution of 7.15 g. (0.025 mole) of I in 25 ml. of acetic acid at 10° was added 5 ml. of concentrated nitric acid dropwise during 5 minutes. The mixture turned red, and nitric oxide fumes were evolved. The product (6 g.) which separated as an orange-red solid upon addition of the reaction-mixture to 100 ml. of ice-water, was removed by filtration and washed with 15 ml. of cold water. Crystallization from petroleum ether (b.p. 30–60°) gave red platelets, m.p. 67–70°.

*Anal.* Calcd. for $C_6H_2F_8N_4$: F, 53.88; N, 19.86. Found: F, 53.47; N, 19.97.

**3,6-Bis-(difluoromethyl)-*sym*-tetrazine (V).**—Oxidation of II by the same procedure gave a 62% yield of 3,6-bis-(difluoromethyl)-*sym*-tetrazine as red-orange crystals which were recrystallized from cyclohexane; m.p. 103–104°.

*Anal.* Calcd. for $C_4H_2F_4N_4$: C, 26.38; H, 1.11; F, 41.74. Found: C, 26.73; H, 1.42; F, 41.58.

**3,6-Bis-(3,3-difluoroallyl)-*sym*-tetrazine (VI).**—The dihydro derivative III was treated with 2.5 ml. of nitric acid under the conditions employed in preparing IV. After pouring the reaction mixture into ice-water, the resulting red oil was extracted with ether, and the ether extract was shaken with aqueous bicarbonate solution to remove any acid. The ether was removed by distillation and the tetrazine (VI) collected as a deep-red liquid, b.p. 75–80° (1 mm.).

*Anal.* Calcd. for $C_8H_6F_4N_4$: C, 41.01; H, 2.58. Found: C, 41.45; H, 2.82.

**2,3,3,3-Tetrafluoropropionyl Fluoride Hydrazone (VIII).**—Hexafluoropropene (75 g., 0.5 mole) was distilled into an evacuated silver-lined bomb which contained 50 g. (1 mole) of hydrazine hydrate and 100 ml. of ether. The reaction mixture was heated at 60° for 8 hours, then cooled. The hydrazinium fluoride was removed by filtration and the solvent distilled at atmospheric pressure. Fractionation of the residual liquid yielded 54 g. (66%) of 2,3,3,3-tetrafluoropropionyl fluoride hydrazone (VIII). b.p. 58–60° (147 mm.), $n^{25}\mathrm{D}$ 1.3476.

*Anal.* Calcd. for $C_3H_3F_5N_2$: C, 22.23; H, 1.86; N, 17.29; F, 58.62; mol. wt., 162. Found: C, 22.58; H, 1.97; N, 17.25; F, 58.32; mol. wt., 164.

**Conversion of VIII to 1,2-Dihydro-3,6-bis-(1,2,2,2-tetrafluoroethyl)-*sym*-tetrazine.**—A solution of 0.5 g. of the α-fluorohydrazone VIII in 2 ml. of glacial acetic acid was heated at 70° for 10 minutes, cooled, and poured into 3 volumes of ice-water, whereupon the lower melting isomer of I separated, m.p. 106–108°. The infrared spectrum of this product was identical to that of an authentic sample.

**2,3,3,3-Tetrafluoropropionyl Fluoride Phenylhydrazone (IX).**—A mixture of 70 g. (0.65 mole) of phenylhydrazine, 70 g. (0.47 mole) of hexafluoropropene and 150 ml. of water in a silver-lined bomb was kept at room temperature for 5 hours, then heated at 80° for 6 hours. The reaction mixture was extracted with 200 ml. of ether. The ether extract was concentrated, diluted with 100 ml. of petroleum ether and filtered to remove some solid. Fractionation of the filtrate yielded 32 g. (40.5% yield, based on hexafluoropropene) of the colorless oily α-fluorophenylhydrazone, b.p. 76–77° (0.8 mm.), $n^{25}\mathrm{D}$ 1.4832.

*Anal.* Calcd. for $C_9H_7F_5N_2$: C, 45.38; H, 2.96; N, 11.77. Found: C, 45.24; H, 3.23; N, 11.76.

**2,3,3,3-Tetrafluoropropionyl Fluoride Semicarbazone (X).**—A mixture of 100 g. (1 mole) of semicarbazide hydrochloride, 37 g. (0.92 mole) of sodium hydroxide, 75 g. (0.5 mole) of hexafluoropropene and 150 ml. of water was kept in a silver-lined bomb at room temperature for 8 hours, then heated at 50° for 6 hours. A white fluffy solid (10.5 g.) was collected by filtration and extracted with ether. Removal of the ether yielded a colorless crystalline product, m.p. 167–168°.

*Anal.* Calcd. for $C_4H_4F_5N_3O$: C, 23.42; H, 1.96; F, 46.32. Found: C, 23.45; H, 2.13; F, 46.49.

**Reaction of VIII with Benzophenone.**—To a solution of 5.46 g. (0.03 mole) of benzophenone in 20 ml. of ethyl alcohol was added 4.9 g. (0.03 mole) of the α-fluorohydrazone VIII. The mixture was refluxed for 6 hours and cooled. A yellow crystalline solid (6.9 g.) separated, which, on recrystallization from methanol, melted at 165–166° (lit.[18] for benzophenone azine, m.p. 164–165°).

**1,2-Bis-(2,3,3,3-tetrafluoropropionyl)-hydrazine.**—1,2-Dihydro-3,6-bis-(1,2,2,2-tetrafluoroethyl)-*sym*-tetrazine (7.0 g.) was added gradually to 100 ml. of concentrated sulfuric acid with stirring. The mixture was stirred at room temperature for 45 minutes, then at 40° for an additional 45 minutes. The acid solution was cooled to 20°, then slowly poured over 150 g. of crushed ice. The solid which separated was collected by filtration and washed with water. Both the solid and the filtrate were extracted with ether. The combined ether extract was dried and evaporated to dryness, yielding 3.5 g. of crude acylhydrazine. Recrystallization from water yielded almost colorless platelets, m.p. 168–169° (sealed tube). The infrared spectrum shows peaks at 3.1 and 3.25 μ which may be N–H, as well as peaks at 6.1 and 6.6 μ, characteristic of secondary amides.

*Anal.* Calcd. for $C_6H_4N_2O_2F_8$: C, 25.01; H, 1.40; N, 9.73. Found: C, 25.47; H, 1.72; N, 9.53.

The ether-insoluble solid was shown to be hydrazinium sulfate.

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(15) J. L. Anderson, U. S. Patent 2,743,303 (1956).