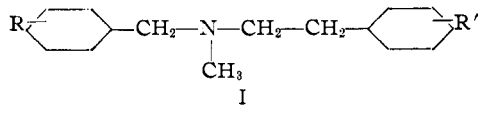
[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Antifibrillatory Agents. The Preparation of Some N-Benzyl-N-methylphenethylamines

BY A. R. SURREY, A. MOORADIAN, R. A. CUTLER, C. M. SUTER AND J. S. BUCK

A series of compounds having the structure I



I

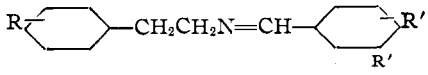
has been synthesized and found to have antifibrillatory action in varying degree.[1]

The compounds described in Table II were synthesized from the appropriate benzaldehydes and phenethylamines by condensation to give the corresponding Schiff bases. In most instances, the latter were not isolated but were reduced directly with palladium–charcoal to the N-benzylphenethylamines. In a few cases, the Schiff bases were isolated and purified (Table I).

The secondary amines were alkylated with formaldehyde and formic acid to give the desired N - benzyl - N - methylphenethylamines. N-(3,4-Dimethoxybenzyl) - N - ethyl - 4 - methoxyphenethylamine, was prepared from the corresponding secondary amine by ethylation with ethyl sulfate in good yield.

TABLE I

SCHIFF BASES

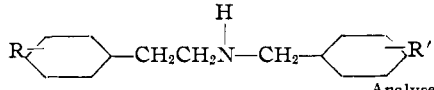


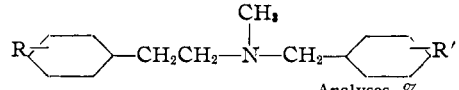
R	R′	M. p., °C.[a]	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
4-OCH_3	3-OCH_3-4-OC_2H_5[b]	68.2–69.4	72.82	72.91	7.40	7.48	4.47	4.34
4-O_2CH_2	4-OCH_3	63.2–63.9	72.09	72.29	6.05	6.09	4.95	4.75
4-O_2CH_2	3,4-di-OCH_3	74.9–76.7	68.99	69.01	6.11	5.90	4.47	4.38

[a] Corrected melting points. [b] All Schiff bases were recrystallized from Skellysolve B.

TABLE II

HYDROCHLORIDES





R	R′	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
H	4-OCH_3	256–259[b]			Cl, 12.77	12.60		
H	3,4-di-OCH_3	212–213[c]					4.55	4.43
4-OCH_3	3-OCH_3	165–166			Cl, 11.52	11.57		
4-OCH_3	4-OCH_3	[c]						
4-OCH_3	3,4-di-OCH_3	224–225[c]			Cl, 10.50	10.45		
4-OCH_3	3,4-O_2CH_2	239–242			Cl, 11.01	11.05		
4-OCH_3	3-OCH_3-4-OC_2H_5	209–210	64.85	65.15	7.45	7.30	3.98	3.84
4-OCH_3	3,4,5-tri-OCH_3	158–160[d]			Cl, 9.67	9.58		
3,4-di-OCH_3	3-OCH_3	138–140[c]			Cl, 10.50	10.55		
3,4-di-OCH_3	4-OCH_3	225–228[c]						
3,4-di-OCH_3	3,4-di-OCH_3	166–168			Cl, 9.67	9.71		
3,4-di-OCH_3	3,4-O_2CH_2	195–198[c]			Cl, 10.10	10.01		
3,4-O_2CH_2	4-OCH_3	248–249	63.45	63.56	6.26	6.11	4.35	4.27
3,4-O_2CH_2	3,4-di-OCH_3	205.5–206	61.45	61.40	6.30	6.06	3.98	3.90
3,4-O_2CH_2	3,4-O_2CH_2	240–241[c]	60.81	61.02	5.40	5.28	4.17	4.30
3,4,5-tri-OCH_3	3-OCH_3	154.5–155	62.03	61.93	7.08	7.09	Cl, 9.67	9.52
		182.4–183.2	64.37	64.55	6.60	6.57	4.17	4.06
		180–181	62.37	62.35	6.61	6.41	3.83	3.64
		205.6–206.6	61.80	61.92	5.76	5.85	4.01	3.89
		166–166.5	62.90	63.25	7.39	7.27	Cl, 9.29	9.29
		145–149			Cl, 12.15	12.00	4.80	4.70
		190.8–191.9	67.17	67.34	7.52	7.31	4.35	4.26
		149–152			Cl, 11.03	10.87	4.35	4.10
		145.5–147.6	67.17	67.24	7.52	7.80	4.35	4.32
		190–192			Cl, 10.10	10.12	3.98	3.99
		169.5–171			Cl, 10.57	10.39	4.16	3.98
		178.4–179.5	65.65	65.61	7.71	7.39	3.93	3.80
		198.8–200[d]			Cl, 9.28	9.38	3.66	3.72
		166.5–167.5			Cl, 10.10	10.09	3.98	3.91
		181–182	64.84	65.03	7.45	7.36	3.98	3.98
		199–201			Cl, 9.30	9.33	3.66	3.65
		190–192	62.37	62.20	6.61	6.66	Cl, 9.72	9.64

[a] Corrected melting points. [b] Shepard and Ticknor, THIS JOURNAL, **38**, 381 (1916). [c] Buck, *ibid.*, **53**, 2192 (1931). [d] Prepared in these Laboratories by Dr. G. Fohlen.

Of the compounds tested thus far, N-3,4-dimethoxybenzyl - N - methyl - 4 - methoxyphenethylamine, and N-3,4-dimethoxybenzyl-N-methyl -3,4-dimethoxyphenethylamine, appear to be the best antifibrillatory agents. In anesthetized cats, the former proved to be 2.3 times more active than quinidine and 1.3 times more active than α-fagarine.[2] The ratio of its toxicity to its activ-

(1) We are indebted to Dr. J. R. DiPalma, Long Island College of Medicine, New York, for the pharmacological results, the details of which will be published elsewhere. The method employed for testing these compounds is described by DiPalma and Lambert, *Science*, **107**, 66 (1948).

(2) J. R. DiPalma, J. J. Lambert, R. A. Reiss and J. E. Schults, to be published in the *Fed. Proc.*, April, 1949.

ity is quite favorable. It is interesting to note that when a tertiary amine is quaternized, its antifibrillatory activity is lost. For example, the methiodide of N-3,4-dimethoxybenzyl-N-methyl-4-methoxyphenethylamine shows no antifibrillatory activity.

Experimental[3]

Preparation of Secondary Amines (Table II) General Procedure.—A mixture of equimolecular quantities of the appropriate benzaldehyde and phenethylamine was allowed to stand at room temperature for twenty hours or heated *in vacuo* for one hour on a steam-bath. The mixture was dissolved in ethanol and reduced catalytically in the presence of palladium–charcoal. After filtering off the catalyst, alcoholic hydrogen chloride solution was added followed by ether where necessary. The solid hydrochloride which precipitated was filtered off, washed with ether, dried and recrystallized from water or isopropyl alcohol.

Preparation of Tertiary Amines (Table II) General Procedure.—A mixture of the secondary amine base (1 mole), 35–40% formaldehyde (1.1 mole) and formic acid (2.5 mole) was heated on the steam-bath for eight to twelve hours. An excess of sodium hydroxide solution was added to the reaction mixture and the base was extracted with ether. Addition of alcoholic hydrogen chloride solution to the dried ether extract yielded the desired tertiary amine hydrochloride. The products were purified by recrystallization either from isopropyl alcohol or a mixture of ethanol and ether.

N-(3,4-Dimethoxybenzyl)-N-ethyl-4-methoxyphenethylamine Hydrochloride.—Twenty grams of 3,4-dimethoxybenzyl-4-methoxyphenethylamine was added to a mixture of 8.1 g. of potassium hydroxide in 60 ml. of water and 120 ml. of acetone and the resulting mixture was refluxed to effect dissolution. Ethyl sulfate (11.5 g.) was added and the mixture refluxed for eight hours, acidified with dilute hydrochloric acid, and the acetone removed by distillation. The residual mixture was diluted with water and extracted with ether to remove a small amount of insoluble oil. The aqueous solution was made basic with sodium hydroxide solution. After ether extracting, the extract was dried and the ether removed by distillation. The residual material (17.5 g.) was dissolved in ethanol, alcoholic hydrogen chloride was added, and the solution was seeded with the hydrochloride of the starting material. On standing, 2 g. of this hydrochloride separated and was filtered off. The filtrate was diluted with ether to yield 16.5 g. of product, melting at 132–135°. After recrystallization from isopropyl alcohol it melted at 134.8–136.6° cor.

Anal. Calcd. for $C_{20}H_{27}NO_3 \cdot HCl$: C, 65.65; H, 7.71; N, 3.83. Found: C, 65.77; H, 7.57; N, 3.70.

N-3,4-Dimethoxybenzyl-N-methyl-4-methoxyphenethylamine Methiodide.—The base from 5 g. of N-3,4-dimethoxybenzyl-N-methyl-4-methoxyphenethylamine hydrochloride was dissolved in 75 ml. of acetone and to it was added 12 ml. of methyl iodide. The mixture was refluxed for two hours, cooled and filtered. The solid (6.2 g.) was triturated with hot acetone, filtered off and washed with acetone and then with ether. After being dried *in vacuo* the product melted at 206–207.2° cor.

Anal. Calcd. for $C_{20}H_{28}INO_3$: I, 27.75; OCH_3, 20.36. Found: I, 28.26; OCH_3, 20.12.

Acknowledgment.—The authors are indebted to M. E. Auerbach and K. D. Fleischer and coworkers for the analyses reported.

Summary

The preparation of a series of N-benzyl-N-methylphenethylamines which has been found to possess antifibrillatory activity in varying degree is described.

The preparation of N-ethyl-N-(3,4-dimethoxybenzyl)-4-methoxyphenethylamine is also reported.

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(3) Melting points are uncorrected unless otherwise specified.

[CONTRIBUTION FROM ROHM & HAAS COMPANY]

Condensation of Acetylenes with Esters. Acetylene and Phenylacetylene with Methyl Benzoate[1]

BY W. J. CROXALL AND J. O. VAN HOOK

The ease with which acetylene[2] and mono substituted acetylenes[1] may be acylated with alkyl carbonates in the presence of quaternary ammonium alkoxides suggested that esters other than alkyl carbonates might also be suitable acylating agents. Accordingly, a number of attempts were made to condense acetylene and phenylacetylene with alkyl acetates in the presence of quaternary ammonium alkoxides. However, it was soon evident that self condensation of these esters in the presence of this base occurred to the exclusion of reaction with the alkyne. We have been able, however, to effect condensation with an ester having no active hydrogen atom, namely, methyl benzoate.

Similar condensations have been effected with esters of this general category. Ethyl benzoate[3] and ethyl cinnamate[4] have been reported to condense with sodium phenylacetylide to give phenylbenzoylacetylene and phenylcinnamoylacetylene, respectively. However, Nightingale and Wadsworth[5] have proven the latter product to be bis-phenylethynylstyrylcarbinol rather than phenylcinnamoylacetylene. Ethyl propiolate[6] has been shown to undergo a Claisen-type condensation with ethyl benzoate in the presence of metallic sodium. The use of quaternary ammonium alkoxides as condensation bases for reaction between alkyl benzoates and alkynes does not appear to have been tried before.

(1) For the second paper of this series see, Croxall and Fegley, THIS JOURNAL, **71**, 1261 (1949).

(2) Croxall and Schneider, *ibid.*, **71**, 1257 (1949).

(3) Moureu and De Lange, *Compt. rend.*, **134**, 45 (1902).

(4) Worrall, THIS JOURNAL, **60**, 1266 (1938).

(5) Nightingale and Wadsworth, *ibid.*, **69**, 1181 (1947).

(6) Ingold, *J. Chem. Soc.*, **127**, 1199 (1925).