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[CONTRIBUTION FROM ABBOTT LABORATORIES]

Anticonvulsant Drugs. VI. Some 1-Substituted Biurets[1]

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A series of 1-substituted biurets has been prepared, generally by the action of amines on nitrobiuret. Half of the compounds gave good protection against electroshock. They were less effective against psychomotor shock and generally ineffective against Metrazol.

In the search for more effective drugs it is only natural for investigators to focus attention on structures of proven value and to ponder what elements of such structures may give rise to the observed activity. Thus, in the anticonvulsant field, amides[2] and acylureas[3] have been subjected to thorough examination because they may be visualized as fragments of substituted hydantoins in which the 1–5 bond has been severed. Apparently, however, no one has yet reported a systematic study of products hypothetically obtained by rupture of the 4–5 bond of 5-substituted hydantoins.[4] Although the 1-alkyl(or aryl)-3-formylureas which formally result do not lend themselves well to such a study, abstraction of the formyl group or addition of a terminal amino group leads to substituted ureas and biurets—and these derivatives are worthy of examination for anticonvulsant activity. It is the object of this report to present data on such 1-substituted biurets.[5]

More than half a dozen distinctly different methods have been used in the past to prepare 1-alkyl (or aryl)-biurets. Three can be considered to be of wide applicability: (1) reaction of allophanyl chloride with amines,[6] (2) ammonolysis or aminolysis of allophanates,[7] and (3) reaction of nitrobiuret with amines.[8]

The first method suffers from the disadvantage that allophanyl chloride is difficult to obtain and handle. Nothing is known about the efficiency of this reaction inasmuch as the authors who described it failed to indicate yield. The utility of the second method is limited by the fact that the yields are often low and other products frequently are obtained.

We feel that Davis and Blanchard's nitrobiuret synthesis is the method of choice for the simple laboratory preparation of the majority of biurets. Although the yields are often poor, the starting material is readily available and the reaction is generally not complicated by secondary products. Unreacted amine can easily be recovered and retreated if desired. Most of our products were obtained by the use of this method.

Since *s*-carbinylamines gave poorer results than less highly branched amines, we did not attempt to apply the Davis–Blanchard synthesis to *t*-carbinylamines. *t*-Carbinylbiurets may be obtained by an interesting application of the Ritter reaction, using dicyandiamide and branched alkenes[9] or tertiary alcohols.

(1) Preceding paper in this series, M. A. Spielman, W. J. Close and I. J. Wilk, THIS JOURNAL, **73**, 1775 (1951).

(2) (a) J. H. Billman and P. H. Hidy, *ibid.*, **65**, 760 (1943); (b) J. H. Billman, T. G. Ward and P. H. Hidy, *ibid.*, **67**, 130 (1945); (c) C. O. Wilson, *J. Am. Pharm. Assoc., Sci. Ed.*, **38**, 466 (1949); (d) S. Kushner, R. I. Cassell, J. Morton and J. H. Williams, *J. Org. Chem.*, **16**, 1283 (1951); (e) L. M. Long, Abst. of papers, 121st Meeting A. C. S., Milwaukee, Wis., 1952, p. 8J.

(3) (a) M. A. Spielman, A. O. Geiszler and W. J. Close, THIS JOURNAL, **70**, 4189 (1948); (b) L. S. Goodman, J. E. P. Toman and E. A. Swinyard, *Arch. intern. pharmacodyn.*, **78**, 144 (1949); (c) E. A. Swinyard and J. E. P. Toman, *J. Pharmacol. Exper. Ther.*, **100**, 151 (1950); (d) R. Hazard, J. Cheymol, P. Chabrier and K. Smarzewska, *Therapie*, **6**, 129 (1951); (e) R. Hazard, J. Cheymol and P. Chabrier, *Compt. rend.*, **232**, 658 (1951).

(4) This thought apparently provided the stimulus for the study of some of the derivatives of benzhydrylamine reported by R. Duschinsky, Abstracts of Papers, XIIth Intern. Cong. Chem., New York, 1951, p. 323.

(5) The anticonvulsant action of four biurets was reported by H. H. Anderson, C. H. Ch'eng and P. P. T. Sah, *Rec. trav. chim.*, **68**, 111 (1949). Only one of these (1,1-pentamethylenebiuret) was of the type considered here.

(6) J. Bougault and J. Leboucq, *Compt. rend.*, **188**, 1406 (1929); *Bull. soc. chim.*, [4] **47**, 594 (1930).

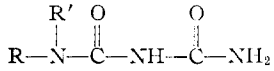
(7) (a) F. B. Dains and E. Wertheim, THIS JOURNAL, **42**, 2303 (1920); (b) H. Biltz and A. Jeltsch, *Ber.*, **56**, 1914 (1923); (c) E. S. Gatewood, THIS JOURNAL, **47**, 407 (1925); (d) E. Wertheim, *ibid.*, **53**, 200 (1931); (e) J. A. Murray and F. B. Dains, *ibid.*, **56**, 144 (1934); (f) Chabrier, *Compt. rend.*, **214**, 495 (1942).

(8) T. L. Davis and K. C. Blanchard, THIS JOURNAL, **51**, 1801 (1929).

(9) J. J. Ritter and P. P. Minieri, *ibid.*, **70**, 4045 (1948).

TABLE I

SUBSTITUTED BIURETS,



R	R′	M.p., °C.	Lit., m.p., °C.	Ref.[a]	Formula	Anal., N Calcd.	Found	E.S.	Activity[b] Met.	P.S.
CH_3	H	167–168	166.5–167	A				1	1	1
CH_3	CH_3	176–176.5	141	A	$C_4H_9N_3O_2$	32.1	31.8	1	1	1
C_2H_5	H	154–155	154–154.5	A				1	1	1
C_2H_5	C_2H_5	138–139	139–139.2	A				1	1	2B
n-C_3H_7	H	145–146	147.2–147.6	A				4B	1	2A
i-C_3H_7	H	132–133			$C_5H_{11}N_3O_2$	29.0	29.3	1	1	1
n-C_4H_9	H	128–129	129.1–129.5	A				4C	1	4C
i-C_4H_9	H	108–109			$C_6H_{13}N_3O_2$	26.4	26.5	2C	3C	2A
t-C_4H_9	H	176–177			$C_6H_{13}N_3O_2$	26.4	26.2	1	1	1
n-C_5H_{11}	H	79–80			$C_7H_{15}N_3O_2$	24.3	24.4	2D	1	1
i-C_5H_{11}	H	127–128	118	B	$C_7H_{15}N_3O_2$	24.3	24.4	4D	2D	4D
t-C_5H_{11}	H	151–152	148.5–149	C				1	1	1
n-C_6H_{13}	H	127–128			$C_8H_{17}N_3O_2$	22.4	22.4	1	1	1
$(C_2H_5)_2CHCH_2$	H	128–129			$C_8H_{17}N_3O_2$	22.4	22.3	1	1	1
Cyclo-C_6H_{11}	H	153–154	195	B	$C_8H_{15}N_3O_2$	22.7	22.5	4C	1	4C
C_6H_5	H	172–173[c]	165–166	A,D				4C	1	4C
C_6H_5	CH_3	160–161	156; 168	B,E				4C	2C	2C
C_6H_5	C_2H_5	146–147	155.2–155.8	A				1	1	1
$C_6H_5CH_2$	H	174–175	174.5–175	A				4B	1	1
$C_6H_5CH_2$	CH_3	155–156			$C_{10}H_{13}N_3O_2$	20.3	20.5	4C	2C	4C
$C_6H_5CH_2$	C_2H_5	120–121			$C_{11}H_{15}N_3O_2$	19.0	19.0	4C	1	2B
$C_6H_5(CH_3)_2CH$	H	110–111			$C_{10}H_{14}N_3O_2$	20.3	20.1	4B	2C	1
$(C_6H_5)_2CH$	H	168–169			$C_{15}H_{16}N_3O_2$	15.6	15.8	1	1	1

[a] The letters refer to the following: A, ref. 8; B, ref. 6; C, ref. 9; D, ref. 7c; E, H. Thate, *Rec. trav. chim.*, **48**, 116 (1929). [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] A lower crystallographic modification melts at 165°.

Pharmacological data on the biurets were obtained through published procedures[10] by Drs. R. K. Richards and G. M. Everett, assisted by J. S. Goodsell and A. H. Smith, Jr. The compounds were primarily effective against electroshock, which is to be anticipated from their structures. In purely aliphatic compounds highest activity was obtained with alkyl substituents of three to five carbons in length and, of these, the less-branched chains were superior. Nearly all of the biurets derived from N-phenyl- and N-benzylbiurets were active. The most notable exception is benzhydrylbiuret, which may be considered an open chain analog of Phenytoin. Many of the compounds protecting against electroshock also gave protection against psychomotor shock. Anti-Metrazol action was generally absent throughout. The pharmacological data are summarized in Table I.

Experimental[11]

With the exception of the compounds specifically mentioned below, the biurets were all prepared by the general procedure described under method A. The properties of the compounds are given in Table I.

Method A.—Nitrobiuret[8] and an equimolar quantity of the amine were brought together in water, generally about 50 ml. for a 0.05 mole run. The mixture was allowed to stand for one hour with occasional shaking. Stirring was employed for water-insoluble amines. The mixture was then heated gradually to boiling and refluxed from 20 minutes to one hour, depending on the reactivity of the amine. The product crystallized upon cooling; in the case of more water-soluble biurets concentration was necessary. The products were recrystallized to constant melting point in alcohol–water mixtures. The yields were generally 30–90%. The lower yields were obtained in the cases of the more volatile amines and secondary carbinylamines.

It was apparent that the success of the reaction was dependent upon the quality of the nitrobiuret used. Acid-free nitrobiuret melting about 163° was found to be satisfactory.

***t*-Butylbiuret and *t*-Amylbiuret.**—To an ice-cooled, stirred mixture of 33.6 g. (0.4 mole) of dicyandiamide and 38.1 g. (0.4 mole) of *t*-butyl alcohol was added over a one-hour period a mixture of 40 g. (0.4 mole) of sulfuric acid and 80 ml. of glacial acetic acid. After an additional hour of cooling and stirring the mixture was heated to 60° for four more hours, during which time the mixture became homogeneous. The solution was cooled, poured on cracked ice and neutralized with ammonium hydroxide. The crude solid was separated by filtration. More product was obtained by concentrating and cooling the mother liquors. The product was recrystallized from absolute ethanol to constant melting point. A total of 19.8 g., m.p. 176–177°, was obtained.

***t*-Amylbiuret** was prepared in a similar manner from *t*-amyl alcohol.

Phenylbiuret.—This derivative was prepared originally according to the directions of Gatewood.[7c] Although she as well as numerous other authors had found the melting point to be about 165°, our product melted substantially higher (172–173°). However, correct analytical values were obtained.

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.7; H, 5.1. Found: C, 53.8; H, 5.0.

A sample was next prepared by the Davis–Blanchard procedure.[8] It melted at 164–165°. A mixture of the two products melted at 170–172°, confirming the essential identity of the two substances.

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

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