test for chloride ion. This was followed by washing with distilled water until the eluate became neutral. After removal of catalyst by filtration, the hydrogenation mixture was diluted with 100 ml. of water and passed through the washed column. Six fractions of 40 ml. each, ranging in *p*H from 9.2 to 10.9, were saved and combined. Concentration on the steam-bath under reduced pressure yielded an oil which was taken up in 100 ml. of absolute ethanol and dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated to 30 ml. and treated with dry ether to precipitate the crude quaternary salt, m.p. 198–201°. Three recrystallizations from an isopropyl alcohol–ether mixture gave 0.2 g. of the monohydrate of the methochloride analog of I, m.p. 208–209°. When mixed with a sample of I, m.p. 211–212°, the resulting melting point was depressed to 187–191°.

Anal. Calcd. for $C_{20}H_{33}ClN_2O\cdot H_2O$: C, 64.75; H, 9.51; N, 7.55; Cl, 9.56. Found: C, 64.28; H, 9.60; N, 7.70; Cl, 9.07.

Conversion of I to the Corresponding Chloride by IR-45 Treatment.—A solution of 3.2 g. (0.008 mole) of I in 200 ml. of 50% aqueous methanol was passed through a 100-ml. column of IR-45 resin at a rate of about one drop per second. The eluate was concentrated to dryness under reduced pressure and the semi-solid residue was taken up in 100 ml. of absolute ethanol. After drying with anhydrous sodium sulfate and removing the drying agent by filtration, the solution was concentrated to 30 ml., cooled and treated with dry ether to precipitate the crude quaternary salt. Two recrystallizations from isoproyl alcohol–ether gave 1.7 g. of the methochloride monohydrate, m.p. 208–209°. A mixture of this material with the product obtained from the hydrogenation of VI melted at 208–209°, and the infrared spectra (mull) of the two samples were qualitatively identical.

Anal. Calcd. for $C_{20}H_{33}ClN_2O\cdot H_2O$: C, 64.75; H, 9.51; N, 7.55; Cl, 9.56. Found: C, 64.89; H, 9.62; N, 7.47; Cl, 9.22.

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NORTH CHICAGO, ILLINOIS

[CONTRIBUTION FROM ABBOTT LABORATORIES]

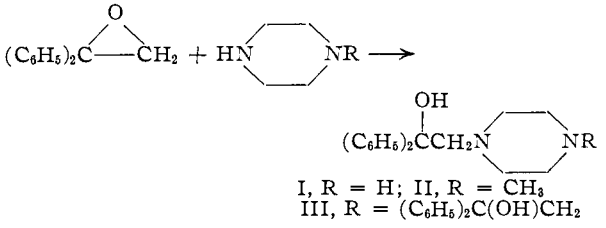
Tertiary Carbinols of the Piperazine Series. III. Reaction of 1,1-Diphenylethylene Oxide with Piperazines and Other Polyamines

BY HAROLD E. ZAUGG AND RAYMOND J. MICHAELS

RECEIVED DECEMBER 16, 1957

1,1-Diphenylethylene oxide reacts with piperazine and 1-methylpiperazine to give good yields of the carbinols I and II, respectively. A minor by-product of the reaction with piperazine is the dicarbinol III. This reaction has been extended to include several other substituted piperazines and a number of mono-primary and mono-secondary di- and triamines. Although diethylaminoethyl mercaptan gave the expected aminohydroxy thioether, tertiary aminoalkanols could not be made to yield the analogous O-ethers. A modified method for the preparation of 1,1-diphenylethylene oxide is reported.

During the search for a more convenient method for the preparation of certain of the pharmacologically interesting piperazinecarbinols previously reported,[1] the reaction of 1,1-diphenylethylene oxide with piperazines was examined. Gilman and Wanser[2] had shown that N-methylethanolamine attacked this epoxide at the 2-carbon atom. In the present work it was found that piperazine and 1-methylpiperazine reacted analogously to give 82 and 90% yields, respectively, of the carbinols I and II, identical with the compounds previously obtained by other methods.[1] As an expected by-



I, R = H; II, R = CH_3
III, R = $(C_6H_5)_2C(OH)CH_2$

product of the reaction with piperazine, the symmetrically disubstituted product III was obtained in 14% yield when a 3:1 molar excess of piperazine was employed. Lowering this ratio led to higher yields of III at the expense of I. A recent work[3] reports the reaction of 1-*n*-butyl-1-ethylethylene oxide with piperazine to give a 52% yield of the symmetrical N,N′-disubstituted piperazine as the only isolated product. Methylation of I with formaldehyde and formic acid gave an 80% yield of II, thus providing a route to II utilizing piperazine in place of the more costly 1-methylpiperazine.

The extension of this reaction to other substituted piperazines is summarized in Table I. Of the three methylated piperazines used, in which both nitrogens were unsubstituted, only 2,5-dimethylpiperazine gave any isolable disubstituted by-product. The carbinols derived from 2-methyl and 2,6-dimethylpiperazine are structurally ambiguous. However, since it was found that 2,3,5,6-tetramethylpiperazine would not react with diphenylethylene oxide under the conditions used, and since only one product was obtained in each case, the structures indicated in Table I, arising from attack by the less hindered nitrogen, have been assigned to them.

Table II lists the products obtained by the reaction of 1,1-diphenylethylene oxide with a number of di- and triamines. The yields reported are lower than those obtained in the preparation of the carbinols I and II. However, it is felt that most of these yields could be improved by a more careful study of conditions for each reaction. As indicated in Table II a low yield of product, not obtainable analytically pure, was secured from the reaction

(1) H. Zaugg, *et al.*, THIS JOURNAL, **80**, 2763 (1958).
(2) H. Gilman and C. Wanser, *ibid.*, **73**, 4030 (1951).
(3) L. Dedussenko and M. Mowssumsade, *Chem. Zentr.*, **127**, 13126 (1956).

TABLE I

AMINOCARBINOLS OF TYPE, $(C_6H_5)_2CCH_2N(R_1)(R_2)CH_2CH_2NR_3R_4$

Compound R1	R2	R3	R4	Form	M.p.,[a] °C.	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Activity[h]
H	H	H	H	Base[b]	135–136	82	$C_{18}H_{22}N_2O$	76.56	7.85	9.92	76.61	7.60	9.80	3.0(1)
H	H	$C_{14}H_{13}O$[c]	H	Base	220–221	14	$C_{32}H_{34}N_2O_2$	80.30	7.16	5.85	80.34	7.00	5.86	0(200)
H	H	CH_3	H	2HCl	226–227	90	$C_{19}H_{26}Cl_2N_2O$	61.78	7.10	7.59	61.49	7.07	7.53	3.0(5)
H	CH_3	H	H	2HCl	223–225	51	$C_{19}H_{26}Cl_2N_2O$	61.78	7.10	7.59	61.67	7.21	7.70	2.5(100)
H	CH_3	CH_3	H	2HCl	170–172	72[d]	$C_{20}H_{28}Cl_2N_2O$	62.66	7.36	7.31	62.55	7.38	7.33	1.0(50)
				$(CH_3)_2SO_4$	149–150	[e]	$C_{22}H_{32}N_2O_5S$	60.52	7.39	6.42	60.70	7.33	6.43	
CH_3	H	H	CH_3	Base	74–75	29	$C_{20}H_{26}N_2O$	77.38	8.44	9.03	77.57	8.58	9.14	
				2HCl	335–336[f]		$C_{20}H_{28}Cl_2N_2O$	62.66	7.36	7.31	61.07	7.42	7.35	0(100)
CH_3	H	$C_{14}H_{13}O$[c]	CH_3	Base	238–239	1	$C_{34}H_{38}N_2O_3$	80.59	7.56	5.53	80.57	7.61	5.63	
H	CH_3	H	CH_3	Base	72–73	41	$C_{20}H_{28}N_2O$	77.38	8.44	9.03	77.53	8.47	9.07	1.5(50)
H	H	$HOCH_2CH_2$	H	2HCl	219–220	77	$C_{20}H_{26}Cl_2N_2O_2$	60.15	7.07	7.02	60.15	7.26	6.83	2.5(50)
H	H	C_5H_4N[g]	H	Base	123–124	53	$C_{23}H_{25}N_3O$	76.85	7.01	11.69	76.59	7.11	11.72	0(25)

[a] Uncorrected. [b] The dihydrochloride, m.p. 247–249°, is reported in Table II of paper I of this series.[1] [c] $(C_6H_5)_2C(OH)CH_2$– the product formed by substitution of the epoxide at both nitrogens of the piperazine ring. [d] Prepared by methylation of the preceding compound; see Experimental. [e] Prepared by quaternization of the preceding compound; see Experimental. [f] With decomposition after darkening at 225–250°. [g] 2-Pyridyl. [h] See text for explanation.

TABLE II

AMINOCARBINOLS OF TYPE, $(C_6H_5)_2C(OH)CH_2R$

Compound R	Form	M.p.,[a] °C.	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Activity[i]
$-NHCH_2CH_2N(CH_3)_2$	Base	93–94	52	$C_{18}H_{24}N_2O$	76.02	8.51	9.85	75.59	8.29	9.46	
	2HCl	234–235		$C_{18}H_{26}Cl_2N_2O$	60.67	7.36	7.86	60.82	7.04	7.68	3.0(25)
$-NHCH_2CH_2CH_2N(CH_3)_2$	2HCl	254–255	46	$C_{19}H_{28}Cl_2N_2O$	61.45	7.60	7.55	61.78	7.48	7.44	1.5(50)
$-NHCH_2CH_2N(C_2H_5)_2$	2HCl	218–219	31	$C_{20}H_{30}Cl_2N_2O$	62.33	7.85	7.27	62.29	7.75	7.33	2.5(50)
$-NHCH_2CH_2CH_2N(C_2H_5)_2$	2HCl	152–153	37	$C_{21}H_{32}Cl_2N_2O$	60.43	8.21	6.71	60.49	8.43	6.51	2.0(20)
$-NHCH_2C(CH_3)_2N(CH_3)_2$	2HCl	180–181	45	$C_{20}H_{30}Cl_2N_2O$	62.33	7.85	7.27	62.31	7.78	7.15	2.5(20)
$-N(CH_3)CH_2CH_2NHCH_3$	2HCl	217–218	63	$C_{18}H_{26}Cl_2N_2O$	60.67	7.36	7.86	61.16	7.23	7.83	0.5(50)
$-N(CH_3)CH_2CH_2N(CH_3)_2$	2HCl	238–239	46	$C_{19}H_{28}Cl_2N_2O$	61.45	7.60	7.55	61.43	7.61	7.49	1.5(50)
$-NHCH_2CH_2NC_4H_8$[b]	2HCl	235–236	38	$C_{20}H_{28}Cl_2N_2O$	62.66	7.36	7.31	62.75	7.22	7.30	2.0(50)
$-NHCH_2CH_2NC_5H_{10}$[c]	Base	57–58	31	$C_{21}H_{28}N_2O$	77.73	8.70	8.64	78.04	8.85	8.63	1.0(50)
$-NH(CH_2)_3NC_4H_8O$[d]	2HCl	228–229	69	$C_{21}H_{30}Cl_2N_2O_2$	61.01	7.32	6.78	60.79	7.45	6.62	1.0(50)
$-NH(CH_2)_3NC_6H_{12}O$[e]	2HCl	172–173	34	$C_{23}H_{34}Cl_2N_2O_2$	62.58	7.76	6.35	62.36	8.04	6.15	1.0(25)
$-NHCH_2CH_2NC_4H_8NCH_3$[f]	3HCl	247–248	33	$C_{21}H_{32}Cl_3N_3O$	56.19	7.19	9.36	56.26	7.17	9.28	0(20)
$-NH(CH_2)_3NC_4H_8NCH_3$[f]	3HCl	284–285	51	$C_{22}H_{34}Cl_3N_3O$[g]	57.08	7.40	9.08	57.29	7.47	9.08	0(50)
$-SCH_2CH_2N(C_2H_5)_2$	HCl	178–179	18	$C_{20}H_{28}ClNOS$[h]	65.64	7.71	3.83	68.02	7.34	3.92	1.0(50)

[a] Uncorrected. [b] NC_4H_8 = pyrrolidyl. [c] NC_5H_{10} = piperidyl. [d] NC_4H_8O = morpholyl. [e] $NC_6H_{12}O$ = 2,6-dimethylmorpholyl. [f] $NC_4H_8NCH_3$ = 1-methyl-4-piperazyl. [g] *Anal.* Calcd.: Cl, 22.98; O, 3.46. Found: Cl, 22.98; O, 3.50. [h] *Anal.* Calcd.: Cl, 9.69; S, 8.76. Found: Cl, 10.28; S, 10.34. [i] See text for explanation.

with β-diethylaminoethyl mercaptan. Attempts to extend the reaction further to several dialkylaminoalkanols failed, even when the corresponding sodium alkoxides were used to promote the reaction.

The method for the preparation of 1,1-diphenylethylene oxide was also examined. The requisite intermediate, 2-chloro-1,1-diphenylethanol, was first prepared by Klages and Kessler[4] by the reaction of phenylmagnesium bromide with ethyl chloroacetate but no yield was reported. In our hands a 52% yield appeared to be optimal. Gilman and Wanser[2] treated phenacyl chloride with phenyllithium at −70° and obtained a 78% yield of the chlorohydrin. We have found that a comparable yield (73%) can be obtained from phenacyl chloride and phenylmagnesium bromide at 0°. Conversion of the chlorohydrin to 1,1-diphenylethylene oxide was carried out previously[2,4] by the action of alcoholic sodium ethoxide. We have found that aqueous sodium hydroxide serves the purpose equally well.

In preparing many of the compounds reported herein, the direct reaction of the amine with 2-chloro-1,1-diphenylethanol without the intermediate use of the epoxide could probably be employed successfully. In the one case attempted in the present work, reaction of piperazine with the chlorohydrin gave the carbinol I in a 61% yield.

Pharmacology.—The compounds listed in the two tables were tested for their ability to antagonize the tremor-producing effects of Tremorine[5] (20 mg./kg. i.p.) in mice. In the last column of both tables, the numbers in parentheses indicate the dosage of the compounds in mg./kg. given subcutaneously to the mice. The other numbers represent the protective effect of the given dose in

(4) A. Klages and J. Kessler, *Ber.*, **39**, 1753 (1906).

(5) G. Everett, L. Blockus and I. Shepperd, *Science*, **124**, 79 (1956).

an arbitrary scale ranging from zero to complete protection at the value of 3.0. For the purpose of comparison it can be said that the most active member of the series, compound I, is about twice as effective as atropine in antagonizing the effects of Tremorine, but at the same time possesses only about one-eightieth of the potency of atropine in antagonizing the effect of acetylcholine on the isolated rabbit ileum. The augmented activity of compound I on the central nervous system thus appears to have been brought about at the expense of its peripheral effects.

Experimental

Amines.—N-β-Aminoethylpyrrolidine,[6] N-β-aminoethylpiperidine,[6] N,N'-dimethylethylenediamine,[7] β-dimethylaminoisobutylamine,[8] trimethylethylenediamine,[9] 1-(β-aminoethyl)-4-methylpiperazine,[10] 1-(γ-aminopropyl)-4-methylpiperazine,[10] 1-(2'-pyridyl)-piperazine[11] and 2-methylpiperazine[12] were prepared by published methods. Other amines were obtained from commercial sources.

2-Chloro-1,1-diphenylethanol.—To a stirred solution of 77.5 g. (0.5 mole) of phenacyl chloride in 750 ml. of dry ether was added dropwise over a period of 1.5 hr., a solution of phenylmagnesium bromide previously prepared from 24 g. (1.0 mole) of magnesium and 157 g. (1.0 mole) of bromobenzene in 375 ml. of dry ether (total volume of Grignard solution = 425 ml.). The temperature of the reaction mixture was maintained at 0 to −5° and the reaction was protected by an atmosphere of dry nitrogen. At intervals during the addition, samples of the reaction mixture were removed and tested for unreacted Grignard reagent.[13] After 245 ml., corresponding to about 0.58 mole of Grignard reagent, had been added a positive color test was obtained. Addition was stopped and the mixture was stirred for another 30 minutes at 0°. To the cold reaction mixture was then added dropwise, with stirring, a solution of 100 g. of ammonium chloride in 400 ml. of water. The insoluble magnesium salts were removed by filtration and washed with ether. The ether layer was separated and the aqueous layer was extracted with 300 ml. of ether. The combined ether extracts were washed once with 250 ml. of water and dried over anhydrous sodium sulfate. Filtration and removal of the ether by distillation gave a crude residue which was fractionated under reduced pressure. After a forerun of 20.6 g., b.p. 92–154° (1.5 mm.), there was obtained 85.1 g. (73.4%) of 2-chloro-1,1-diphenylethanol, b.p. 154–156° (1.5 mm.). The product which solidified on standing, m.p. 52–57°, was pure enough for use in the next step. The pure chlorohydrin melts at 64–65°.

When ethyl chloroacetate was substituted for the phenacyl chloride in the above procedure and a 3:1 ratio of Grignard reagent was used, a 52% yield of 2-chloro-1,1-diphenylethanol was obtained.

1,1-Diphenylethylene Oxide.—A suspension of 23.2 g. (0.1 mole) of 2-chloro-1,1-diphenylethanol in 40 ml. of water containing 8 g. (0.2 mole) of sodium hydroxide was stirred and heated at 60–65° for 30 minutes. The cooled mixture was extracted with two 150-ml. portions of ether and the combined extracts were concentrated to dryness to give the crude epoxide, m.p. 49–52°. One recrystallization from absolute ethanol gave 16.5 g. (84%) of 1,1-diphenylethylene oxide, m.p. 52–54°. This material was pure enough for further use. The pure epoxide melts at 56–57°.[2,4]

1-(2',2'-Diphenyl-2'-hydroxyethyl)-piperazine (I). A. From 1,1-Diphenylethylene Oxide.—A solution of 7.8 g. (0.04 mole) of 1,1-diphenylethylene oxide and 23.3 g. (0.12 mole) of piperazine hexahydrate in 40 ml. of 95% ethanol was refluxed with stirring for 18 hr. The insoluble 1,4-disubstituted piperazine by-product III (1.4 g., 14%, m.p. 220–221°, see Table I) was removed by filtration of the warm reaction mixture and washed with 20 ml. of ethanol which was combined with the filtrate and cooled in ice. The desired carbinol crystallized from this solution to give 7.8 g. of material, m.p. 132–135°, in a first crop and 1.5 g. more of m.p. 130–132° in a second. The total of 9.3 g. represents a yield of 82%. The analytically pure carbinol, m.p. 135–136° (Table I), was obtained by recrystallization from 95% ethanol. The corresponding dihydrochloride, m.p. 247–249° (m.p. varies slightly with the rate of heating), was obtained by dissolving 5 g. of the base in 20 ml. of methanol and adding 15 ml. of a methanolic solution containing 0.15 g. of hydrogen chloride per ml.

B. **From 2-Chloro-1,1-diphenylethanol.**—A solution of 70.6 g. (0.36 mole) of piperazine hexahydrate and 21.1 g. (0.09 mole) of 2-chloro-1,1-diphenylethanol in 100 ml. of 95% ethanol was stirred and refluxed for 18 hr. The reaction mixture was worked up as in A to yield 2.1 g. (9.6%) of the 1,4-disubstituted product III, m.p. 220–221°, and 16.7 g. (61%) of 1-(2',2'-diphenyl-2'-hydroxyethyl)-piperazine (I), m.p. 132–135°.

Reaction of 1,1-Diphenylethylene Oxide with Diamines. 3-Dimethylaminopropylamine.—The following procedure serves as an example of the procedure employed, with minor variations, for the preparation of most of the compounds reported in the two tables. A mixture of 2.9 g. (0.015 mole) of diphenylethylene oxide and 4.6 g. (0.045 mole) of 3-dimethylaminopropylamine was treated with 2–3 drops of water and heated on the steam-bath for 16 hr. To the cooled reaction mixture was added about 50 ml. of water and the insoluble oil was taken up in several portions of ether. The combined extracts were dried over anhydrous sodium sulfate. After filtration and removal of the ether by distillation, the residual oil was taken up in 30 ml. of isopropyl alcohol and an excess of a solution of hydrogen chloride in isopropyl alcohol was added to form the dihydrochloride salt of N-(2,2-diphenyl-2-hydroxyethyl)-N',N'-dimethyl-1,3-propylenediamine, which was recrystallized three times from methanol, m.p. 254–255° dec., yield 2.6 g., 46% (see Table II).

In a few cases where removal of the ether from the extract gave a solid residue, the diaminocarbinol was isolated as the free base. In many cases only a 2:1 molar ratio of amine to epoxide was employed with little effect on the yield. Symmetrical dimethylethylenediamine, like piperazine and 2,5-dimethylpiperazine, can react with the epoxide at both nitrogen atoms. However, from the ethylenediamine only the product of reaction at one nitrogen was isolated in 63% yield (Table II). Likewise, from 2-methyl and 2,6-dimethylpiperazines, only monosubstitution products could be isolated. The above general procedure was used with some success in the reaction of the epoxide with β-diethylaminoethyl mercaptan. However, the aminoalcohols N-hydroxyethylpyrrolidine, N-hydroxyethylpiperidine and diethylaminoethanol either alone or in the presence of the corresponding sodium alkoxide failed to react with the epoxide to give the desired aminohydroxyethers. Two amines, β-dimethylaminoisopropylamine and the hindered 2,3,5,6-tetramethylpiperazine, also failed to yield the expected diaminocarbinols.

1-(2',2'-Diphenyl-2'-hydroxyethyl)-3,4-dimethylpiperazine.—A mixture of 4.2 g. (0.014 mole) of 1-(2',2'-diphenyl-2'-hydroxyethyl)-3-methylpiperazine (prepared from 1,1-diphenylethylene oxide and 2-methylpiperazine), 1.4 g. (0.16 mole) of 35% aqueous formaldehyde and 1.2 g. (0.02 mole) of 90% formic acid was heated on the steam-bath for 2 hr. and then refluxed for 4 hr. To the cooled reaction was added 1.1 ml. of concentrated hydrochloric acid and the mixture was concentrated to dryness under reduced pressure. The residue was taken up in 75 ml. of water and the resulting clear solution was made strongly alkaline with 40% aqueous sodium hydroxide solution. The precipitated oil was taken up in several portions of ether and the combined extracts were dried over anhydrous sodium sulfate. The residual oil, obtained after removal of the drying agent by filtration and the solvent by distillation, could not be made to crystallize. Therefore, it was dissolved in 100 ml. of dry ether and treated with an excess of ethereal hydrogen chloride. Filtering and recrystallizing the precipitated product twice from absolute ethanol gave 3.9 g. (72%) of the

(6) R. Reitsema, U. S. Patent 2,476,914 (1949); *C. A.*, **44**, 4043 (1950).

(7) W. Boon, *J. Chem. Soc.*, 307 (1947).

(8) Z. Welvart, *Compt. rend.*, **238**, 2536 (1954).

(9) O. Hromatka and C. Skopalik, *Monatsh.*, **83**, 38 (1952).

(10) British Patent 676,812 (1952); *C. A.*, **47**, 3884 (1953).

(11) A. Weston and K. Hamlin, U. S. Patent 2,636,032 (1953); *C. A.*, **48**, 6473 (1954).

(12) K. Beck, K. Hamlin and A. Weston, THIS JOURNAL, **74**, 605 (1952).

(13) H. Gilman and F. Schulze, *ibid.*, **47**, 2002 (1925).

dihydrochloride of the above-named compound, m.p. 170–172°. Conversion of 1.5 g. of the dihydrochloride to the free base followed by treatment with 0.5 g. of dimethyl sulfate in methyl ethyl ketone in the usual way[1] gave 0.8 g. of the corresponding quaternary methomethyl sulfate, m.p. 149–150° (Table I).

In a similar manner to the above, treatment of 1-(2′,2′-diphenyl-2′-hydroxyethyl)-piperazine (I) with formaldehyde and formic acid gave an 80% yield of 1-(2′,2′-diphenyl-2′-hydroxyethyl)-4-methylpiperazine (II) isolated as the dihydrochloride, m.p. 226–227°.

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NORTH CHICAGO, ILLINOIS

[CONTRIBUTION FROM ABBOTT LABORATORIES]

Tertiary Carbinols of the Piperazine Series. IV. Products Derived from the Nucleophilic Condensations of 2-Methylpyrazine and 1-Methyl-4-phenylacetylpiperazine

BY H. E. ZAUGG, R. W. DENET AND M. FREIFELDER

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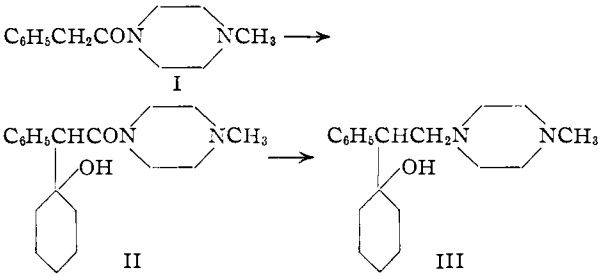
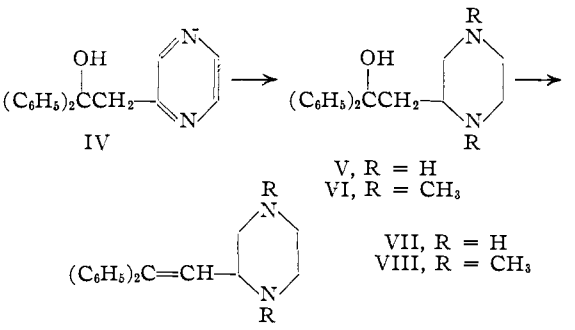
1-Methyl-4-phenylacetylpiperazine (I) undergoes an Ivanov-type reaction with cyclohexanone, but the reaction does not appear to be general. The sodium derivative of 2-methylpyrazine adds to benzophenone to give the carbinol IV. The preparation from these condensation products of compounds of potential pharmacological interest is reported.

The original Ivanov reaction of the halomagnesium derivatives of phenylacetic acid salts with carbonyl compounds has been shown by Blicke and Zinnes[1] to be extendible to analogous acids with suitably activated α-hydrogens. In the present work, it was found that the substituted phenylacetamide I will add to cyclohexanone under Ivanov conditions to give a 32% yield of the carbinol II. However, attempts to extend the reaction to cyclopentanone and *n*-butyraldehyde were not successful. Reduction of the amide carbonyl group of II with lithium aluminum hydride gave



III, the monoquaternary salt of which differs from TRAL[2,3] only in the shifting of the hydroxyl group by one carbon atom away from the central nitrogen.

The addition of the sodium derivatives of 2- and 4-picoline to benzophenone is well-known.[4] It was found in the present work that the sodium derivative of 2-methylpyrazine could be made to add to benzophenone to give IV, albeit in only 23% yield. As in the pyridine series,[4] the pyrazine ring could be hydrogenated selectively to give V in which, unlike piperazine carbinols previously reported,[2] the diphenylethanol substituent is attached to a carbon atom rather than to a nitrogen of the piperazine ring. Methylation and dehydration of V gave VI and VII, respectively, and methylation of VII led to VIII.



Pharmacology.—Compounds II and III and their corresponding quaternary salts showed activities of the order of one-tenth to one-twentieth that of atropine against acetylcholine induced spasm of the isolated rabbit ileum. All of the other compounds were practically inactive. Likewise, none of the compounds showed more than minimal activity in antagonizing the effects of Tremorine[5] in mice.

Experimental

1-Methyl-4-phenylacetylpiperazine (I).—A solution of 100 g. (1.0 mole) of 1-methylpiperazine in 200 ml. of dry ether was added dropwise with stirring to a cooled solution of 77.2 g. (0.5 mole) of phenylacetyl chloride in 200 ml. of dry ether. Enough water was added to dissolve the precipitated hydrochloride, and the ether layer was separated. The aqueous layer was saturated with solid potassium carbonate and the oil which separated was taken up in ether, combined with the original ether layer and dried over anhydrous magnesium sulfate. Filtration, removal of the ether by distillation, and fractional distillation of the residue gave 65 g. (60%) of I, b.p. 135–145° (0.5 mm.), $n^{25}D$ 1.5480. A sample was converted to the hydrochloride which melted at 209–210° after two recrystallizations from dry ethanol.

Anal. Calcd. for $C_{13}H_{19}ClN_2O$: C, 61.29; H, 7.52; N, 11.00. Found: C, 61.58; H, 7.65; N, 10.92.

Ivanov Reaction of I with Cyclohexanone. Preparation of the Carbinol II.—To the Grignard reagent prepared from 1.8 g. (0.075 mole) of magnesium and 9.3 g. (0.075 mole) of isopropyl bromide in 100 ml. of dry ether was added a solution of 11 g. (0.05 mole) of 1-methyl-4-phenylacetylpiperazine (I) in 100 ml. of dry benzene. After the ether was removed by distillation, the mixture was stirred and refluxed for 3 hr. Then a solution of 7.3 g. (0.075 mole) of cyclohexanone in 50 ml. of dry benzene was added and stirring and refluxing was continued for another 3 hr.

(1) F. Blicke and H. Zinnes, THIS JOURNAL, **77**, 5399, 6051, 6247 (1955).

(2) H. Zaugg, *et al.*, *ibid.*, **80**, 2763 (1958).

(3) Registered trademark of Abbott Laboratories, North Chicago, Ill.

(4) See C. Tilford and M. Van Campen, THIS JOURNAL, **76**, 2431 (1954).

(5) G. Everett, L. Blockus and I. Shepperd, *Science*, **124**, 79 (1956)