223.5–225.5°). The formyl compound (V*a*) was acetylated (see III) and the product was recrystallized from methanol to yield 3.7 g (66%, m.p. 148–149.5°) of diacetate V*b*. Recrystallization from the same solvent gave pure crystals melting at 150.5–151.5°; $[\alpha]_D^{23}$ −21.4° (*c*, 1.27); $\nu_{max}^{CHCl_3}$ 1 770, 1 726, and 1 656 cm^{-1}.

Anal. Found: C, 71.48; H, 8.67. $C_{24}H_{34}O_5$ requires C, 71.61; H, 8.51.

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THE SYNTHESIS OF SUBSTITUTED BIURETS[1]

H. STOLLAR, R. J. RANZ, AND FRANCIS L. CHUBB

In a previous communication (1) the synthesis and pharmacology of some 1-substituted biurets were described. We now report the synthesis of a new series of mono- and poly-substituted biurets (Table I), some of which were synthesized by a novel method. This method, while being generally applicable to the synthesis of biurets, is particularly suitable for the synthesis of 1,5-disubstituted biurets.

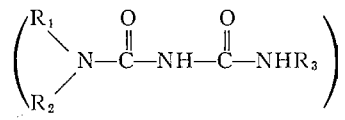
Most of the biurets herein reported were synthesized by the reaction of nitrobiuret with a primary or secondary amine (2), or by the reaction of a 1,1-disubstituted-5-nitrobiuret (Table II) with a primary amine (3). However, there are no reports in the literature of this method having been used for the synthesis of 1,5-disubstituted biurets (4, 5). We found that the reaction of 1-methyl-5-nitrobiuret with phenethylamine gave very low yields of the required 1-methyl-5-phenethylbiuret.

The reaction of allophanic esters with amines has been used to prepare some 1,5-disubstituted biurets, but has been found to be of limited usefulness (4). When we attempted to prepare 1,5-disubstituted biurets by causing methyl-4-phenethylallophanate to react with various amines, we were successful only in the case of methylamine and benzylamine.

Another method which has been used for the synthesis of 1,5-disubstituted biurets is the condensation of an isocyanate with an O-alkyl-N-substituted isourea to yield an isobiuret,

[1]*Presented at the 150th meeting of the American Chemical Society, September 1965, Atlantic City, New Jersey.*

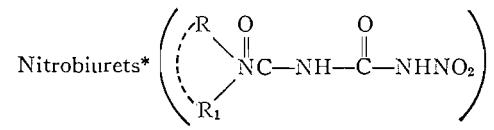
TABLE I

Substituted biurets 

FWH No.	R_1	R_2	R_3	Method of preparation*	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Melting point (°C)
503	CH_3	CH_3	ϕCH_2CH_2	B	9	$C_{12}H_{17}N_3O_2$	61.25	7.28	17.86	60.95	7.19	18.27	104–106
505	$(CH_2)_2O(CH_2)_2$		ϕCH_2CH_2	A, B	83, 78	$C_{14}H_{19}N_3O_3$	60.63	6.91	15.13	60.77	6.87	15.26	135–136
506	$(CH_2)_5$		ϕCH_2CH_2	A, B	65.74	$C_{16}H_{21}N_3O_2$	65.42	7.69	15.26	65.51	7.75	14.97	110–111
507	$(CH_2)_6$		ϕCH_2CH_2	B	38	$C_{16}H_{23}N_3O_2$	66.72	8.01	14.52	66.71	7.92	14.99	95–96
509	$(CH_2)_4$		ϕCH_2CH_2	B	79	$C_{14}H_{19}N_3O_2$	64.36	7.33	16.08	63.98	7.32	15.99	163–164
510	C_2H_5	C_2H_5	ϕCH_2CH_2	B	86	$C_{14}H_{21}N_3O_2$	63.86	8.04	15.96	64.22	8.17	16.05	79–80
535	C_2H_5	C_2H_5	ϕCH_2	B	80	$C_{13}H_{19}N_3O_2$	62.64	7.68	16.86	62.65	7.88	16.45	92–94
538	C_2H_5	C_2H_5	$\phi(CH_2)_4$	B	45	$C_{16}H_{26}N_3O_2$	65.95	8.65	14.42	66.36	8.65	14.09	63–64
547	C_2H_5	C_2H_5	$\phi(CH_2)_3$	B	24	$C_{15}H_{23}N_3O_2$	64.95	8.36	15.15	65.26	8.44	15.44	52–53
548	C_3H_7	C_3H_7	ϕCH_2	B	27	$C_{15}H_{23}N_3O_2$	64.95	8.36	15.15	64.72	8.48	14.98	71–72.5
549	C_3H_7	C_3H_7	$\phi(CH_2)_3$	B	21	$C_{17}H_{27}N_3O_2$	66.85	8.91	13.76	66.77	8.79	13.85	58–59
550	C_2H_7	C_3H_7	$\phi(CH_2)_4$	B	23	$C_{18}H_{29}N_3O_2$	67.68	9.15	13.15	68.05	9.33	13.42	50–50.5
567	C_2H_5	C_2H_5	p-$ClC_6H_4CH_2CH_2$	B	79	$C_{14}H_{20}N_3O_2Cl$	56.45	6.77	14.11	56.64	6.89	13.91	102–104
558	p-$ClC_6H_4CH_2CH_2$	H	H	B	81	$C_{10}H_{12}N_3O_2Cl$	49.69	5.01	17.38	49.82	4.88	17.22	174–175
560	p-$AcNHC_6H_4$	H	H	B	81	$C_{10}H_{12}N_4O_3$	50.84	5.12	23.72	50.87	5.72	23.75	>300
561	o-$AcNHC_6H_4$	H	H	B	43	$C_{10}H_{12}N_4O_3$	50.84	5.12	23.72	50.61	5.13	23.88	200
546	n-C_3H_7	n-C_3H_7	H	B	75	$C_8H_{17}N_3O_2$	51.31	9.15	22.44	51.45	9.12	22.10	130.5–132
574	ϕCH_2CH_2	C_2H_5	H	B	74	$C_{12}H_{17}N_3O_2$	61.24	7.28	17.85	61.07	7.49	18.12	154–156
579	ϕCH_2CH_2	n-C_3H_7	H	B	68	$C_{13}H_{19}N_3O_2$	62.63	7.68	16.86	62.71	7.56	16.94	119–120
580	ϕCH_2CH_2	n-C_4H_9	H	B	88	$C_{14}H_{21}N_3O_2$	63.86	8.04	15.96	63.82	8.00	16.22	93–94
528	ϕCH_2CH_2	H	CH_3	C	60	$C_{11}H_{15}N_3O_2$	59.70	6.83	19.00	59.89	6.95	19.25	119.5–120.5
529	ϕCH_2CH_2	H	ϕCH_2	C	64	$C_{17}H_{19}N_3O_2$	68.68	6.44	14.14	69.17	6.20	14.08	158–160
541	$\phi(CH_2)_3$	H	$\phi(CH_2)_3$	A	37	$C_{20}H_{26}N_3O_2$	70.78	7.43	12.38	70.82	7.45	12.57	84–85
564	$\phi(CH_2)_2$	H	n-C_4H_9	A	55	$C_{14}H_{21}N_3O_2$	63.86	8.04	15.96	63.65	8.26	15.93	89–90
570	$\phi(CH_2)_2$	H	n-C_3H_7	A	61	$C_{13}H_{19}N_3O_2$	62.63	7.68	16.86	62.37	7.70	16.65	89–90
573	ϕCH_2CH_2	H	n-C_8H_7	A	78	$C_{18}H_{29}N_3O_2$	67.67	9.15	13.15	67.48	9.17	12.95	60–61
576	ϕCH_2	H	n-C_3H_7	A	86	$C_{12}H_{17}N_3O_2$	61.24	7.28	17.85	61.20	7.40	18.26	85–87

*A, azide method; B, nitrobiuret method; C, allophanic ester method.

TABLE II

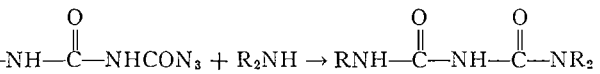
Nitrobiurets* 

R_1, R	Decomposition point (°C)	Yield of crude product
$(CH_2)_2O(CH_2)_2$	113–115	50%
$(CH_2)_4$	107–108	Quantitative
$(CH_2)_5$	107–108	Quantitative
$(CH_2)_6$	108–110	Quantitative

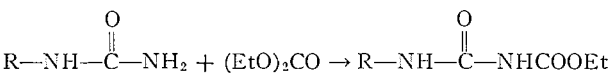
*These rather unstable compounds were used in the next step without further purification or analysis.

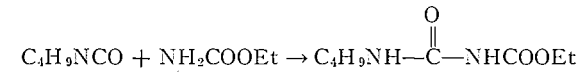
which was then hydrolyzed to the biuret (4). This method necessitates the synthesis of both the required isocyanates and isoureas, and the reported yields were low.

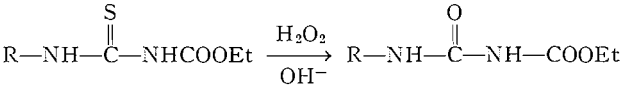
Lipschitz (6) has reported biuret to be the only product of the reaction of allophanyl azide with ammonia. We have found that 4-substituted allophanyl azides react smoothly with primary amines to yield 1,5-disubstituted biurets. In general, allophanyl azide or 4-substituted allophanyl azides react with primary or secondary amines to give high yields of the corresponding substituted biurets.

[1] 

Key intermediates required for the preparation of allophanyl azides were the corresponding allophanic esters (Table III). Three different methods of synthesis were investigated. The most convenient and generally applicable synthesis was the base-catalyzed condensation of diethyl carbonate with the appropriate substituted urea (eq. [2]) according to the procedure of a German patent (7). Ethyl 4-*n*-butylcarbamate was synthesized by the reaction of butyl isocyanate with ethyl carbamate (eq. [3]), but this method was not found to be generally applicable. A third method investigated was the oxidative desulfurization of 4-substituted-3-thioallophanic esters. Dixon and Taylor (8) reported that methyl 4,4-diphenyl-3-thioallophanate was resistant to heavy metal desulfurization. We have found that oxidative desulfurization of 4-substituted-3-thioallophanates by hydrogen peroxide (eq. [4]) worked in the case of the 4-*n*-butyl and 4-*n*-propyl derivatives, but we did not investigate the method any further since it was not as convenient as the ethyl carbonate method.

[2] 

[3] 

[4] 

The allophanic esters were then converted into hydrazides (Table IV), which were in

TABLE III

Substituted allophanates $\left(\begin{matrix} & X \\ & \| \\ RNHC—NHCOOR_1 & \end{matrix}\right)$

R	X	R_1	Method of preparation*	Yield (%)	Melting point (°C)	Formula	Analyses (%) Calcd. C	H	N	S	Found C	H	N	S
C_2H_5	O	C_2H_5	A	74	74–75†	$C_6H_{12}N_2O_3$	—	—	—	—	—	—	—	—
n-C_3H_7	O	C_2H_5	A, C	57,53	75–77	$C_7H_{14}N_2O_3$	48.26	8.10	16.09	—	47.80	8.27	15.95	—
n-C_3H_7	S	C_2H_5	D	38	45–46	$C_7H_{14}N_2O_2S$	44.16	7.41	14.72	16.85	43.70	7.39	14.37	16.78
n-C_4H_9	O	CH_3	B	50	69–70	$C_7H_{14}N_2O_3$	48.26	8.10	16.09	—	47.98	8.47	15.81	—
n-C_4H_9	O	C_2H_5	A, B, C	77, 54, 34	61	$C_8H_{16}N_2O_3$	51.04	8.56	14.89	—	51.31	8.42	15.09	—
n-C_4H_9	S	C_2H_5	D	40	38–39	$C_8H_{16}N_2O_2S$	47.03	7.90	13.72	15.70	47.03	7.76	13.57	15.91
ϕCH_2CH_2	O	C_2H_5	A	57	90	$C_{12}H_{16}N_2O_3$	60.98	6.83	11.86	—	60.76	6.92	11.75	—
ϕCH_2CH_2	S	CH_3	D	27	109–110	$C_{11}H_{14}N_2O_2S$	55.43	5.92	11.76	13.45	55.59	5.77	12.03	13.59
ϕCH_2CH_2	S	C_2H_5	D	65	92–93	$C_{12}H_{16}N_2O_2S$	57.12	6.39	11.11	12.71	56.86	6.22	11.24	12.89
$\phi(CH_2)_3$	O	C_2H_5	A	62	76.5–77	$C_{13}H_{18}N_2O_3$	62.38	7.25	11.19	—	62.43	7.27	11.01	—

*A, ethyl carbonate method; B, isocyanate method; C, oxidative desulfurization method; D, method of Elmore and Ogle (9).
†Literature (12) m.p. 72°.

turn converted into the corresponding azides (Table V). The crude azides were sufficiently pure for conversion into biurets as described above.

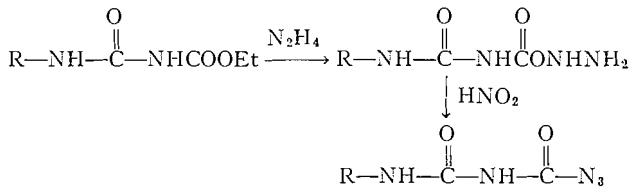
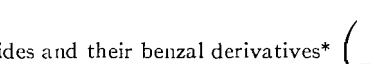
[5] 

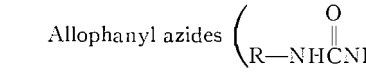
TABLE IV

Allophanyl hydrazides and their benzal derivatives* 

R	Yield (%)	Melting point (°C)	Formula	Analyses (%) Calcd. C	H	N	Found C	H	N
C_2H_5	78	146–147	$C_4H_{10}N_4O_2$	32.86	6.90	38.32	33.12	7.00	38.43
n-C_3H_7	70	154–155	$C_5H_{12}N_4O_2$						
		166–169	$C_{12}H_{16}N_4O_2$*	58.03	6.50	22.56	57.70	6.64	22.47
n-C_4H_9	70	154–155	$C_6H_{14}N_4O_2$	41.37	8.10	32.17	41.47	7.84	31.99
ϕCH_2CH_2	71	153	$C_{10}N_{14}N_4O_2$	54.04	6.35	25.22	53.96	6.74	25.36
$\phi(CH_2)_3$	77	146–146.5	$C_{11}H_{16}N_4O_2$						
		141–142	$C_{18}H_{20}N_4O_2$*	66.65	6.22	17.28	66.83	6.35	17.47

*Benzal derivatives were prepared in cases where a good analysis was not obtainable on the hydrazide.

TABLE V

Allophanyl azides 

R	Yield (%)	Melting point (°C)	Formula	Analyses (%) Calcd. C	H	N	Found C	H	N
C_2H_5	80	119–124	$C_4H_7N_5O_2$	30.58	4.49	44.59	30.75	4.78	44.74
n-C_3H_7	80	90–98	$C_5H_9N_5O_2$	35.08	5.30	40.92	35.28	5.25	41.17
n-C_4H_9	78	85–91	$C_6H_{11}N_5O_2$	38.90	5.99	37.82	38.88	6.09	38.15
ϕCH_2CH_2	94	153–155	$C_{10}H_{11}N_5O_2$	51.48	4.75	30.03	51.51	5.05	29.67
$\phi(CH_2)_3$	94	95–97	$C_{11}H_{13}N_5O_2$	53.42	5.30	28.32	53.35	5.25	28.08

EXPERIMENTAL

Melting points are uncorrected. Microanalyses were carried out by C. Daessle, 5757 Decelles, Montreal.

4-Substituted Allophanic Esters

The synthesis of ethyl 4-*n*-butylallophanate by the three methods used is given by way of illustration.

Ethyl 4-n-Butylallophanate

Procedure A.—N-Butylurea (7.3 g, 0.046 mole) and diethyl carbonate (5.9 ml, 0.048 mole) were added to a solution of 1.05 g (0.046 mole) sodium in 25 ml of absolute alcohol. After the solution was refluxed for 45 min it was evaporated to near dryness. The residue was dissolved in water and the aqueous solution was acidified with acetic acid, causing an oil to separate which soon solidified. The precipitate was filtered, and when water was added to the filtrate a second crop of product was obtained. The total yield of crude product was

5.2 g (77%), m.p. 54–60°. Recrystallization from *n*-hexane yielded a product, m.p. 60–61°, whose infrared spectrum was identical with that of the analytical sample.

Procedure B.—A mixture of 89 g (1 mole) of ethyl carbamate, 99 g (1 mole) of *n*-butyl isocyanate, and 5 drops of triethylamine was heated on the steam cone overnight. The cooled solid residue was recrystallized twice from *n*-hexane to yield 103 g (54%) of ethyl 4-*n*-butylallophanate, m.p. 55–61°. Repeated recrystallization from *n*-hexane gave the analytical sample, m.p. 61°; ν_{max}^{Nujol} 3 330, 1 730, and 1 710 cm^{-1}.

Procedure C.—To a mixture of ethyl 4-*n*-butyl-3-thioallophanate (3 g, 0.015 mole) prepared according to the procedure of Elmore and Ogle (9), 5 ml of concentrated ammonia, and 50 ml of alcohol in a three-necked flask was added 7 ml of 30% hydrogen peroxide at such a rate that the temperature was prevented from rising above 30°. After the mixture was stirred for 2 h it was made acidic with hydrochloric acid. When the solution was concentrated and cooled 1.2 g of crude product was obtained. One recrystallization from alcohol yielded 0.95 g (33.5%) of ethyl-4-*n*-butylallophanate, m.p. 57–60°, whose infrared spectrum was identical with that of the analytical sample.

Allophanyl Hydrazides

The 4-substituted allophanyl hydrazides (Table IV) were prepared according to the procedure of Audrieth and Gordon (10). Analytical samples were prepared by careful recrystallization from low-boiling solvents such as methanol–water or methylene chloride – hexane.

Allophanyl Azides

The 4-substituted allophanyl azides (Table V) were prepared according to the procedure of Audrieth and Gordon (10).

Substituted Biurets

1-Benzyl-5-n-propylbiuret (Azide Method)

A mixture of 10.7 g (0.1 mole) of benzylamine and 17.1 g (0.1 mole) of 4-*n*-propylallophanyl azide in 150 ml of benzene was stirred for 30 min at room temperature. The mixture was then heated to reflux on the steam cone. After evaporation of the solvent under reduced pressure the residue was recrystallized from water–alcohol to yield 20.2 g (86%) of 1-benzyl-5-*n*-propylbiuret, m.p. 85–87°.

Nitrobiuret Method

These biurets were prepared by the reaction of amines with nitrobiuret or a 1,1-disubstituted-5-nitrobiuret according to the procedure of Davis and Blanchard (2) as modified by Dunnigan and Close (11).

1-Methyl-5-phenethylbiuret (Allophanic Ester Method)

Methyl 4-phenethylallophanate (5 g, 0.0225 mole) was heated with an excess of anhydrous methylamine at 120–125° for 3 h in a Parr pressure reaction apparatus. After the solution was cooled, the excess amine was evaporated and the residue was recrystallized from methanol–water to yield 3.0 g (60%) of 1-methyl-5-phenethylbiuret, m.p. 105–110°.

Two recrystallizations from methanol–water gave the analytical sample, m.p. 119.5–120.5°.

1,1-Disubstituted-5-nitrobiurets

These derivatives (Table II) were prepared according to the procedure of Davis and Constan (3).

ACKNOWLEDGEMENT

The assistance of Mr. Brine Kirk is gratefully acknowledged.

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