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Dialkylacetyl Biurets

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In spite of the considerable success of the hypnotics of the acetamide, acyl urea, and barbituric acid types, a need still exists for less toxic compounds with hypnotic properties. The structural features which appear to account for the pharmacological action of the above-mentioned compounds are two: one or more -CONH- groups, and branched-chain alkyl groups whose function is apparently to confer high lipoid-solubility on the molecules of which they are a part. Biuret, $NH_2CONHCONH_2$, has the significant -CONH- group repeated within its structure, and furthermore has been demonstrated to have a very low toxicity. It was to be expected, therefore, that acyl biurets containing branched-chain alkyl groups might combine high hypnotic effectiveness with low toxicity. Accordingly a number of dialkylacetyl biurets were prepared with a view to the study of their pharmacological properties. The dialkylacetyl groups were chosen for their demonstrated value in the acetamide and acyl urea series.

A survey of the literature shows that two approaches to the acyl biurets have been most extensively employed. Acetyl, benzoyl, and phenacetyl biurets have been prepared by the direct acylation of biuret with the acid chlorides[2,3,4,5] and benzoyl biuret has been prepared by the treatment of urea with benzoyl chloride in the presence of pyridine.[4,6] However, attempts to reproduce these results, and to extend the method to the preparation of dialkylacetyl biurets, were disappointing, the yields being very low. Attention was therefore directed to the development of a new synthesis of acyl biurets.

The work of Billeter[7] on the preparation of acyl isocyanates, and the reaction of these compounds with amines and alcohols, together with a number of patents[8,9,10,11] on the preparation of acyl ureas and acyl urethans by these reactions, suggested the possibility of carrying out the reaction

$$RCONCO + R'NHCONH_2 \longrightarrow RCONHCONHCONHR'$$

Accordingly, a series of dialkylacetyl isocyanates was prepared by the modification of Billeter's method patented by Baeyer and Co.,[12] and these isocyanates were allowed to react with urea, substituted ureas, and thiourea, in ether or benzene suspension, and the desired biurets were obtained in yields as high as 83% of the theoretical.

Experimental

Dialkylacetyl Chlorides.—The dialkylacetic acids used were prepared by the method of Levene and Cretcher,[13] with the exception of phenylethylacetic acid, which was prepared by the saponification and subsequent decarboxylation of phenylethylmalonic ester. The acids were converted to the corresponding acid chlorides by allowing them to stand with a 100% excess of thionyl chloride for twelve hours, then refluxing to complete the reaction. The acid chlorides were purified by distillation through a packed column under vacuum.

Dialkylacetyl Isocyanates.—The appropriate acid chloride was dissolved in five volumes of carefully dried diethyl ether and added slowly during stirring to a slight excess of freshly prepared silver cyanate suspended in dry ether. A round-bottomed flask fitted with a sealed stirrer and a reflux condenser carrying a calcium chloride tube was found to be convenient as a reaction vessel. In every case reaction commenced spontaneously and was completed by refluxing the reaction mixture gently for one to three hours. The suspension was then quickly filtered through a Büchner funnel to remove the silver chloride, and the ether was removed from the filtrate in the usual manner. The resi-

TABLE I[a]

Acyl isocyanate	B. p., °C.	Yield, %
Diethylacetyl[b]	59–61° at 31 mm.	90
n-Butylethylacetyl	78–85° at 20 mm.	81
s-Butylethylacetyl	55–56° at 11 mm.	59
Isoamylethylacetyl	100–105° at 30 mm.	82
Dibutylacetyl	68–73° at 12 mm.	74
Phenylethylacetyl	111–115° at 11 mm.	42
Allylethylacetyl	83–85° at 34 mm.	65
Ethyldimethylacetyl	65–70° at 10 mm.	70
Benzoyl[b]	88–91° at 20 mm.	50
Phenacetyl[b]	116–120° at 20 mm.	40

[a] By reason of the high reactivity of acyl isocyanates with atmospheric moisture, direct analysis of these compounds was impracticable. They were characterized through their derivatives with urea. [b] Previously reported.

(1) From a dissertation submitted by William M. Degnan to the Faculty of the Graduate School of Yale University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Ostrogovich, *Ann.*, **288**, 318 (1895).

(3) Ostrogovich, *ibid.*, **291**, 377 (1896).

(4) Ostrogovich, *Bul. soc. stiinte Cluj*, **4**, 528 (1929).

(5) Ostrogovich and Tanislau, *Gazz. chim. ital.*, **64**, 800 (1934).

(6) Bloch and Sobotka, THIS JOURNAL, **60**, 1656 (1938).

(7) Billeter, *Ber.*, **36**, 3213 (1903).

(8) German Patent 271,682.

(9) German Patent 275,200.

(10) German Patent 316,902.

(11) U. S. Patent 1,424,236.

(12) German Patent 275,215.

(13) Levene and Cretcher, *J. Biol. Chem.*, **33**, 505 (1918).

due was then distilled under vacuum. The isocyanates must be carefully protected from moisture throughout the course of preparation and purification, as they react vigorously with water to give the corresponding acetamides and carbon dioxide. The yields in this preparation ranged from 40–90%. Table I lists the acyl isocyanates prepared.

Substituted Ureas.—Monoethyl and diethyl urea were prepared by the nitrourea dearrangement method of Davis and Blanchard.[14] Other ureas were prepared by the conventional treatment of the amine hydrochlorides with potassium cyanate.

Dialkylacetyl Biurets.—These compounds were prepared by the reaction of the appropriate isocyanate with urea or a substituted urea in diethyl ether or petroleum ether. The general technique employed was as follows: the urea was suspended (or dissolved where soluble) in dry ether or petroleum ether in an Erlenmeyer flask. Slightly less than one equivalent of the acyl isocyanate dissolved in dry ether was then added quickly. A reflux condenser carrying a calcium chloride tube was attached to the flask and the suspension (or solution) was refluxed gently until the characteristic odor of the isocyanate had disappeared. The heating time varied from three to forty-eight hours. When reaction was complete the suspension (or solution) was cooled and filtered if the product appeared only slightly soluble in cold ether, or the ether was removed by distillation if the product appeared appreciably soluble. The residue was then crystallized from hot water, hot alcohol, or hot dilute alcohol. Two recrystallizations usually sufficed.

Dialkylacetyl Thiobiurets.—It was found that the dialkylacetyl isocyanates reacted slowly or not at all with thiourea at the temperature of boiling ether, so reactions in this series were carried out in boiling benzene. Thiourea was suspended in dry benzene and exactly one equivalent of the isocyanate was added. The suspension was heated for twelve hours, during which time the thiourea disappeared and a clear yellow solution with a characteristic unpleasant odor was formed. This was cooled in an ice-bath to precipitate a jelly-like material which was filtered off with some difficulty. Attempts to crystallize this crude product from water, alcohol, dilute alcohol, benzene, and dilute acetone failed, amorphous solids being obtained in each case. The acyl thiobiurets were purified by dissolution in cold alcohol, followed by precipitation by the addition of an equal volume of cold water. Several repetitions of this operation gave products which melted sharply. The acyl thiobiurets were obtained as slightly yellow amorphous powders with marked pyroelectric properties. Yields in this series were low, due primarily to handling losses during purification.

Table II lists the acyl biurets prepared. Benzoyl biuret and phenacetyl biuret are not new, having been prepared primarily for comparison with the products reported by Ostrogovich and his co-workers.[3,5] Benzoyl biuret prepared from the isocyanate was shown by mixed melting point to be identical with a sample prepared by the direct benzoylation of biuret with benzoyl chloride.

(14) Davis and Blanchard, THIS JOURNAL, **51**, 1797 (1929).

TABLE II

Biuret	Yield, %	M. p., °C.	Nitrogen, % Calcd.	Found
Diethylacetyl	70	178	20.89	20.89
n-Butylethylacetyl	52	106	18.34	18.24
s-Butylethylacetyl	..	89	18.34	18.19
Isoamylethylacetyl	34	177	17.35	17.21
Dibutylacetyl	61	158	16.34	16.21
Phenylethylacetyl	83	154	16.83	16.90
Allylethylacetyl	..	106	19.71	19.56
Benzoyl[a]	33	233	20.20	20.29
Phenacetyl[a]	66	203	19.00	18.87
Ethyldimethylacetyl	..	171	20.89	20.95
1-Diethylacetyl-5-ethyl	..	245	18.34	18.30
1-Diethylacetyl-5,5-diethyl	20	104	16.34	16.39
1-Diethylacetyl-5-*p*-phenacetyl	79	127	14.14	14.20
1-Diethylacetyl-5,5-cyclopentamethylene	..	113	15.61	15.68
Ethylene-*bis*-diethylacetyl[b]	66	246	19.55	19.65
1-Diethylacetyl-4-thio-	..	132	19.20	19.35
1-Isoamylethylacetyl-4-thio-	..	123	16.22	16.36
1-Allylethylacetyl-4-thio-	..	123	18.34	18.40

[a] Previously reported. [b] Crystallized from glacial acetic acid.

Pharmacological Results

Preliminary pharmacological tests[15] indicate that these compounds compare favorably with sodium barbital in hypnotic effectiveness. They do not show any anesthetic (depressor) action. The toxicities of these compounds, with the exception of those of the thiobiurets, are remarkably low; doses as high as 500 mg./kg. have no permanent ill effects on the test animals. The presence of branched chains in the acyl radical increases effectiveness. Alkylation in the 5-position of the biuret chain also increases effectiveness, 1-diethylacetyl-5,5-cyclopentamethylene biuret being the most active of the compounds tested.

Summary and Conclusions

1. A series of acyl biurets, including dialkylacetyl biurets, 1-dialkylacetyl-5-alkyl biurets, alkylarylacetyl biurets, and 1-dialkylacetyl-4-thiobiurets, has been synthesized by the reactions of appropriate acyl isocyanates upon urea, substituted ureas, and thiourea.

2. Preliminary pharmacological investigation indicates that these compounds possess a moderate hypnotic activity, accompanied by extremely low toxicity. The high margin of safety afforded would indicate that members of this series should be valuable sedatives.

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(15) The pharmacological tests were carried out by the Calco Chemical Co. Division of American Cyanamid and Chemical Corp.