[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORIES OF THE SCHERING CORPORATION]

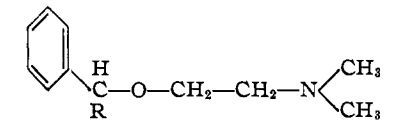
The Chemistry of the Benzyl Pyridines. IV. *p*-(α-and β-Dimethylaminoethyl)-2-benzylpyridines and *p*-(β-Dimethylaminoethyl)-diphenylmethane

BY FRANK J. VILLANI, MARY S. KING, JOSEPH LANG AND DOMENICK PAPA

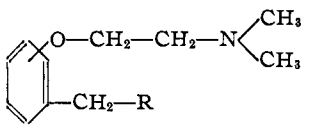
RECEIVED MARCH 19, 1954

The nuclearly substituted β-dimethylaminoethyl isomer of 3-phenyl-3-(2-pyridyl)-N,N-dimethylpropylamine and several related compounds have been prepared and pharmacologically evaluated as histamine antagonists.

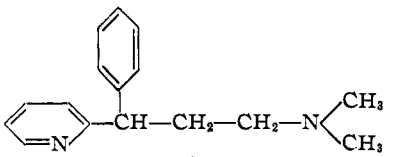
The transposition of the β-dimethylaminoethoxy group of β-dimethylaminoethyl benzhydryl ether[1] and its 2-pyridyl analog[2] from a methylene to a benzenoid carbon has given compounds III and IV having substantially the same antihistaminic potency in experimental animals as the parent compounds. It therefore appeared of interest to prepare and examine pharmacologically the nuclear substituted β-dimethylaminoethyl isomer VI of 3-phenyl-3-(2-pyridyl)-N,N-dimethylpropylamine (V), Trimeton, in order to determine whether



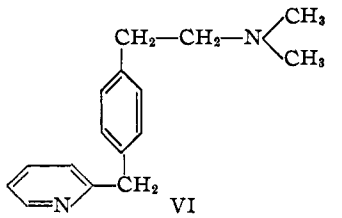
I, R = C_6H_5
II, R = 2-C_5H_4N



III, R = C_6H_5
IV, R = 2-C_5H_4N



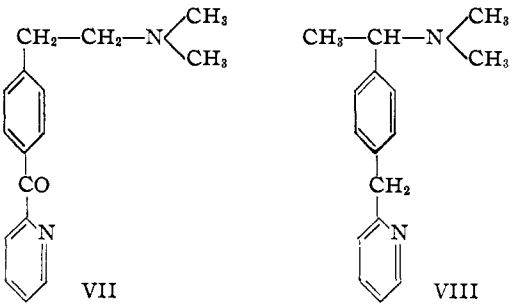
V



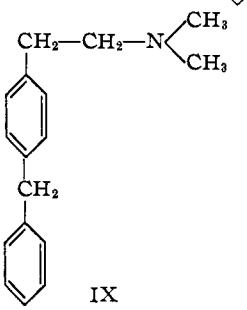
VI

the pharmacological effect of shifting the alkamine residue of the propylamine-type antihistamines would parallel that reported for the alkamine ethers I and II. Included in this structure–activity study are several compounds related to VI.

The most direct approach to the synthesis of VI was through the Friedel–Crafts reaction which has been employed successfully in the synthesis of benzoylpyridines.[3] Accordingly picolinoyl chloride was condensed with N,N-dimethyl-β-phenethylamine to yield *p*-(β-dimethylaminoethyl)-2-benzoyl-

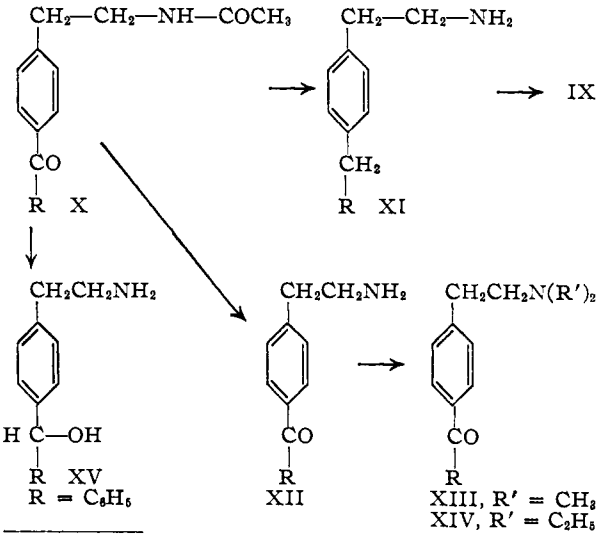


VII VIII



IX

pyridine (VII). Wolff–Kishner reduction of VII yielded VI in 40% yield. The isomeric *p*-(α-dimethylaminoethyl)-2-benzylpyridine (VIII) was prepared by converting *p*-acetyl-2-benzylpyridine[4] to *p*-(α-aminoethyl)-2-benzylpyridine by the Leuckart reaction and dimethylating the latter amine with formic acid and formaldehyde. The diphenyl compound IX was prepared by the Friedel–Crafts reaction of N-acetyl-β-phenethylamine with benzoyl chloride and the resulting acetylamino ketone X, on reduction by the Wolff–Kishner method,



XV, R = C_6H_5
XII
XIII, R′ = CH_3
XIV, R′ = C_2H_5

(1) L. C. Cheney, R. R. Smith and S. B. Binkley, THIS JOURNAL, **71**, 60 (1949); W. B. Wheatley, L. C. Cheney and S. B. Binkley, *ibid.*, **71**, 64 (1949).

(2) D. Papa, N. Sperber and M. Sherlock, *ibid.*, **73**, 1279 (1951).

(3) R. Wolffenstein and F. Hartwich, *Ber.*, **48**, 2043 (1915); F. J. Villani, M. S. King and D. Papa, *J. Org. Chem.*, **17**, 249 (1952).

(4) F. J. Villani and D. Papa, THIS JOURNAL, **72**, 2722 (1950).

yielded the primary amine XI.[5] With formic acid and formaldehyde, XI was converted smoothly to IX. The benzoyl analog of IX was obtained by hydrolysis of X to the amino ketone XII, which was converted into the tertiary aminoketones XIII and XIV. The amino carbinol XV was obtained in 33% yield by reduction of X with zinc dust in alkaline solution.

Pharmacology.—The compounds were assayed as histamine antagonists in guinea pigs by intravenous injection of histamine diphosphate one hour after the oral administration of the test compound. Compound V was used as the standard. Compound VI was the most active of the series, its potency being $^1/_2$ to $^3/_4$ that of V. Compound VII and its phenyl analog showed a very weak antihistaminic effect, approximately $^1/_{25}$th that of V. The diphenyl compound XI and compound VIII had an activity one one-hundredth of the standard.

Acknowledgment.—The authors wish to express their appreciation to Dr. S. Margolin of our Pharmacology Laboratories for permission to publish the preliminary data on the compounds. We are also grateful to Mr. Edwin Conner of our Micro-Analytical Laboratory for the analyses reported herein.

Experimental

p-(β-**Dimethylaminoethyl**)-**phenyl 2-Pyridyl Ketone** (**VII**).—To 129 g. (1.04 moles) of picolinic acid contained in a three-liter three-necked flask, equipped with stirrer, dropping funnel and condenser, 750 ml. of purified thionyl chloride was added dropwise with stirring and cooling. After one and one-half hours, most of the thionyl chloride (80%) was removed under vacuum, and to the dark purple residue was added 500 ml. of dry nitrobenzene. The mixture was cooled in an ice-bath, 144 g. (0.9 mole) of N,N-dimethyl-β-phenethylamine was added slowly, followed by the addition of 396 g. of anhydrous aluminum chloride over a period of 2–2.5 hours. The dark red mixture was allowed to warm to room temperature and then heated on the steam-bath for 8 hours. After cooling, the mixture was poured into ice (2 kg.) and concentrated hydrochloric acid (about 200 ml.) and steam distilled to remove the nitrobenzene. The residue from the steam distillation was cooled, made strongly alkaline with 50% sodium hydroxide and extracted with ether. The ether extracts were dried, the ether removed and the residue distilled, yield 26.5 g. (10%), b.p. 185–187° (1.5 mm.). The viscous oil solidified and after recrystallization from ethanol melted at 147.5–148°.

Anal. Calcd. for $C_{16}H_{18}ON_2$: N, 11.02. Found: N, 10.80.

p-(β-**N-Acetylaminoethyl**)-**benzophenone** (**X**).—To 46.4 g. (0.33 mole) of freshly distilled benzoyl chloride and 49 g. (0.3 mole) of N-acetyl-β-phenethylamine in 200 ml. of dry nitrobenzene, there was added in small portions, with stirring and cooling, 60 g. of anhydrous aluminum chloride. The mixture was heated for eight hours on the steam-bath, poured into ice and concentrated hydrochloric acid and the nitrobenzene removed by steam distillation. The residue from the steam distillation was cooled and extracted with ether. The ether extracts were combined, washed with 10% sodium hydroxide and with water, dried over sodium sulfate and distilled; yield 47 g. (69%), b.p. 235–245° (1 mm.). The product, on trituration with ether, solidified, m.p. 80–82°.

Anal. Calcd. for $C_{16}H_{15}ON$: N, 6.22. Found: N, 6.47.

The oxime prepared in the usual manner melted at 174–176°.

Anal. Calcd. for $C_{17}H_{18}O_2N_2$: N, 9.93. Found: N, 9.50.

p-(β-**Dimethylaminoethyl**)-**phenyl-2-pyridylmethane** (**VI**).—To a solution of 10.5 g. of sodium metal dissolved in 500 ml. of ethylene glycol, 21 g. of hydrazine hydrate and 25 g. (0.1 mole) of VII was added. The mixture was heated under reflux for 40 hours, cooled, poured into two liters of ice-water and the solution extracted several times with ether. The ether extracts were washed repeatedly with water and, after drying, the ether was removed and the product distilled; yield 12.6 g. (40%), b.p. 145–151° (1 mm.), $n^{25}D$ 1.5618.

Anal. Calcd. for $C_{16}H_{20}N_2$: C, 79.96; H, 8.30. Found: C, 80.17; H, 8.42.

p-(β-**Aminoethyl**)-**diphenylmethane** (**XI**).—Sodium (35 g.) was dissolved in one liter of ethylene glycol. Hydrazine hydrate (45 g.) and 26.6 g. (0.1 mole) of X were added and the mixture was processed as in the preceding example; yield 17.8 g. (85%), b.p. 135–140° (3 mm.), $n^{31}D$ 1.5743. The free base absorbs carbon dioxide from the air very rapidly and therefore was converted into the hydrochloride salt and analyzed; m.p. 232–233°; literature[5] m.p. 222–224°.

Anal. Calcd. for $C_{15}H_{18}NCl$: N, 5.65. Found: N, 5.63.

p-(β-**Dimethylaminoethyl**)-**diphenylmethane** (**IX**).—To a cooled solution of 20.4 g. (0.4 mole) of 90% formic acid, 17 g. (0.08 mole) of XI was added, followed by the portionwise addition of 18 g. of 40% formalin. The mixture was heated on the steam-bath under reflux for five hours. After cooling, 40 ml. of 4 *N* hydrochloric acid was added and the solvents removed under reduced pressure. The residue was dissolved in water, made basic with sodium hydroxide and extracted with water. The ether extracts were combined, dried and the residue distilled; yield 15 g. (79%), b.p. 136–140° (1 mm.), $n^{25}D$ 1.5534.

Anal. Calcd. for $C_{17}H_{21}N$: C, 85.33; H, 8.85; N, 5.58. Found: C, 85.41; H, 8.89; N, 5.85.

p-(β-**Dimethylaminoethyl**)-**benzophenone** (**XIII**).—A mixture of 14 g. (0.05 mole) of X, 14 ml. of ethanol and 14 ml. of concentrated hydrochloric acid was heated under reflux for four hours. After cooling, the mixture was poured into water, made basic with sodium hydroxide and extracted with ether. The ether solution was extracted several times with dilute (10%) hydrochloric acid. The acid extracts were washed with ether, basified with dilute sodium hydroxide solution and extracted with ether. The latter ether extracts were combined, washed with water, dried and the ether was removed. The crude residual oil was methylated by the procedure described above; yield 6 g. (46%), b.p. 166–169° (1 mm.), $n^{25}D$ 1.5790.

Anal. Calcd. for $C_{17}H_{19}ON$: N, 5.53. Found: N, 5.24.

p-(β-**Diethylaminoethyl**)-**benzophenone** (**XIV**).—Twenty-one grams (0.079 mole) of X was saponified as described in the preceding paragraph. The crude amine (12.5 g.) was suspended in a solution of 3 g. of sodium hydroxide in 60 ml. of water. The flask was cooled in an ice-bath, while 4.3 g. of diethyl sulfate was added slowly with stirring. After one hour, the mixture was allowed to warm to room temperature and heated on the steam-bath overnight. The oily layer was separated with ether, the ether solution dried and then 10 ml. of acetyl chloride added. The ethereal mixture was allowed to stand at room temperature for one hour and then extracted several times with dilute hydrochloric acid. The acid extracts were basified with dilute sodium hydroxide and the oil which separated was extracted with ether. The ether solutions were washed with water, dried and distilled; yield 2 g. (13%), b.p. 176–183° (2 mm.), $n^{23}D$ 1.5858.

Anal. Calcd. for $C_{19}H_{23}ON$: N, 4.97. Found: N, 4.87.

p-(β-**Aminoethyl**)-**diphenylcarbinol** (**XV**).—To a solution of 17.8 g. (0.066 mole) of X in 200 ml. of ethanol containing 18 g. of sodium hydroxide, 18 g. of zinc dust was added and the mixture refluxed for three hours. The mixture was filtered and the filter cake was washed with 100 cc. of hot ethanol. The alcoholic solution was poured into two liters of ice-water, neutralized with acetic acid and extracted with ether. The ether extracts were combined, washed with water, dried over sodium sulfate and distilled; yield 5 g. (33%), b.p. 205–206° (1 mm.).

(5) J. H. Speer and A. J. Hill, *J. Org. Chem.*, **2**, 139 (1937), synthesized XI by reacting the magnesium derivative of *p*-bromodiphenylmethane with ethylene oxide to give the corresponding primary alcohol. The latter compound then was converted *via* the bromide to the primary amine XI.

Anal. Calcd. for $C_{15}H_{17}ON$: C, 79.25; H, 7.54. Found: C, 79.30; H, 7.65.

p-(α-Aminoethyl)-phenyl-2-pyridylmethane.—This compound was prepared by a modification of the procedure described by Ingersoll[6] for the synthesis of α-phenethylamine.

Twenty-one grams (0.1 mole) of *p*-acetyl-2-benzylpyridine and 25 g. (0.4 mole) of freshly prepared ammonium formate was heated with a free flame in a small round-bottom flask, equipped with a condenser set for distillation and a thermometer extending just above the bottom of the flask. The temperature was raised slowly to 150–155° and after the initial reaction had subsided the temperature was kept at 190–200° for 2 hours. After cooling, the mixture was shaken with water several times to remove the inorganic salts, the water solutions extracted with benzene, and the benzene extracts added to the residue in the flask. The benzene was removed by vacuum concentration on the steam-bath, 150 ml. of concentrated hydrochloric acid added to the residue and the mixture warmed on the steam-bath for two hours. After cooling and basification with concentrated aqueous sodium hydroxide, the organic material was extracted with ether. The ether extracts were combined and washed with water, dried and distilled; yield 11 g. (52.4%), b.p. 154–160° (2 mm.), $n^{28}D$ 1.5762.

Anal. Calcd. for $C_{14}H_{16}N_2$: N, 13.27. Found: N, 13.41.

The *p*-(α-Dimethylaminoethyl)-phenyl-2-pyridylmethane (VIII).—Ten grams of the amine, described in the preceding paragraph, was dimethylated by the formic acid–formaldehyde procedure. There was obtained 6 g. (55.5%) of a colorless liquid boiling at 157–161° (3 mm.), $n^{27}D$ 1.5592.

Anal. Calcd. for $C_{16}H_{20}N_2$: N, 11.67. Found: N, 12.00.

BLOOMFIELD, NEW JERSEY

(6) A. W. Ingersoll, "Org. Syntheses," Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 503.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Piperidine Derivatives. XXV. The Reaction of Certain 3-Substituted-1-methyl-4-piperidones with Organometallic Compounds

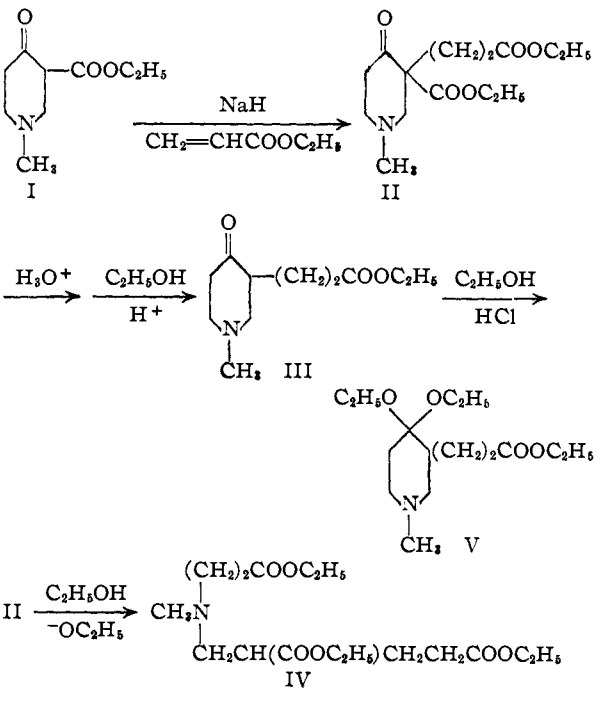
BY S. M. MCELVAIN, WILLIAM B. DICKINSON[1] AND ROBERT J. ATHEY[2]

RECEIVED JULY 15, 1954

1-Methyl-4-piperidones containing the 3-substituents, $-CH_2CH_2R$, in which R is $-COOC_2H_5$ (III), $-CONC_5H_{10}$ (XI), $-CH_2NC_5H_{10}$ (XVII) and $-CH_2OCOC_6H_5$ (XXII), react with phenylmagnesium bromide or phenyllithium to give principally the metal enolate of the ketone; with XVII this is the only reaction. With III the addition of the organometallic compound that does occur takes place on the ester group in preference to or together with addition to the ketone group. With XI and XXII addition of the Grignard reagent occurs only at the ketone group. The 1-methyl-3-substituted-4-phenyl-4-hydroxypiperidines, VIII, XII, XXIII and XXIV, have been isolated and characterized.

The high analgesic activity of certain 4-phenylpiperidines, particularly 1,3-dimethyl-4-phenyl-4-propionyloxypiperidine,[3] indicated that the preparation and pharmacological evaluation of a wider variety of 3-substituted-1-methyl-4-phenyl-4-acyloxypiperidines would be desirable. The present paper reports some work in this direction, in which certain of these types have been prepared in low yields *via* the addition of phenyllithium or phenylmagnesium bromide to the ketonic groups of 1,3-disubstituted-4-piperidones. The main products formed from these reactants, however, were the result of attacks of the organometallic compounds at other more reactive centers of these 4-piperidones.

The keto ester III, which was the principal intermediate in this work, was prepared from the carbethoxypiperidone I by the sequence of reactions shown. The latter keto ester could be used directly as it was obtained from the Dieckmann cyclization of methyldi-(β-carbethoxyethyl)-amine[3] if the precaution was taken to remove the alcohol produced in the cyclization by azeotropic distillation with benzene after neutralization of the reaction mixture with acetic acid. If this precaution was not taken, the reaction product was the triester IV, resulting from the ethanolysis of II in the presence of the base required for its formation. The keto ester III was converted readily to the ketal V; indeed this could be done simply by recrystallization of the hydrochloride of III from ethanol.



The reaction of the keto ester III with phenylmagnesium bromide, either by direct or inverse mixing of the reactants, produced approximately 50% of a magnesium enolate of III as determined by the isolation of both benzene before the enolate was decomposed and of unchanged III after hydrolysis of the initial reaction product. The only other

(1) E. I. du Pont de Nemours and Company Fellow, 1949–1950.

(2) Wisconsin Alumni Research Foundation Research Assistant, 1951–1952; Socony-Vacuum Oil Company Fellow, 1952–1953.

(3) A. Ziering and J. Lee, *J. Org. Chem.*, **12**, 911 (1947).