[Chem. Pharm. Bull. 19(19)2643—2644(1971)]

UDC 547.854.5.057

A Convenient Synthesis of 1,3-Dialkyl-5,5-dichlorobarbituric Acids

KEITARO SENGA

Pharmaceutical Institute, School of Medicine, Keio University[1]

(Received July 5, 1971)

A convenient new method for the introduction of two chlorine atoms into the 5 position of pyrimidines has been found in the reaction of 1,3-dialkyluracils or 1,3-dialkylbarbituric acids with sulfuryl chloride which gave 1,3-dialkyl-5,5-dichlorobarbituric acids. These 5,5-dichlorobarbituric acids have customarily been prepared by the reaction of 1,3-dialkylbarbituric acids with chlorine[2a,b] or by that of tetraalkylalloxantines with phosphorus pentachloride.[3a,b] It is well known that one of the chlorine atoms in 5,5-dichlorobarbituric acids has strong reactivity.[4] Therefore, 1,3-dialkyl-5,5-dichlorobarbituric acids would be of interest as versatile synthetic intermediates.[5]

Treatment of 1 part of 6-amino-1,3-dimethyluracil (I)[6] with 10 parts of sulfuryl chloride at room temperature for 30 min gave 5,5-dichloro-1,3-dimethylbarbituric acid (VII)[2b,3a,3b] which is isolated by evaporation of the sulfuryl chloride and addition of water in quantitative yield. In complete analogy with the above result, 6-chloro-1,3-dimethyluracil (II)[7] and 1,3-dimethylbarbituric acid (III)[7] were converted into VII in high yields. The reaction was extended successfully to 6-amino-1,3-diethyluracil (VI)[6] to give 5,5-dichloro-1,3-diethylbarbituric acid (VIII)[2a] (see Table I).

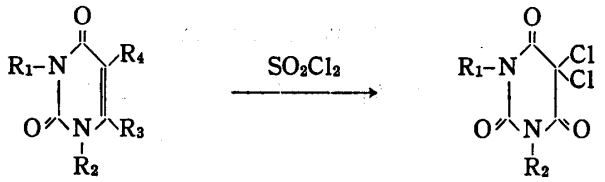
It will be noted that the reaction of 6-amino-1,3-dimethyl-5-phenylazouracil (IV)[8] or 1,3-dimethyl-5-phenylazobarbituric acid (V)[8] with sulfuryl chloride gave VII. It is well known that the halogenation of 5-substituted barbituric acid and uracil derivatives such as

TABLE I. Reaction of 1,3-Dialkyluracils or 1,3-Dialkylbarbituric Acids with Sulfuryl Chloride

Starting material	Reaction		Product	Yield (%)
	Time (min)	Temp. (°C)		
I	30	25	VII	100
II	5	25	VII	92
III	5	25	VII	98
IV	10	25	VII	73
V	10	80	VII	57
VI	30	25	VIII	89

1) Location: *35, Shinanomachi, Shinjuku-ku, Tokyo.*
2) *a*) K. Sembritzki, *Ber.*, **30**, 1814 (1897); *b*) H. Biltz and T. Humberger, *Ber.*, **49**, 635 (1916).
3) *a*) W. Techow, *Ber.*, **27**, 3083 (1894); *b*) A.C. Cope, D. Heyl, D. Peck, C. Eide and A. Arroyo, *J. Am. Chem. Soc.*, **63**, 356 (1941).
4) D.J. Brown, "The Chemistry of Heterocyclic Compounds, The Pyrimidines," Interscience Publishers, A. Weissberger, Ed., 1962, p. 162.
5) For example, Tishler, *et al.* reported that the synthesis of alloxazines and isoalloxazines in the reaction of 5,5-dichlorobarbituric acid with *o*-phenylenediamines: M. Tishler, J.W. Wellman and K. Ladenberg, *J. Am. Chem. Soc.*, **67**, 2165 (1945).
6) J.H. Speer and A.L. Raymond, *J. Am. Chem. Soc.*, **75**, 114 (1953).
7) W, Pfleiderer and K.H. Shündehütte, *Ann.*, **612**, 158 (1958).
8) M. Ishidate, M. Sekiya, Y. Osaki and Y. Harada, *Yakugaku Zasshi*, **76**, 1107 (1956).

5-nitroso-,[2b] 5-nitro,[9] 5-acetyl-,[10] 5-benzylidenebarbituric aicd[11] and uracil-5-carboxylic acid[12] gave 5,5-dihalogenopyrimidines. However, there seem to be no previous instances recorded in the literature for the dichlorination with replacement of phenylazo group.



I : $R_1=R_2=CH_3$, $R_3=NH_2$, $R_4=H$
II : $R_1=R_2=CH_3$, $R_3=Cl$, $R_4=H$
III : $R_1=R_2=CH_3$, $R_3=OH$, $R_4=H$
IV : $R_1=R_2=CH_3$, $R_3=NH_2$, $R_4=N_2C_6H_5$
V : $R_1=R_2=CH_3$, $R_3=OH$, $R_4=N_2C_6H_5$
VI : $R_1=R_2=C_2H_5$, $R_3=NH_2$, $R_4=H$

VII : $R_1=R_2=CH_3$
VIII : $R_1=R_2=C_2H_5$

Chart 1

Experimental[13]

General Procedure for Synthesis of 1,3-Dialkyl-5,5-dichlorobarbituric Acids (VII and VIII)——A mixture of 0.003 mole of 1,3-dialkyluracils or 1,3-dialkylbarbituric acids and 10 parts of SO_2Cl_2 was allowed to stand at room temperature as described in Table I (As one exception, a mixture of V and SO_2Cl_2 was heated for 10 min at 80°). After excess of SO_2Cl_2 was removed under reduced pressure, 10 ml of chilled H_2O was added. After standing for 1 hr at room temperature, separated crystals were collected by filtration, washed with H_2O and dried to give corresponding 5,5-dichlorobarbituric acid.

5,5-Dichloro-1,3-dimethylbarbituric Acid (VII): Recrystallization from EtOH gave colorless scales, mp 156—157° (Lit. mp 157—158°[3a,b]). *Anal.* Calcd. for $C_6H_6O_3N_2Cl_2$: C, 32.02; H, 2.68; N, 12.45. Found C, 32.27; H, 2.57; N, 12.51.

5,5-Dichloro-1,3-diethylbarbituric Acid (VIII): Recrystallization from EtOH–H_2O gave colorless needles, mp 89—90° (Lit. mp 87.5°[2a]). *Anal.* Calcd. for $C_8H_{10}O_3N_2Cl_2$: C, 37.96; H, 3.98; N, 11.07. Found: C, 38.03; H, 4.05; N, 11.03.

9) A.V. Baeyer, *Ann.*, **127**, 199 (1863).
10) H. Biltz and H. Wittek, *Ber.*, **54**, 1035 (1921).
11) W. Bock, *Ber.*, **55**, 3400 (1922).
12) T.B. Johnson, *J. Am. Chem. Soc.*, **65**, 1218 (1943).
13) All melting points are uncorrected.