[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

# The Preparation and Reactions of Some Fluorine-containing Nitro Compounds

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Heptafluorobutanal hydrate has been condensed with nitromethane, nitroethane and 1-nitropropane to give the corresponding fluorine-containing nitroalcohols while fluoral hydrate has been condensed with nitromethane to give 1,1,1-trifluoro-3-nitro-2-propanol. Dehydration of the several fluorinated nitroalcohols has resulted in the preparation of the following fluorinated nitroölefins: 3,3,4,4,5,5,5-heptafluoro-1-nitro-1-pentene, 4,4,5,5,6,6,6-heptafluoro-2-nitro-2-hexene and 5,5,6,6,7,7,7-heptafluoro-3-nitro-3-heptene. The Michael addition of nitromethane, several Grignard reagents and diethyl malonate to the nitroölefins has been found to proceed in good yield while the reduction of the fluorinated nitroölefins with lithium aluminum hydride at −50° has given good yields of the fluorinated nitroalkanes. The addition of nitromethane to ethyl 4,4,4-trifluorobutenoate and ethyl 4,4,5,5,6,6,6-heptafluoro-2-hexenoate in the presence of triethylamine has given 65% yields of ethyl 4,4,4-trifluoro-3-nitromethylbutyrate and ethyl 4,4,5,5,6,6,6-heptafluoro-3-nitromethylhexanoate.

## Introduction

The present study was undertaken in order to prepare a number of compounds containing both fluorine and a nitro group. The various methods studied of preparing these materials have included the addition of nitroalkanes to fluorinated aldehydes, ketones and unsaturated esters. The preparation of a number of fluorinated nitroalcohols was accomplished and led to the preparation of fluorinated nitroölefins which have been found to be quite reactive in the Michael type of reaction with other nitroalkanes, Grignard reagents and diethyl malonate. The use of the method recently described by Gilsdorf and Nord[1] has made possible the reduction of the fluorinated nitroölefins to the fluorinated nitroalkanes with lithium aluminum hydride in yields of 50–70%. A number of the fluorinated nitro compounds have been reduced to the corresponding amines by low pressure hydrogenation using Raney nickel and platinum catalysts, or lithium aluminum hydride.

In a manner analogous to the method described by Burkett, *et al.*, for the condensation of nitromethane with chloral hydrate,[2] heptafluorobutyral and fluoral hydrates have been condensed with several nitroalkanes. These compounds together with their properties are listed in Table I.

TABLE I

NEW COMPOUNDS

| | Formula | Yield, % | B.p. °C. | B.p. Mm. | M.p., °C. | $n^{20}D$ | Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $C_3F_7CHOHCH_2NO_2$ | 75 | 56 | 2 | | 1.3522 | 23.16 | 23.29 | 1.54 | 1.54 | 5.40 | 5.43 |
| 2 | $CF_3CHOHCH_2NO_2$ | 47 | 84 | 17 | | 1.3771 | 22.64 | 22.63 | 2.51 | 2.62 | 8.80 | 8.85 |
| 3 | $C_3F_7CHOHCH(CH_3)NO_2$ | 70 | 55 | 1 | | 1.3589 | 26.37 | 26.22 | 2.19 | 2.36 | 5.12 | 5.18 |
| 4 | $C_3F_7CHOHCH(C_2H_5)NO_2$ | 78 | 73 | 5 | | 1.3657 | 29.26 | 29.38 | 1.79 | 1.98 | 4.87 | 5.00 |
| 5 | $C_3F_7C(CH_3)OHCH_2NO_2$ | 28 | 68 | 8 | | 1.3624 | 26.14 | 26.43 | 2.19 | 2.32 | 5.12 | 5.21 |
| 6 | $C_3F_7CH{=}CHNO_2$ | 68 | 122 | | | 1.3403 | 24.90 | 25.14 | 0.83 | 0.97 | 5.80 | 5.78 |
| 7 | $C_3F_7CH{=}C(CH_3)NO_2$ | 63 | 136 | | | 1.3534 | 28.23 | 28.66 | 1.57 | 2.03 | 5.48 | 5.64 |
| 8 | $C_3F_7CH{=}C(C_2H_5)NO_2$ | 78 | 78 | 75 | | 1.3574 | 31.22 | 31.24 | 2.23 | 2.33 | 5.20 | 5.32 |
| 9 | $C_3F_7CH_2CH_2NO_2$ | 51 | 68 | 33 | | 1.3335 | 24.69 | 25.02 | 1.64 | 2.06 | 5.76 | 5.78 |
| 10 | $C_3F_7CH_2CH(CH_3)NO_2$ | 51 | 64 | 23 | | 1.3412 | 28.00 | 28.49 | 2.32 | 2.46 | 5.44 | 5.55 |
| 11 | $C_3F_7CH_2CH(C_2H_5)NO_2$ | 69 | 60 | 9 | | 1.3493 | 31.00 | 31.21 | 2.95 | 2.84 | 5.17 | 5.19 |
| 12 | $C_3F_7CH(CH_3)CH_2NO_2$ | 38 | 53 | 15 | | 1.3447 | 28.00 | 28.08 | 2.32 | 2.38 | 5.44 | 5.32 |
| 13 | $C_3F_7CH(C_2H_5)CH_2NO_2$ | 53 | 56 | 18 | | 1.3543 | 31.00 | 30.95 | 2.95 | 3.01 | 5.17 | 5.19 |
| 14 | $C_3F_7CH(CH_2CH_2C_3F_7)CH_2NO_2$ | 23 | 80 | 3 | | 1.3361 | 27.30 | 27.30 | 1.57 | 1.77 | 3.19 | 3.25 |
| 15 | $C_3F_7CH(CH_2NO_2)_2$ | 68 | | | 62–62.5 | | 23.84 | 23.94 | 1.65 | 1.86 | 9.26 | 9.47 |
| 16 | $C_3F_7CH[CH(CO_2C_2H_5)_2]CH_2NO_2$ | 49 | 145 | 9 | | 1.3904 | 35.91 | 36.11 | 3.49 | 3.51 | 3.49 | 3.68 |
| 17 | $C_3F_7CH(OC_2H_5)CH_2NO_2$ | 35 | 76 | 29 | | 1.3488 | 29.26 | 29.51 | 2.78 | 3.18 | 4.87 | 4.96 |
| 18 | $C_3F_7CH(NHC_6H_4COOH)CH_2NO_2$ | 61 | | | 125.5–126.5 | | 38.09 | 38.31 | 2.37 | 2.59 | 7.40 | 7.22 |
| 19 | $C_3F_7CH(NHC_6H_4COOH)CH(CH_3)NO_2$ | 60 | | | 149–150 | | 39.90 | 39.75 | 2.80 | 2.80 | 7.14 | 7.16 |
| 20 | $CF_3CH(CH_2NO_2)CH_2CO_2C_2H_5$ | 68 | 105 | 9 | | 1.4008 | 36.68 | 36.64 | 4.37 | 4.37 | 6.11 | 6.34 |
| 21 | $C_3F_7CH(CH_2NO_2)CH_2CO_2C_2H_5$ | 64 | 96 | 5 | | 1.3770 | 32.82 | 32.80 | 3.04 | 3.10 | 4.25 | 4.21 |
| 22 | $C_3F_7CH(CH_2NO_2)CH_2COOH$ | 48 | | | 46.5–48 | | 27.91 | 28.00 | 1.98 | 2.04 | 4.65 | 4.67 |
| 23 | $C_3F_7CH(C_2H_5)CH_2NH_2$ | 39 | 68 | 81 | | 1.3443 | 34.85 | 35.26 | 4.14 | 4.50 | 5.81 | 6.14 |
| 24 | $C_3F_7CH_2CH(C_2H_5)NH_2$ | 50 | 60 | 82 | | 1.3388 | 34.85 | 35.03 | 4.14 | 4.46 | 5.81 | 5.60 |
| 25 | $CF_3CH(OH)CH_2NH_2 \cdot HCl$ | 50 | | | 154–155[a] | | 22.08 | 22.06 | 4.30 | 4.40 | 8.58 | 8.55 |
| 26 | $C_3F_7CH(OH)CH_2NH_2 \cdot HCl$ | 95 | | | 133–135 | | 22.64 | 22.55 | 2.64 | 2.78 | 5.28 | 5.29 |
| 27 | $C_3F_7CH(OH)CH(CH_3)NH_2 \cdot HCl$ | 97 | | | 228–230 | | 25.80 | 25.78 | 3.22 | 3.81 | 5.02 | 5.24 |
| 28 | $C_3F_7CH(OH)CH(C_2H_5)NH_2 \cdot HCl$ | 30 | | | 197–198 | | 28.67 | 28.65 | 3.75 | 3.81 | 4.77 | 4.87 |
| 29 | $C_3F_7CH(OH)CH_2NH_2$ | 84 | | | 68–69 | | 26.20 | 26.16 | 2.62 | 2.82 | 6.11 | 6.24 |
| 30 | $C_3F_7CH(OH)CH(CH_3)NH_2$ | 65 | | | 82–83 | | 29.62 | 29.69 | 3.29 | 3.30 | 5.76 | 5.75 |

[a] R. Jones, THIS JOURNAL, **70**, 143 (1948), reports m.p. 147–148° and the dibenzoyl derivative m.p. 126.5–127.5°. The same derivative prepared in this Laboratory has a m.p. 124.5–125°.

A number of attempts to condense nitromethane with a fluorinated ketone was made but the reaction was found to be only moderately successful in one case, that of 3,3,4,4,5,5,5-heptafluoro-2-pentanone. A 27% yield of the compound, 3,3,4,4,5,5,5-heptafluoro-2-methyl-1-nitro-2-pentanol was obtained.

The dehydration of the fluorinated nitroalcohols has been found to proceed with a number of dehydrating agents. Acetic anhydride, propionic

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[1] R. T. Gilsdorf and F. F. Nord, THIS JOURNAL, **74**, 1837 (1952).

[2] M. Compton, H. Higgins, L. MacBeth, J. Osborn and H. Burkett, *ibid.*, **71**, 3229 (1949).

anhydride, benzoic anhydride and phosphorus pentoxide were all useful as reagents. The methods for the dehydration by acetic anhydride and phosphorus pentoxide are recorded in the Experimental section. Although 3,3,4,4,5,5,5-heptafluoro-1-nitro-2-pentanol can be dehydrated with phosphorus pentoxide in 68% yield with no difficulty, 1,1,1,2,2,3,3-heptafluoro-5-nitro-4-heptanol dehydrates with decomposition when heated with the oxide. No decomposition occurred when acetic anhydride was used for the dehydrating agent with any of the fluorinated nitroalcohols. The fluorinated nitroolefins obtained by these methods are yellow lachrymatory liquids with the intensity of the odor decreasing as the chain length increases.

A study of the addition reactions of the fluorine-containing nitroölefins has shown little reactivity with acid-catalyzed reagents under the conditions employed while the base-catalyzed reagents react readily. Several attempts to add hydrogen bromide to 3,3,4,4,5,5,5-heptafluoro-1-nitro-1-pentene in a manner described by Heath and Rose[3] for the addition of hydrogen chloride to $\alpha$-unsaturated nitroölefins proved unsuccessful with recovery of the olefin unchanged. The impossibility of obtaining any successful Nef or modified Nef reactions with the fluorinated nitroölefins, nitroalcohols or nitroalkanes was also observed.

In contrast, the base-catalyzed addition of lithium aluminum hydride,[1] the addition of various Grignard reagents following the procedure of Buckley and Ellery[4] and the addition of nitromethane according to the method of Lambert and Piggott[5] to the various nitroölefins has resulted in fair to good yields of the several mono- and dinitroalkanes.

In one example it was shown that the addition of ethylmagnesium bromide to 3,3,4,4,5,5,5-heptafluoro-1-nitro-1-pentene has followed a 1:4 mechanism by preparing the other possible product from 1,1,1,2,2,3,3-heptafluoro-5-nitro-4-heptanol through dehydration to the olefin and subsequent saturation with lithium aluminum hydride. Although these two compounds have about the same boiling points, there is a noticeable difference in their refractive indices. (See compounds 11 and 13 and also compounds 10 and 12 in Table I.) Further evidence of the difference in these two compounds was shown by the preparation of the two different amines (compounds 23 and 24 in Table I), which were characterized by the preparation of their benzamides. From this evidence, the addition of methylmagnesium bromide and 3,3,4,4,5,5,5-heptafluoropentylmagnesium bromide to 3,3,4,4,5,5,5-heptafluoro-1-nitro-1-pentene have also followed a 1:4 mechanism. Diethyl malonate has been found to undergo an apparent 1:4 addition reaction with the same nitroölefin in 50% yield to give diethyl (2,2,3,3,4,4,4-heptafluoro-1-nitromethylbutyl)-malonate.[6]

The addition of ethyl alcohol and $p$-aminobenzoic acid to 3,3,4,4,5,5,5-heptafluoro-1-nitro-1-pentene has given the two derivatives, 1,1,1,2,2,3,3-heptafluoro-4-ethoxy-5-nitropentane and 1,1,1,2,2,3,3-heptafluoro-4-$p$-carboxyanilino-5-nitropentane. Although McBee, Pierce and Smith[7] have found that water will add to ethyl 4,4,4-trifluorocrotonate to form the $\beta$-hydroxyester, the fluorinated nitroölefins will not add water under the basic conditions employed.

Although Kloetzel[8] was unable to add 1-nitropropane to methyl crotonate with triethylamine as the catalyst, Leonard and Felley[9] have been able to condense nitromethane with ethyl crotonate in low yield using diethylamine and higher yield using trimethylbenzylammonium butoxide. Ethyl 4,4,4-trifluoro-2-butenoate and ethyl 4,4,5,5,6,6,6-heptafluoro-2-hexenoate[10] were condensed with nitromethane in a manner analogous to the method used by Kloetzel[8] resulting in a 65% yield of ethyl 4,4,4-trifluoro-3-nitromethylbutyrate and ethyl 4,4,5,5,-6,6,6-heptafluoro-3-nitromethylhexanoate. Apparently the lack of reaction of methyl crotonate with nitroalkanes in the presence of triethylamine is not due to steric hindrance alone since the trifluoromethyl and heptafluoropropyl groups should offer a greater steric effect than the methyl group. However, a strong inductive effect would enhance a carbanion attack on the beta carbon. This observation agrees with other reports[11] which postulate that if the $\alpha$- or $\beta$-substituents on acrylic esters are negative groups such as cyano or carbethoxy, the Michael addition reaction is not inhibited to the extent which would be expected from the steric effect. Attempts to obtain the acid from ethyl 4,4,5,5,6,6,6-heptafluoro-3-nitromethylhexanoate by saponification in base gave only a tar while acid saponification gave no product. A transesterification of this ester with 98% formic acid gave the solid acid, 4,4,5,5,6,6,6-heptafluoro-3-nitromethylhexanoic acid.

Reduction studies of chlorinated nitroalcohols by Burkett[2] have shown that catalytic reduction of 1,1,1-trichloro-3-nitro-2-propanol with Raney nickel resulted in hydrogenolysis to give 1,1-dichloro-3-amino-2-propanol. Similar studies with 3,3,4,4,5,5,5-heptafluoro-1-nitro-2-pentanol, 4,4,5,5,6,6,6-heptafluoro-2-nitro-3-hexanol, 1,1,1,2,2,3,3-heptafluoro-5-nitro-4-heptanol and 1,1,1-trifluoro-3-nitro-2-propanol have shown that the fluorine-containing nitroalcohols can be reduced to the corresponding aminoalcohol and isolated as the hydrochloride in 97% yield with no evidence of hydrogenolysis. The free aminoalcohols were prepared by neutralization with sodium carbonate or ammonium hydroxide. These compounds are listed in Table I.

The reduction of 1,1,1,2,2,3,3-heptafluoro-4-nitromethylhexane to the amine was accomplished by catalytic reduction with platinum in ethanol. A similar attempt to reduce 1,1,1,2,2,3,3-heptafluoro-5-nitroheptane was unsuccessful. The de-

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[3] R. L. Heath and J. D. Rose, *J. Chem. Soc.*, 1485 (1947).

[4] G. D. Buckley and E. J. Ellery, *ibid.*, 1497 (1947).

[5] A. Lambert and H. A. Piggott, *ibid.*, 1489 (1947).

[6] A similar directive influence with 4,4,4-trifluorocrotonate derivatives has been shown by H. M. Walborsky and M. Schwarz, THIS JOURNAL, **75**, 3241 (1953).

[7] E. T. McBee, O. R. Pierce and D. D. Smith, private communication.

[8] M. C. Kloetzel, THIS JOURNAL, **70**, 3571 (1948).

[9] N. J. Leonard and D. L. Felley, *ibid.*, **71**, 1758 (1949).

[10] Supplied by D. D. Smith, see ref. 6.

[11] (a) C. K. Ingold, E. A. Parren and J. F. Thorpe, *J. Chem. Soc.*, **121**, 1771 (1922); (b) R. Connor and W. R. McClellan, *J. Org. Chem.*, **3**, 570 (1938); **3**, 470 (1939).

sired amine was prepared by reduction of 5,5,6,6,7,7,7-heptafluoro-3-nitro-3-heptene with lithium aluminum hydride at room temperature according to the method of Gilsdorf and Nord.[12] These amines were characterized by the formation of their hydrochlorides and benzoyl derivatives.

## Experimental[13]

**Starting Materials.**—The perfluoroacetic and perfluorobutyric acids were obtained from the Minnesota Mining and Manufacturing Company, St. Paul, Minnesota, and were converted to fluoral and heptafluorobutyral by a modification of the method described by Husted and Ahlbrecht.[14] The perfluoroaldehydes were hydrated by adding the calculated amount of water to the ice-cooled aldehyde contained in a flask equipped with a stirrer and a Dry Ice-cooled reflux condenser. The conversion of the anhydrous aldehyde to the hydrate was quantitative.

3,3,4,4,5,5,5-Heptafluoro-2-pentanone was prepared in a manner described by McBee, *et al.*,[15] for the condensation of fluorinated esters with ethyl acetate in the presence of sodium hydride, while ethyl 4,4,4-trifluoro-2-butenoate and ethyl 4,4,5,5,6,6,6-heptafluoro-2-hexenoate were obtained by the method of McBee, Pierce and Smith.[7] The preparation of 3,3,4,4,5,5,5-heptafluoro-1-bromopentane has been described by Pierce, McBee and Kline.[16] The nitroalkanes used were obtained from the Commercial Solvents Corporation.

**Fluorinated Nitroalcohols.**—The condensation of the hydrated fluorinated aldehydes and ketone with various nitroalkanes have all followed the same general procedure. The description of the preparation of the following two compounds will suffice to illustrate the method. The properties and yields of these compounds are listed in Table I.

**3,3,4,4,5,5,5-Heptafluoro-1-nitro-2-pentanol.**—One hundred and eleven grams (0.51 mole) of heptafluorobutanal hydrate was stirred with 34 g. of nitromethane (0.57 mole) in the presence of 1.06 g. of anhydrous potassium carbonate. After heating the mixture at 50–60° for three hours, the potassium carbonate was washed out with water, the water extracted with ether and the ether–oil fractions combined and dried. Upon distillation through a modified Claisen head, 101 g. of the product was obtained, b.p. 48–52° (1 mm.). This material was then rectified to obtain a pure product.

**3,3,4,4,5,5,5-Heptafluoro-2-methyl-1-nitro-2-pentanol.**—Twenty-one and two-tenths grams (0.1 mole) of 3,3,4,4,5,5,5-heptafluoro-2-pentanone was dissolved in 85 g. (1.1 moles) of nitromethane and refluxed through a Soxhlet extractor which contained 0.6 g. of anhydrous potassium carbonate. The refluxing was continued for 7 hours with some polymerization noted in the flask. The reaction mixture was then washed with two 100-ml. portions of water and the combined water washings extracted with ether twice. The ether extract and residual oil were combined and dried over Drierite. After removal of the ether, the excess nitromethane was removed by distillation through a 30-cm. column filled with Heli-Pack. The remaining substance was distilled in a modified Claisen flask resulting in 7.6 g., b.p. 33–41° (1 mm.). This substance was purified by rectification.

**Fluorinated Nitroölefins.**—The fluorine-containing nitroalcohols have been found susceptible to dehydration when heated with acetic anhydride, propionic anhydride, benzoic anhydride and phosphorus pentoxide. Dehydration with phosphorus pentoxide (method A) was found useful for the conversion of only 3,3,4,4,5,5,5-heptafluoro-1-nitro-2-pentanol to the olefin while the acetic anhydride (method B) was found to be a general method for all the nitroalcohols. In this method the acetoxy intermediate was not isolated but treated immediately with sodium carbonate to form the olefin.

A. **3,3,4,4,5,5,5-Heptafluoro-1-nitro-1-pentene.**—Forty-three grams of 3,3,4,4,5,5,5-heptafluoro-1-nitro-2-pentanol (0.166 mole) was mixed with 26 g. of phosphorus pentoxide in a flask equipped with a reflux condenser. The mixture was brought to gentle reflux for 1.5 to 2 hours during which time the olefin formed. After cooling the reaction mixture the excess phosphorus pentoxide was destroyed by slowly adding water. The olefin was extracted from the water with ether, dried over anhydrous magnesium sulfate and distilled through a heated 35-cm. Vigreux column after removal of the ether. The olefin distilled at 117–119° and weighed 26.6 g. (68%). Purification of the substance was accomplished by rectification.

B. **5,5,6,6,7,7,7-Heptafluoro-3-nitro-3-heptene.**—Fifty-six grams (0.195 mole) of 1,1,1,2,2,3,3-heptafluoro-5-nitro-4-heptanol was mixed with 9 drops of concentrated sulfuric acid, and 30.6 g. (0.3 mole) of acetic anhydride was added dropwise with stirring so the temperature of the mixture did not go above 90°. The mixture was then heated at 80–90° for six hours, cooled and hydrolyzed in 600 ml. of water for 30 minutes. The mixture of olefin and acetoxy derivative was extracted twice with 150-ml. portions of ether and dried over anhydrous magnesium sulfate. After removal of the ether the product was treated with 21 g. of anhydrous sodium carbonate and heated gently for 1 to 2 hours. During this time a solid mass formed and care was taken not to use excessive heat. Compound 1 dehydrates exothermally and needs cooling when started. The formation of the olefin was noted by the formation of a yellow color. Upon cooling, the olefin was extracted from the solid residue with anhydrous ether (500–600 ml.) and the ether removed from the olefin. The olefin was distilled through a 35-cm. heated Vigreux column to give 40.8 g. of product, b.p. 70–71° (51 mm.). A purified sample was obtained by rectification.

**Fluorinated Nitroalkanes *via* Lithium Aluminum Hydride Reduction of the Olefin.**—The description of one such reduction will be sufficient to illustrate the method. Compounds 10 and 11 were made in an analogous manner.

**1,1,1,2,2,3,3-Heptafluoro-5-nitropentane.**—Thirty-five grams (0.145 mole) of 3,3,4,4,5,5,5-heptafluoro-1-nitro-1-pentene was dissolved in 200 ml. of anhydrous ether and cooled to −50°. To this cooled solution, 1.75 g. of lithium aluminum hydride dissolved in 100 ml. of anhydrous ether was added dropwise. The time of addition was 1.5 hours and the temperature was maintained below −50°. The reaction mixture was then allowed to come to room temperature and hydrolyzed with 20 ml. of concentrated hydrochloric acid in 150 ml. of water. The green ether solution which resulted was washed twice with water and dried with anhydrous magnesium sulfate. After removal of the ether the residue was distilled through a 30-cm. Vigreux column. A fraction b.p. 91–99° (100–102 mm.) which weighed 17.9 g. was recovered and was purified by rectification.

**Fluorinated Nitroalkanes *via* the Addition of Grignard Reagents to an Olefin.**—One such reaction is described below. Compounds 12 and 14 were prepared in a similar manner. In the preparation of compound 14 a lower boiling fraction, b.p. 57–58° (12 mm.) and $n^{20}\mathrm{D}$ 1.3108, was isolated which proved to be the coupled product 1,1,1,2,2,-**3,3,8,8,9,9,10,10,10-tetradecafluorodecane.** *Anal.* Calcd. for $C_{10}H_8F_{14}$: C, 30.45; H, 2.03. Found: C, 30.23; H, 2.27.

**1,1,1,2,2,3,3-Heptafluoro-4-nitromethylhexane.**—The Grignard reagent was prepared from 40 g. of ethyl bromide and 10.5 g. of magnesium in 150 ml. of anhydrous ether. Fifty-nine grams (0.245 mole) of 3,3,4,4,5,5,5-heptafluoro-1-nitro-1-pentene was dissolved in 200 ml. of anhydrous ether and cooled in an ice-bath to 0–10°. The Grignard reagent was added dropwise over a 2-hour period to maintain a temperature below 10°. The mixture was then heated to reflux for 1 hour and allowed to come to room temperature. Upon cooling in ice and neutralizing with a solution of 19.6 ml. of acetic acid in 160 ml. of water the ether was separated from the water and the water layer extracted once with ether. The two ether fractions were combined and washed with sodium carbonate solution and once with water. After drying over magnesium sulfate and removal of the ether, 34.8 g. (53%) of an oil, b.p. 52–58° (9–10 mm.), was obtained by distillation through a modified Claisen head and was rectified for further purification.

**1,3-Dinitro-2-perfluoropropylpropane.**—A solution of sodium methoxide was prepared by dissolving 3.2 g. (0.14 mole) of sodium in 95 ml. of absolute methanol. The solu-

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(12) R. T. Gilsdorf and F. F. Nord, *ibid.*, **15**, 807 (1950).

(13) All melting points and boiling points are uncorrected. Rectifications were conducted in a Podbielniak Miniature Hyper Cal Assembly.

(14) D. R. Husted and A. H. Ahlbrecht, THIS JOURNAL, **74**, 5422 (1952).

(15) E. T. McBee, O. R. Pierce, H. Kilbourne and E. R. Wilson, *ibid.*, **75**, 3152 (1953).

(16) O. R. Pierce, E. T. McBee and R. Kline, *ibid.*, **75**, 5618 (1953).

tion was cooled to 10–15° and 10.2 g. (0.167 mole) of nitromethane added. Twenty-seven and one-half grams (0.113 mole) of 3,3,4,4,5,5,5-heptafluoro-1-nitro-1-pentene was added to the stirred solution dropwise at such a rate the temperature was maintained at 10–15°. A yellow solid formed which slowly turned brown. After the addition of the olefin, the mixture was brought to room temperature and allowed to stir for 2.5 hours. The reaction mass was then poured into 500 ml. of water and made just acidic with 2 *N* hydrochloric acid. A dark brown solid formed which was collected by filtration. The weight of this crude material was 23.3 g. (68%). When this product was recrystallized from 150 ml. of pet. ether–benzene (2:1) 11.4 g. of a product with a m.p. of 59–60° was obtained. A recrystallization of 1 g. of this substance in a solution of 10 ml. of petroleum ether (90–100°) and 3 ml. of benzene gave cream colored, mica crystals which melted at 62–62.5°.

**Diethyl (2,2,3,3,4,4,4-Heptafluoro-1-nitromethylbutyl)-malonate.**—Sodium ethoxide was prepared by dissolving 2.9 g. (0.126 mole) of sodium in 100 ml. of absolute ethanol. This solution was cooled to 10–15° and 23.5 g. (0.15 mole) of diethyl malonate added. Over a period of 1.5 hours 25 g. (0.102 mole) of 3,3,4,4,5,5,5-heptafluoro-1-nitro-1-pentene was added to the cooled mixture at such a rate the temperature did not go above 15°. At the end of this time the solution was allowed to come to room temperature and stirred for another 1.5 hours. The alcoholic solution was then poured into 600 ml. of water resulting in a yellow suspension which on acidification with concentrated hydrochloric acid gave a clear oil. The oil was extracted with ether, dried over anhydrous magnesium sulfate and distilled through a modified Claisen head after removal of the ether. A forerun up to 100° (3 mm.) weighed 12.5 g. while 20.0 g. (49%) of the product was recovered which distilled at 112–115° (3 mm.).

A rectification of the forerun gave another 2 g. of product for a total yield of 54%. When the product was redistilled through a 30-cm. heated Vigreux column the compound distilled at 144–145° (8–9 mm.).

**1,1,1,2,2,3,3-Heptafluoro-4-ethoxy-5-nitropentane.**—Ten grams (0.04 mole) of 3,3,4,4,5,5,5-heptafluoro-1-nitro-1-pentene was dissolved in 50 ml. of absolute ethanol and refluxed for 48 hours. The liquid was rectified through a Todd Monel metal spiral column to separate the low boiling fraction. The remaining oil was transferred to a small flask equipped with a modified Claisen head and distilled under reduced pressure. Four grams of a product was obtained, b.p. 90° (58 mm.). This sample was purified by rectification.

**1,1,1,2,2,3,3-Heptafluoro-4-*p*-carboxyanilino-5-nitropentane.**—In a manner described by Brower and Burkett[17] 5.0 g. (0.021 mole) of 3,3,4,4,5,5,5-heptafluoro-1-nitro-1-pentene was treated with 3 g. (0.022 mole) of *p*-aminobenzoic acid in a solution of 25 ml. of absolute ethanol. The solution was refluxed for 45 minutes and allowed to stand overnight. With the addition of 10 ml. of water and cooling in ice, 2.1 g. of a white crystalline product formed. A second crop weighed 2.7 g. A sample of this product when recrystallized had a m.p. 125.5–126.5°.

Compound 19 was prepared in a manner analogous to the above preparation.

**Fluorinated Nitroesters.**—The addition of nitromethane in an apparent 1:4 manner to ethyl 4,4,4-trifluorobutenoate is described below. Compound 21 was made in a similar manner except that it was allowed to stand at 23–24° for 100 hours.

**Ethyl 4,4,4-Trifluoro-3-nitromethylbutyrate.**—Thirty-three and six-tenths (0.2 mole) grams of ethyl 4,4,4-trifluorobutenoate was mixed with 36.4 g. (0.6 mole) of nitromethane and 10 g. of triethylamine. This mixture was allowed to stand at 23–24° for 47 hours and the low-boiling components then distilled from the mixture at a pressure of 15 mm. The product was recovered by distillation through a modified Claisen head as an oil b.p. 78–88° (3–4 mm.) and weighed 30 g. (68%). A more viscous oil remained in the distillation pot which is believed to result from the addition of two ester molecules to nitromethane. This substance was not obtained in a state pure enough for analysis. The product was purified by rectification.

**4,4,5,5,6,6,6-Heptafluoro-3-nitromethylhexanoic Acid.**—Sixteen and one-half grams of ethyl 4,4,5,5,6,6,6-heptafluoro-3-nitromethylhexanoate (0.05 mole) was mixed with 8 g. (0.15 mole) of 98% formic acid and refluxed through a 30-cm. Vigreux column for 6 hours. During this time some low-boiling ethyl formate was removed. The residue was then transferred to a Claisen head flask and the ethyl formate and excess formic acid removed under pressure of 15–20 mm. with gentle heat. The oily residue was crystallized from 30 ml. of petroleum ether (b.p. 90–100°) and 20 ml. of benzene. An oil formed which became crystalline on cooling in ice. The total yield after obtaining a second crop of crystals was 7.2 g. A recrystallization of 1 g. of this product from a mixture of 20 ml. of petroleum ether and 5 ml. of benzene gave white, greasy plates, m.p. 46.5–48°.

**1-Amino-2-ethyl-3,3,4,4,5,5,5-heptafluoropentane.**—Ten grams of 1,1,1,2,2,3,3-heptafluoro-4-nitromethylhexane was dissolved in 75 ml. of absolute ethanol and reduced under a pressure of 55 lb. of hydrogen in the presence of 0.1 g. of platinum. After the calculated pressure drop was obtained, the alcohol was removed through a 30-cm. Vigreux column and the resulting amine distilled through a heated Vigreux column. The b.p. was 68° (81 mm.). Some decomposition was noted.

**The hydrochloride** of this compound was formed by passing dry HCl into an ether solution of the amine and after recrystallization from ethyl acetate–ethanol melted at 232.5–235° in a sealed tube.

*Anal.* Calcd. for $C_7H_{11}NClF_7$: C, 30.32; H, 3.97; N, 5.05. Found: C, 30.00; H, 4.24; N, 4.90.

**The benzamide** was formed by reaction of the hydrochloride with benzoyl chloride in sodium hydroxide solution. Recrystallization gave crystals melting at 43–45°.

*Anal.* Calcd. for $C_{14}H_{14}ONF_7$: C, 48.69; H, 4.05; N, 4.05. Found: C, 48.72; H, 4.00; N, 4.07.

**1-Amino-1-ethyl-3,3,4,4,5,5,5-heptafluoropentane.**—Twelve and one-half grams of 5,5,6,6,7,7,7-heptafluoro-3-nitro-3-heptene (0.046 mole) was dissolved in 180 ml. of absolute ethyl ether and added dropwise to a stirred suspension of 3.8 g. of lithium aluminum hydride (0.1 mole) in 150 ml. of absolute ether at such a rate that gentle reflux was maintained. At the end of this time the excess lithium aluminum hydride was hydrolyzed with about 20 ml. of 95% ethanol, and 250 ml. of a 20% sodium potassium tartrate solution was added to the mixture. The ether layer was separated from the mixture and the water layer was extracted twice with 150-ml. portions of ether. The ether layers were combined and dried over anhydrous magnesium sulfate. The ether was removed through a 30-cm. Vigreux column and the residue distilled through a heated Vigreux column at 63–72° (84–85 mm.) with $n^{20}_D$ 1.3390. The yield was 5.5 g. (50%). The product was purified by rectification.

**The hydrochloride** of this compound was prepared and found to melt at 236–238°.

*Anal.* Calcd. for $C_7H_{11}NClF_7$: C, 30.32; H, 3.97; N, 5.05. Found: C, 30.02; H, 4.18; N, 5.05.

**The benzamide** of this compound was found to melt at 90–91°.

*Anal.* Calcd. for $C_{14}H_{14}ONF_7$: C, 48.69; H, 4.05; N, 4.05. Found: C, 48.71; H, 3.98; N, 3.90.

**Fluorinated Aminoalcohols.**—The reduction of the fluorinated nitroalcohols all follow the same procedure and the illustration of one such reduction will suffice for all. The properties of the fluorinated aminoalcohols and their hydrochlorides are given in Table I.

**3,3,4,4,5,5,5-Heptafluoro-1-amino-2-pentanol Hydrochloride.**—Fifteen grams (0.058 mole) of heptafluoro-1-nitro-2-pentanol was dissolved in 50 ml. of absolute ethanol and reduced under 34–47 lb. of hydrogen in the presence of 3–4 g. of Raney nickel. After 3.5 hours the pressure drop was equal to a molar ratio of 1:3. Fifteen milliliters of concentrated hydrochloric acid was added to the alcoholic solution and the solvents removed under reduced pressure of the aspirator. White, greasy flat crystals were collected and dried. The total weight of the aminoalcohol hydrochloride was 13.6 g. Recrystallization from ethyl acetate–ethanol solution gave a product which melted on a Fisher–Johns block at 133.5–135.5°.

**3,3,4,4,5,5,5-Heptafluoro-1-amino-2-pentanol.**—Ten grams of 3,3,4,4,5,5,5-heptafluoro-1-amino-2-pentanol hydrochloride was dissolved in 50 ml. of water and treated

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(17) F. Brower and H. Burkett, This Journal, **75**, 1082 (1952).

with a solution of 5 g. of sodium carbonate in 50 ml. of water. After several minutes a solid gelatinous precipitate formed which was recovered by filtration and dried. The weight of the precipitate was 5.5 g. and an additional 1.4 g. was obtained on cooling the water solution in ice (84%). A sample of this substance was recrystallized from water-alcohol to give a white crystalline solid m.p. 68–69°.

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LAFAYETTE, IND.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

# Amides of Ethylenediamines. II. Substituted Cinnamides as Local Anesthetic Agents[1]

BY FRANK J. VILLANI, JOSEPH LANG AND DOMENICK PAPA

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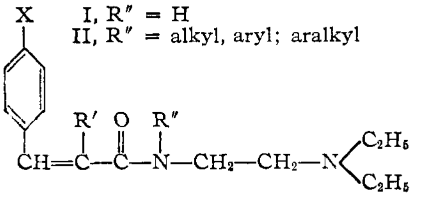
Several cinnamamides of substituted ethylenediamines were prepared and evaluated for their local anesthetic action. N'-Benzyl-N'-cinnamoyl-N,N-diethylethylenediamine was the most active compound in this series.

The local anesthetic activity of dialkylaminoalkyl cinnamamides of formula I has been reported some time ago in the patent literature.[2] As part of a program on the synthesis of amides of substituted ethylenediamines,[3] it was of interest to prepare and evaluate pharmacologically a series of cinnamamides, wherein the amide nitrogen is further substituted by alkyl, aryl, or aralkyl groups, as shown in formula II. This paper describes the synthesis and local anesthetic activity of a number of these compounds, as well as cinnamamides having substituents in the *para* position of the phenyl ring. Included in this study are compounds with substituents, such as methyl and phenyl, on the alpha carbon of the cinnamic acid.

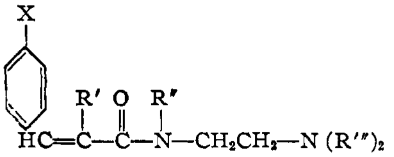


I, R'' = H
II, R'' = alkyl, aryl; aralkyl

The amides (Table I) were prepared by the reaction of the cinnamoyl chloride and the appropriately substituted ethylenediamine in benzene with pyridine as the acid acceptor. N'-*p*-Aminocinnamoyl-N'-benzyl-N,N-diethylethylenediamine was prepared from the corresponding *p*-nitro derivative by reduction with ammoniacal ferrous sulfate.

TABLE I

COMPOUNDS OF THE FORMULA



| No. | X | R' | R'' | R''' | B.p. °C. | Mm. | Yield, % | $n_D$ | $t$ | Formula | Nitrogen, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | H | H | $C_2H_5$ | 184–187 | 1 | 70 | 1.5665 | 21 | $C_{15}H_{22}ON_2$ | 11.38 | 11.59 |
| 2 | H | H | *n*-$C_3H_7$ | $C_2H_5$ | 191–196 | 3 | 58 | 1.5463 | 27 | $C_{18}N_{28}ON_2$ | 9.72 | 9.42 |
| 3 | H | H | $C_6H_5$ | $C_2H_5$ | 200–207 | 1 | 70 | 1.5868 | 27 | $C_{21}H_{26}ON_2$ | 8.69 | 8.60 |
| 4 | H | H | $C_6H_5CH_2$ | $CH_3$ | 220–225 | 0.5 | 73 | 1.595 | | $C_{20}H_{24}ON_2$ | 9.08 | 9.11 |
| 5 | H | H | $C_6H_5CH_2$ | $C_2H_5$ | 225–232 | 0.5 | 62 | 1.583 | | $C_{22}H_{28}ON_2$ | 8.32 | 8.51 |
| 6 | Cl | H | $C_6H_5CH_2$ | $C_2H_5$ | 236–241 | 1 | 64 | 1.5891 | 28 | $C_{22}H_{27}ON_2Cl$ | 7.56 | 7.68 |
| 7 | $NO_2$ | H | $C_6H_5CH_2$ | $C_2H_5$ | *a* | | *b* | | | $C_{22}H_{27}O_3N_3$ | 11.62 | 11.99 |
| 8 | $NH_2$ | H | $C_6H_5CH_2$ | $C_2H_5$ | *c* | | *b* | 1.5863 | 26 | $C_{22}H_{29}ON_3$ | 11.96 | 11.68 |
| 9 | $(CH_3)_2CH$– | H | $C_6H_5CH_2$ | $C_2H_5$ | 228–231 | 1 | 55 | 1.5717 | 23 | $C_{25}H_{34}ON_2$ | 7.61 | 7.94 |
| 10 | H | $CH_3$ | $C_6H_5CH_2$ | $C_2H_5$ | 198–201 | 0.5 | 67 | 1.5625 | 24 | $C_{23}H_{30}ON_2$ | 7.99 | 8.49 |
| 11 | H | $C_6H_5$ | $C_6H_5CH_2$ | $C_2H_5$ | 247–252 | 1 | 63 | 1.5917 | 29 | $C_{28}H_{32}ON_2$ | 6.79 | 7.07 |
| 12 | Cl | $C_6H_5$ | $C_6H_5CH_2$ | $C_2H_5$ | 258–261 | 1 | 39 | 1.5993 | 23 | $C_{28}H_{31}ON_2Cl$ | 6.28 | 6.74 |
| 13 | H | H | *p*-$OCH_3$–$C_6H_4CH_2$ | $CH_3$ | 265–270 | 1 | 34 | 1.5928 | 27 | $C_{21}H_{26}O_2N_2$ | 8.28 | 8.32 |

[a] M.p. 72–73°. [b] See Experimental section. [c] 230–239° (3 mm). (dec.).

To ascertain whether or not unsaturation in these compounds was essential for local anesthetic activity, one hydrocinnamoyl amide was synthesized for comparative purposes. A furan substituted compound also was prepared in order to determine structure–activity relationships.

The amides listed in Table I were obtained as light yellow, high boiling, viscous oils, readily soluble in dilute hydrochloric acid.

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[1] Presented in abstract before the Division of Medicinal Chemistry of the American Chemical Society, Atlantic City, New Jersey, September, 1952.

[2] W. A. Lott, U. S. Patents 2,103,265 (1937); 2,139,687 (1938); 2,251,287 (1941); 2,251,946 (1941); 2,310,973 (1943).

[3] For paper I in this series, see F. J. Villani, N. Sperber, J. Lang and D. Papa, THIS JOURNAL, **72**, 2724 (1950).