[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Antispasmodics. IV[1]

BY F. F. BLICKE AND F. B. ZIENTY[2]

In this paper, a continuation of our studies of antispasmodics,[3] there has been described a number of mixed tertiary amines of the general formula CH_3NRR' in which R represents a β-cyclohexylethyl and R' an alkyl, cycloalkylalkyl or arylalkyl group.

These compounds were prepared since it was of interest to determine the extent to which antispasmodic activity would be retained by the replacement of one of the β-cyclohexylethyl radicals in methyldi-β-cyclohexylethylamine by some other group. Methyldi-β-cyclohexylethylamine was chosen since this compound was found to be a strong antispasmodic early in our investigation.

Furthermore, we wished to obtain data with regard to the relative activities of the mixed amine, CH_3NRR', and the corresponding amines CH_3NR_2 and $CH_3NR'_2$. So far, six instances have been found in which the mixed amine exhibited strong activity while one or both of the amines of types CH_3NR_2 and $CH_3NR'_2$ proved to be weak antispasmodics.

From the data in Table I[4] it can be seen that active antispasmodics are obtained by the substitution of one β-cyclohexylethyl group in methyldi-β-cyclohexylethylamine by the *n*-octyl, cinnamyl, γ-cyclohexylpropyl, δ-cyclohexylbutyl or β-phenylethyl radical. Antispasmodics, weak in activity, are produced when one β-cyclohexylethyl group is replaced by a *n*-hexyl, 2-(6-methyl-5-heptenyl), cyclohexyl, cyclohexylmethyl, β-cyclopentylethyl, γ-phenoxypropyl or a benzyl radical.

However, if the carbon chain in the β-cyclohexylethyl radical is lengthened by one or two carbon atoms the cyclohexyl and cyclohexylmethyl groups may be used effectively; thus, the tertiary amines methylcyclohexyl-δ-cyclohexylbutyl, methylcyclohexylmethyl-δ-cyclohexylpropyl and methylcyclohexylmethyl-δ-cyclohexylbutylamine are strong antispasmodics.

(1) This article is part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by F. B. Zienty in partial fulfilment of the requirements for the degree of Doctor of Philosophy, in the University of Michigan.

(2) Frederick Stearns and Company Fellow.

(3) Blicke and Monroe, THIS JOURNAL, **61**, 91 (1939); Blicke and Zienty, *ibid.*, **61**, 93, 771 (1939).

(4) We are indebted to Dr. C. W. Geiter of Frederick Stearns and Company for the pharmacological evaluation of the amines.

Experimental Part

All of the amines, except those described below, were prepared by the general procedures described previously.

The amine hydrochlorides were obtained by treatment of an ether solution of the base with hydrogen chloride.

Methyldicinnamylamine.—A mixture of 9.3 g. of methylamine, 70 cc. of alcohol, 35 cc. of benzene and 10.6 g. of anhydrous sodium carbonate was cooled and stirred and 19.7 g. of cinnamyl bromide, dissolved in 35 cc. of benzene, added from a dropping funnel. The material was heated for five hours on a steam-bath, the solvents removed and excess hydrochloric acid added to the residue. After the unchanged bromide had been extracted with ether, sodium hydroxide solution was added and the oily amines were dissolved in ether. The ether solution was dried with fused sodium sulfate and the solvent removed. Upon distillation there was obtained 5.0 g. of the tertiary amine, b. p. 180–185° at 5 mm., and 2.6 g. of methylcinnamylamine, b. p. 102–104° at 5 mm.[5]

The gummy, very hygroscopic hydrochloride of methyldicinnamylamine precipitated when hydrogen chloride was passed into an ether solution of the base. The product was washed with absolute ether and then dissolved in acetone. Upon addition of ether the hydrochloride precipitated as an oil which solidified after some time. The material was dissolved again in acetone and precipitated with ether. After this process had been repeated three times, crystalline hydrochloride was obtained. The latter becomes oily but does not dissolve when water is added to it.

Methyldi-2-cyclohexanonylmethylamine.—A mixture of 30 g. of trioxymethylene, 34 g. of methylamine hydrochloride, 196 g. of cyclohexanone and 200 cc. of alcohol was heated just to the boiling point; the reaction began and proceeded, vigorously, to completion without further application of heat. After about five minutes the trioxymethylene had disappeared. The solution was filtered, the alcohol removed, the residue cooled to about 30° and extracted with ether to remove cyclohexanone. The product was treated with 25% sodium hydroxide solution, the amines extracted with ether and the ether solution dried with fused sodium sulfate. After removal of the solvent the oily material was kept at 0° for twelve hours; absolute ether was added and the crystalline compound filtered; yield 14 g. Mannich and Braun[6] prepared the amine with the use of aqueous formaldehyde solution but obtained a yield of only 6 g. The base was recrystallized from methyl alcohol or benzene.

Hydrogen chloride was passed into a warm solution of 4 g. of the base in 125 cc. of benzene, the solvent decanted from the precipitated oily hydrochloride and dry ether added. The salt, which soon became crystalline, was purified by the gradual addition of anhydrous ether to 5 g. of the crude product dissolved in 20 cc. of absolute alcohol.

(5) Von Braun and Engel (*Ann.*, **436**, 313 (1924)) reported the boiling point to be 110-112° at 12 mm.

(6) Mannich and Braun, *Ber.*, **53**, 1877 (1920).

TABLE I

AMINES AND AMINE HYDROCHLORIDES

The hydrochlorides were recrystallized in the following manner: compounds 3, 7, 8, 9, 16, 17, 18 and 21 were recrystallized from acetone; compounds 4, 11, 12, 13, 14 and 20 from 1,4-dioxane; compound 6 from carbon tetrachloride; compound 15 from alcohol; compounds 1, 5, 10 and 19 from a mixture of acetone and alcohol; compound 2 was precipitated from an acetone solution by addition of dry ether. The chloroaurates of compounds 24 and 25 were recrystallized from dilute alcohol.

	Amine (tertiary)	Antispasmodic activity	Prepared from	B. p. of fraction used °C.	Mm.	Amine hydrochloride M. p., °C.	Formula	% Cl Calcd.	Found
1	Methyldibenzyl	(Stimulant)	Methylamine	161–162	12[a]	200–201[b]	$C_{15}H_{18}NCl$	14.32	14.33
2	Methyldicinnamyl	Weak	Methylamine	180–185	5	148–149	$C_{19}H_{22}NCl$	11.83	11.90
3	Methyl-cinnamyl-benzyl	Weak	Methylcinnamylamine[c]	175–180	10	141–142	$C_{17}H_{20}NCl$	12.96	13.01
4	Methyl-cinnamyl-γ-phenoxypropyl	Weak	Methylcinnamylamine	195–198	4	130–131	$C_{19}H_{24}ONCl$	11.16	11.19
5	Methyl-cinnamyl-cyclohexylmethyl	Inactive	Methylcinnamylamine	166–169	9	185–186	$C_{17}H_{26}NCl$	12.68	12.73
6	Methyl-cinnamyl-β-cyclohexylethyl	Active	Methyl-β-cyclohexylethylamine[d]	175–180	8	211–212	$C_{18}H_{28}NCl$	12.07	11.99
7	Methyl-cinnamyl-β-cyclopentylethyl	Weak	Methylcinnamylamine	164–167	8	183–184	$C_{17}H_{26}NCl$	12.68	12.73
8	Methyl-cyclohexyl-β-cyclohexylethyl	Weak	Methylcyclohexylamine[e]	133–137	6	201–202	$C_{15}H_{30}NCl$	13.66	13.55
9	Methyl-cyclohexyl-δ-cyclohexylbutyl	Active	Methylcyclohexylamine	151–155	4	184–185	$C_{17}H_{34}NCl$	12.32	12.30
10	Methyl-cyclohexylmethyl-β-cyclohexylethyl	Weak	Methyl-β-cyclohexylethylamine	144–146	6	250–251	$C_{16}H_{32}NCl$	12.95	12.91
11	Methyl-cyclohexylmethyl-γ-cyclohexylpropyl	Active	Methylcyclohexylmethylamine[f]	140–145	6	199–200	$C_{17}H_{34}NCl$	12.32	12.29
12	Methyl-cyclohexylmethyl-δ-cyclohexylbutyl	Active	Methylcyclohexylmethylamine	154–157	6	179–180	$C_{18}H_{36}NCl$	11.74	11.94
13	Methyl-β-cyclohexylethyl-hexyl	Weak	Methyl-β-cyclohexylethylamine	113–117	5	203–204	$C_{15}H_{32}NCl$	13.55	13.51
14	Methyl-β-cyclohexylethyl-octyl	Active	Methyl-β-cyclohexylethylamine	139–141	5	170–171	$C_{17}H_{36}NCl$	12.24	12.19
15	Methyl-β-cyclohexylethyl-benzyl	Weak	Methyl-β-cyclohexylethylamine	140–142	4	242–243	$C_{16}H_{26}NCl$	13.24	13.19
16	Methyl-β-cyclohexylethyl-β′-phenylethyl	Active	Methyl-β-cyclohexylethylamine	150–152	4	205–206	$C_{17}H_{28}NCl$	12.58	12.54
17	Methyl-β-cyclohexylethyl-γ′-phenoxypropyl	Weak	Methyl-β-cyclohexylethylamine	168–171	5	142–143	$C_{18}H_{30}ONCl$	11.37	11.38
18	Methyl-β-cyclohexylethyl-β′-cyclopentylethyl	Weak	Methyl-β-cyclohexylethylamine	137–139	6	251–252	$C_{16}H_{32}NCl$	12.95	13.11
19	Methyl-β-cyclohexylethyl-2-methylcyclohexylmethyl	Inactive	Methyl-β-cyclohexylethylamine	137–139	5	230–231	$C_{17}H_{34}NCl$	12.32	12.33
20	Methyl-β-cyclohexylethyl-γ′-cyclohexylpropyl	Active	Methyl-β-cyclohexylethylamine	153–156	6	228–229	$C_{18}H_{36}NCl$	11.75	11.79
21	Methyl-β-cyclohexylethyl-δ′-cyclohexylbutyl	Active	Methyl-δ-cyclohexylbutylamine[g]	160–165	4	191–192	$C_{19}H_{38}NCl$	11.16	11.38
22	Methyl-β-cyclohexylethyl-2-(6-methyl-5-heptenyl)-	Weak	Methyl-2-(6-methyl-5-heptenyl)-amine[h]	140–145	5	Oil	$C_{17}H_{33}N$	N, 5.58	5.38
23	Methyl-β-hydroxyethyl-β′-(β″-cyclohexyl-ethoxy)-ethyl	Weak	Methyldi-β-hydroxyethylamine[i]	142–143	5	Oil	$C_{13}H_{27}O_2N$	N, 6.12	6.28
24	Methyldi-γ-phenylpropyl	Active	Methylamine	182–184	6	127–128[l]	$C_{19}H_{26}NCl_4Au$	Au, 32.47	32.37
25	Methyldi-δ-phenylbutyl	Active	Methylamine	193–195	6	113–114[l]	$C_{21}H_{30}NCl_4Au$	Au, 31.04	31.00
26	Methyldi-2-cyclohexanonylmethyl	Weak	Methylamine	(M. p. 170–172[j])		195–197[k]	$C_{15}H_{26}O_2NCl$	12.32	12.04

[a] Wegler and Frank (*Ber.*, **69**, 207 (1936)) reported 165° (15 mm.). [b] Hughes and Ingold (*J. Chem. Soc.*, 75 (1933)) described the hydrobromide and picrate. [c] Von Braun and Engel, *Ann.*, **436**, 312 (1924). [d] Blicke and Monroe, THIS JOURNAL, **61**, 92 (1939). [e] Sabatier and Maillie, *Compt. rend.*, **153**, 1207 (1911). [f] Blicke and Zienty, THIS JOURNAL, **61**, 94 (1939). [g] Blicke and Monroe, *ibid.*, **61**, 92 (1939). [h] German Patent 617,536, *C. A.*, **30**, 731 (1936). [i] Knorr and Matthes, *Ber.*, **31**, 1069 (1898). [j] Mannich and Braun (*ibid.*, **53**, 1877 (1920)) found 172°. They prepared the hydrochloride also but merely stated that it is very hygroscopic. [k] With effervescence. [l] M. p. of chloroaurate.

Mannich and Braun[6] stated that the hydrochloride is hygroscopic; no melting point was reported by them.

Analysis of Amine Hydrochlorides.—We found the Fajans method[7] very suitable and advantageous for the determination of chlorine in many of our amine hydrochlorides. Since the method requires some modification in the case of an amine salt, the whole procedure is described below.

In order to carry out the analysis successfully the liberated amine must be extracted with ether. In the event that the amine base is very insoluble in water, ether can be added to the neutralized solution and titration performed without removal of the ether later. If the base is somewhat soluble, as is the case with methylcyclohexylmethylamine, the amine must be extracted and the ether layer removed, otherwise enough of the amine remains in the aqueous layer to obscure the end-point. When an amine was found to be very soluble in water it was so difficult to remove it completely from the water layer that the Fajans method was not used.

A mixture of the amine hydrochloride, which weighed 0.2–0.3 g., 15 cc. of water and one drop of phenolphthalein indicator was made alkaline with 2% chloride-free sodium hydroxide solution. If the amine hydrochloride is insoluble in water, sufficient alcohol may be added to effect solution or the alkali may be added in portions and the mixture agitated or warmed until the red color has disappeared before each addition of the alkali. The liberated amine is extracted three times with 50-cc. portions of ether, the ether layer removed carefully by decantation and the slight amount of solvent which remains can be evaporated on a steam-bath. The cold solution is neutralized with 1:50 nitric acid and diluted to about 75 cc. Ten drops of dichlorofluorescein indicator and 5 cc. of 2% dextrin solution are added and the solution titrated with 0.1 *N* silver nitrate. Calcd. for $C_{23}H_{38}NCl$ (benzyldi-β-cyclohexylethylamine hydrochloride): Cl, 9.75. Found: Cl, 9.73, 9.76.

(7) See Willard and Furman, "Elementary Quantitative Analysis," D. Van Nostrand Co., New York, 1935, p. 138.

Summary

A number of mixed amines of the general type CH_3NRR' have been described in which R and R′ represent alkyl, cycloalkylalkyl and arylalkyl groups. Eleven of the amines were found to be strong antispasmodics.[8]

(8) A very recent contribution to the field of antispasmodics is the paper by Buth, Külz and Rosenmund (*Ber.*, **72**, 19 (1939)).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

Substituted Vinyl Barbituric Acids. III. Derivatives Containing a Dialkylvinyl Group Having Five or More Carbon Atoms

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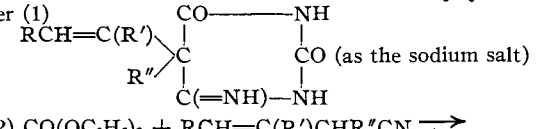
The recent syntheses of a number of (dialkylvinyl) alkyl cyanoacetic esters in which the substituted vinyl groups contain five, six and seven carbon atoms,[1] furnished the intermediates necessary for the syntheses of corresponding barbituric acids, which are described in this paper.

The substituted vinyl alkyl cyanoacetic esters condense with urea readily, giving imino barbituric acids which can be hydrolyzed to the barbituric acids. In each case a side reaction occurs during the condensation, in which part of the ester undergoes alcoholysis and loses a carbethoxy group as ethyl carbonate, forming a nitrile.

$$RCH{=}C(R')C(R'')(CN)COOC_2H_5 + H_2NCONH_2 + NaOC_2H_5 \longrightarrow$$

either (1)



or (2) $CO(OC_2H_5)_2 + RCH{=}C(R')CHR''CN \rightleftharpoons$

I (β, γ) $RCH_2C(R'){=}C(R'')CN$ II (α, β)

(1) Cope and Hancock, THIS JOURNAL, **60**, 2903 (1938).

The nitriles which are produced may have structures corresponding to either I or II, or may be composed of mixtures of the α,β- and β,γ-unsaturated isomers. After loss of a carbethoxy group the double bond can shift through the migration of hydrogen. Nitriles similar in structure to these have been observed to reach equilibrium in the presence of sodium ethoxide as a catalyst.[2] The structures of the nitriles and their synthesis by the alcoholysis of substituted vinyl alkyl cyanoacetic esters will be the subject of a future communication.

In order to produce barbituric acid derivatives according to equation (I) in good yield, it is essential that the alcoholysis (equation II) be minimized. One method by which this may be accomplished is by the substitution of sodium isopropoxide in isopropyl alcohol for the sodium ethoxide in ethyl alcohol usually employed as a condensing agent. Another method which was employed in some cases was to substitute guani-

(2) *Cf.* Kandiah and Linstead, *J. Chem. Soc.*, 2139 (1929); Letch and Linstead, *ibid.*, 443 (1932); Letch and Linstead, *ibid.*, 612 (1933).