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1-*n*-Alkyl-5,5-ethyl-isobutyl Barbituric Acids

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A number of 1-*n*-alkyl-5,5-dialkyl barbituric acids has been described, but, with the exception of 1-*n*-amylbarbital,[1] none contains more than four carbon atoms in the 1-*n*-alkyl group. The authors therefore prepared a series of eleven 1-*n*-alkyl-5,5-ethyl-isobutyl barbituric acids, the 1-*n*-alkyl group ranging from *n*-amyl to *n*-docosyl. The alkyl groups on the 5 carbon atom were selected, after some trials, as ethyl and isobutyl, so as to give reasonably marked hypnotic action and to avoid, as far as possible, oily products.

The object of the work was fourfold: (a) to determine the limits of the usual substituted malonic ester-urea condensation; (b) to ascertain the physical nature of the compounds; (c) to examine the compounds pharmacologically; and (d) to determine the point, if any, at which the hypnotic effect finally disappears.[2] It was found (a) that the size of the *n*-alkyl group on the substituted urea makes little difference in the ease of the condensation; (b) that the eleven compounds examined are all relatively low melting, three being oils and eight being crystalline solids, and that their solubilities are such as to render them unsatisfactory for pharmacological work; (c) that the series of compounds offers no promise as hypnotics; and (d) that the hypnotic effect disappears at about the *n*-nonyl compound, mol. wt. 338.

The alkyl ureas, prepared as intermediates, show a surprising constancy of melting point. From methyl urea to *n*-docosyl urea only two ureas (ethyl urea, m. p. 96°, and *n*-butyl urea, m. p. 92°) fall outside the range 100–115° (see Table I).

Experimental

Amines.—*n*-Amylamine and *n*-heptylamine were purchased. *n*-Hexylamine was prepared by a Hofmann reaction (using 10% excess sodium hypochlorite) on heptylic amide. The other amines were all prepared by sodium–alcohol reduction of the corresponding nitriles,[3] the higher amines being isolated as the bases, after removal of the alcohol by steam. The nitriles were obtained from the amides by the action of thionyl chloride[4] in benzene, while the amides were made conveniently from the acid chlorides and ammonia, by the Aschan[5] or the Fileti and Ponzio[6] methods. The yields at each stage are very good. *n*-Docosylamine was not isolated in a pure state but was analyzed as the urea.

***n*-Alkyl Ureas.**—The amines were converted into the ureas by means of nitrourea in alcohol.[7] Some of the ureas are new, and these, together with a few from the literature, are tabulated below. Recrystallized from aqueous alcohol, they all form white, crystalline compounds, soluble in hot benzene, soluble in alcohol (the solubility decreasing with increase in length of chain), slightly soluble in ether and in hexane, and (above *n*-heptyl urea) practically insoluble in water. With the exception of the *n*-octyl compound, which has a burning taste, the ureas described are practically tasteless. They all melt within a narrow range of temperature (100 to 115°).

1-*n*-Alkyl-5,5-ethyl-isobutyl Barbituric Acids.—These barbituric acids were prepared in the usual way, by the condensation of one mol of ethyl ethylisobutylmalonate[8] with one mol of the *n*-alkyl urea, in the presence of four mols of sodium ethylate, for four and one-half hours.

The *n*-amyl, *n*-hexyl and *n*-heptyl compounds were purified by extracting the alkaline solution with ether, and then saturating the aqueous layer with carbon dioxide, the products being purified by crystallization from pentane at 0°. The *n*-octyl compound, after purification *via* the alkaline solution, was distilled *in vacuo*. It was not possible to purify efficiently the higher homologs by precipitation from alkaline solution, on account of the soapy nature of the solutions and the solubility of the sodium salts in organic solvents. The *n*-nonyl and *n*-decyl compounds were therefore purified by distillation at low pressure and the higher homologs by recrystallization from pentane at 0°.

It was intended originally to examine the urea–ester condensation quantitatively, but this idea was abandoned as the varied and sacrificial treatment of the products deprived the yields of quantitative significance. In a qualitative sense, however, all the condensations took place with about equal facility.

The properties of the barbituric acids, together with references, mostly indirect, to the intermediates, are given in Table II. All react with cold 5% sodium hydroxide solution, the lower homologs being completely soluble, while the higher ones form soapy, frothy solutions, the effect increasing with the molecular weight. At the same time, as the series is ascended, the sodium salts become increasingly soluble in organic solvents such as ether, and the solubility in water decreases.

Pharmacological Properties.—The physical properties of the 1-*n*-alkyl-5,5-ethyl-isobutyl barbituric acids are so unfavorable for pharmacological testing that the com-

(1) Buck and Hjort, THIS JOURNAL, **59**, 2567 (1937).
(2) Dox, *J. Am. Pharm. Assoc.*, **12**, 602 (1923).
(3) Krafft and Moye, *Ber.*, **22**, 811 (1889).
(4) Michaelis and Siebert, *Ann.*, **274**, 312 (1893).
(5) Aschan, *Ber.*, **31**, 2344 (1898).
(6) Fileti and Ponzio, *Gazz. chim. ital.*, **23**, II, 382 (1893); *cf.* ref. 13.
(7) Buck and Ferry, THIS JOURNAL, **58**, 854 (1936).
(8) Shonle and Moment, *ibid.*, **45**, 243 (1923).

TABLE I

n-ALKYL UREAS

Urea	Formula	Analyses, %N Calcd.	Found	M. p., °C.	Appearance
n-Amyl[9]				100	
n-Hexyl[9]				110	
n-Heptyl[9]				113	
n-Octyl	$C_9H_{20}ON_2$	16.27	16.37	102.5	Long, thin silky plates
n-Nonyl	$C_{10}H_{22}ON_2$	15.04	14.98	108	Small, glittering, felted flat needles
n-Decyl	$C_{11}H_{24}ON_2$	13.98	14.02	113	Felted, silky, thin plates
n-Dodecyl	$C_{13}H_{28}ON_2$	12.27	12.39	107	Glittering, long, flat plates
n-Tetradecyl	$C_{15}H_{32}ON_2$	10.93	11.06	114.5	Fluffy, glittering, long, thin plates
n-Pentadecyl[10]				109	
n-Hexadecyl[11]	$C_{17}H_{36}ON_2$	9.85	9.97	108.5	Glittering, silky, thin plates
n-Heptadecyl[12]				109	
n-Octadecyl[13]	$C_{19}H_{40}ON_2$	8.97	8.88	111.5	Silky clumps of tiny plates
n-Eicosyl[14]				111.5	
n-Docosyl	$C_{23}H_{48}ON_2$	7.60	7.45	115	Clumps of tiny ill-defined flakes

TABLE II

1-*n*-ALKYL-5,5-ETHYL-ISOBUTYL BARBITURIC ACIDS

1-Alkyl group and references to intermediates	Formula	Analyses Calcd. %C	%H	Found %C	%H	M. p. or b. p., °C.	Appearance
n-Amyl[9]	$C_{14}H_{24}O_3N_2$	63.78	9.29	63.94	9.24	49	Meshed tiny needle prisms
n-Hexyl[9,18]	$C_{15}H_{26}O_3N_2$	64.82	9.53	64.85	9.65	55–56	Clumps of tiny needle prisms
n-Heptyl[9]	$C_{17}H_{30}O_3N_2$	65.76	9.75	65.97	9.75	52–53	Meshed small prisms
n-Octyl[5,15a,b]	$C_{18}H_{32}O_3N_2$	66.61	9.95	66.43	10.21	198–200/2.5	Colorless, thick oil (cryst. below room temp.)
n-Nonyl[15c,d,18]	$C_{19}H_{34}O_3N_2$	67.40	10.13	67.15	10.20	190–193/0.5	Colorless thick oil
n-Decyl[15e,f,17]	$C_{20}H_{36}O_3N_2$	68.12	10.30	67.98	10.23	215/1.5	Colorless thick oil
n-Dodecyl[13,19,20]	$C_{22}H_{40}O_3N_2$	69.38	10.64	69.46	10.96	43	Bulky aggregates of tiny spherules
n-Tetradecyl[19,20,21]	$C_{24}H_{44}O_3N_2$	70.53	10.86	70.55	10.98	54	Clumps of tiny spherules
n-Hexadecyl[5,11,15g,19]	$C_{26}H_{48}O_3N_2$	71.49	11.09	71.42	11.28	60	Chalky powder of tiny spherules
n-Octadecyl[5,13,15h,19,22]	$C_{28}H_{52}O_3N_2$	72.57	11.28	72.46	11.53	66	Bulky aggregates of tiny spherules
n-Docosyl[5,15i,23]	$C_{32}H_{60}O_3N_2$	73.78	11.53	73.83	11.76	69	Nodules of tiny plates

pounds could be evaluated only approximately. The compounds were used in aqueous solution containing 10% excess over the theoretical of sodium hydroxide, and were injected intraperitoneally into white mice, in 0.075 or less molar concentration. Only the solution of the *n*-amyl compound remained permanently clear, and this compound was the only one to show a more rapid action than barbital. The hydrolysis in the other solutions, which increased with the molecular weight of the solute, caused slow absorption, with prolonged action and delayed deaths. The M. H. D. (mM/kg.) increased from 0.8 for the *n*-amyl compound to well over 1.25 for the *n*-decyl compound. Beyond this, the low solubility rendered results meaningless. All the compounds are fatal at the M. H. D. Hypnotic action is clearly marked in the *n*-octyl compound (mol. wt. 324) and is still questionably present in the *n*-decyl compound (mol. wt. 352).

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(10) Jeffreys, *Ber.*, **30**, 898 (1897).
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(12) Turpin, *Ber.*, **21**, 2486 (1888).
(13) Adam, *Proc. Roy. Soc.* (London), **A101**, 452 (1922).
(14) Adam and Dyer, *J. Chem. Soc.*, **127**, 70 (1925).
(15) Beilstein's "Handbuch," **4** Auf., II, p. 324; (a) II, p. 349; (b) IV, p. 196; (c) II, p. 353; (d) II, p. 354; (e) II, p. 356; (f) IV, p. 199; (g) II, p. 374; (h) II, p. 384; (i) II*, p. 180.
(16) v. Braun and Sobecki, *Ber.*, **44**, 1464 (1911).
(17) Krafft and Koenig, *ibid.*, **23**, 2382 (1890).
(18) Caspari, *Am. Chem. J.*, **27**, 303 (1902).
(19) Krafft and Stauffer, *Ber.*, **15**, 1728 (1882); *cf.* ref. 18.
(20) Krafft, *ibid.*, **23**, 2360 (1890).
(21) Blau, *Monatsh.*, **26**, 89 (1905).
(22) Gaade, *Rec. trav. chim.*, **55**, 541 (1936).
(23) Levene and Taylor, *J. Biol. Chem.*, **59**, 905 (1924).

Summary

A series of eleven 1-*n*-alkyl-5,5-ethyl-isobutyl barbituric acids has been prepared and described, the 1-*n*-alkyl group ranging from *n*-amyl to *n*-docosyl. Pharmacologically they are unpromising, but hypnotic action is clearly shown up to the *n*-octyl compound (mol. wt. 324). Eight new *n*-alkyl ureas also are described.

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