Reaction of 4-Phenylazo-2-phenyloxazolin-5-one with Methanolic Ammonia.—Seven grams (0.026 mole) of 4-phenylazo-2-phenyloxazolin-5-one was dissolved in 200 cc. of methanol and 200 cc. of 25% ammonium hydroxide. The solution was heated under reflux for 5 minutes and then evaporated to crystallization. Recrystallization from methanol gave 5.5 g., 79.7% yield, of platelets melting at 198–199°.

Anal. Calcd. for $C_{15}H_{12}N_4O$: C, 68.2; H, 4.6; N, 21.2. Found: C, 68.2; H, 4.5; N, 21.2.

Decarboxylation of 1,5-Diphenyl-3-carboxy-1*H*-1,2,4-triazole.—Five grams (0.019 mole) of 1,5-diphenyl-1*H*-1,2,4-triazole from the preceding experiment was heated to 185° in an oil-bath until the decarboxylation started. The temperature was then lowered and held at 170° until evolution of gas had ceased. The resinous residue was extracted twice with 100-cc. portions of cyclohexane. Evaporation of the solvent left 2.1 g. of crude material melting at 76–80°. Recrystallized from water, 1.6 g., 38%, of colorless needles, m.p. 90–91°, was obtained.

Anal. Calcd. for $C_{14}H_{11}N_3$: C, 76.0; H, 5.0; N, 19.0. Found: C, 75.8; H, 4.9; N, 18.6.

The picrate melted at 139–140°; Thompson reports 140–141°.[8]

Esterification of 1,5-Diphenyl-3-carboxy-1*H*-1,2,4-triazole.—Two grams (0.0075 mole) of 1,5-diphenyl-3-carboxy-1*H*-1,2,4-triazole was refluxed 1 hr. with 20 cc. of methanol containing a drop of sulfuric acid. The reaction mixture was poured into water and the crude ester collected. Recrystallization from methanol gave 1.4 g., 68%, of colorless platelets, m.p. 158–159°.

Ammonolysis of the Ester.—One gram (0.0036 mole) of the ester was refluxed 1 hr. with 20 cc. of methanol and 20 cc. of 25% ammonium hydroxide. The reaction mixture was evaporated nearly to dryness. The precipitate was collected and was recrystallized from methanol; yield 0.59 g., 62%, of colorless platelets, m.p. 198–199°. This product gave no depression in melting point when mixed with the product of direct ammonolytic rearrangement of 4-phenylazo-2-phenyloxazolin-5-one.

1,5-Diphenyl-3-carbamido-1*H*-1,2,4-triazole has been previously prepared by Bladin[7] by oxidation of the corresponding cyanotriazole.

(8) Q. E. Thompson, THIS JOURNAL, **73**, 5914 (1951).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WESTERN ONTARIO]

Toxic Fluorine Compounds. XIV.[1] Some ω-Fluoroalkyl Nitrogen Compounds

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Some ω-fluoroalkyl isocyanates, isothiocyanates, urea derivatives and barbiturates have been prepared and their toxicities determined. None of the compounds were outstandingly toxic. The activity of the fluorobarbiturates as depressants of the central nervous system was less than that of their non-fluorinated analogs.

In continuation of the study of toxic fluorine compounds, certain nitrogen compounds were prepared and examined (Table I). These included: three isocyanates, two isothiocyanates and four urea derivatives, all of which were prepared for comparison with the corresponding ω-fluoroalkylamines[2]; and two ω-fluoroalkylbarbituric acids,[3] for testing as depressants of the central nervous system.

Preparation.—The ω-fluoroalkyl isocyanates were prepared by means of the Curtius rearrangement.[5,6] ω-Fluorocarboxylic acid chlorides,[7] available in high yield from the corresponding acids,[8] were treated with activated sodium azide[9] to form the acid azides, which in turn were rearranged to the isocyanates. 2-Fluoroethyl, 3-fluoropropyl and 4-fluorobutyl isocyanates were thus obtained in yields of 44, 49 and 85%, respectively. Fluoromethyl isocyanate could not be prepared by this procedure; the product of the reaction boiled over a wide temperature range and, on standing, deposited a high melting solid, which was insoluble in common organic solvents. An attempt was then made to form the fluoromethyl derivative using fluoroacetic anhydride instead of fluoroacetyl chloride, but the results were equally indefinite. These observations suggest that fluoromethyl isocyanate is inherently unstable.

Since prolonged contact with air resulted in polymerization and urea formation, the isocyanates were distilled in an atmosphere of nitrogen and handled in a closed system. For this purpose, an assembly was devised which served both as a receiver on the Todd still and as a manifold for transferring the materials to sealed ampoules.

The N-ω-fluoroalkyl-N′-phenylureas, prepared as a means of characterizing the ω-fluoroalkyl isocyanates, were obtained from the latter by treatment with aniline. N,N′-Bis-4-fluorobutylurea was prepared from 4-fluorobutyl isocyanate by treatment with water.

The ω-fluoroalkyl isothiocyanates were prepared[10,11] from the corresponding amines by conversion to the sodium dithiocarbamates, followed by treatment with ethyl chloroformate. It was necessary to carry out these reactions at −15° to avoid the formation of impurities which co-distilled with the main product. 5-Fluoroamyl and 6-fluorohexyl isothiocyanates were thus obtained in yields of 56 and 48%, respectively.

The two ω-fluoroalkylbarbituric acids were prepared[3] in low yield from diethyl ethylmalonate by

(1) Issued as DRB Report No. SW-32. Part XIII, *Can. J. Chem.*, **35**, 141 (1957).

(2) F. L. M. Pattison, W. C. Howell and R. W. White, THIS JOURNAL, **78**, 3487 (1956).

(3) F. L. M. Pattison, *Nature*, **174**, 737 (1954).

(4) W. F. Bruce and R. deV. Huber, THIS JOURNAL, **75**, 4668 (1953); U. S. Patent 2,721,201 (Oct. 1955).

(5) J. W. Boehmer, *Rec. trav. chim.*, **55**, 379 (1936).

(6) P. A. S. Smith, *Organic Reactions*, **3**, 337 (1946).

(7) F. L. M. Pattison, R. R. Fraser, G. J. O'Neill and J. F. K. Wilshire, *J. Org. Chem.*, **21**, 887 (1956).

(8) F. L. M. Pattison, S. B. D. Hunt and J. B. Stothers, *ibid.*, **21**, 883 (1956).

(9) J. Nelles, *Ber.*, **65B**, 1345 (1932).

(10) K. H. Slotta and H. Dressler, *ibid.*, **63B**, 888 (1930).

(11) M. L. Moore and F. S. Crossley, *Org. Syntheses*, **21**, 81 (1941).

TABLE I

PHYSICAL CONSTANTS, TOXICITY AND ANALYTICAL DATA

Compound	Formula	B.p. °C.	Mm.	$n^{25}D$ or m.p., °C.	L.D. 50 for mice (intraperitoneal), mg./kg.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
2-Fluoroethyl isocyanate	$F(CH_2)_2NCO$	100–101		....[a]	16.5	40.45	40.68	4.49	4.70	15.73	15.82
3-Fluoropropyl isocyanate	$F(CH_2)_3NCO$	126		....[a]	10–20	46.60	46.89	5.83	5.81	13.59	13.84
4-Fluorobutyl isocyanate[b]	$F(CH_2)_4NCO$	72–72.5	42	....[a]	4.7	51.28	50.86	6.84	6.86	11.97	11.51
5-Fluoroamyl isothiocyanate	$F(CH_2)_5NCS$	104.5–105	9	1.4917	67	48.98	49.11	6.80	6.98	9.52	9.40
6-Fluorohexyl isothiocyanate	$F(CH_2)_6NCS$	116–116.5	8	1.4882	11.2	52.18	52.26	7.45	7.53	8.69	8.83
N-2-Fluoroethyl-N′-phenylurea	$F(CH_2)_2NHCONHC_6H_5$			144–145	>100					15.38	15.54
N-3-Fluoropropyl-N′-phenylurea	$F(CH_2)_3NHCONHC_6H_5$			105–105.5	...					14.29	14.00
N-4-Fluorobutyl-N′-phenylurea	$F(CH_2)_4NHCONHC_6H_5$			117.5–118	16.8					13.33	13.56
N,N′-Bis-4-fluorobutylurea	$F(CH_2)_4NHCONH(CH_2)_4F$			67–67.5	4.4					13.46	13.20
Diethyl ethyl-4-fluorobutylmalonate	$F(CH_2)_4CEt(COOEt)_2$	140–142	10	1.4277	>500	59.54	59.54	8.78	8.64		
Diethyl ethyl-5-fluoroamylmalonate[c]	$F(CH_2)_5CEt(COOEt)_2$	152–153	12	1.4286	>100	60.87	60.67	9.06	9.16	6.87[d]	6.75[d]
5-Ethyl-5-(4′-fluorobutyl)-barbituric acid	$F(CH_2)_4CEt(CONH)_2CO$			141.5–142	>100	52.18	52.35	6.52	6.45	12.17	12.37
5-Ethyl-5-(5′-fluoroamyl)-barbituric acid[e]	$F(CH_2)_5CEt(CONH)_2CO$			118–118.5	...					11.47	11.28

[a] The refractive index was not determined because of the pronounced lachrymatory action of the isocyanates. [b] 4-Fluorobutyl isocyanate has been used as an intermediate in the preparation of N-4-fluorobutylacetamide.[2] [c] Bruce and Huber[4] report b.p. 135–138° (4 mm.) and $n^{25}D$ 1.4294. [d] Fluorine, %. [e] Bruce and Huber[4] report, m.p. 120–122°.

reaction with the appropriate ω-fluoroalkyl halides[12] and then by treatment of the resultant esters with urea in the usual way. Shortly after the completion of this work in 1953, Bruce and Huber described[4] the preparation and properties of various barbiturates containing the 3-fluoropropyl or 5-fluoroamyl group.

Properties.—The ω-fluoroalkyl isocyanates are powerful lachrymators; this, together with their instability in moist air, precluded the determination of their refractive indices. When stored under dry nitrogen in a sealed ampoule, they exist as stable, colorless liquids. That these isocyanates undergo the characteristic reactions of the non-fluorinated members is indicated by the formation of the substituted urea derivatives mentioned above and by the conversion[2] of 4-fluorobutyl isocyanate to N-4-fluorobutylacetamide on treatment with methylmagnesium chloride.

The two ω-fluoroalkyl isothiocyanates failed to react with aniline, α- and β-naphthol and anhydrous ammonia. Because of this lack of reactivity in the NCS group of both 5-fluoroamyl and 6-fluorohexyl isothiocyanate, it was necessary to resort to infrared spectroscopy as a means of characterization. Both the isothiocyanates show strong bands at 2920 and 1453 (CH_2), 2100 (NCS), 1350 (C=S) and 980–1060 (C–F), with weak bands at 1715 and 1772 cm.$^{-1}$ attributable to carbonyl-containing impurities which could not be completely removed by repeated fractionations.

It is interesting to note the similarity in toxicity of 4-fluorobutyl isocyanate and N,N′-bis-4-fluorobutylurea and that the former is readily converted to the latter simply by treatment with water. These two observations provide evidence that isocyanates are initially converted *in vivo* to the corresponding symmetrical ureas before undergoing further change.

The activity of the two fluorinated barbiturates as depressants of the central nervous system was considerably less than that of non-fluorinated analogs such as neonal and amytal, and their toxicity was relatively low. These conclusions conform to the observations of Bruce and Huber[4] regarding various 5-(3′-fluoropropyl)- and 5-(5′-fluoroamyl)-barbituric acids. The intermediate fluoro-esters obtained in our syntheses were non-toxic; this is consistent with the observation[13] that alkylated malonic acids are not extensively utilized *in vivo*, being excreted in the urine in large quantities.

Experimental[14]

4-Fluorobutyl Isocyanate.—Activated sodium azide was prepared by the method of Nelles.[9] Commercial sodium azide (10 g.) was triturated with hydrazine hydrate (0.5 ml.), and the moist powder was allowed to stand overnight in the air. It was then dissolved in a minimum quantity of hot water and precipitated by the addition of acetone (*ca.* 2

(12) F. L. M. Pattison and W. C. Howell, *J. Org. Chem.*, **21**, 748 (1956).

(13) See, for example, G. D. Greville and H. B. Stewart, *Ann. Repts. on Progr. Chem.* (*Chem. Soc. London*), **50**, 301 (1953).

(14) (a) The majority of the microanalyses were performed by Mr. J. F. Alicino, Metuchen, N. J., and the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y. Results are listed in Table I. (b) Physical constants and toxicity data are listed in Table I. (c) Melting points and boiling points are uncorrected.

l.). The fine powder so formed was filtered, washed with ether and stored in a desiccator.

5-Fluorovaleryl chloride[7] (12.7 g., 0.092 mole), freshly activated sodium azide (7.2 g., 0.11 mole) and anhydrous benzene (50 ml.) were heated sufficiently to cause gentle evolution of nitrogen. Heating was discontinued when the evolution of nitrogen ceased (*ca.* 4 hr.). The mixture was filtered, and the cake was washed with anhydrous benzene. The washings and filtrate were fractionated through a Todd still in an atmosphere of pure nitrogen, using purified nitrobenzene (30 ml.) as a chaser. The isocyanate was redistilled and sealed into an ampoule using vacuum line techniques which maintained the sample out of contact with the air at all stages of the purification process. 4-Fluorobutyl isocyanate (9.1 g., 85%) was thus obtained as a colorless, mobile, lachrymatory liquid.

2-Fluoroethyl isocyanate (4.6 g., 44%) was prepared similarly from 3-fluoropropionyl chloride[7,15] (13 g., 0.12 mole) and freshly activated sodium azide (4.2 g., 0.14 mole). Nitrobenzene (50 ml.) was used as solvent. The reaction was initiated by gentle heating, after which it proceeded spontaneously and vigorously, being kept under control by means of a cold water-bath. Gentle heat was again applied toward the end of the reaction until the evolution of nitrogen ceased.

3-Fluoropropyl isocyanate (3.0 g., 49%) was prepared similarly from 4-fluorobutyryl chloride[7] (7.5 g., 0.060 mole) and freshly activated sodium azide (3.92 g., 0.060 mole) in anhydrous benzene (50 ml.). The reaction was vigorous, and the procedure described in the preparation of 2-fluoroethyl isocyanate was followed. Purified nitrobenzene was used as a chaser in the fractionation.

If the isocyanates were required for immediate use, they were purified in an atmosphere of nitrogen by conventional means, without recourse to vacuum line techniques.

5-Fluoroamyl Isothiocyanate.—A mixture of carbon disulfide (9.4 g., 0.124 mole), sodium hydroxide (4.96 g., 0.124 mole) and water (50 ml.) was cooled to −15° in an ice–HCl-bath, and a solution of 5-fluoroamylamine[2] (13 g., 0.124 mole) in water (30 ml.) was added over 30 minutes. The mixture, which turned red as the addition neared completion, was warmed to room temperature to complete the reaction and again cooled to −15°, and ethyl chloroformate (13.5 g., 0.124 mole) was added with stirring over 30 minutes. The mixture was then warmed to room temperature and stirred for a further 30 minutes. Ether was added to remove the isothiocyanate layer, and the aqueous layer was extracted with several portions of ether. The extracts were dried over anhydrous sodium sulfate. Fractionation of the dried product through a modified Podbielniak column yielded four fractions, at half-degree intervals, over 2°; the refractive indices of these differed considerably. By repeated fractionation of the cut with the highest refractive index until this value was constant, 5-fluoroamyl isothiocyanate (10.1 g., 56%) was obtained.

6-Fluorohexyl isothiocyanate (6.5 g., 48%) was prepared similarly, using carbon disulfide (6.4 g., 0.084 mole), sodium hydroxide (3.4 g., 0.084 mole) in water (23 ml.), 6-fluorohexylamine[2] (10.0 g., 0.084 mole) in water (18 ml.) and ethyl chloroformate (9.1 g., 0.084 mole). The infrared spectra of both isothiocyanates are described in the Discussion.

N-2-Fluoroethyl-N'-phenylurea.—A solution of freshly distilled aniline in petroleum ether was added to a solution of 2-fluoroethyl isocyanate in benzene. Reaction took place immediately, with the formation of a white, crystalline solid. After standing overnight, the solid was filtered, washed with ether, recrystallized from aqueous ethanol and dried in a desiccator.

N-3-Fluoropropyl-N'-phenylurea and N-4-fluorobutyl-N'-phenylurea were prepared similarly.

N,N'-Bis-4-fluorobutylurea.—4-Fluorobutyl isocyanate and water were mixed and allowed to stand at room temperature for several hours. White, crystalline needles were formed, which, after separation, were recrystallized from benzene–petroleum ether.

Diethyl Ethyl-4-fluorobutylmalonate.—Diethyl ethylmalonate (29.4 g., 0.156 mole) and 4-fluorobutyl iodide[12] (31.3 g., 0.155 mole) were added dropwise and with stirring to sodium (5.4 g., 0.235 g. atom) in absolute ethanol (90 ml.). The mixture was then heated under reflux for 3 hr. Most of the alcohol was removed by distillation. The mixture was cooled and diluted with water. The ester layer was separated, and the aqueous layer was extracted with ether. The combined ester and extracts were washed with 5% sodium thiosulfate and dried over calcium chloride. Fractionation from silver crystals (prepared by immersing copper wire in aqueous silver nitrate) gave the fluoroester (32.0 g., 79%).

Diethyl ethyl-5-fluoroamylmalonate (21.0 g., 48%) was obtained in essentially the same manner from diethyl ethylmalonate (30.0 g., 0.159 mole), 5-fluoroamyl bromide[12] (26.9 g., 0.158 mole) and sodium methylate (8.5 g., 0.158 mole) in absolute ethanol (80 ml.).

5-Ethyl-5-(4'-fluorobutyl)-barbituric Acid (fluoroneonal).—This preparation was adapted from the procedure described by Layraud.[16] Sodium (1 g.) was dissolved in absolute ethanol (50 ml.). Urea (2.2 g.) was added and the mixture was heated until the urea had dissolved. Diethyl ethyl-4-fluorobutylmalonate (6 g.) was added, and the mixture was heated with gentle agitation in a small stainless steel autoclave for 5 hr. at 110°. The excess alcohol was removed by distillation, cold water was added and the fluoroneonal was precipitated by the addition of 6 *N* hydrochloric acid. The crude material (3.45 g.) was dissolved in a minimum quantity of aqueous sodium hydroxide. The solution was extracted with ether and then reacidified. The resultant colorless solid was recrystallized from very dilute aqueous ethanol, giving pure fluoroneonal (1.9 g., 36%).

5-Ethyl-5-(5'-fluoroamyl)-barbituric acid has been prepared by Bruce and Huber[4]; our procedure was essentially the same as that described by these authors.

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(15) F. L. M. Pattison, W. J. Cott, W. C. Howell and R. W. White, THIS JOURNAL, **78**, 3484 (1956).

(16) E. Layraud, U. S. Patent 1,609,520 (Dec. 7, 1926).