5-FLUORO-4-ALKYL(ARYL)BARBITURIC ACIDS

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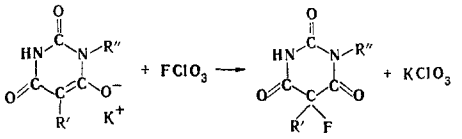
Fluorobarbituric acids are formed as a result of the reaction of 5-alkyl(aryl)barbituric acid salts with perchloryl fluoride.

While 5-chloro- and 5-bromobarbituric acids are readily formed by halogenation of the corresponding barbiturates [1], there is not information available regarding the fluorination of barbituric acids. We have found that perchloryl fluoride readily reacts with salts of 5-monosubstituted barbituric acids (I) to give 5-fluorobarbituric acids (II) via the scheme



I II

I, II a $R' = C_2H_5$, $R'' = H$; b $R' = i\text{-}C_3H_7$, $R'' = H$; c $R' = n\text{-}C_4H_9$, $R'' = H$; d $R' = s\text{-}C_4H_9$, $R'' = H$; e $R' = i\text{-}C_5H_{11}$, $R'' = H$; f $R' = C_3H_5$, $R'' = H$; g $R' = CH_2C_6H_5$, $R'' = H$; h $R' = C_6H_5$, $R'' = H$; i $R' = n\text{-}C_4H_9$, $R'' = CH_3$

The nature of the grouping in the 5-position does not have an appreciable effect on the yields of the fluorobarbiturates. The starting acids are obtained from the salts of 5,5-disubstituted barbituric acids.

The fluorobarbituric acids are white crystalline substances that are only slightly soluble in cold water and chloroform and moderately soluble in alcohol and acetone. They readily react with sodium alkoxides to give water-soluble salts.

Fluorobarbiturates II are not toxic to white mice when they are injected intraperitoneally as aqueous solutions of the sodium salts; their LD_{50} exceeds 1000 mg/kg. Their depressive action is considerably less than that of amobarbital.

TABLE 1. 5-Fluorobarbituric Acids (II)

Compound	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
			F	N	F	N	
IIa	202*	$C_6H_7FN_2O_3$	11,0	16,2	10,9	16,1	67
IIb	215—216	$C_7H_9FN_2O_3$	10,0	14,9	10,1	14,9	80
IIc	185—187	$C_8H_{11}FN_2O_3$	9,7	13,8	9,4	13,9	67
IId	177—178	$C_8H_{11}FN_2O_3$	9,4	13,8	9,4	13,9	68
IIe	213—214	$C_9H_{13}FN_2O_3$	9,4	12,5	8,8	13,0	70
IIf	163—164	$C_7H_7FN_2O_3$	10,2	14,8	10,2	15,0	60
IIg	224—225	$C_{11}H_9FN_2O_3$	7,8	11,5	8,1	11,9	73
IIh	240—242	$C_{10}H_7FN_2O_3$	9,2	12,5	8,5	12,6	72
IIi	92—93	$C_9H_{13}FN_2O_3$	8,5	12,4	8,8	13,0	62

*According to [2], this compound has mp 204-205°C.

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EXPERIMENTAL

The starting 5-monosubstituted barbituric acids were obtained by condensation of urea or methylurea with the appropriate monosubstituted malonic esters in butyl alcohol at 110-115°C in the presence of sodium butoxide. The salts (I) were obtained from the 5-monosubstituted barbituric acids by the action of KOH or CH_3COOK in alcohol.

5-Butyl-5-fluorobarbituric Acid (IIc). A total of 2 liters (88 mmole) of perchloryl fluoride was passed into a suspension of 12.5 g (68 mmole) of salt Ic in 100 ml of methanol with vigorous stirring while maintaining the temperature at no higher than 20°. After removal of the methanol, the residue was suspended in 150 ml of water, and the solid material was removed by filtration, washed with water, and dried. Recrystallization from alcohol gave 7.7 g (67%) of acid IIc. UV spectrum (in methanol): λ_{max} 210 nm (log ε 4.0).

The remaining 5-fluorobarbituric acids, which are presented in Table 1, were similarly obtained.

LITERATURE CITED

1. R. Ya Levina and F. K. Velichko, Usp. Khim., 29, 957 (1960).
2. Pennsalt Chemicals Co., British Patent No. 865,321 (1961); Chem. Abstr., 56, 3331 (1962).