substitution of the non-penetration ion (or for electron transfer) might still result in a system which would be fairly labile with respect to change. In view of the fact that Co^{+++} associating with F^- forms a complex in which the paramagnetic state is the ground state, while with NH_3 the diamagnetic state is the ground state, it would not be surprising if with the ligand H_2O, which is intermediate in polarizability between F^- and NH_3, the two states have nearly the same energy.

GEORGE HERBERT JONES LABORATORIES
UNIVERSITY OF CHICAGO
CHICAGO 37, ILL.

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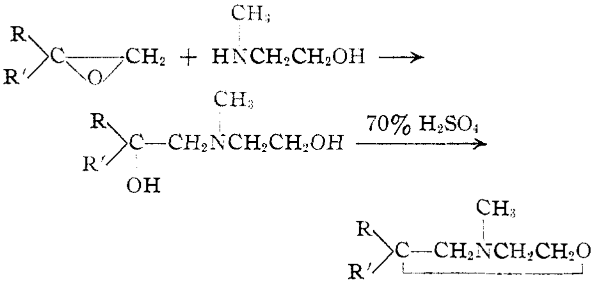
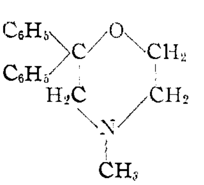
Some 2-Substituted-4-methylmorpholines

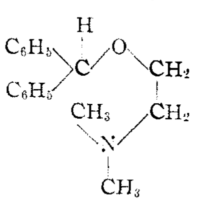
BY HENRY GILMAN AND CALVIN C. WANSER

In connection with the extensive search for compounds possessing antihistaminic activity, it appeared desirable to synthesize a number of 2-substituted-4-methylmorpholines where the substituents were aryl groups. These morpholines were prepared by the dehydration of the corresponding dialkanolamines, which were obtained in good yields by the addition of methylethanolamine to the appropriate olefin oxide. Of particular interest was the synthesis of 2,2-diphenyl-4-methylmorpholine (I), a cyclic structure differing from Benadryl[1] (II) only by the removal of two hydrogen atoms. The antihistaminic activity of (II) is well known and a comparison of the activity of (I) with its linear analog is being made.





I



II

A new method of synthesis for one of the intermediates, 2-chloro-1,1-diphenylethanol, was investigated and found to work quite smoothly. Klages and Kessler[2] first prepared the compound by the reaction of phenylmagnesium bromide with ethyl chloroacetate but no yield was reported. During the course of this study, we found that the compound could be conveniently prepared in good yield by the addition of phenyllithium to phenacyl chloride at −70°.

An attempt was made to prepare 1,1-diphenylethylene oxide by the epoxidation of 1,1-diphenylethylene with monoperphthalic acid. The reaction yielded a small amount of product, m. p. 54–55°. A mixed melting point of this compound with 1,1-diphenylethylene oxide, prepared by the dehydrohalogenation of 2-chloro-1,1-diphenylethanol with sodium ethoxide and melting at 56–57°, showed a depression. Newbold and Spring[3] studied the reaction of perbenzoic acid with 1,1-diphenylethylene and obtained none of the expected epoxide.

Cottle and co-workers[4] synthesized a number of C-alkylmorpholines by the dehydration of the corresponding dialkanolamines with 95% sulfuric acid at elevated temperatures. The C-arylmorpholines described here were prepared by a modification of that procedure. Cyclization was effected with 70% sulfuric acid at temperatures ranging from 100–150°.

Experimental

The following experiments are typical of those given in Tables I and II. All melting points and boiling points are uncorrected.

2-Chloro-1,1-diphenylethanol.—To a stirred solution of 15.5 g. (0.1 mole) of phenacyl chloride in 150 ml. of anhydrous ether cooled to −70° was added dropwise 0.19 mole of phenyllithium in ether under an atmosphere of nitrogen. The phenyllithium was added until a positive Color Test I[5] was obtained. The reaction mixture was allowed to warm to −20° and then hydrolyzed with ammonium chloride solution. The ether layer was separated and the aqueous layer was extracted with ether. The combined extracts were washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was distilled under reduced pressure to yield 18.1 g. (78%) of colorless liquid, b.p. 139–140° (0.1 mm.), which solidified to a white crystalline mass, m.p. 61–63°. The product, after several recrystallizations from petroleum ether (b.p. 60–70°), melted at 64–65°. The reported[2] boiling point and melting point are 150–180° (11 mm.) and 66°, respectively. Treatment of 2-chloro-1,1-diphenylethanol with diethylamine by the method of Klages and Kessler[2] yielded 2-diethylamino-1,1-diphenylethanol, m.p. 47–48°. The reported[2] melting point of this compound is 49°.

1,1-Diphenylethylene Oxide.—The 1,1-diphenylethylene oxide was prepared from 2-chloro-1,1-diphenylethanol by the method of Klages and Kessler[2] in yields ranging from 66–70%, m.p. 56–57°.

Reaction of 1,1-Diphenylethylene with Monoperphthalic Acid.—The reaction was patterned after the procedure of Böhme[6] for the oxidation of ethylenic double bonds. Eighteen grams (0.1 mole) of 1,1-diphenylethylene,[7] in 20 ml. of ether was added dropwise with stirring to 0.14 mole of an ether solution of monoperphthalic acid[8] at −10°. The reaction mixture was kept at approximately 10° after the addition. After seventy-two hours the theoretical amount of peracid was consumed. The ether solution was extracted with 10% sodium bicarbonate, washed with water and dried over anhydrous sodium sulfate. The solvent was removed and the residue dissolved in absolute ethanol. Two grams

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(1) For general references to Benadryl and related types see: G. Rieveschl, Jr., U. S. Patent 2,421,714 (1947) [*C. A.*, **41**, 5550 (1947)]; G. Rieveschl, Jr., and O. M. Gruhzit, *Federation Proc.*, **4**, 150 (1945); E. R. Loew, *et al.*, *J. Pharmacol.*, **83**, 120 (1945); and E. R. Loew, *Physiol. Revs.*, **27**, 542 (1947). In certain other antihistaminic types, K. E. Hamlin, *et al.*, THIS JOURNAL, **71**, 2731 (1949), the introduction of a *p*-chlorophenyl group was found to enhance the activity. In this regard, the synthesis of 2-phenyl-2-*p*-chlorophenyl-4-methylmorpholine is in progress.

(2) A. Klages and I. Kessler, *Ber.*, **39**, 1753 (1906).

(3) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 247 (1945).

(4) D. L. Cottle, *et al.*, *J. Org. Chem.*, **11**, 286 (1946).

(5) H. Gilman and F. Schulze, THIS JOURNAL, **47**, 2002 (1925).

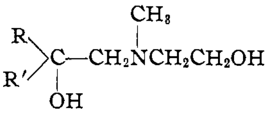
(6) H. Böhme, *Ber.*, **70**, 379 (1937).

(7) Prepared by the procedure of C. F. H. Allen and S. Converse, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 226.

(8) Obtained by the method of H. Böhme, *Org. Syntheses*, **20**, 70 (1940), and the modifications of G. B. Bachman and D. E. Cooper, *J. Org. Chem.*, **9**, 302 (1944).

TABLE I

N-METHYLDIETHANOLAMINES



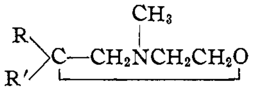
$$\mathrm{RR'C(OH)\text{—}CH_2N(CH_3)CH_2CH_2OH}$$

R	R'	Yield, %	B.p., °C.	B.p., Mm.	n^{20}_D	d^{20}_{20}	Formula	Nitrogen, %[a] Calcd.	Nitrogen, %[a] Found
C_6H_5	H	89.9[b]	152	0.9	1.5365	1.090	$C_{11}H_{17}O_2N$	7.18	7.45[c]
C_6H_5	C_6H_5	85	M. p. 110–111				$C_{17}H_{21}O_2N$	5.17	5.33
$C_6H_5CH_2$	H	85[d]	154	0.1	1.5271	1.065	$C_{12}H_{19}O_2N$	6.70	6.66[e]

[a] Analyses for nitrogen were performed by the micro Dumas method. [b] The styrene oxide was added dropwise to the methylethanolamine with the temperature kept below 45°. [c] Calcd. *MR*$_D$, 56.45; neut. equiv., 195. Found: *MR*$_D$, 55.89; neut. equiv., 193. [d] The conditions were the same as in (*b*). The intermediary 1-phenyl-2,3-epoxypropane was prepared by the dehydrohalogenation of 3-chloro-1-phenyl-2-propanol, which was kindly furnished by J. B. Honeycutt, Jr. A ring closure procedure described by H. Gilman, C. S. Sherman, C. C. Price, R. C. Elderfield, J. T. Maynard, R. H. Reitsema, L. Tolman, S. P. Massie, Jr., F. J. Marshall and L. Goldman, THIS JOURNAL, **68,** 1291 (1946), was utilized and the yield was 66%. See also E. Fourneau and M. Tiffeneau, *Compt. rend.*, **140**, 1596 (1905), for the preparation of this epoxide. [e] Calcd.: *MR*$_D$, 61.07. Found: *MR*$_D$, 60.58.

TABLE II

2-SUBSTITUTED-4-METHYLMORPHOLINES



$$\mathrm{RR'C\text{—}CH_2N(CH_3)CH_2CH_2O}$$

R	R'	Yield, %	B.p. °C.	B.p. Mm.	n^{20}_D	d^{20}_{20}	Formula	Nitrogen, %[a] Calcd.	Nitrogen, %[a] Found
C_6H_5	H	62[b]	115–118	0.5–0.8	1.5279	1.026	$C_{11}H_{15}ON$	7.91	9.16[c]
$C_6H_5CH_2$	H	32[d]	93–97	0.1	1.5239	1.021	$C_{12}H_{17}ON$	7.33	7.67[e]
C_6H_5	C_6H_5	71	M. p. 76–77				$C_{17}H_{19}ON$	5.53	5.52

[a] Analyses for nitrogen were performed by the micro Dumas method. [b] After the dropwise addition of the β-phenyl-N-methyldiethanolamine to the 70% sulfuric acid (the molar ratio of amine to acid was 1 to 3), the mixture was heated at 135–155° for 5.5 hours. [c] Calcd. *MR*$_D$, 52.84; neut. equiv., 177. Found: *MR*$_D$, 53.14; neut. equiv., 174. [d] Same as in (*b*) except that the mixture was heated at 140–150° for 4 hours. [e] Calcd.: *MR*$_D$, 57.46. Found: *MR*$_D$, 57.33. The picrate was prepared in 95% ethanol, m.p. 172–173.5°. Calcd. for $C_{18}H_{20}O_8N_4$: N, 13.33. Found: N, 13.09.

of product was obtained by low temperature crystallization,[9] m.p. 54–55° and the mixed m.p. with 1,1-diphenylethylene oxide was 33–36°. Two-tenths gram of the product was refluxed with 10 ml. of 25% potassium hydroxide in methanol for one hour. The mixture was cooled and diluted with water. A small amount of neutral compound precipitated, m.p. 69–70°. The same compound, as shown by m.p. and mixed m.p., was obtained when the oxidation product (m.p. 54–55°) was treated with semicarbazide hydrochloride and sodium acetate in dilute ethanol. The structures of the oxidation product and of its hydrolysis product are under investigation.

β,β-Diphenyl-N-methyldiethanolamine.—Nine grams (0.12 mole) of methylethanolamine[10] containing 1 ml. of water was stirred while 13 g. (0.066 mole) of 1,1-diphenylethylene oxide was added portionwise. The mixture was heated on the steam-bath overnight and the resulting oil solidified on cooling. Crystallization from a mixture of petroleum ether (b.p. 60–70°) and absolute ethanol gave 15.3 g. of the product. The N-methyldiethanolamines prepared are listed in Table I.

2,2-Diphenyl-4-methylmorpholine.—In a 250-ml. 3-necked flask equipped with a stirrer, solid addition funnel and condenser set for downward distillation was placed 5 ml. of 70% sulfuric acid. To the well-stirred, ice-cold acid was added portionwise 5.4 g. (0.02 mole) of β,β-diphenyl-N-methyldiethanolamine. The mixture was heated on the steam-bath for three hours upon completion of the addition. It was made basic with sodium hydroxide, and the basic solution extracted with ether. The ether extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed and the residue solidified on cooling. A single crystallization from dilute ethanol gave 3.6 g. of pure white product. Slight modifications in the preparation of the other substituted morpholines are given in the footnotes to Table II.

Acknowledgment.—The authors are grateful to Burt Hofferth for assistance. They also wish to express their appreciation to Parke, Davis and Company for arranging for the pharmaceutical tests, details of which will be published elsewhere.

CHEMICAL LABORATORY
IOWA STATE COLLEGE
AMES, IOWA

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Cleavage of the Silicon–Silicon Bond in Hexaphenyldisilane

BY HENRY GILMAN AND T. C. WU

It is well known that hexaarylethanes dissociate into triarylmethyl radicals and react readily with halogens, oxygen and alkali metals.[1] It has also been shown that the central metal–metal bonds of hexaphenyldilead,[2] hexamethylditin[3] and hexaphenyldigermanium[4] can be cleaved with sodium in liquid ammonia. However, attempts to cleave the silicon–silicon bonds in some hexasubstituted disilanes by sodium in liquid ammonia,[5] lithium in ethylamine,[5] and iodine[6] or oxygen[6,7] in boiling xylene have been reported to be unsuccessful. Kipping,[8] after treating some hexasubstituted disilanes with aqueous or alcoholic alkali and with concentrated sulfuric acid, found that the silicon–silicon bonds of the disilanes were intact. The organometallic compounds of silicon have been made from

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[9] The technique is described by H. Adkins and R. H. Gillespie, *Org. Syntheses*, **29**, 81 (1949).

[10] Generously supplied by the Carbide and Carbon Chemical Corporation, New York.

[1] See Chapter by W. E. Bachmann in H. Gilman, "Organic Chemistry, An Advanced Treatise," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 585 ff.

[2] L. S. Foster, W. M. Dix and I. J. Gruntfest, THIS JOURNAL, **61**, 1685 (1939).

[3] C. C. Kraus and W. V. Sessions, *ibid.*, **47**, 2361 (1925).

[4] C. A. Kraus and L. S. Foster, *ibid.*, **49**, 462 (1927).

[5] C. A. Kraus and W. K. Nelson, *ibid.*, **56**, 195 (1934).

[6] H. Gilman and G. E. Dunn, *ibid.*, **73**, 3404 (1951).

[7] W. Schlenk, J. Renning and G. Racky, *Ber.*, **44**, 1178 (1911).

[8] F. S. Kipping, *J. Chem. Soc.*, **119**, 647 (1921).