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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[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

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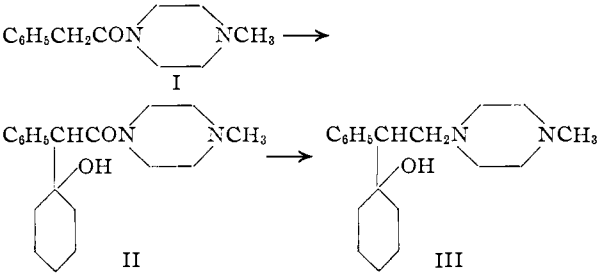
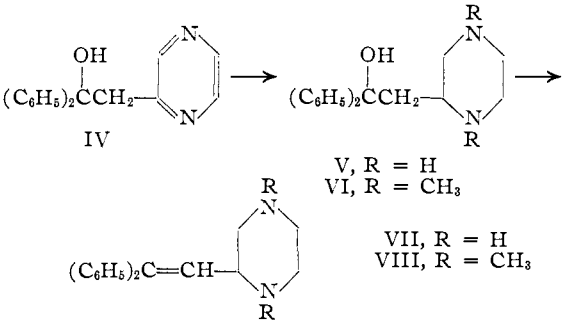
1-Methyl-4-phenylacetylpiperazine (I) undergoes an Ivanov-type reaction with cyclohexanone, but the reaction does not appear to be general. The sodium derivative of 2-methylpyrazine adds to benzophenone to give the carbinol IV. The preparation from these condensation products of compounds of potential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

After standing at room temperature for several days, the mixture was cooled and treated slowly with a saturated aqueous solution of ammonium chloride. After separation of the benzene, the aqueous layer was extracted with ether which was combined with the benzene. The organic extract was washed thoroughly with water to remove unreacted I and then extracted with dilute hydrochloric acid, shaken with charcoal, filtered and made strongly alkaline with aqueous potassium hydroxide. The precipitated oil was taken up in ether and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave a viscous residue which was dissolved in hot hexane (Skellysolve B), treated with charcoal, filtered and concentrated. Cooling in ice and scratching to induce crystallization gave 5.1 g. (32%) of II, m.p. 120°. Two more recrystallizations of a sample for analysis raised the m.p. to 122–123°.

Anal. Calcd. for $C_{19}H_{28}N_2O_2$: C, 72.11; H, 8.92; N, 8.85. Found: C, 72.14; H, 9.20; N, 8.88.

II Methiodide Hemihydrate, m.p. 165° with softening at 135°. *Anal.* Calcd. for $C_{20}H_{31}IN_2O_2 \cdot {}^1/_2H_2O$: C, 51.39; H, 6.90; N, 5.99; O, 8.55; I, 27.16. Found: C, 51.41; H, 6.98; N, 6.13; O, 8.57; I, 27.11.

II Methobromide, m.p. 223–224° (from ethanol–ether). *Anal.* Calcd. for $C_{20}H_{31}BrN_2O_2$: C, 58.39; H, 7.59; N, 6.81. Found: C, 58.30; H, 7.54; N, 7.01.

Attempts to prepare carbinols from I using cyclopentanone or *n*-butyraldehyde in place of cyclohexanone in the above procedure failed.

Reduction II to III.—A mixture of 6.2 g. (0.0196 mole) of the carbinol II and 3.04 g. (0.08 mole) of lithium aluminum hydride was refluxed in ether for 4 hr., allowed to stand over a week-end at room temperature, and refluxed for another 4 hr. The stirred mixture was treated slowly with water until it no longer refluxed spontaneously. Insoluble salts were removed by filtration and washed with ether. The combined filtrate and washings were dried over anhydrous potassium carbonate. Filtration and removal of the ether by distillation gave a solid residue which was recrystallized once from hexane (Skellysolve B) to give 4.5 g. (72%) of the carbinol III, m.p. 104–105°.

Anal. Calcd. for $C_{19}H_{30}N_2O$: C, 75.45; H, 9.99; N, 9.26. Found: C, 75.72; H, 9.87; N, 9.40.

The monomethiodide of III was prepared by treating a sample of III with an equivalent quantity of methyl iodide in chloroform solution at room temperature, m.p. 190–191° (from ethanol–ether).

Anal. Calcd. for $C_{20}H_{33}IN_2O$: C, 54.05; H, 7.48; N, 6.30. Found: C, 54.00; H, 7.76; N, 6.41.

Condensation of 2-Methylpyrazine with Benzophenone. Preparation of IV.—To a suspension of 15 g. (0.35 mole) of sodamide in 47 g. (0.5 mole) of 2-methylpyrazine[6] was added dropwise with stirring a solution of 23 g. (0.125 mole) of benzophenone in 14 g. (0.3 mole) of 2-methylpyrazine. The temperature during the addition rose to 65° and after addition was complete the temperature was maintained at 65–70° for 1 hr. by means of a warm water-bath. The thick black reaction mixture was poured over ice and allowed to stand overnight. The oily solid was collected at the filter and suspended in ether, filtered again and washed with ether. There was obtained 8 g. (23%) of the carbinol IV, m.p. 140–143°. One recrystallization from dry ethanol gave 5.1 g., m.p. 149–150°.

Anal. Calcd. for $C_{18}H_{16}N_2O$: C, 78.23; H, 5.83; N, 10.14. Found: C, 78.33; H, 5.93; N, 9.95.

A larger run employing 1 mole of 2-methylpyrazine, 0.5 mole of benzophenone and 0.8 mole of sodamide gave 32 g. of the carbinol IV, representing an exact duplication of the above yield.

Hydrogenation of IV to V.—A solution of 24 g. (0.087 mole) of the pyrazine IV, m.p. 148–149°, in 250 ml. of absolute ethanol containing 0.9 mole of dry hydrogen chloride and 25 ml. of glacial acetic acid was treated with 0.75 g. of platinum oxide catalyst and hydrogenated at 60° and 40 pounds pressure. Reduction was complete in several hours. Enough water was added to dissolve precipitated hydrochloride and the catalyst was removed by filtration. The filtrate was concentrated nearly to dryness, 300 ml. of water and 4 g. of charcoal (Darco) were added and, after standing 15 minutes, the mixture was filtered. The filtrate was made strongly alkaline and the precipitated base which solidified slowly was collected at the filter and washed with water. One recrystallization of the dried product from absolute ethanol gave 13 g. (53%) of the carbinol V, m.p. 190–191°. Several more recrystallizations for analysis gave m.p. 194–195°.

Anal. Calcd. for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92; O, 5.67. Found: C, 76.50; H, 7.68; N, 9.96; O, 5.94.

Reductive Methylation of V to VI.—A solution of 5.0 g. (0.0177 mole) of V in 75 ml. of 95% ethanol containing 10 ml. of 37% aqueous formaldehyde was treated with 0.5 g. of a 5% palladium–charcoal catalyst and hydrogenated at room temperature and 40 pounds pressure. Absorption of hydrogen appeared complete in 48 hr. Nevertheless, the old catalyst was removed by filtration, fresh catalyst was added and hydrogenation was resumed for another 18 hr. The catalyst was removed by filtration and to the filtrate was added an alcoholic solution containing 0.0354 mole of hydrogen chloride. Concentration to dryness, treatment of the residue with benzene, concentration once more to dryness, trituration of the residue with ether, collection of the product at the filter, and recrystallization from isopropyl alcohol gave 4.0 g. of **VI dihydrochloride**, m.p. 231–232°.

Anal. Calcd. for $C_{20}H_{28}Cl_2N_2O$: C, 62.61; H, 7.36; N, 7.31. Found: C, 62.26; H, 7.30; N, 7.10.

A sample was converted to the free base VI, m.p. 138–139° (from Skellysolve B).

Anal. Calcd. for $C_{20}H_{26}N_2O$: C, 77.33; H, 8.44; N, 9.03; O, 5.20. Found: C, 77.78; H, 8.12; N, 9.14; O, 5.28.

An attempt to methylate V by means of formaldehyde and formic acid, the method used for the conversion of VII to VIII, proved fruitless.[4]

2-(α-Phenylstyryl)-piperazine (VII).—A mixture of 4 g. of V and 20 ml. of 85% sulfuric acid was warmed in hot water for several minutes until solution was complete. After standing for several more minutes, the deep red solution was poured over ice. The solid which formed was dissolved by slight warming and the solution was made strongly alkaline with aqueous sodium hydroxide. The resulting base solidified to give 3.0 g. of crude product, m.p. 65–70°. One recrystallization from cyclohexane gave 1.6 g. of VII, m.p. 103–104°.

Anal. Calcd. for $C_{18}H_{20}N_2$: C, 81.78; H, 7.62; N, 10.60. Found: C, 81.66; H, 7.91; N, 10.59.

1,4-Dimethyl-2-(α-phenylstyryl)-piperazine (VIII).—A mixture of 1.4 g. of VII, 20 ml. of 37% aqueous formaldehyde and 10 ml. of 90% formic acid was refluxed for 16 hr., cooled, treated with excess of dilute hydrochloric acid and concentrated to dryness under reduced pressure. The residue was taken up in water and made strongly alkaline with aqueous potassium hydroxide. Extracting the base with ether followed by drying over anhydrous magnesium sulfate, filtering and adding excess of ethereal hydrogen chloride gave the dihydrochloride of VIII, m.p. 249–250° (from ethanol–ether).

Anal. Calcd. for $C_{20}H_{26}Cl_2N_2$: C, 65.75; H, 7.17; N, 7.67; Cl, 19.44. Found: C, 65.04; H, 7.47; N, 7.67; Cl, 19.65.

Attempts to prepare VIII by dehydration of VI under the same conditions used for converting V to VII were unsuccessful.

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(6) Obtained from the Wyandotte Chemical Corp.