crystallized from acetone–hexane to afford 0.683 g (71.5% yield) of white crystals: mp 169–170°; identical, by mixture melting point and nmr comparison, with III prepared above.

**C. By Diels–Alder Addition of Methyl Acrylate to IV.**—A mixture of 0.311 g of IV, 1.3 ml of freshly distilled methyl acrylate, and 10 mg of hydroquinone was sealed in a glass tube, under reduced pressure. After the tube had been heated at 120° for 96 hr, it was cooled and then opened. The contents were concentrated under reduced pressure. The residue was chromatographed over 20 g of Merck acid-washed alumina. Elution with benzene–ethyl acetate afforded 0.319 g of material which crystallized from acetone–hexane to afford 0.288 g of white flakes, mp 171–172°. The identity of this material with the 14α,17α-etheno-16α-carbomethoxypregn-4-ene-3,20-dione obtained in A was demonstrated by nmr spectroscopy and by a mixture melting point determination.

**4,14,16-Pregnatriene-3,20-dione (IV).**—A mixture of 1.93 g of 5,14,16-pregnatrien-3β-ol-20-one, 13.0 ml of cyclohexanone, and 300 ml of toluene was dried by refluxing under a Dean–Stark head until no further water separated (4 hr). The mixture was then cooled to room temperature, and 2.03 g of aluminum isopropoxide was added. The reactants were heated under reflux for 1 hr. After the toluene had been distilled under reduced pressure, the residue was partitioned between $CHCl_3$ and aqueous HCl. The chloroform solution was then dried ($MgSO_4$), filtered, and evaporated to dryness under reduced pressure. The residue, in benzene solution, was chromatographed over 210 g of Merck acid-washed alumina. Benzene (150 ml) eluted 200 mg of impurities followed by 334 mg of impure product. A solution (150 ml) of 5% ethyl acetate in benzene followed by 100 ml of 10% ethyl acetate in benzene then eluted 1.32 g of semisolid material which crystallized from acetone to afford 1.22 g of an acetone complex of IV as pale yellow crystals, mp 105–106°.

*Anal.* Calcd for $C_{21}H_{26}O_2 \cdot 0.5C_3H_6O$: C, 79.61; H, 8.61. Found: C, 79.72, 79.54; H, 8.53, 8.37.

The product was recrystallized from ethanol to afford an ethanol complex as pale yellow crystals: mp 114–115°; $\nu^{Nujol}$ 1669, 1647, 1629, 1618 $cm^{-1}$. The nmr spectrum had a singlet at 2.33 (21-$CH_3$) and peaks in the vinyl proton region at 5.80, 6.07, and 7.28 (doublet, $J$ = 2 cps).

*Anal.* Calcd for $C_{21}H_{26}O_2 \cdot 0.5C_2H_6O$: C, 79.24; H, 8.77. Found: C, 79.47; H, 8.53.

# Derivatives of Piperazine. XXXV.[1a] Synthesis of 2-Phenylpiperazine and Some Derivatives

WILLIAM R. RODERICK,[1b] HOWARD J. PLATTE,[1c] AND C. B. POLLARD[1d]

*Department of Chemistry, University of Florida, Gainesville, Florida*

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Three methods for the synthesis of 2-phenylpiperazine (**3**), two of them new, have been investigated. One method concerned the condensation of ethyl α-bromophenylacetate with ethylenediamine to form 3-oxo-2-phenylpiperazine (**4**) followed by hydride reduction to **3**. This method was superior to the condensation of styrene oxide with ethylenediamine, previously employed. The second method involved condensation of ethyl glycinate, cyanide, and benzaldehyde to ethyl N-(α-cyanobenzyl)glycinate (**5**), which was hydrolyzed to the amido ester **6**. The latter was cyclized by sodium hydride to 3,5-dioxo-2-phenylpiperazine (**7**) which was reduced to **3**. The 1-alkyl derivatives of **3** were obtained unambiguously by alkylation of 3-oxo-2-phenylpiperazine followed by hydride reduction. The 4-alkyl and 1,4-dialkyl derivatives were prepared by alkylation of **3**.

Of the very large number of derivatives of piperazine, many of which have been investigated for various pharmacological activities, relatively few C-substituted derivatives have been studied.[2] Aside from the 2,5-disubstituted piperazines obtained by dehydration of amino acids to diketopiperazines followed by reduction, the synthesis of C-substituted piperazines offers several difficulties.[3] The first synthesis of 2-phenylpiperazine (**3**) was reported in 1943[4]; no other synthesis or papers concerning this compound have appeared, although related keto derivatives and further C-substituted derivatives have been reported. The structure of **3**, since it contains the phenethylamine moiety of the sympathomimetic amines, should be of special interest to medicinal chemistry. We report here an improved synthesis of **3** and the synthesis of some N-alkyl and oxo derivatives, prepared for pharmacological evaluation.

The first method of synthesis of **3** consisted of the reaction of styrene oxide with excess ethylenediamine to form N-(β-hydroxy-β-phenethyl)ethylenediamine (**1**) which was catalytically cyclodehydrated at high pressure in the presence of Raney nickel. The adducts of styrene oxide and amines have been assumed to result from attack at the β-carbon of styrene oxide.[5] For the reaction of several amines with styrene oxide, the major but not exclusive product has been shown to result from attack at the less substituted carbon atom.[6] This method of synthesis of **3** was reinvestigated in an attempt to improve the yield, and data were obtained to support the structure previously assigned (without proof) to the styrene oxide–ethylenediamine adduct.

From the reaction of 1 mole of styrene oxide with 2 moles of ethylenediamine, the 1:1 adduct (**1**) was obtained in 60% yield based on styrene oxide. A 2:1 adduct (**2**) was also obtained, in 11% yield based on styrene oxide. The structures of **1** and **2** were based on elemental analyses, nmr spectral comparisons, and the absence of primary amine in **2** as shown by the Hinsberg test. The nmr spectrum of **1** showed the

(1) (a) Part XXXIV: C. B. Pollard, W. M. Lauter, and N. O. Nuessle, *J. Org. Chem.*, **24**, 764 (1959). (b) Communications regarding this paper should be addressed to the Department of Organic Chemical Research, Abbott Laboratories, North Chicago, Ill. 60064. (c) This paper was abstracted from the Ph.D. Dissertation, University of Florida, June 1962. (d) Deceased; formerly Professor of Chemistry, University of Florida.

(2) E. Jucker and E. Rissi, *Helv. Chim. Acta*, **45**, 2383 (1962).

(3) For example, the synthesis of N-phenylpiperazines from arylamines and diethanolamine hydrochloride could not be extended to the synthesis of C-substituted piperazines: J. P. Bain and C. B. Pollard, *J. Am. Chem. Soc.*, **61**, 2704 (1939).

(4) L. J. Kitchen, Ph.D. Dissertation, University of Florida, Feb. 1943; C. B. Pollard and L. J. Kitchen, U. S. Patent 2,400,022 (1946); *Chem. Abstr.*, **40**, 5074 (1946); L. J. Kitchen and C. B. Pollard, *J. Am. Chem. Soc.*, **69**, 854 (1947).

(5) W. S. Emerson, *ibid.*, **67**, 516 (1945).

(6) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

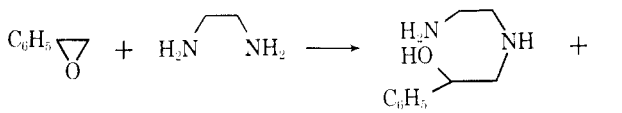
TABLE I

PROTON NMR SPECTRA OF PHENETHANOLAMINES[a]

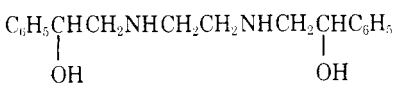
| Structure | Chemical shifts, cps[b] $H_x$ | $H_{a,b}$ | N–H, O–H |
|---|---|---|---|
| $C_6H_5$—C($H_x$)(OH[c])—C($H_a$)($H_b$)—$NH_2$ | 240 (q) | 220 (q) | 210–250 (s) |
| $C_6H_5$—C($H_x$)(HO)—C($H_a$)($H_b$)—$NH_2$ | 274 (q) | 169 (t) | 140 (s) |
| $C_6H_5$—C($H_x$)(HO)—C($H_a$)($H_b$)—$NHCH_3$ | 286 (d) | 163 (q) | 147 (s) |
| $C_6H_5$—C($H_x$)(HO)—C($H_a$)($H_b$)—$NHCH_2CH_2NH_2$ | 283 (q) | *Ca.* 168[d] | 132 (s) |

[a] Spectra were determined in $CDCl_3$ on a Varian Associates A-60 spectrometer by Dr. R. W. Mattoon and associates of Abbott Laboratories, to whom the authors are grateful. [b] s, singlet; d, doublet; t, triplet; q, quartet. [c] Synthesized by the procedure of S. Gabriel and J. Colman, *Ber.*, **47**, 1866 (1914). [d] Assumed to be a multiplet with one peak at 171 cps and others hidden under the absorption of the other four methylene protons at 163 cps.

expected ABX pattern for the three protons on the carbon atoms $\alpha$ and $\beta$ to the benzene ring. Comparison of the chemical shifts of these protons with the shifts of the corresponding protons in the two isomeric phenethanolamines clearly showed that **1** is a derivative of $\alpha$-hydroxy-$\beta$-aminoethylbenzene (see Table I). The nmr spectrum of **2** could not be obtained owing to its low solubility. It is probable, however, that both molecules of styrene oxide react in the same manner, thus forming the symmetrical structure **2**.



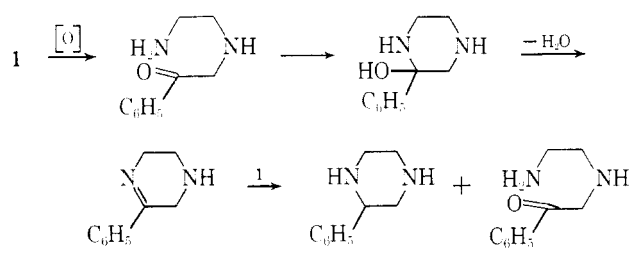
**1**



**2**

The cyclodehydration of **1** probably proceeds *via* dehydrogenation of the alcohol to a ketone, cyclization, dehydration, and reduction by a second molecule of alcohol, in a chain reaction requiring a trace of ketone to initiate the reaction (see Chart I). This sequence has been well established for alkylation of amines by alcohols,[7] and the isolation of a tetrahydropyrazine from cyclodehydration of a substituted N-($\beta$-hydroxyethyl)ethylenediamine supports this mechanism.[8]

CHART I



**3**

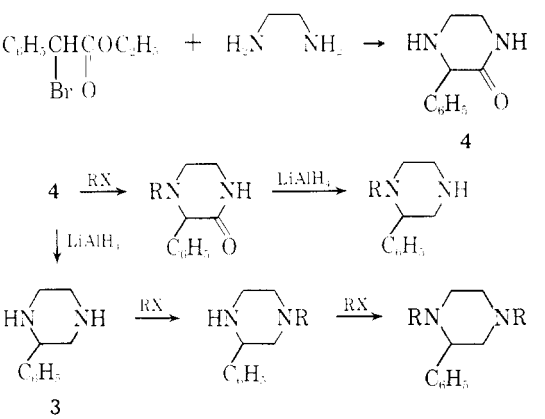
(7) E. F. Pratt and E. J. Frazza, *J. Am. Chem. Soc.*, **76**, 6174 (1954).

(8) L. T. Plante, W. G. Lloyd, C. E. Schilling, and L. B. Clapp, *J. Org. Chem.*, **21**, 82 (1956).

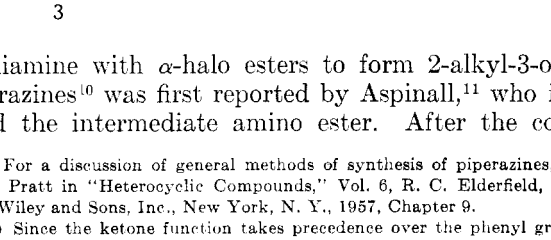
In our hands the cyclodehydration of **1** gave 2-phenylpiperazine (**3**) in yields of 25–30%, 50–70% of **1** being recovered. The over-all yield for the two-step synthesis of **3** was 7–15%. The presence of sodium sulfate, added to remove water and shift equilibrium, resulted in a lower yield. Cyclodehydration was attempted at atmospheric pressure without Raney nickel under three types of experimental conditions: oxidizing agents to form the intermediate ketone, benzalaniline and alkoxide to dehydrogenate the alcohol, and solvents to remove water as an azeotrope. In none of these experiments was **3** formed.

Several of the many other syntheses of the piperazine ring[9] were studied as routes to **3**; two methods were found to be effective. The first method, the one used in the synthesis of all the compounds reported in this paper, is shown in Chart II. The reaction of ethyl-

CHART II



**4**



**3**

enediamine with $\alpha$-halo esters to form 2-alkyl-3-oxopiperazines[10] was first reported by Aspinall,[11] who isolated the intermediate amino ester. After the com-

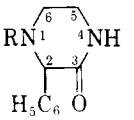
(9) For a discussion of general methods of synthesis of piperazines, see Y. T. Pratt in "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, Chapter 9.

(10) Since the ketone function takes precedence over the phenyl group, the oxo derivative of 2-phenylpiperazine is correctly named as 2-oxo-3-phenylpiperazine. To avoid confusion, however, the "2-phenyl" nomenclature will be employed throughout this paper.

(11) S. R. Aspinall, *J. Am. Chem. Soc.*, **62**, 1202 (1940).

TABLE II

3-OXO-2-PHENYLPIPERAZINES



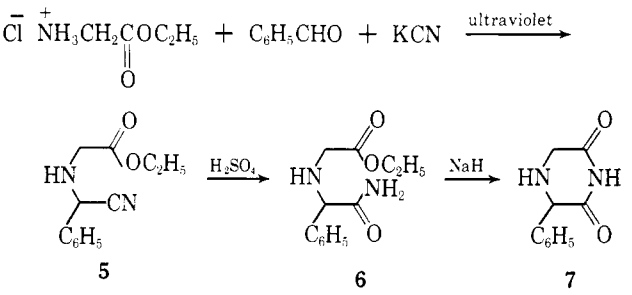
| No. | R | Yield, % | Mp, °C | Formula | Carbon, % Calcd | Carbon, % Found | Hydrogen, % Calcd | Hydrogen, % Found | Nitrogen, % Calcd | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| 4 | H | 50 | 139.0–139.5 | $C_{10}H_{12}N_2O$ | 68.16 | 68.44 | 6.86 | 7.02 | 15.90 | 15.62 |
| 8 | $CH_3$ | 20 | 130–132 | $C_{11}H_{14}N_2O$ | 69.44 | 69.50 | 7.42 | 7.44 | 14.73 | 15.05 |
| 9 | $C_2H_5$ | 81 | 99–101 | $C_{12}H_{16}N_2O$ | 70.56 | 70.27 | 7.90 | 7.71 | 13.72 | 13.69 |
| 10 | $n$-$C_3H_7$ | 71 | 89.5–92.0 | $C_{13}H_{18}N_2O$ | 71.52 | 71.60 | 8.31 | 8.35 | 12.83 | 13.01 |
| 11 | $C_6H_5CH_2$ | 82 | 224–226 dec | $C_{17}H_{18}N_2O$ | 76.66 | 76.61 | 6.81 | 6.89 | 10.52 | 10.34 |
| 12 | $C_6H_5CH_2CH_2$[a] | 50 | 144–145 | $C_{18}H_{20}N_2O$ | 77.11 | 77.33 | 7.19 | 7.15 | 9.99 | 9.60 |
| 13 | $CH_3CO$ | 54 | 161–162 | $C_{12}H_{14}N_2O_2$ | 66.03 | 66.04 | 6.46 | 6.53 | 12.83 | 13.03 |

[a] The 4-phenyl derivative of compound **12**, 1-(β-phenethyl)-3-oxo-2,4-diphenylpiperazine, has been reported: O. E. Fancher, S. Hayao, and W. G. Strycker, *J. Med. Chem.*, **7**, 154 (1964).

pletion of the present study, the synthesis of 3-oxo-2-phenylpiperazine (**4**)[10] from a reaction differing from that shown in Chart II only in the use of the methyl instead of the ethyl ester was reported.[12] Reduction of **4** by lithium aluminum hydride gave 2-phenylpiperazine; the over-all yield for these two steps was 47–56%.

It was also desired to prepare 2-(substituted phenyl)-piperazines, *e.g.*, 2-(*o*-methoxyphenyl)piperazine, which would be more likely to have useful pharmacological activity. Attempts at direct substitution of 2-phenylpiperazine and syntheses *via* ring-substituted α-halophenylacetates were unsuccessful. The sequence shown in Chart III was investigated since it appeared that it could be easily modified by using substituted benzaldehydes to achieve the desired goal.

CHART III



The formation of **5** and its conversion to the amido ester (**6**) have been reported.[13–15] The amido ester was prepared using a slight modification of the literature procedure. Cyclization to the imide **7** could not be effected by pyrolysis, although the imide has been reported as the product of thermal dehydration of the carbobenzyloxy derivative of the amido acid corresponding to **6** followed by hydrogenolysis.[16] The amido ester was converted to the diamide, but this derivative was also resistant to thermal cyclization. Cyclization of the amido ester was effected by sodium hydride, and reduction of the resultant imide with lithium aluminum hydride gave 2-phenylpiperazine. Since the over-all yield for the sequence of reactions was quite low, no studies with substituted benzaldehydes were carried out.

Both 1-alkyl and 4-alkyl derivatives of **3** were prepared. Monoalkylation of **3** would be expected, as a result of steric factors, to occur predominantly in the 4-position, as has been shown for 2-methylpiperazine,[17] and this was found to be the case. The synthesis of 1-substituted 2-phenylpiperazines would thus require the use of a blocking group in the 4-position, such as benzyl,[18] ethoxycarbonyl,[17,19,20] benzyloxycarbonyl,[19] acetyl,[20] or nitroso.[20] However, alkylation of a 2-substituted 3-oxopiperazine would give 1-alkylation without the use of an added protecting group. Thus, by alkylation of 3-oxo-2-phenylpiperazine, followed by reduction, it was possible to obtain 1-alkyl derivatives, whereas alkylation of **3** gave 4-alkyl derivatives. The 1,4-dialkyl-2-phenylpiperazines were obtained by alkylation of **3** using excess alkylating agent (see Chart II). The compounds prepared in this way are summarized in Tables II and III.

**Pharmacological Evaluation.**—Preliminary pharmacological screening showed central nervous system effects from several compounds in both the 3-oxo-2-phenylpiperazine[21] and 2-phenylpiperazine series. Mild analgetic activity in the guinea pig was shown by 2-phenylpiperazine (**3**). 1,4-Dimethyl-2-phenylpiperazine (**16**) showed moderate analgetic activity in the mouse and rat but was inactive in the guinea pig. Compounds **22** and **24** showed moderate cerebral stimulation. Moderate anticonvulsant activity against seizures induced by electroshock was exhibited by compounds **10** and **11**, but no antimetrazole activity was observed. Compounds **11** and **14** had moderate and weak hypotensive activity, respectively, at high dosages. None of these activities was sufficient to justify further interest. None of the compounds showed antibacterial activity.

(12) S. Kawahara and H. Kawakami, Japanese Patent 4540 (1962); *Chem. Abstr.*, **58**, 10214 (1963); the 2-(*p*-chlorophenyl) derivative was also prepared.

(13) G. L. Stadnikov, *J. Russ. Phys. Chem. Soc.*, **40**, 1638 (1908); *Ber.*, **41**, 4364 (1908).

(14) F. E. King, J. R. Marshall, and P. Smith, *J. Chem. Soc.*, 239 (1951).

(15) H. Scheibler and P. Baumgarten, *Ber.*, **55**, 1358 (1922).

(16) S. R. Safir, J. J. Hlavka, and J. H. Williams, U. S. Patent 2,763,652 (1956); *Chem. Abstr.*, **51**, 3675 (1957).

(17) K. M. Beck, K. E. Hamlin, and A. W. Weston, *J. Am. Chem. Soc.*, **74**, 605 (1952).

(18) J. S. Buck and R. Baltzly, U. S. Patent 2,415,786 (1947); *Chem. Abstr.*, **41**, 3133 (1947).

(19) W. O. Foye and L. R. Fedor, Jr., *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 412 (1959); *Chem. Abstr.*, **53**, 21981 (1959).

(20) M. Harfenist and E. Magnien, *J. Am. Chem. Soc.*, **79**, 2215 (1957).

(21) 3-Oxo-2-phenylpiperazine (**4**) has been reported[12] to have analgetic and antispasmodic activity.

TABLE III

2-PHENYLPIPERAZINES

| No. | R | R′ | Yield, % | Mp or bp (mm), °C | Formula | Carbon, % Calcd | Carbon, % Found | Hydrogen, % Calcd | Hydrogen, % Found | Nitrogen, % Calcd | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | H | H | 93 | 87–88 | $C_{10}H_{14}N_2$ | 74.03 | 74.29 | 8.70 | 8.73 | 17.27 | 17.47 |
| 14 | H | $CH_3$ | 51 | 95 (0.4–0.5) | $C_{11}H_{16}N_2$ | 74.95 | 74.81 | 9.15 | 8.96 | 15.90 | 15.83 |
| 15 | $CH_3$ | H | 50 | 78–80 (0.1) | $C_{11}H_{16}N_2$ | 74.95 | 74.91 | 9.15 | 9.17 | 15.90 | 15.76 |
| 16 | $CH_3$ | $CH_3$ | 60 | 88 (0.5) | $C_{12}H_{18}N_2$ | 75.74 | 75.76 | 9.54 | 9.56 | 14.72 | 14.50 |
| 17 | H | $C_2H_5$ | 82 | 91–93 (0.7–0.8) | $C_{12}H_{18}N_2$ | 75.74 | 75.36 | 9.54 | 9.46 | 14.72 | 15.10 |
| 18 | $C_2H_5$ | H | 65 | 90 (0.5) | $C_{12}H_{18}N_2$ | 75.74 | 75.75 | 9.54 | 9.51 | 14.72 | 14.83 |
| 19 | $C_2H_5$ | $C_2H_5$ | 83 | 93–95 (0.3–0.4) | $C_{14}H_{22}N_2$ | 77.01 | 77.07 | 10.16 | 10.05 | 12.83 | 13.01 |
| 20 | H | $n$-$C_3H_7$ | 65 | 91–94 (0.3–0.4) | $C_{13}H_{20}N_2$ | 76.42 | 76.24 | 9.87 | 9.95 | 13.71 | 13.83 |
| 21 | $n$-$C_3H_7$ | H | 83 | 61.5–66.5 | $C_{13}H_{20}N_2$ | 76.42 | 76.59 | 9.87 | 9.98 | 13.71 | 13.60 |
| 22 | $n$-$C_3H_7$ | $n$-$C_3H_7$ | 68 | 106–110 (0.7–0.9) | $C_{16}H_{26}N_2$ | 77.99 | 77.75 | 10.64 | 10.36 | 11.56 | 11.37 |
| 23 | H | $C_6H_5CH_2$ | 63 | 110 (1.5), 55–63 | $C_{17}H_{20}N_2$ | 80.91 | 80.79 | 7.99 | 7.76 | 11.10 | 11.15 |
| 24 | $C_6H_5CH_2$ | H | 61 | 101.5–102.5 | $C_{17}H_{20}N_2$[a] | 75.52 | 75.65 | 8.22 | 8.19 | 10.36 | 10.36 |
| 25 | $C_6H_5CH_2$ | $C_6H_5CH_2$ | 65 | 109.5–110.5 | $C_{24}H_{26}N_2$ | 84.17 | 84.26 | 7.65 | 7.86 | 8.18 | 8.19 |

[a] Monohydrate.

## Experimental Section[22]

**2-Phenylpiperazine (3). I. Method of Kitchen and Pollard.[4] A. N-(β-Hydroxy-β-phenethyl)ethylenediamine (1).**—A solution of 270 g (2.25 moles) of styrene oxide in 500 ml of methanol was added slowly to a stirred solution of 256 ml (4.5 moles) of ethylenediamine and 500 ml of methanol in a 3-l. flask fitted with condenser, thermometer, and stirrer. The mixture was left for 4 hr, during which time it warmed to reflux, and a colorless precipitate (38 g, 11%) of the 2:1 adduct formed. The mixture was filtered, and the filtrate was distilled. The crude **1** was collected at 151–160° (0.8–1.0 mm) as a yellow liquid which solidified in the receiver; yield 242 g (60%). Recrystallization from hexane–ethanol, as used by Kitchen and Pollard, gave gummy or oily crystals. Since the product is very hygroscopic, the difficulties appeared to result from the presence of water. The product was dissolved in benzene, water was removed by azeotropic distillation, and the solution was cooled to give colorless crystals melting at 88.5–91.0°. The 2:1 adduct (**2**) was crystallized from dimethylformamide to give colorless flakes with mp 230–232°.

*Anal.* Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 72.42; H, 8.18; N, 9.00.

**B. Conversion of 1 to 3.**—To an autoclave of 1.5–2.0-l. capacity were added 132 g of **1**, 600 ml of dioxane, and 20 g of Raney nickel. The autoclave was charged with hydrogen to 500 psig and maintained at 200° for 4 hr with continuous rocking. The catalyst was removed by filtration, and the filtrate was distilled at atmospheric pressure to remove dioxane–water azeotrope and dioxane. Fractional distillation at reduced pressure gave 25–30% of **3**, bp 110–130° (4 mm), and unchanged **1**, bp 170–175° (4 mm) (50–70% recovery). Compound **3** was recrystallized three times from *n*-hexane to give crystals of mp 87–88° (lit.[4] 87.5–87.8°).

**II. From Ethyl α-Bromophenylacetate. A. 3-Oxo-2-phenylpiperazine (4).**—To a stirred solution of 68 ml (1.0 mole) of ethylenediamine in 750 ml of absolute ethanol was added 122 g (0.5 mole) of ethyl α-bromophenylacetate.[23] After the addition was completed, a solution of sodium ethoxide (prepared from 11.5 g, 0.5 g-atom, of sodium and 100 ml of absolute ethanol) was added, and the mixture was warmed on the steam bath for 2 hr. The ethanol and excess ethylenediamine were removed by distillation at reduced pressure. The yellow-orange residue was extracted with boiling acetone to give 44–53 g (50–60%) of **4** contaminated with a small amount of NaBr. Crystallization from benzene and then from acetone gave a product melting at 139.0–139.5° (lit.[12] 141–142°). Further recrystallization (three times from water and twice from acetone) gave a product with a satisfactory analysis.

*Anal.* Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.44; H, 7.02; N, 15.62.

For characterization, 1-acetyl-3-oxo-2-phenylpiperazine was prepared by acetylation of **4** with acetic anhydride (55% yield). The product was crystallized from water to give colorless plates of mp 161–162°.

*Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.46; N, 12.83. Found: C, 66.04; H, 6.53; N, 13.03.

**B. Conversion of 4 to 3.**—Reduction of **4** by lithium aluminum hydride as described under the preparation of 1-alkyl-2-phenylpiperazines gave **3** (see Table III for data).

**III. From Benzaldehyde. A. Ethyl N-(α-Cyanobenzyl)glycinate (5).**—A slurry of 14.0 g (0.10 mole) of ethyl glycinate hydrochloride, 10.2 ml (0.10 mole) of benzaldehyde, and 200 ml of ether was mixed with 6.5 g (0.10 mole) of KCN in 10 ml of water. The mixture was irradiated for 12 hr by an ultraviolet lamp immersed in the continuously stirred suspension. The reaction mixture was dried with $Na_2SO_4$ and filtered. Distillation of the ether left a residue (19.7 g, 90%) of crude ester nitrile, used without purification for conversion to the amido ester.

**B. Ethyl N-(α-Carboxamidobenzyl)glycinate (6).**—The crude ester nitrile from A (5.0 g, 0.023 mole) was added dropwise with constant stirring to 22 ml of concentrated $H_2SO_4$. The resulting red-brown viscous solution was left for 20 hr, then added dropwise to 50 ml of absolute ethanol at 0–15°. The ethanolic solution was neutralized with a solution of ammonia in absolute ethanol, the temperature being kept below 15°. The mixture was filtered to remove $(NH_4)_2SO_4$, and the ethanol was distilled from the filtrate. The residue was crystallized from acetone to give 2.83 g (52%) of colorless needles, mp 133.5–134.0° (lit.[11] 135°).

**C. 3,5-Dioxo-2-phenylpiperazine (7).**—A mixture of 3.9 g (0.02 mole) of **6** from B, 0.8 g (0.03 mole) of sodium hydride, and 50 ml of xylene freshly distilled from sodium hydride was refluxed under nitrogen for 20 hr. The solution was acidified with 2 ml of acetic acid, heated to 100°, and filtered. Crystals formed as the xylene solution cooled. They were collected and washed with ether, giving 0.8 g (25%), mp 121–124° (lit.[16] 125–127°). The infrared spectrum had bands at 5.79 and 5.95 μ consistent with a cyclic imide structure.

**D. Conversion of 7 to 3.**—A mixture of 100 mg of **7** from C, 90 mg of lithium aluminum hydride, and 50 ml of ether was refluxed for 8 hr. The isolated product was 50 mg of an oil which partially crystallized. An infrared spectrum of the oil contained all of the major bands of 2-phenylpiperazine plus a carbonyl band, indicating incomplete reduction. Sublimation gave crystalline **3**.

*Anal.* Calcd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 73.93; H, 8.40; N, 17.14.

**1-Alkyl-2-phenylpiperazines.**—A solution of 8.75 g (0.050 mole) of 3-oxo-2-phenylpiperazine, 0.055 mole of the alkyl halide, and

(22) Melting points and boiling points are not corrected. Elemental analyses were performed by Drs. Weiler and Strauss, Oxford, England, and by the Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(23) E. Schwenk and D. Papa, *J. Am. Chem. Soc.*, **70**, 3626 (1948).

21 ml (0.15 mole) of triethylamine in 100 ml of acetone or toluene was refluxed several hours. The reaction mixture was filtered and the solvent was removed by distillation. The residue was crystallized from benzene, hexane, or acetone. Methylation was effected with formaldehyde–formic acid in water.[24] The reductions were carried out by refluxing for 24 hr a solution or slurry of 0.016 mole of the 1-alkyl-3-oxo-2-phenylpiperazine and 0.063 mole of lithium aluminum hydride in 250 ml of ether. The products were isolated by standard methods.

**4-Alkyl- and 1,4-Dialkyl-2-phenylpiperazines.**—The 4-alkyl derivatives were prepared by alkylation of 2-phenylpiperazine, with 1 equiv of alkylating agent by the general procedure given above. The 4-methyl derivative was prepared using methyl iodide since formaldehyde–formic acid gave some disubstitution. The 1,4-dialkyl derivatives were obtained using 3 equiv of alkylating agent. The products were purified by distillation at reduced pressure.

(24) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

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# Derivatives of 2-Azabicyclo[2.2.2]octane. I

FRANK J. VILLANI AND CLAIRE A. ELLIS

*Medicinal Chemical Research Department, Schering Corporation, Bloomfield, New Jersey*

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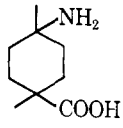
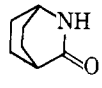
2-Azabicyclo[2.2.2]octan-3-one (isoquinuclidone), prepared by pyrolysis of *cis*-4-aminocyclohexanecarboxylic acid, was reduced in excellent yield to 2-azabicyclo[2.2.2]octane (isoquinuclidine). The isoquinuclidyl ring was substituted for the dimethylamino group in a limited number of clinically effective agents. The following compounds were prepared: N-[3-(*p*-chlorophenyl)-3-(2-pyridyl)propyl]isoquinuclidine (VI), N-[2-(*p*-chlorobenzhydryloxy)ethyl]isoquinuclidine (VII), and 10-[3-(N-isoquinuclidyl)propyl]-2-chlorophenothiazine (VIII). These compounds showed the same type of biological activity as their dimethylamino prototypes but were less active. N-[2-(Guanidino)ethyl]- and N-[3-(guanidino)propyl]isoquinuclidine sulfates were also prepared.

The biological properties of a series of compounds, wherein the bulky bicyclic ring, 2-azabicyclo[2.2.2]-octane, commonly known as isoquinuclidine[1] was substituted for the dimethylamino moiety in a number of clinically active agents, were studied.

Isoquinuclidine (III) was prepared by pyrolysis of *cis*-4-aminocyclohexanecarboxylic acid (I)[2] to the cyclic lactam, 2-azabicyclo[2.2.2]octan-3-one (II),[3] followed by reduction with lithium aluminum hydride.[4] This series of reactions establishes the conformation of the *cis* acid (I), since the *trans* form cannot be so converted and serves as a convenient method for the preparation of the bicyclic amine (III).




I

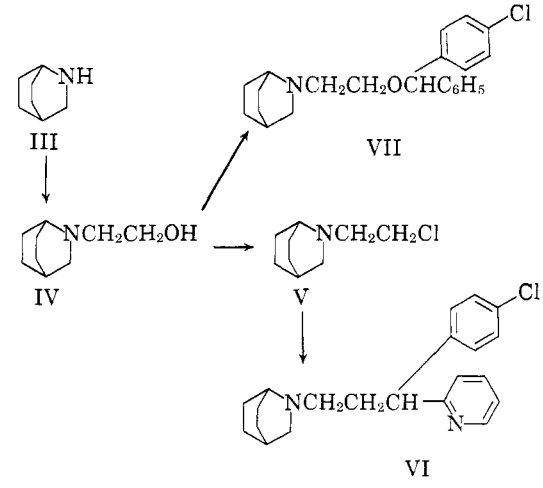



II

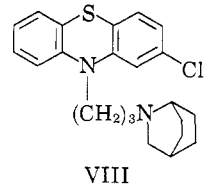

III

The preparation of the isoquinuclidyl analogs of the propylamine and aminoalkyl ether types of antihistaminic agents of which chlorpheniramine[5a] and chlordiphenhydramine[5b] are the prototypes is shown in Chart I. Isoquinuclidine (III) was converted into N-(2-hydroxyethyl)isoquinuclidine (IV) by reaction with ethylene oxide. Reaction of IV with thionyl chloride gave the chloride V. Alkylation of 2-(*p*-chlorobenzyl)-pyridine with V in the presence of potassium amide gave the desired N-[3-(*p*-chlorophenyl)-3-(2-pyridyl)-propyl]isoquinuclidine (VI). Compound VII was prepared by heating a dilute xylene solution of IV with *p*-chlorobenzhydryl bromide in the presence of potassium carbonate.

CHART I




The preparation of the isoquinuclidyl analog VIII of the central nervous system depressant, chlorproma-




VIII

(1) Throughout this manuscript, the common name isoquinuclidine is used instead of the more cumbersome chemical name.

(2) F. J. Villani and C. A. Ellis, *J. Org. Chem.*, **29**, 2585 (1964).

(3) E. Ferber and H. Bruckner, *Ber.*, **76**, 1019 (1943).

(4) (a) L. H. Werner and S. Ricca, *J. Am. Chem. Soc.*, **80**, 2733 (1958), were unable to effect this reduction. (b) W. Schneider and R. Dillmann, *Chem. Ber.*, **96**, 2377 (1963), prepared this compound in 40% yield using $LiAlH_4$ in tetrahydrofuran. (c) Compound III is unstable and a sample of analytical purity could not be obtained. The compound sublimes quite readily and absorbs $CO_2$ from the air. See ref 4a and 4b.

(5) (a) 1-(*p*-Chlorophenyl)-1-(2-pyridyl)-3-dimethylaminopropane, Chlor-Trimeton®, Schering Corporation; (b) 2-(*p*-chlorobenzhydryloxy)-N-dimethylethylamine; (c) 10-(3-dimethylaminopropyl)-2-chlorophenothiazine; (d) [2-(octahydro-1-azocinyl)ethyl]guanidine.