tained at 12–16° while 1.08 g. (0.01 mole) of ethyl chloroformate was added dropwise. After the addition was completed, the stirred suspension was kept at the same temperature for an additional 15 min. and then a stream of ammonia gas was passed through the solution for 3 min. The suspension was allowed to warm to room temperature and remained there for 4 hr., after which time the solvent was removed by evaporation. The resulting solid residue was recrystallized from hot ethanol by the addition of water until the solution became opalescent and then cooled.

Synthesis of *cis*-6-Styrylnicotinic Acid and Derivatives.—To 0.50 g. (0.002 mole) of 6-phenethynylnicotinic acid suspended in 50 ml. of methanol was added 1 drop of quinoline and 0.1 g. of deactivated 10% palladium-on-charcoal catalyst.[8] The mixture was stirred in an atmosphere of hydrogen until 0.002 mole was taken up. The catalyst was then removed by filtration and the filtrate evaporated *in vacuo*. The residue was recrystallized from hot methanol by the addition of water and cooling to give 0.35 g. (69%) of a crystalline solid which melted at 148–150°. Upon cooling, the liquid in the melting point tube resolidified and remelted at 222–225°, which was the melting point of the *trans* isomer.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.67; H, 5.17; N, 6.24.

Similar hydrogenation of the previously prepared amides of 6-phenethynylnicotinic acid yielded the corresponding amides of *cis*-6-styrylnicotinic acid (see Table IV).

Conclusions

Of those compounds tested, only 6-phenethylnicotinyl pyrrolidide exhibited a stimulant effect upon the uterus; but in order to produce such action, a dose was required that was (on a weight basis) approximately 50 times the dose of ergonovine needed to provoke a vigorous response. It did not display the smooth muscle selectivity characteristic of ergonovine, for at doses somewhat below those required for uterine stimulation, it increased gut motility. Ethyl 6-(*o*-aminophenethyl)-nicotinate, which in itself produces no effects on either uterus or gut, consistently abolished the uterine contractions previously initiated by ergonovine. The nature and specificity of this antagonism remains to be determined. The other compounds affected neither normal uterus nor uterus previously stimulated by ergonovine. These last three compounds all depressed gut activity, however. Under the conditions described, none of the substances examined evoked responses that compare favorably with the uterotropic action of ergonovine.

4-Alkyl- (or Aralkyl) 1-Aryl-2-piperazinones

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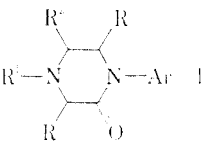
A number of 4-alkyl- (or aralkyl) 1-aryl-2-piperazinones were prepared as potential analgesics. These compounds were prepared either by catalytic debenzylation or pyrolytic debenzylation (or demethylation) of 1,1-dialkyl- (or 1,1-diaralkyl) 3-oxo-4-arylpiperazinium halides.

In the course of our search for new nonnarcotic type analgesics, we have synthesized a group of 4-alkyl- (or aralkyl) 1-aryl-2-piperazinones (I). 1,4-Diaryl-,[1] 1,4-diaralkyl-, and 1,4-dialkyl-2-piperazinones[2] having identical substituents at the 1 and 4 positions, 3-substituted 2-piperazinones,[3] and 3,3-disubstituted-2-piperazinones[4] have been reported. 1-Cyclohexyl-2-piperazinone[5] and 4-alkyl-3-oxo-1-piperazinylalkylphenothiazines[6] have been described. However, no 4-alkyl- (or aralkyl) 1-aryl-2-piperazinones have been recorded in the literature except for six compounds disclosed in our patent.[7] Recently very similar compounds, 1-(2-phenethyl)-4-(lower alkyl)-2-piperazinones,[8] were reported.

The following compounds have been prepared for analgetic screening.



Ar = C_6H_5, 4-$CH_3OC_6H_4$, 3-$CH_3OC_6H_4$, 4-ClC_6H_4; R = H, CH_3, C_6H_5; R^1 = H, CH_3, $C_6H_5CH_2$, $C_6H_5CH_2CH_2$, $C_6H_5CH_2CH(CH_3)$, 3,4-$(CH_3O)_2C_6H_3CH_2CH(CH_3)$, $(C_2H_5)_2NCH_2CH_2$; R^2 = H, CH_3, C_6H_5; R^3 = H, CH_3

The synthesis of these compounds was carried out as follows with final conversion to the desired piperazinones *via* either catalytic hydrogenolysis or pyrolytic distillation.

The ease of cyclization to form piperazinium halides (III) from the reaction of the diamines (II) and chloroacetyl chloride, α-bromopropionyl chloride, or α-chlorophenylacetyl chloride seems to depend on steric factors. When IIa was treated with chloroacetyl chloride in benzene under Schotten–Baumann conditions, IIIa precipitated from the benzene solution on standing at room temperature. When α-bromopropionyl chloride was used, it was necessary to heat the benzene solution under reflux before cyclization took place. The same

(1) (a) C. A. Bischoff and O. Nastrogel, *Ber.*, **22**, 1783 (1889); *ibid.*, **23**, 2026, 2031, 2035 (1890); (b) C. A. Bischoff and Ch. Trapesonzjanz, *ibid.*, **25**, 2931 (1892).

(2) W. B. Martin, Jr., and A. E. Martell, *J. Am. Chem. Soc.*, **72**, 4301 (1950).

(3) (a) H. Moureu, P. Chovin, and L. Petit, *Compt. Rend.*, **243**, 910 (1956), *Chem. Abstr.*, **51**, 5769 (1957); (b) A. P. Phillips, U. S. Patent 2,958,693 (Nov. 1, 1960), *Chem. Abstr.*, **55**, 9438 (1961).

(4) (a) J. S. Strong, W. E. Craig, and V. T. Elkind, U. S. Patent 2,649,450 (Aug. 18, 1953), *Chem. Abstr.*, **48**, 8271 (1954); (b) G. Melone, A. Vecchi, and G. Maffii, British Patent 870,888 (June 21, 1961), *Chem. Abstr.*, **56**, 482 (1962); (c) J. S. Strong, W. E. Craig, and T. V. Elkind, U. S. Patent 2,700,668 (Jan. 25, 1955), *Chem. Abstr.*, **50**, 413 (1956); (d) T. Kametani, W. Taub, and D. Ginsburg, *Bull. Chem. Soc. Japan*, **31**, 860 (1958); (e) S. R. Aspinall, *J. Am. Chem. Soc.*, **62**, 1202 (1940).

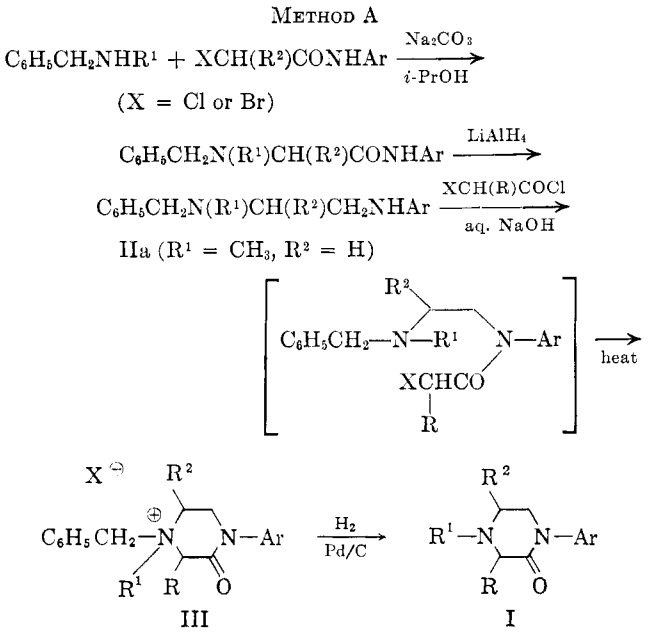
(5) J. Honzl, *Collection Czech. Chem. Commun.*, **25**, 2651 (1960), *Chem. Abstr.*, **55**, 3603 (1963).

(6) J. W. Cusic, H. S. Lowrie, and H. W. Sause, U. S. Patent 2,778,617 (April 2, 1957); *Chem. Abstr.*, **51**, 12155 (1957).

(7) O. E. Fancher and S. Hayao, U. S. Patent 3,072,658 (Jan. 8, 1963).

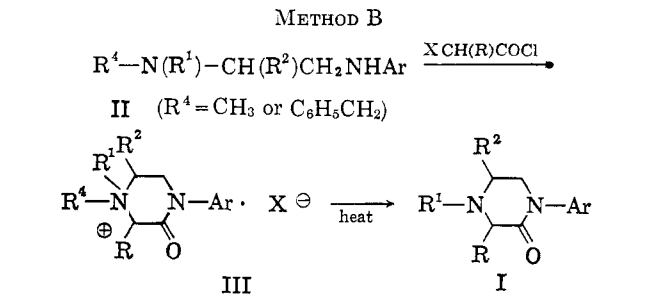
(8) S. Archer, U. S. Patent 3,062,821 (Nov. 6, 1962).

Method A



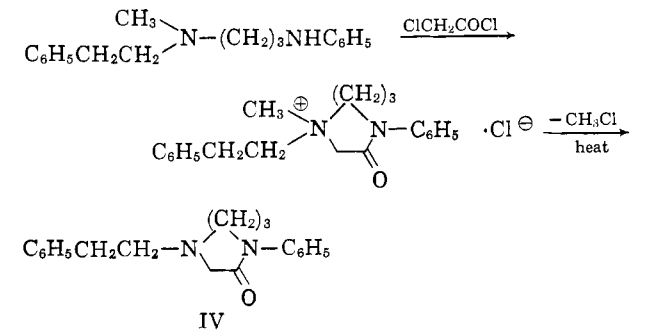
IIIa (R = R^2 = H, R^1 = CH_3)
IIIb (R = R^1 = CH_3, R^2 = H)
IIIc (R = H, R^1 = R^2 = CH_3)
IIId (R = CH_3, R^1 = $C_6H_5CH_2CH_2$, R^2 = H)
IIIe (R = H, R^1 = $C_6H_5CH_2CH_2$, R_2 = CH_3)

Method B



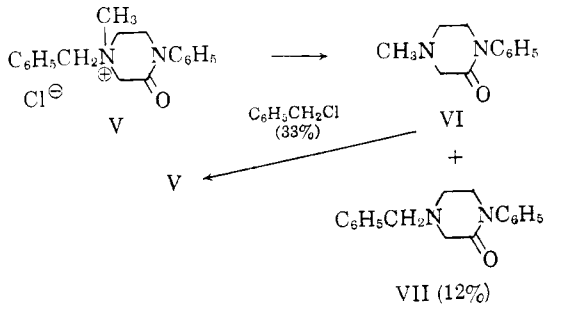
IIIf (R = H, R^1 = $C_6H_5CH_2CH_2$, R^2 = C_6H_5, R^4 = $C_6H_5CH_2$)
IIIg (R = R^2 = CH_3, R^1 = $C_6H_5CH_2CH_2$, R^4 = $C_6H_5CH_2$)
IIIh (R = R^2 = H, R^1 = R^4 = $C_6H_5CH_2$)

4-Phenethyl-1-phenyl-2-homopiperazinone (IV) was prepared by method B.



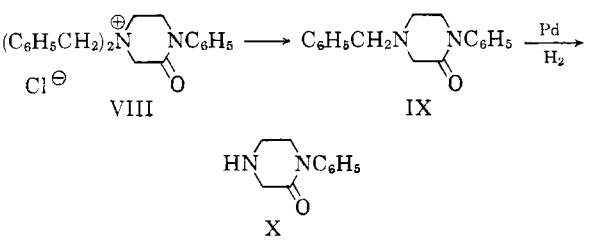
conditions were required for the formation of IIIc and IIId. On the other hand, IIIe, IIIf, IIIg, and IIIh were obtained only when their benzene solutions were evaporated and the remaining sirups were heated at 200° for a few hours in a wax bath.

1-Benzyl-1-methyl-3-oxo-4-phenylpiperazinium chloride (V) was distilled pyrolytically to determine whether methyl chloride or benzyl chloride would be eliminated. At first, benzyl chloride and 4-methyl-1-phenyl-2-piperazinone (VI) distilled together and reacted in a receiver to give V in 33% yield after recrystallization;



then 4-benzyl-1-phenyl-2-piperazinone (VII) distilled at a higher temperature in 12% yield.

The elimination of benzyl chloride also occurred on pyrolytic distillation of 1,1-dibenzyl-3-oxo-4-phenylpiperazinium chloride (VIII) to give 4-benzyl-1-phenyl-2-piperazinone (IX) in 87% yield. The hydrochloride of IX was debenzylated by hydrogenolysis with palladium-on-carbon catalyst to give 1-phenyl-2-piperazinone (X).

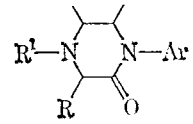


The presence of the 2-piperazinone ring system was established by lithium aluminum hydride reduction of 4-phenethyl-1-phenyl-2-piperazinone to 4-phenethyl-1-phenylpiperazine. The reduction product was prepared independently from 1-phenylpiperazine and phenethyl bromide.

Pharmacology.—All the 4-alkyl- (or aralkyl) 1-aryl-2-piperazinones (I) described in this paper showed very little or no hypotensive activity in pentobarbitalized dogs (intravenous route) at 5 mg./kg., almost no sedative activity by the rotarod test[9] or hexobarbital sleeping time test,[10] and very little or no anti-inflammatory activity against rat-foot inflammation induced by the injection of yeast solution.[11] However, some of these compounds, **4** (I, Ar = C_6H_5, R = R_2 = H, R^1 = R^3 = CH_3), **6** (I, Ar = C_6H_5, R = R^2 = R^3 = H, R^1 = $C_6H_5CH_2CH_2$), **5** (I, Ar = C_6H_5, R = R^2 = R^3 = H, R^1 = $C_6H_5CH_2$), **13** (I, Ar = 4-$CH_3OC_6H_4$, R = R^3 = H, R^2 = CH_3, R^1 = $C_6H_5CH_2CH_2$), and **23** (I, Ar = R = C_6H_5, R^1 = R^2 = CH_3, methiodide) showed borderline analgetic activity by the phenylquinone[12] writhing test in mice at 100 mg./kg. (subcutaneous route). The Randall–Selitto[13] method showed that **6** had moderate analgetic activity comparable to aminopyrine at 100 mg./kg. in rats (oral route).

(9) N. W. Dunham and T. S. Miya, *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 208 (1957).
(10) C. A. Winter, *J. Pharmacol. Exptl. Therap.*, **94**, 7 (1948).
(11) L. O. Randall, J. J. Selitto, and J. Valdes, *Arch. Intern. Pharmacodyn.*, **113**, 233 (1957).
(12) L. C. Hendelshot and J. Forsaith, *J. Pharmacol. Exptl. Therap.*, **125**, 237 (1959).
(13) L. O. Randall and J. J. Selitto, *Arch. Intern. Pharmacodyn.*, **111**, 409 (1957).

TABLE I



No.	Method[a]	Ar	R	R¹	R²	R³	Formula	M.p., °C.	% calcd. C	% calcd. H	% calcd. N	% calcd. HCl	% found C	% found H	% found N	% found HCl
1	B	C_6H_5	H	H	H	H	$C_{10}H_{12}N_2O\cdot HCl$	181–182	56.4	6.11	13.2	17.2	55.8	6.55	13.0	17.2
2	A	C_6H_5	H	CH_3	H	H	$C_{11}H_{14}N_2O\cdot C_4H_4O_4$[b]	129.5–130.5	58.8	5.88	9.15		58.9	6.02	9.14	
3	A	C_6H_5	H	CH_3	CH_3	H	$C_{12}H_{16}N_2O$	126–135 (0.2 mm.)[d]			6.86[c]				6.70	
							$C_{12}H_{16}N_2O\cdot C_2H_2O_4$[c]	125–126	57.2	6.13	9.53		57.0	6.25	9.38	
4	A	C_6H_5	H	CH_3	H	CH_3	$C_{12}H_{16}N_2O$	128–135 (0.45 mm.)[d]			6.86[c]				6.71	
							$C_{12}H_{16}N_2O\cdot C_2H_2O_4$	84–88			9.52				9.80	
5	A	C_6H_5	H	$C_6H_5CH_2$	H	H	$C_{17}H_{18}N_2O$	105–105.5[f]	76.7	6.77	10.5		76.4	7.01	10.6	
							$C_{17}H_{18}N_2O\cdot HCl$	210–212	67.4	6.29	9.25	12.1	67.7	5.97	9.41	12.2
6	A, B	C_6H_5	H	$C_6H_5CH_2CH_2$	H	H	$C_{18}H_{20}N_2O$	83–84	77.2	7.15	10.0		76.8	7.15	10.1	
							$C_{18}H_{20}N_2O\cdot HCl$	222.5–223.5 dec.	68.2	6.63	8.85	11.5	68.1	6.82	8.78	11.6
7	A	C_6H_5	CH_3	$C_6H_5CH_2CH_2$	H	H	$C_{19}H_{22}N_2O$	200–203 (0.2 mm.)[d]			4.76[c]				4.73	
							$C_{19}H_{22}N_2O\cdot C_2H_2O_4$	201–201.5 dec.	65.6	6.25	7.29		65.6	6.15	7.27	
8	A	C_6H_5	H	$C_6H_5CH_2CH_2$	CH_3	H	$C_{19}H_{22}N_2O$[g]	97–99	77.5	7.49	4.76[c]		77.0	7.52	4.70	
							$C_{19}H_{22}N_2O\cdot C_2H_2O_4$	130–132 dec.	65.6	6.25	7.29		65.2	6.22	7.40	
9	B	C_6H_5	H	$C_6H_5CH_2CH_2$	H	CH_3	$C_{19}H_{22}N_2O$[h]	101–102	77.5	7.49	9.53		77.0	7.84	9.51	
							$C_{19}H_{22}N_2O\cdot HCl$	224–226	68.9	6.95	8.46	11.1	68.4	6.92	8.93	11.1
10	A, B	C_6H_5	CH_3	$C_6H_5CH_2CH_2$	CH_3	H	$C_{20}H_{24}N_2O$[i]	190–196 (0.4 mm.)[d]			4.54[c]				4.52	
11	B	C_6H_5	H	*dl*-$C_6H_5CH_2CH(CH_3)$	H	H	$C_{19}H_{22}N_2O$	200–207 (0.25 mm.)[d]			...				...	
							$C_{19}H_{22}N_2O\cdot C_2H_2O_4$	170–171 dec.	65.6	6.25	7.30		65.0	6.18	7.28	
12	A	4-$CH_3OC_6H_4$	H	$C_6H_5CH_2CH_2$	H	H	$C_{19}H_{22}N_2O_2$	230–234 (0.35 mm.)[d]			...				...	
							$C_{19}H_{22}N_2O_2\cdot HCl$	222	65.9	6.64	8.08	10.5	66.1	6.99	8.00	10.5
13	B	4-$CH_3OC_6H_4$	H	$C_6H_5CH_2CH_2$	CH_3	H	$C_{20}H_{29}N_2O_2$[j]	89–91			4.32[c]				4.22	
							$C_{20}H_{29}N_2O_2\cdot C_2H_2O_4$	126–127	63.0	7.40	6.77		63.0	6.15	6.91	
14	B	4-$CH_3OC_6H_4$	CH_3	$C_6H_5CH_2CH_2$	CH_3	H	$C_{21}H_{26}N_2O_2$[i]	212–214 (0.15 mm.)[d]			4.14[c]				4.13	
15	B	3-$CH_3OC_6H_4$	H	$C_6H_5CH_2CH_2$	CH_3	H	$C_{20}H_{24}N_2O_2$	212–219 (0.23 mm.)[d]			4.32[c]				4.26	
							$C_{20}H_{24}N_2O_2\cdot HCl$	61–63 dec.				10.4				9.98
16	B	C_6H_5	H	4-$CH_3OC_6H_4CH_2CH_2$	H	H	$C_{19}H_{22}N_2O_2$	80–83			...				...	
							$C_{19}H_{22}N_2O_2\cdot HCl$	240–241	65.9	6.64	8.48	10.5	65.6	6.93	8.48	10.5
17	B	C_6H_5	H	4-$CH_3OC_6H_4CH_2CH_2$	CH_3	H	$C_{20}H_{24}N_2O_2$	214–241 (0.4 mm.)[d]			4.32[c]				4.42	
							$C_{20}H_{24}N_2O_2\cdot C_2H_2O_4$	84–86			6.76				6.99	
18	B	C_6H_5	H	3,4-$(CH_3O)_2C_6H_3CH_2CH(CH_3)$	H	H	$C_{21}H_{26}N_2O_3\cdot C_2H_2O_4$	189.5–191.5 dec.	62.3	6.32	6.31		62.4	6.17	6.42	
19	B	4-ClC_6H_4	H	$C_6H_5CH_2CH_2$	CH_3	H	$C_{19}H_{21}ClN_2O$	99–102	69.3	6.38	8.51		68.8	6.60	8.53	
							$C_{19}H_{21}ClN_2O\cdot HCl$	223.5–225.5 dec.				10.0				10.0
20	B	C_6H_5	H	$C_6H_5CH_2CH_2$	C_6H_5	H	$C_{24}H_{24}N_2O$	216–239 (0.4 mm.)[d]			...				...	
							$C_{24}H_{24}N_2O\cdot C_2H_2O_4$	185–185.5	69.9	5.82	6.27		69.6	5.72	6.32	
21	B	C_6H_5	C_6H_5	$C_6H_5CH_2CH_2$	H	H	$C_{24}H_{24}N_2O$	196–235 (0.35 mm.)[d]			3.93[c]				3.86	
							$C_{24}H_{24}N_2O\cdot HCl$	215–217 dec.	73.4	6.36	7.13	9.30	72.8	6.05	7.24	9.13
22	B	C_6H_5	C_6H_5	$C_6H_5CH_2CH_2$	CH_3	H	$C_{25}H_{26}N_2O$	216–236 (0.5 mm.)[d]			...				...	
							$C_{25}H_{26}N_2O\cdot HCl$	144–146	73.6	6.64	6.88	8.95	72.9	6.79	6.85	8.80
23	A	C_6H_5	C_6H_5	CH_3	CH_3	H	$C_{18}H_{20}N_2O$	198–202 (1.2 mm.)[d]			10.0				9.99	
							$C_{18}H_{20}N_2O\cdot CH_3I$[k]	226–227 dec.	54.0	5.45	6.64		54.5	5.85	6.51	
24	A	C_6H_5	H	$(C_2H_5)_2NCH_2CH_2$	H	H	$C_{16}H_{25}N_3O$	188–202 (0.45 mm.)[d]			...				...	
							$C_{16}H_{25}N_3O\cdot 2C_2H_2O_4$	172–174 dec.			9.24				9.42	

[a] Method A: catalytic debenzylation by hydrogenolysis. Method B: pyrolytic debenzylation or demethylation. [b] Maleate. [c] Oxalate. [d] B.p., °C. [e] Basic nitrogen by $HClO_4$ titration. [f] B.p. 184–207° (0.2–0.5 mm.). [g] 190–196° (0.35 mm.). [h] 191–199° (0.6 mm). [i] Free base decomposed rapidly at room temp., no solid salt obtained. [j] 185–230° (0.2 mm.). [k] Methiodide.

Experimental[14]

4-Benzyl-1-phenyl-2-piperazinone. A.—To an ice-cold solution of N-phenyl-N′,N′-dibenzylethanediamine (71.0 g., 0.224 mole) in a mixture of 150 ml. of benzene and 200 ml. of 20% aqueous sodium hydroxide was added dropwise a solution of chloroacetyl chloride (25.5 g., 0.225 mole) in 100 ml. of benzene during 15 min. with vigorous stirring. Stirring was continued for an additional 60 min. and then the benzene layer was separated. The aqueous layer was extracted with ether and the combined extracts were dried over anhydrous magnesium sulfate. After concentration *in vacuo* the residue was heated in a wax bath at 200° for 5 hr. to give a dark semisolid. This was dissolved in 700 ml. of methanol and hydrogenated at room temperature with 5 g. (5% by wt.) of palladium-on-charcoal catalyst under 50 lbs. (3.52 kg./cm.^{2}) of hydrogen during a 30-hr. period. The solvent was removed *in vacuo* and the residue was distilled to give a light yellow liquid of b.p. 175–202° (0.4–0.5 mm.), yield 37.6 g. The product solidified in a receiver and was recrystallized from benzene–Skelly B to give a pale yellow solid of m.p. 100–103°, yield 22.6 g. A sample was again recrystallized to give a colorless solid of m.p. 105–105.5°.

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.7; H, 6.77; N, 10.5. Found: C, 76.4; H, 7.01; N, 10.6.

The free base (21.3 g.) was converted to the hydrochloride, m.p. 210–212°, yield 19.5 g.

Anal. Calcd. for $C_{17}H_{19}ClN_2O$: C, 67.4; H, 6.29; N, 9.25; HCl, 12.1. Found: C, 67.7; H, 5.97; N, 9.41; HCl, 12.2.

4-Benzyl-1-phenyl-2-piperazinone. B.—To an ice-cold solution of N-phenyl-N′,N′-dibenzylethanediamine (147.9 g., 0.468 mole) in 150 ml. of benzene and 150 ml. of 20% aqueous sodium hydroxide was added a solution of chloroacetyl chloride (53.2 g., 0.47 mole) in 100 ml. of benzene during 15 min. to give a milky solution which was stirred for 60 min. The benzene layer was separated and the aqueous layer was extracted with ether. The combined organic solutions were dried and the solvent was removed *in vacuo*, leaving a light tan sirup which was heated in a wax bath at 190° for 17 hr. The dark melt gave a tan solid mass on cooling. This was distilled pyrolytically under reduced pressure to give at first benzyl chloride (36.6 g.) and then a yellow viscous liquid of b.p. 215–244° (0.8–1.7 mm.), yield 109.3 g. (87.2%). The latter product was redistilled to give a light yellow liquid of b.p. 184–207° (0.2–0.15 mm.), yield 105.4 g. It was dissolved in 300 ml. of hot benzene and added to 200 ml. of 2-propanol saturated with dry hydrogen chloride (30.0 g., 0.82 mole) to give a colorless powder, yield 98.0 g. One recrystallization from aqueous methanol–ether gave 88.9 g. of hydrochloride melting at 207–211°. A sample was again recrystallized for analysis, m.p. 210–212°. A mixture melting point with the sample from method A showed no depression

Anal. Calcd. for $C_{17}H_{19}ClN_2O$: HCl, 12.1. Found: HCl, 12.2 (titration).

1-Phenyl-2-piperazinone.—The aqueous solution of the above hydrochloride (40.0 g., 0.132 mole) was hydrogenated with 5 g. (5% by weight) of palladium-on-charcoal catalyst at room temperature under 50 lbs. (3.52 kg./cm.^{2}) of hydrogen The calculated amount of hydrogen was taken up in 2 hr. Another sample (48.6 g., 0.16 mole) of the hydrochloride was debenzylated in the same manner. The combined solution was concentrated *in vacuo* and made alkaline with sodium hydroxide solution. The mixture was extracted with chloroform, and the combined extracts were dried and added to 200 ml. of 2-propanol saturated with dry hydrogen chloride to give a colorless solid, yield 28.5 g. (46%), m.p. 178–179°. One recrystallization from methanol–ethyl acetate gave 18.2 g. of pure product melting at 181–182°.

Anal. Calcd. for $C_{10}H_{13}ClN_2O$: C, 56.4; H, 6.11; N, 13.2; HCl, 17.2. Found: C, 55.8; H, 6.55; N, 13.0; HCl, 17.2.

N^1-Methyl-N^1-phenethyl-N^2-phenyl-1,2-propoanediamine.—To an ice-cold mixture of N-methylphenethylamine (54.0 g., 0.4 mole) in 100 ml. of benzene and 150 ml. of 20% sodium hydroxide solution was added a solution of 2-bromopropionyl chloride (72.6 g., 0.4 mole) in 100 ml. of benzene during 30 min. with vigorous stirring. After an additional 20 min., the benzene layer was separated and the aqueous layer was extracted with benzene. The combined extracts were dried and aniline (74.5 g., 0.8 mole) was added. The solution was stirred under reflux for 15 hr. and aniline hydrobromide (47.3 g., 68% yield) was removed by filtration. The filtrate was concentrated *in vacuo* to give a viscous liquid which was dissolved in 250 ml. of tetrahydrofuran (THF) and added to a slurry of lithium aluminum hydride (15.2 g., 0.4 mole) in 400 ml. of THF during 40 min. The mixture was stirred under reflux for 8 hr. and set aside overnight. The excess hydride was decomposed as usual and the solution was concentrated *in vacuo* to leave a dark sirup which was distilled, b.p. 150–152° (0.3–0.35 mm.), yield 63.3 g. (59.2%).

Anal. Calcd. for $C_{18}H_{24}N_2$: N (basic), 5.22. Found: N (basic), 5.38 (titration).

6-Methyl-4-phenethyl-1-phenyl-2-piperazinone.—To an ice-cold solution of the above diamine (60.1 g., 0.23 mole) in 100 ml. of benzene and 100 ml. of 20% sodium hydroxide solution was added with stirring a solution of chloroacetyl chloride (25.5 g., 0.23 mole) in 50 ml. of benzene during 5 min. The resulting milky solution was stirred for 30 min., the benzene layer was separated, and the aqueous layer was extracted with ether. The combined extracts were dried and then heated on a steam bath to give a slurry of solid and a hard glassy precipitate. The solid was collected on a filter, yield 25.5 g., m.p. 174–186° dec. The precipitate was dissolved in a small amount of hot methanol and added to the above filtrate. The clear amber solution was heated on a steam bath for 5 hr. to give 21.0 g. of the solid product. The filtrate was refluxed overnight to furnish an additional 4.2 g. of product. Thus, the total yield was 50.7 g. (65.2%). The crude solid was heated under vacuum to eliminate methyl chloride and the resulting liquid was distilled, b.p. 191–199° (0.6–0.3 mm.), yield 33.8 g. It solidified at once in the receiver and was recrystallized from benzene–Skelly B to give a slightly tan solid of m.p. 97–101°, yield 29.9 g. A sample was recrystallized from benzene–Skelly B, m.p. 101–102° $\nu_{max}^{CHCl_3}$ 1645 cm.$^{-1}$ (amide C=O).

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.5; H, 7.49; N, 9.53. Found: C, 77.0; H, 7.52; N, 9.51.

The hydrochloride melted at 224–226° dec. after recrystallization from methanol–ether.

Anal. Calcd. for $C_{19}H_{23}ClN_2O$: C, 68.9; H, 6.95; N, 8.46; HCl, 11.1. Found: C, 68.4; H, 6.92; N, 8.93; HCl, 11.1.

Pyrolysis of 1-Benzyl-1-methyl-3-oxo-4-phenylpiperazinium Chloride.—The piperazinium chloride (57.9 g., 0.182 mole) was heated under vacuum to give the following fractions: (1) b.p. 115–142° (3.2–2.5 mm.), 8.0 g.; (2) b.p. 143–160° (2.5–1.7 mm.), 13.2 g., (3) b.p. 161–171° (1.7–2.4 mm.), 20.1 g.; (4) b.p. 213–206° (0.8 mm.), 5.8 g. The first three fractions solidified in the receiver. They were combined and recrystallized from methanol–ethyl acetate to give a colorless solid of m.p. 205–206° dec., yield 19.1 g. (33% recovery). This was identical with the starting 1-benzyl-1-methyl-3-oxo-4-phenylpiperazinium chloride. The last fraction (5.8 g., 12%) was dissolved in methanol, saturated with dry hydrogen chloride, and diluted with ethyl acetate to give a hydrochloride of m.p. 209–211°, yield 3.8 g. The mixture m.p. with authentic 4-benzyl-1-phenyl-2-piperazinone hydrochloride was not depressed.

N^3-Methyl-N^3-phenethyl-N^1-phenyl-1,3-propanediamine.—A mixture of 3-bromopropionanilide (91.3 g., 0.4 mole), anhydrous sodium carbonate (56.7 g., 0.42 mole), and N-methylphenethylamine (54.0 g., 0.4 mole) in 350 ml. of 2-propanol was heated under reflux with stirring for 18 hr. The mixture was filtered and the filtrate was concentrated *in vacuo* to leave a viscous amide. The material was dissolved in 150 ml. of THF and added dropwise to a slurry of lithium aluminum hydride (22.8 g., 0.4 mole) in 300 ml. of THF, and the mixture was heated for 6 hr. The reaction mixture was treated with 23 ml. of water, 23 ml. of 20% aqueous sodium hydroxide, and 71 ml. of water, respectively. It was filtered and the filtrate was evaporated to dryness *in vacuo*, leaving a residue which was distilled to give a liquid of b.p. 151–160° (0.30–0.45 mm.), yield 77.4 g. (72.2%).

Anal. Calcd. for $C_{18}H_{24}N_2$: N(basic), 10.45. Found: N (basic), 10.41 (titration).

1-Phenyl-2-oxo-4-phenethyl-1,4-homopiperazine.—A solution of chloroacetyl chloride (42.4 g., 0.375 mole) in 50 ml. of benzene was added slowly to an ice-cold mixture of N^3-methyl-N^3-phenethyl-N^1-phenyl-1,3-propanediamine (93.0 g., 0.375 mole) in 250 ml. of benzene and 80 ml. of 20% sodium hydroxide solution. Stirring was continued for an additional hour and then the benzene layer was separated. This was dried and concentrated on a steam bath to give a viscous liquid which solidified on cooling. Pyrolytic distillation under vacuum gave a liquid of b.p. 202–203°

(14) All melting points were determined in a Büchi apparatus (Switzerland) and corrected. Infrared spectra were measured by a Perkin-Elmer Spectracord Model 137 and Perkin-Elmer 237 grating infrared spectrophotometer. Titrations were done by a Sargent Model D recording titrator.

(0.4–0.5 mm.), yield 15 g. (13%) $\nu_{max}^{CHCl_3}$ 1650 cm.$^{-1}$ (amide C=O) no amide II band.

Anal. Calcd. for $C_{19}H_{22}N_2O$: N(basic), 4.76. Found: N(basic), 4.65 (titration).

The base was dissolved in ether and treated with 10 g. (0.11 mole) of oxalic acid in ether to form a pale yellow solid. This was recrystallized from methanol–ether to give a colorless solid of m.p. 147–149° dec.

Anal. Calcd. for $C_{19}H_{22}N_2O \cdot C_2H_2O_4$: C, 65.6; H, 6.25; N, 7.29. Found: C, 65.5; 64.8; H, 6.22, 6.10; N, 7.23.

1-Methyl-3-oxo-1-phenethyl-4-phenylpiperazinium chloride.—To an ice-cold solution of N^1-methyl-N^1-phenethyl-N^2-phenyl-1,2-ethanediamine (83.4 g., 0.328 mole) in 150 ml. of benzene and 100 ml. of 20% sodium hydroxide solution was added a solution of chloroacetyl chloride (37.1 g., 0.33 mole) in 100 ml. of benzene during 45 min. The milky solution was stirred for an additional 30 min. and the benzene layer was separated. A small amount of benzene insoluble oil was extracted with chloroform. The combined extracts were dried quickly over anhydrous magnesium sulfate and heated in an open flask on a steam bath for 5 hr. The clear solution soon became cloudy and a brown oil began to precipitate which became a colorless solid after 2 hr. heating with occasional scratching. The solid was collected, washed with ethyl acetate–ether, and dried in the air; yield 91.3 g. (78.2%), m.p. 210–211° dec. A small sample was recrystallized from a methanol–ethyl acetate–ether mixture to give a colorless solid of m.p. 212–213° dec., ν_{max}^{KCl} 1660 cm.$^{-1}$ (amide C=O).

Anal. Calcd. for $C_{19}H_{23}ClN_2O$: C, 68.9; H, 6.95; N, 8.46. Found: C, 69.0; H, 6.60; N, 8.20.

The filtrate was heated again for 5 hr. on a steam bath to give another 2.5 g. of the product of m.p. 209–210° dec.; thus the total yield was 93.8 g. (87.0%).

4-Phenethyl-1-phenyl-2-piperazinone.—The piperazinium chloride (92.0 g., 0.278 mole) was distilled pyrolytically to give a fraction boiling at 203–211° (0.7–1.3 mm.), yield 63.5 g. (81.5%). It solidified in the receiver and was recrystallized from acetone–Skelly B to give a light tan crystalline solid of m.p. 84–85°, yield 51.7 g. The filtrate was concentrated to give a milky solution which rendered an additional 8.6 g. of product on cooling. Thus, the total yield was 60.3 g. A sample of the first crop was recrystallized from acetone–Skelly B to give pale tan plates of m.p. 83–84°. $\nu_{max}^{CHCl_3}$ 1655 cm.$^{-1}$ (amide C=O), no N–H or amide II band.

Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.2; H, 7.15; N, 10.0. Found: C, 76.8; H, 7.15; N, 10.1.

4-Phenethyl-1-phenylpiperazine.—A solution of the above piperazinone (58.7 g., 0.21 mole) in 150 ml. of THF was added dropwise to a slurry of lithium aluminum hydride (11.4 g., 0.3 mole) in 150 ml. of THF during 60 min. to give a gray suspension which was refluxed with stirring for 6 hr. and set aside overnight. The reaction mixture was treated with 12 ml. of water, 12 ml. of 20% sodium hydroxide solution, and 35 ml. of water, respectively. The inorganic salt was filtered and the light tan solution was evaporated to dryness *in vacuo* to give an amber liquid which solidified on cooling. This was distilled to give a pale yellow liquid of b.p. 162–165° (3.0–1.75 mm.), yield 48.9 g. It solidfied at once in the receiver and was recrystallized from aqueous methanol to furnish a light yellow solid of m.p. 75–77°, yield 40.3 g. It was again recrystallized to yield 32.5 g. of a colorless solid of m.p. 76–77°.

Anal. Calcd. for $C_{18}H_{22}N_2$: C, 81.3; H, 8.27; N, 10.5. Found: C, 81.6; H, 8.27; N, 10.5.

The mixture m.p. with an authentic sample (m.p. 78–79°) prepared from phenethyl bromide and 1-phenylpiperazine was not depressed (m.p. 76–79°). The infrared spectra of the two samples were identical.

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The Metabolism of Carbazole in Rats and Rabbits[1]

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3-Hydroxycarbazole, conjugated with glucuronic acid, has been shown to be the major urinary metabolite in rats and rabbits after administration of carbazole. Hydroxylation at position 3 is in accordance with an attack by oxidizing enzymes at the position of highest electron density in the molecule.

Previous studies[2] in this laboratory on the metabolism of ergometrine and lysergic acid diethylamide showed that these complex indole derivatives undergo metabolism in the rat by hydroxylation in the aromatic ring of the indole skeleton, followed by conjugation of this phenol with glucuronic acid. The major metabolite from ergometrine, after hydrolysis with dilute hydrochloric acid or β-glucuronidase, could not be separated from synthetic 12-hydroxyergometrine on a number of chromatographic systems, and it has been tentatively suggested that hydroxylation occurs at position 12.

The need for developing unambiguous methods for the synthesis of all the possible metabolites of such complicated structures, *viz.* all the possible hydroxylated ergometrine derivatives, would be reduced if the mechanism and, hence, the likely position of hydroxylation were known. This paper deals with an investigation to ascertain the position of hydroxylation in the indole nucleus by a study of more simple indoles.

Indole itself is metabolized mainly to indoxyl (3-hydroxyindole)[3] which is excreted conjugated with both glucuronic and sulfuric acids. The reactivity of position 3 in the indole nucleus to oxidation prevents extensive hydroxylation in the aromatic ring and is of little use in determining the position of hydroxylation in that ring. The increase in conjugates, however, after the administration of indole to rats[4] cannot be explained alone by indoxyl formation and 5-hydroxyindole has been suggested as a minor metabolite.

A more suitable compound for comparison with the indole alkaloids is skatole, which has the 3-position blocked to oxidation. Skatole has been extensively

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