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Anticonvulsant Drugs. VII. Some Monosubstituted Isocyanurates[1]

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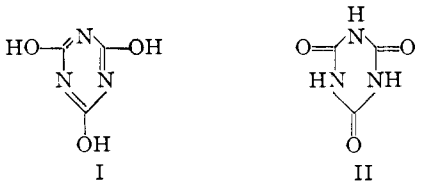
The preparation of monosubstituted isocyanurates by a variety of synthetic paths was studied. The condensation of monosubstituted biurets with ethyl carbonate was found to be far superior to alternative methods. Several of the products had some anticonvulsant action, but none was outstanding.

2,4,6-Trihydroxy-1,3,5-triazine exists in both the enol form (cyanuric acid, I) and the keto form (isocyanuric acid, II). Derivatives of both forms are known, and recently it was discovered that the alkyl derivatives of the former (cyanurates) have anticonvulsant action.[2] Alkyl derivatives of the latter (isocyanurates), then, should provide a fertile field of exploration for new antiepileptic agents, the more so since the isocyanurates are very similar structurally to the barbiturates, a group of compounds widely used in the treatment of epilepsy. It is the object of this report to present the synthesis and properties of several monosubstituted isocyanurates.



I II

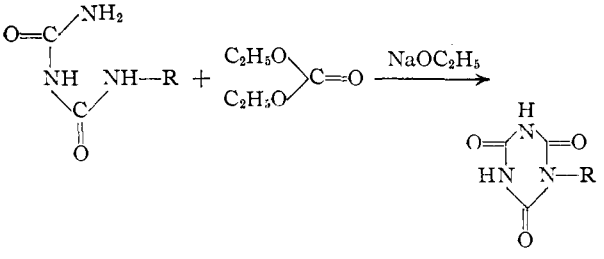
Few monosubstituted isocyanurates have appeared in the chemical literature. Fischer and Frank[3] prepared the first member of the series from ω,ω'-dimethylcarbonyldiurea, either by heating in a sodium hydroxide solution, or by nitrosating and heating the nitrosated product. Monophenyl isocyanurate has been obtained from phenyl-substituted ammelines through hydrolysis with strong acids.[4,5] The same compound was obtained by Dains and co-workers[6] in more modern times by heating phenyl isocyanate with urethan and by treating carbonyldiurethan with aniline. The latter reaction was said to give, among other things, 1-carbethoxy-5-phenylbiuret, which upon dissolution in sodium hydroxide yielded the product. Other aryl amines behaved in an analogous manner.

The carbonyldiurethan method of Dains and his collaborators at first seemed to offer a possible approach to the synthesis of additional isocyanurates. However, we were unable to repeat his preparation of monophenyl isocyanurate by following the conditions specified and only a low yield could be obtained by making appropriate modifications. The reaction failed when applied to two alkyl amines. Dains[6,7] likewise did not obtain isocyanurates or the intermediate carbethoxy alkyl biurets with alkyl amines. It was apparent, therefore, that the usefulness of the Dains procedure was limited.

A logical route to the isocyanurates appears to lie in the condensation of an alkyl azamalonic ester with urea, after the fashion of the classic barbiturate synthesis. Tompkins and Degering[8] have found that substituted azamalonic esters are not as readily obtainable as the corresponding malonic esters, and, furthermore, the products do not undergo condensation with urea. We have confirmed their observations. Some qualified success was obtained by using unsubstituted azamalonic ester and substituted ureas, but the yields were low and results variable.

Since urea is known to yield cyanuric acid upon heating, and alkyl ureas have been reported to yield disubstituted isocyanurates,[9] it seemed probable that monosubstituted isocyanurates could be obtained by heating a mixture of urea and an alkyl urea in the proper proportions. Indeed, a 1:2 mixture of methylurea and urea did yield 30% of monomethyl isocyanurate. The yields, however, fell precipitously with higher homologs.

A method was ultimately discovered which appears to be widely applicable and which gives consistently high yields. The method involves the condensation of monosubstituted biurets with ethyl carbonate in the presence of sodium ethoxide, as shown in the accompanying equation. Of the ten biurets subjected to this treatment, only the hindered *t*-butyl derivative failed to yield the isocyanurate.



The monosubstituted isocyanurates are all high-melting solids, insoluble in water. They dissolve easily without decomposition in dilute bases in keeping with their acidic character. The compounds were tested by described methods[10] for their ability to modify electroshock seizures, to antagonize the action of Metrazol, and to protect against "psychomotor seizures." A few exhibited distinct anticonvulsant action, but most were essentially inactive. As a class the isocyanurates were mildly

(1) Preceding paper in this series, D. A. Dunnigan and W. J. Close, THIS JOURNAL, **75**, 3615 (1953).

(2) M. A. Spielman, W. J. Close and I. J. Wilk, *ibid.*, **73**, 1775 (1951).

(3) E. Fischer and F. Frank, *Ber.*, **30**, 2604 (1897).

(4) B. Rathke, *ibid.*, **20**, 1065 (1887); **21**, 867 (1888).

(5) A. Smolka and A. Friedreich, *Monatsh.*, **11**, 8 (1890).

(6) F. B. Dains, H. W. Greider and C. H. Kidwell, THIS JOURNAL, **41**, 1004 (1919).

(7) J. A. Murray and F. B. Dains, *ibid.*, **56**, 144 (1934).

(8) L. G. R. Tompkins and E. F. Degering, *ibid.*, **69**, 2616 (1947).

(9) A. W. Hofmann, *Ber.*, **19**, 2061 (1886).

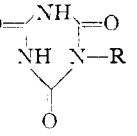
(10) J. E. P. Toman, G. M. Everett and R. K. Richards, *Texas Rpts. Biol. Med.*, **10**, 96 (1952).

hypnotic. The pharmacological data are summarized in Table I, and are reproduced through the kind permission of Dr. R. K. Richards, Dr. G. M. Everett and their staff.

Experimental[11]

The four main procedures for the preparation of monosubstituted isocyanurates which were studied are given below. Only (A) gave satisfactory results, and ultimately nearly all of the compounds were prepared by this method (see Table I).

TABLE I

ISOCYANURATES, 

R	M.p., °C.	Yield, %[a]	Formula	Nitrogen Calcd.	Nitrogen Found	Activity[b] E.S.	Activity[b] Met.	Activity[b] P.S.
CH_3	275-285[c]	31[d]				1	1	1
C_2H_5	230-231	82	$C_5H_7N_3O_3$	26.8	26.7	2A	1	1
n-C_3H_7	226-227	85	$C_6H_9N_3O_3$	24.6	24.7	4C	3B	4C
n-C_4H_9	226-227	86	$C_7H_{11}N_3O_3$	22.7	23.0	1	3D	2C
s-C_4H_9	239-240	2[d]	$C_7H_{11}N_3O_3$	22.7	22.7			
i-C_4H_9	266-267	81	$C_7H_{11}N_3O_3$	22.7	22.8	1	1	1
n-C_5H_{11}	229-230	95	$C_8H_{13}N_3O_3$	21.1	21.4	1	1	2B
i-C_5H_{11}	232-233	95	$C_8H_{13}N_3O_3$	21.1	21.3	1	2A	4C
n-C_6H_{13}	226-227	94	$C_9H_{15}N_3O_3$	19.7	20.0	4D	3B	4B
C_6H_5	310-311[e]	89				1	1	1
$C_6H_5CH_2$	244-245	73	$C_{10}H_9N_3O_3$	19.2	19.2	4B	2C	1

[a] The yields reported are for preparational method A, except where otherwise indicated. [b] In this code system the numbers refer to degree of activity, 1 designating no protection, 4 complete protection, and 2 and 3 representing intermediate degrees of protection. The letters refer to side effects, A designating no symptoms, D severe symptoms, and B and C intermediate degrees of abnormal behavior. The abbreviations in the column headings stand for electroshock, Metrazol, and psychomotor shock, respectively. [c] Fischer and Frank (ref. 3) record 297°. [d] Prepared by method C. [e] Dains, *et al.* (ref. 6) give 290–300°. The m.p. obtained here was taken in a Pyrex tube.

(A) Condensation of Substituted Biurets with Ethyl Carbonate.—A solution of sodium ethoxide was prepared by dissolving 0.46 g. (0.02 mole) of sodium in 20 cc. of absolute alcohol. The substituted biuret[1] (0.01 mole) was added, together with 2.4 g. (0.02 mole) of ethyl carbonate. The mixture was stirred under reflux for one to 20 hours.[12]

The reaction mixture was cooled and filtered. Dry ether was used as required to facilitate transfer of the solid. The sodium salt so obtained was dissolved in water and any insoluble material (unreacted biuret) was removed by filtration.[13] The product was precipitated from the aqueous solution with hydrochloric acid. The isocyanurates usually separated in a pure state; where necessary they were recrystallized from alcohol. The yields ranged from 73 to 95%.

(B) Dains[6] Carbonyldiurethan Reaction.—The procedure described by Dains for the preparation of phenyl isocyanurate from aniline and carbonyldiurethan was followed in detail. The intermediate 1-carbethoxy-5-phenylbiuret could not be obtained; only starting material was isolated. Extending the time of reaction, decreasing the proportion of aniline, or adding alcohol as a solvent did not improve the reaction. However, when equimolar amounts of the reagents were heated at 100° overnight in a small amount of ethylene glycol, 16% of product was obtained.

In an attempted preparation of *n*-amyl isocyanurate equimolar proportions of carbonyldiurethan and *n*-amylamine were refluxed overnight in alcohol. Alcoholysis occurred to give ethyl carbonate and ethyl allophanate; no product could be isolated.

An attempt to condense *n*-butylamine with carbonyldiurethan also failed.

(C) Fusion of Alkyl Ureas with Urea.—Methylurea (18.5 g.) was heated with 30 g. of urea for 40 minutes at 200°, then the temperature was slowly brought to 250° over a one-hour period and maintained at 250° for 20 minutes. The melt was triturated with water and filtered. The residue, consisting of cyanuric acid and methyl isocyanurate, was separated into its components by selective extraction with dilute sodium hydroxide solution (sodium salt of product much more soluble than sodium cyanurate). A total of 11.2 g. (31%) of product melting about 275–285° was obtained. The melting point could not be greatly improved by recrystallization and presumably the product contained some cyanuric acid. However, the analyses were satisfactory.

Anal. Calcd. for $C_4H_5N_3O_3$: C, 33.6; H, 3.5. Found: C, 33.9; H, 3.5.

A similar procedure with ethylurea gave 4% of product; with *s*-butylurea 2% of product was obtained.

(D) Condensation of Azamalonic Esters with Ureas.—A mixture of 8.1 g. of azamalonic ester[8] and 8.0 g. of *n*-amylurea was heated carefully with a free flame. When the temperature of the melt reached 160° alcohol began distilling. The temperature gradually rose to 250° over a half-hour period as the low-boiling liquid was removed. The reaction mixture was cooled, leached with water, and recrystallized from alcohol. The cyanuric acid present was largely removed during the recrystallization (sparingly soluble in hot alcohol). A total of 2.5 g. (25%) of crude *n*-amyl isocyanurate, m.p. 224–226°, was obtained.

Similar procedures gave 15% yields of the *n*-propyl and *n*-butyl isocyanurates.

A single attempt to condense azamalonic ester with *n*-butylurea in absolute alcohol with sodium ethoxide as catalyst failed. Several attempts to condense a substituted azamalonic ester[8] with urea itself using typical barbituric acid procedures failed.

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(11) Microanalyses by E. F. Shelberg and staff.

(12) The ethyl derivative formed in one hour; 20 hours were required for the phenyl compound. The time was not critically examined for others, but refluxing was generally continued overnight.

(13) The general impression gained from the literature is that biurets are quite soluble in dilute bases [see, for example, J. Bougault and J. Leboucq, *Bull. soc. chim.*, [4] **47**, 594 (1930) and E. S. Gatewood, THIS JOURNAL, **45**, 146 (1923)]. Although the biurets are more soluble in bases than in water, they cannot be considered generally soluble in the usual sense of the word. Thus, phenylbiuret, described as soluble by Gatewood, was found to be approximately 1% soluble in a small excess of 2% sodium hydroxide, and less than 3% soluble in 8% sodium hydroxide at room temperature. When titrated electrometrically, it behaved as a neutral substance.