reactant. The solid was added by distillation over the reaction mixture. Stirring and a condenser cooled by ice-water were used in all reactions. Three methods of reaction were used, as shown in the following examples. All appear to be about equivalent.

Method A. N-Methyl-N-cyanomethylcyanamide.—To a solution of sarcosine nitrile (28.6 g., 0.4 mole) in 100 ml. of benzene was added cyanogen chloride (13 g., 0.2 mole on a purity basis) as a gas over a period of 20 minutes at 5–10°. After stirring for one hour at room temperature, the reaction mixture was filtered to yield 23 g. of sarcosine nitrile hydrochloride. The benzene solution was distilled through a 25-cm. Vigreux column to yield 15.1 g. (80%) of product boiling at 147–148° at 13 mm.

Method B. N-Methyl-N-α-cyanopropylcyanamide.—To a mixture of α-N-methylaminobutyronitrile (74.4 g., 0.75 mole) and anhydrous potassium carbonate (51.8 g., 0.375 mole) suspended in 150 ml. of benzene and 37.5 ml. of water was added cyanogen chloride (49.5 g., 0.75 mole on a purity basis) as a gas over a period of one-half hour at 10–25°. After stirring for one-half hour, the mixture was filtered and the benzene layer separated and distilled. There was obtained 88.6 g. (96%) of the product as a colorless liquid distilling at 100° at 1.6 mm.

Method C. N-*n*-Butyl-N-cyanomethylcyanamide.—To a solution of cyanogen chloride (32.2 g., 0.5 mole on a purity basis) in 50 ml. of benzene was added a solution of N-*n*-butylaminoacetonitrile (56.1 g., 0.5 mole) in 100 ml. of benzene over a period of 25 minutes at 20–30°. The hydrochloride of the aminonitrile precipitated during reaction. To this mixture was added a solution of anhydrous potassium carbonate (34.5 g., 0.25 mole) in 35 ml. of water over a 15-minute period at 20–25°. After stirring for one-half hour, the mixture was filtered and the benzene layer distilled to yield 64.7 g. (94%) of the product as a colorless oil boiling at 118° at 0.6 mm.

The preparation of bis-4,6-diamino-1,3,5-triazines is illustrated by the following preparations:

α-(N-Methylmelamino)-isobutyroguanamine (III, R = R_1 = R_2 = CH_3).—To a well-stirred suspension of N-methyl-N-(α-cyanoisopropyl)-cyanamide (36.9 g., 0.3 mole) and dicyandiamide (55.4 g., 0.66 mole) in 65 ml. of isopropyl alcohol at reflux, was added over a 10-minute period a solution of potassium hydroxide (9.9 g., 0.15 mole on a purity basis) in 150 ml. of isopropyl alcohol. Almost all of the solids went into solution, and toward the end of addition precipitation began. After a 20-hour reflux period, the mixture was cooled and filtered. The solid product was washed twice with 250-ml. portions of water at 70° to remove unreacted dicyandiamide, refiltered and dried to give 64.5 g. (74%) of the colorless high-melting product.

α-(N-Methylmelamino)-butyroguanamine.—To a mixture of N-methyl-N-α-cyanopropylcyanamide (61.6 g., 0.5 mole), dicyandiamide (92.5 g., 1.1 moles) and 240 ml. of isopropyl alcohol was added at reflux a solution of potassium hydroxide (16.5 g., 0.25 mole on a purity basis) in 270 ml. of isopropyl alcohol over a period of 50 minutes. After a 4.5-hour reflux period, the cooled product was filtered off and washed with 1500 ml. of hot methanol. The colorless solid weighed 99 g. (96%) and corresponded in analysis to the mono-triazine (see Table II, footnote *b*). A mixture of this mono-triazine (41.4 g., 0.2 mole) and dicyandiamide (18.5 g., 0.22 mole) in 96 ml. of methyl cellosolve was brought to reflux (115°) and to it was added a solution of potassium hydroxide (6.6 g., 0.1 mole on a purity basis) in 90 ml. of methyl cellosolve. After 24 hours reflux, the solid material, which was mainly dicyandiamide, was filtered from the cold solution and the methyl cellosolve stripped off under reduced pressure. The residue was washed with 250 ml. of water at 65° and filtered to yield 33.7 g. of the bis-triazine melting at 255–260°.

Mono-triazines.—(1) From N-1,1,3,3-tetramethylbutyl-N-cyanomethylcyanamide: The reaction of this cyanamide with dicyandiamide, carried out in similar fashion to the preparation of α-(N-methylmelamino)-isobutyroguanamine, gave an 86% yield of light tan solid, m.p. 199–201°. *Anal.* Calcd. for $C_{13}H_{23}N_7$: N, 38.2. Found: N, 38.5. (2) From N-methyl-N-1-cyano-1-cyclohexylcyanamide: The reaction of this cyanamide gave an 83% yield of colorless solid, m.p. 257–258°. *Anal.* Calcd. for $C_{11}H_{17}N_7$: N, 39.7. Found: N, 39.3.

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[CONTRIBUTION FROM THE WYETH INSTITUTE OF APPLIED BIOCHEMISTRY]

Fluorine-containing Barbituric Acids[1]

BY WILLIAM F. BRUCE AND RICHARD DEV. HUBER

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Ethyl 3-fluoropropyl diethylmalonate and its allyl and isoamyl analogs, also ethyl 5-fluorodiethylmalonate and its allyl and isoamyl analogs, were obtained by the interaction of the sodio derivatives of the respective malonic esters with 1-bromo-3-fluoropropane and 1-chloro-5-fluoropentane in ethanol. These new esters were treated with urea in an ethanolic solution of sodium ethoxide to secure the corresponding barbituric acids. Attempts to alkylate various sodio alkylmalonic esters with α- or β-fluoroalkyl halides in ethanol or toluene were incomplete because of difficulties encountered in the purification of the products.

Of the halogen-containing barbituric acids described previously, none contain fluorine and only those with halogen in the relatively inert position on a double bond have proved sufficiently useful to be adopted as drugs for clinical use.[2–4] Since the inertness of the halogen thus appears to be a factor in the utility of these compounds, we were interested to examine some barbiturates containing a fluorine–carbon bond, since the halogen is known to be relatively inert and firmly bound in compounds of the fluoro-hydrocarbon type.[5]

The new fluorine-containing barbituric acids prepared during the course of this work were specifically 5-alkyl-5-(ω-fluoroalkyl) derivatives of barbituric acid. They are as follows: 5-ethyl-5-(3′-fluoropropyl)-barbituric acid, 5-allyl-5-(3′-fluoropropyl)-barbituric acid, 5-isoamyl-5-(3′-fluoropropyl)-barbituric acid, 5-ethyl-5-(5′-fluoro-*n*-amyl)-barbituric acid, 5-allyl-5-(5′-fluoro-*n*-amyl)-barbituric acid, and 5-isoamyl-5-(5′-fluoro-*n*-amyl)-barbituric acid. These compounds were prepared by treating the required alkyl-(ω-fluoroalkyl)-malonic

(1) Presented at the Miniature Meeting of the Philadelphia Section of the American Chemical Society, January 29, 1953.

(2) G. S. Skinner, THIS JOURNAL, **59**, 322 (1937).

(3) G. S. Skinner and J. B. Bicking, *ibid.*, **72**, 1140 (1950).

(4) Jenkins and Hartung, "Chemistry of Organic Medicinal Products," Second edition, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 553.

(5) E. H. Rodd, "Chemistry of Carbon Compounds," Vol. 1A, Elsevier Publishing Co., New York, N. Y., 1951, p. 556.

TABLE I

REACTION CONDITIONS, YIELDS AND ANALYSES[c] OF 5-ALKYL-5-ω-FLUOROALKYL)-BARBITURIC ACIDS: R,R'C(CONH)$_2$CO

Product R	Product R'	Quantity of reactants, mole Ester	Urea	Sodium[a]	Reaction conditions Temp., °C.	Time, hr.	Crude product Yield, %[b]	M.p., °C.	Pure product Yield, %[b]	M.p., °C.	Mol. wt. Calcd.	Equiv. wt. Found[d]	Carbon, % Calcd.	Found[d]	Hydrogen, % Calcd.	Found[d]	Nitrogen, % Calcd.	Found[d]
C_2H_5	FC_3H_6	0.040	0.080	0.120	60	14	75	144–150	52	154–155	216	210	50.00	50.28	6.06	5.97	12.96	13.17
C_3H_5	FC_3H_6	.040	.080	.120	60	14					228	219	52.63	52.93	5.74	5.69	12.29	12.55
					90	3	71	135–140	36	145–146								
i-C_5H_{11}	FC_3H_6	.021	.041	.062	65–70	16	57	120–130	9.4	139–141	258	244	55.79	56.31	7.41	7.33	10.85	10.76
C_2H_5	FC_5H_{10}	.027	.054	.081	70–75	9	76	80–110	38	120–122	244	211	54.07	54.64	7.02	7.19	11.47	11.43
C_4H_5	FC_5H_{10}	.028	.056	.084	65–70	19	63	98–102	21	105–106.5	256	245	56.24	56.77	6.69	6.83	10.93	11.30
i-C_5H_{11}	FC_5H_{10}	.022	.044	.066	65–70	11	43	97–108	16	118–120	286	229	58.72	58.61	8.10	8.25	9.79	10.14

[a] Approximately 55 ml. of absolute ethanol was used for each 0.120 mole of sodium. [b] Percentage yields were based on the starting quantity of alkyl-(ω-fluoroalkyl)-malonic ester. [c] All samples were found to contain fluorine. [d] Microanalyses were furnished by Dr. Wilhelm Reiss and assistants.

TABLE II

REACTION CONDITIONS, YIELDS, PHYSICAL PROPERTIES AND ANALYSES OF ALKYL-(ω-FLUOROALKYL)-MALONIC ESTERS: R,R'C($CO_2C_2H_5$)$_2$

Product R	Product R'	Quantity of reactants, mole Ester	Halide	Sodium[a]	Reaction conditions Temp., °C.	Time, hr.	Yields, %, based on Starting ester	Converted ester	Boiling range °C.	Mm.	$d^t/4$	t, °C.	n^tD	t, °C.	Molar refraction Theor.[b]	Obsd.[c]	Carbon, % Calcd.	Found[d]	Hydrogen, % Calcd.	Found[d]	Fluorine, % Calcd.	Found[d]
C_2H_5	FC_3H_6	0.100	0.100	0.110	55	2			96–103	2	1.043	25	1.4245	25	60.77	60.80	58.03	58.70	8.53	8.49	7.65	7.53
					65–70	5	48	60														
C_3H_5	FC_3H_6	.100	.100	.110	50–55	4			121–126	7	1.0414	24	1.4350	24	64.93	65.24	59.97	59.90	8.13	8.04	7.30	7.64
					65–70	2	56	70														
i-C_5H_{11}	FC_3H_6	.085	.085	.090	45–65	1			120–123	6	1.005	25	1.4275	25	74.63	74.33	62.05	61.34	9.38	9.01	6.55	Present
					65	5.5	26	33														
C_2H_5	FC_5H_{10}	.100	.100	.105	55–70	4			135–138	4	1.011	26	1.4294	26	70.01	70.45	60.84	61.29	9.12	9.06	6.88	Present
					75–78	3	29	47														
C_3H_5	FC_5H_{10}	.060	.060	.060	55–60	9	46	..	150–155	5	1.012	25	1.4376	25	74.2	74.8	62.50	62.31	8.75	8.43	6.60	Present
i-C_5H_{11}	FC_5H_{10}	.100	.100	.110	65	5			133–137	2.5	0.9844	26	1.4319	26	83.86	83.92	64.13	63.63	9.82	9.66	5.97	Present
					75	8	24	37														

[a] Approximately 55 ml. of absolute ethanol was used for each 0.110 mole of sodium. [b] Atomic refraction 0.95 for fluorine taken from Grosse and Cady, *Ind. Eng. Chem.*, **39**, 373 (1947). [c] Lorenz–Lorentz equation. [d] Microanalyses were furnished by Dr. Wilhelm Reiss and assistants.

esters with urea in an ethanolic solution of sodium ethoxide (Table I).

The six alkyl-(ω-fluoroalkyl)-malonic esters utilized in the preparation of the acids are likewise new. Their preparation was achieved by treating the required alkylmalonic esters with 1-bromo-3-fluoropropane or 1-chloro-5-fluoropentane in an ethanolic solution of sodium ethoxide (Table II).

The known ω-halo-ω′-fluoroalkanes were prepared from the respective ω,ω′-dihaloalkanes and potassium fluoride according to the method recently described by Hoffmann.[6-8] Our yields were somewhat lower than those recorded in the literature. In three preparations of 1-bromo-3-fluoropropane we secured yields varying from 22–24% compared with 31% reported by Hoffmann, and in our preparations of 1-chloro-5-fluoropentane, 17–20% was obtained compared with 22–39% from the literature. In spite of the low yields, this method appears to be a practical preparative method for these compounds in view of its convenience, availability and low cost of the starting materials.

The treatment of several α- or β-fluoroalkyl halides with various alkyl malonic esters under the same conditions described above gave mixtures from which a pure component was not readily isolated. The sodio derivative of diethyl allylmalonate reacted with 1-chloro-2-fluoroethane and 1-bromo-2-fluoroethane to give a small amount of sodium halide, and an organic mixture which contained fluorine, but which appeared to be composed largely of unchanged starting material. The same observation applies to chlorodifluoromethane and 1-iodo-heptafluoropropane in toluene. The sodio derivative of diethyl *s*-butylmalonate likewise reacted very incompletely with 1-chloro-2,2-difluoropropane. It appears probable that further study of these or analogous systems will yield additional fluoromalonic esters from which new barbiturates can be made for examination of the effect of fluorine substitution on the hypnotic action of barbituric acids.

A preliminary pharmacological evaluation of the new barbiturates for which we are indebted to Dr. Joseph Seifter and his associates showed that they all exhibit sedative action and produce true hypnosis. The compound showing the greatest potency is 5-allyl-5-ω-fluoropropylbarbituric acid. However, further work is needed to find whether a compound which will compare favorably with the best barbiturates now in use can be discovered among the fluorinated barbiturates, for none of those described here show as great potency as the best barbiturates. In view of the small number of compounds examined relative to the number possible in this series, conclusions relating structure to action are premature. The general impression left by the work thus far completed, however, is that replacement of either hydrogen or methyl by fluorine does not give as useful a product as the original. Moreover, fluorine exerts its own characteristic effect on the activity of the barbiturates containing it and these compounds are quite different from their bromine- or chlorine-containing analogs.

(6) F. W. Hoffmann, *J. Org. Chem.*, **15**, 425 (1950).
(7) F. W. Hoffmann, *ibid.*, **14**, 105 (1949).
(8) F. W. Hoffmann, THIS JOURNAL, **70**, 2596 (1948).

Experimental

ω,ω′-Dihaloalkanes.—Trimethylene bromide and pentamethylene dichloride were commercial products distilled before use.

ω-Halo-ω′-fluoroalkanes.—The freshly prepared 1-bromo-3-fluoropropane boiled at 100–105° (764 mm.), $n^{24}D$ 1.4318. The literature values[6] are b.p. 101° (760 mm.), and $n^{23}D$ 1.4295. Freshly prepared 1-chloro-5-fluoropentane boiled at 105–110° (180 mm.), $n^{25}D$ 1.4115. The literature[6] gave b.p. 143° (760 mm.), and $n^{23}D$ 1.4120.

α-Alkylmalonic Esters.—Diethyl ethylmalonate and diethyl allylmalonate were commercial products distilled before use. The commercial diethyl isoamylmalonate was not distilled before use. However, its observed $n^{25}D$ 1.4210 was close to the literature value $n^{25}D$ 1.4230.

Diethyl Ethyl-(5-fluoro-*n*-amyl)-malonate.—The details of the preparation of this malonate and the barbituric acid which follows are given as typical examples of the preparation of the compounds in Tables I and II. Clean, dry sodium metal, 2.42 g. (0.105 mole), was dissolved in 55 ml. of absolute ethanol in a 100-ml., 3-necked flask equipped with a mercury-sealed stirrer, dropping funnel protected by a calcium chloride tube, and a reflux condenser provided with a calcium chloride tube. With a bath temperature of 45–50°, 18.8 g. (0.100 mole) of diethyl ethylmalonate was added dropwise with stirring during 20 min. Then at 45–50°, 12.5 g. (0.100 mole) of 1-chloro-5-fluoropentane was added with stirring during 20 min. Stirring was stopped. The reaction mixture was heated with a water-bath at 55–70° for 4 hr. and at 75–78° for 3 hr. It then stood overnight at room temperature.

The ethanol was distilled at atmospheric pressure employing an oil-bath heated no higher than 130°. The residue was made acid to litmus with 20% hydrochloric acid and shaken with water to dissolve the inorganic salts. After separating the layers, the aqueous layer was extracted with ether, and this extract was added to the organic layer and dried over calcium chloride.

Distillation of the organic layer gave 7.1 g. (0.038 mole) of unchanged malonic ester, b.p. 84–95° (3 mm.), $n^{25}D$ 1.4157, and 8.0 g. (29% yield, 47% yield based on actual conversion) of substantially pure diethyl ethyl-(5-fluoro-*n*-amyl)-malonate, b.p. 135–138° (4 mm.). Physical constants and analyses are given in Table II.

5-Ethyl-5-(5′-fluoro-*n*-amyl)-barbituric Acid.—Clean, dry sodium metal, 1.86 g. (0.081 mole), was dissolved in 43 ml. of absolute ethanol in a 100-ml., 3-necked flask equipped with a mercury-sealed stirrer, dropping funnel protected by a calcium chloride tube, and a reflux condenser provided with a calcium chloride tube. At room temperature and with stirring 3.24 g. (0.054 mole) of fused, powdered urea and 7.5 g. (0.027 mole) of diethyl ethyl-(5-fluoro-*n*-amyl)-malonate were added in order and all at once. When all of the urea was in solution, stirring was stopped, and the reaction mixture was heated with a water-bath at 70–75° for 9 hr.

The ethanol was distilled at 100 mm. pressure employing a water-bath temperature no higher than 60°. The yellow, viscous residue was dissolved in a minimum amount of ice-cold water, extracted once with chloroform, filtered, and acidified with 20% hydrochloric acid until acid to congo red paper. The precipitate was filtered with suction, washed with 20 ml. of cold water and 50 ml. of petroleum ether, and air-dried. The crude product amounted to 5.0 g. (76% yield) and had m.p. 80–110°.

Recrystallization three times from 30% ethanol and then once from absolute ethanol gave 2.5 g. (38% yield) of substantially pure 5-ethyl-5-(5′-fluoro-*n*-amyl)-barbituric acid, m.p. 120–122°.

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