[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

Quaternary Carbon Compounds. III. Trialkylcarbinyl Isocyanates and Trialkylcarbinamines

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It has been reported that trialkylacetamides[1] (I), trialkylethylamines[2] (II) and trialkylacetic acids[3] (III), in which R is a 3, 4 or 5 carbon atom alkyl group and R_3 totals 12–18 carbon atoms, possess musculotropic antispasmodic activity equal to or greater than papaverine. In order to establish whether the structural requirements for antispasmodic activity observed for I, II and III are generally applicable to highly branched, aliphatic compounds, we prepared a series of trialkylcarbinamines (IV) for pharmacological testing: $R_3C—R'$, I, $R'—CONH_2$; II, $R'—CH_2NH_2$; III, R'—COOH; IV, $R'—NH_2$.

Low molecular weight trialkylcarbinamines[4] have been prepared by the Hofmann degradation of the corresponding acetamides (VI) and subsequent acidic hydrolysis of the resulting isocyanates (VII). Trialkylcarbinamines having one long chain alkyl and two methyl groups and aralkyldialkylcarbinamines[5] have been reported. Tertiary alkyl primary amines have also been prepared[6] by the abnormal reaction of one molar equivalent of a nitrile with two molar equivalents of allylmagnesium bromide. This method results in carbinamines containing at least one allyl or propyl group. Recently Ritter and Kalish[7] have described several *t*-carbinamines prepared by the hydrolysis of N-*t*-alkyl formamides.

In this study, the carbinamines (IV) were synthesized by a series of transformations

$$R_3C—CN \xrightarrow{H_2SO_4} R_3C—CONH_2 \xrightarrow{NaOBr}$$

(V) (VI)

$$R_3C—NCO \xrightarrow{HCl} IV$$

(VII)

The trialkylacetonitriles[8] (V) were hydrolyzed to the corresponding acetamides[2] (VI) with hot 80% sulfuric acid and the amides converted to the corresponding isocyanates[4] (VII) in 80–90% yields. The isocyanates (VII) were hydrolyzed to the carbinamines[9] (IV) when heated with 20% hydrochloric acid. The trialkyl isocyanates (Table I) form ureas upon reaction with various amines. In Table II are listed the amines prepared in this investigation.

In general, the trialkylcarbinamines were less spasmolytic and more toxic than the corresponding trialkylethylamines. N,N'-bis-(1,1-Dibutylamyl)-urea was inactive, whereas N-1,1-dibutylamylurea and N-1,1-dibutylamylacetamide possess musculotropic antispasmodic activity in the range of papaverine.

Experimental

The preparation of 1,1-dibutylamylamine will illustrate the general procedures.

Trialkylcarbinyl Isocyanates.[4]—In a 500 cc., three-necked flask cooled in an ice-salt-bath and fitted with an efficient stirrer, condenser and dropping funnel, was placed an ice cold solution of 24 g. of sodium hydroxide in 200 cc. of water. To the rapidly stirred solution, 8 cc. of bromine was added slowly. When the bromine color had disappeared, 22.7 g. (0.1 mole) of finely powdered tributylacetamide was added in one portion and the suspension was stirred vigorously for four hours at 0°. Within one hour, the solid was transformed into an oil. The oil was extracted with ether, the ether layer washed with water, dried over sodium sulfate, the solvent removed *in vacuo* and the residue fractionated. The isocyanate was then redistilled for analysis.

The isocyanate was fairly stable at room temperature, but slowly deposited N,N'-bis-(1,1-dibutylamyl)-urea. The latter was formed by the reaction of 1,1-dibutylamyl isocyanate and 1,1-dibutylamylamine and melted at 127–128°. This urea was also prepared by warming a mixture of 1,1-dibutylamyl isocyanate and 1,1-dibutylamylamine and melted at 127–127.5° after recrystallization from ethanol-water. A mixed melting point of the two samples showed no depression.

Anal. Calcd. for $C_{27}H_{56}N_2O$: N, 6.60. Found: N, 6.43.

The following derivatives of 1,1-dibutylamyl isocyanate were prepared.

N-1,1-Dibutylamylurea.—A mixture of 12 g. of 1,1-dibutylamyl isocyanate and 55 cc. of concentrated ammonia water (28%) was stirred for six hours and stored for four days in a refrigerator. The oily precipitate was filtered, washed with cold, dilute ethanol and recrystallized from a mixture of ethanol-water; weight 4 g.; m. p. 153–153.5°.

Anal. Calcd. for $C_{14}H_{30}N_2O$: N, 11.56. Found: N, 11.75.

N-(β-Diethylaminoethyl)-N'-(1,1-dibutylamyl)-urea hydrochloride: A cold solution of 11.3 g. (0.05 mole) of 1,1-dibutylamyl isocyanate in 25 cc. of benzene was added to a cold solution of 5.8 g. (0.05 mole) of β-diethylaminoethylamine in 25 cc. of benzene. The resulting warm solution was cooled in an ice-bath until the reaction subsided. After standing overnight at room temperature,

(1) Junkmann and Allardt, U. S. Patent 2,186,976 (1940).

(2) Allardt and Junkmann, U. S. Patent 2,361,524 (1944).

(3) Sperber, Papa and Schwenk, THIS JOURNAL, **70**, 3091 (1948).

(4) Montagne and Casteran, *Compt. rend.*, **191**, 139 (1930).

(5) Mentzer, Buu-Hoï and Cagniant, *Bull. soc. chim.*, **9**, 813 (1942); **10**, 141 (1943); Cagniant, Mentzer and Buu-Hoï, *ibid.*, **10**, 145 (1943).

(6) Allen and Henze, THIS JOURNAL, **61**, 1790 (1939); Henze, Allen and Leslie, *ibid.*, **65**, 87 (1943).

(7) Ritter and Kalish, *ibid.*, **70**, 4048 (1948).

(8) Ziegler and Ohlinger, *Ann.*, **495**, 84 (1932); see ref. 3.

(9) Buu-Hoï (*Nature*, **156**, 392 (1945)) found that the primary amines prepared from a series of fatty acids isolated from dead tubercle bacilli were active against tubercle bacilli, although the parent acids and amides were inactive. In addition, a series of fatty acid amines were also bacteriostatic against acid-fast bacteria. Borrows, Hargreaves, Page, Resugg and Robinson (*J. Chem. Soc.*, 197 (1947)) prepared a series of primary, secondary and tertiary amines containing 8–30 carbon atoms and found that amines containing 17–20 carbon atoms were highly active *in vitro* against *Strep. haemolyticus* and *Staph. aureus*. *Mycobacterium tuberculosis* was inhibited by some of these amines.

TABLE I

TRIALKYLCARBINYL ISOCYANATES, RR'R"C—NCO

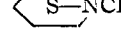
R	R'	R"	B. p., °C.	Mm.	Yield, %		N Analyses, % Calcd.	Found
n-C_3H_7	*n*-C_3H_7	*n*-C_3H_7	65–66	2	90	$C_{11}H_{21}NO$	7.65	7.23
n-C_4H_9	*n*-C_4H_9	*n*-C_4H_9	103–105	1	90	$C_{14}H_{27}NO$	6.22	6.22
n-C_4H_9	*n*-C_5H_{11}	*n*-C_5H_{11}	120–121	2	92	$C_{16}H_{31}NO$	5.53	5.54
n-C_5H_{11}	*n*-C_5H_{11}	*n*-C_5H_{11}	126–127	1	94	$C_{17}H_{33}NO$	5.24	5.17
CH_3	*n*-C_7H_{15}	*n*-C_7H_{15}	130–132	2	68	$C_{17}H_{33}NO$	5.24	5.40
n-C_4H_9	*n*-C_7H_{15}	*n*-C_7H_{15}	176–177	6.5	79	$C_{20}H_{39}NO$	4.53	5.00
n-$(C_2H_5)_2NCH_2$—	*n*-C_4H_9	*n*-C_4H_9	126	4	70	$C_{15}H_{30}N_2O$	11.02	10.45
	*n*-C_4H_9	*n*-C_4H_9	146–148	6	65	$C_{15}H_{30}N_2O$	10.53	10.63

TABLE II

TRIALKYLCARBINAMINES—RR'R"C—NH_2

R	R'	R"	B. p., °C.	Mm.	Yield,[a] %		N Analyses, % Calcd.	Found
n-C_3H_7	*n*-C_3H_7	*n*-C_3H_7	78	13	71	$C_{10}H_{23}N$[b]	8.91	9.04
n-C_4H_9	*n*-C_4H_9	*n*-C_4H_9	78–80	1	72	$C_{13}H_{29}N$	7.30	6.82
n-C_4H_9	*n*-C_5H_{11}	*n*-C_5H_{11}	119	3	80	$C_{15}H_{33}N$	6.16	6.01
n-C_5H_{11}	*n*-C_5H_{11}	*n*-C_5H_{11}	121–122	2	81	$C_{16}H_{35}N$	5.80	5.55
CH_3	*n*-C_7H_{15}	*n*-C_7H_{15}	130–131	2.5	79	$C_{16}H_{35}N$	5.80	5.20
n-C_4H_9	*n*-C_7H_{15}	*n*-C_7H_{15}	147–149	2	89	$C_{19}H_{41}N$	C, 80.48	C, 80.56
							H, 14.57	H, 14.43

[a] Yields are based on distilled products. [b] $n^{21}D$ 1.4349; literature,[6] b. p. 47–48° (5 mm.); $n^{20}D$ 1.4353.

the solution was refluxed for two hours and the solvent was removed *in vacuo*, leaving a gummy sirup. The latter was dissolved in ether and saturated with hydrogen chloride and upon removal of the ether, a gum remained, which was crystallized from ligroin; yield 11 g. (58%), m. p. 91–91.5°.

Anal. Calcd. for $C_{20}H_{44}N_3OCl$: N, 11.13. Found: N, 10.91.

N-Benzyl-N'-1,1-dibutylamylurea.—Upon mixing equivalent quantities of benzylamine and 1,1-dibutylamyl isocyanate the urea crystallized immediately. The solid was recrystallized from a mixture of alcohol and water and appeared as white needles, m. p. 127–128°.

Anal. Calcd. for $C_{21}H_{36}N_2O$: N, 8.40. Found: N, 8.30.

N-(2-Pyridyl)-N'-(1,1-dibutylamyl)-urea.—A solution of 4.7 g. (0.05 mole) of 2-aminopyridine and 12.7 g. (0.05 mole) of 1,1-dibutylamyl isocyanate in 50 cc. of benzene was refluxed for twenty-four hours. The benzene was removed and the residual oil crystallized slowly. The solid was recrystallized twice from a mixture of ethanol and water, m. p. 138–138.5°.

Anal. Calcd. for $C_{19}H_{33}N_3$: N, 13.85. Found: N, 13.53.

Trialkylcarbinamines.—A mixture of 20 g. (0.089 mole) of 1,1-dibutylamyl isocyanate and 70 cc. of 20% hydrochloric acid was heated and stirred for five hours on a steam-bath. Upon cooling 1,1-dibutylamylamine hydrochloride precipitated, yield 16.7 g.; m. p. 68–69°. To an aqueous suspension of the hydrochloride, there was added sodium hydroxide pellets, the liberated amine ether extracted and the ether extracts washed with water. After drying over anhydrous potassium carbonate, the solvent was removed and the residue distilled. A colorless, free-flowing liquid was obtained. In other experiments, the amine hydrochloride was not isolated. After completion of the hydrolysis of the isocyanate to the carbinamine, the mixture was neutralized with sodium hydroxide pellets and the free base taken up in ether and distilled.

The time required for the hydrolysis varied with the molecular weight of the isocyanate. 1,1-Dipropylamyl isocyanate hydrolyzed immediately upon contact with hydrochloric acid, whereas 1-heptyl-1-butyloctyl isocyanate required seven hours to complete the hydrolysis.

N-1,1-Dibutylamylacetamide.—To a solution of 1 cc. of 1,1-dibutylamylamine dissolved in 5 cc. of dry pyridine was added dropwise 2 cc. of acetic anhydride. The warm solution was allowed to stand one hour and then decomposed on ice and water. The white solid was recrystallized from a mixture of ethanol and water, m. p. 80.5–81.5°.

Anal. Calcd. for $C_{15}H_{31}NO$: N, 5.81. Found: N, 5.79.

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Summary

The preparation of a series of trialkylcarbinyl isocyanates and trialkylcarbinamines by the Hofmann degradation of the corresponding acetamides is described.

The trialkylcarbinamines exhibit weaker antispasmodic activity than the corresponding trialkylethylamines.

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