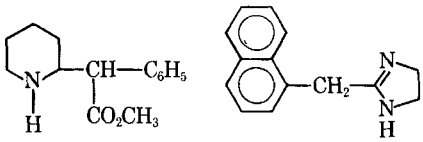
Phenylalkylamines

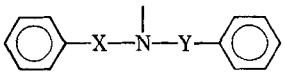
By JOSEPH SAM*

The syntheses of 1- and 2-aralkylpyridines and piperidines and phenylalkylamines are described.

THE ARRAY of compounds which contain the phenylalkylamine moiety and which possess useful biological properties is impressive. The investigation with various phenylalkylamines has culminated in the preparation of compounds with a narrow spectrum of sympathomimetic activity, useful in specific conditions. For example, the incorporation of the alkylamine portion in a heterocyclic molecule such as methyl α-(2-piperidyl)phenylacetate (I) and 2-(1-naphthylmethyl)-2-imidazoline (II) provides compounds with specific central nervous system stimulant (1, 2) and nasal decongestant activity (3, 4), respectively. The preparation of di-(phenylalkyl) amines represented by structure III has led to the development of compounds useful in the management of bronchoconstrictor disorders (5, 6) and in vascular constrictive diseases (7).

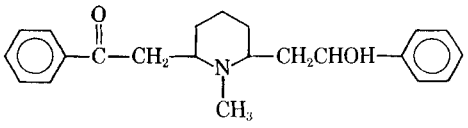


I II



III

Because of the pronounced biological effects exhibited by di-(phenylalkyl)amines (III) and because of the desirable properties elicited by the incorporation of the alkylamine portion in a cyclic structure (8), it was of interest to prepare both mono- and di-(phenylalkyl)amines containing the pyridine and piperidine ring (Tables I and III). The compounds listed in Table III also bear some structural similarity to the alkaloid lobeline (IV) (9).



IV

The pyridine derivatives listed in Table I were prepared by (*a*) the reaction of picolinealdehyde with acetophenones (10), or (*b*) by the reaction of 3,4-dimethoxybenzaldehyde with α-picoline (11), or (*c*) by the reaction of 2-vinylpyridine with *N*-methyl-β-hydroxyphenethylamine (V) (13, 14), or (*d*) by the Pd-C catalyzed reduction of the ethylenic groups of the products obtained in (*a*) and (*b*). (Scheme I.)

The piperidine derivatives (VIII) of Table III were prepared by the catalytic reduction of pyridinium bromides (VII) (Table II). (Scheme II.)

Hypotensive activity (15) and neurosedative activity (16) have been observed recently in similar compounds. Included also in this study are several nonpiperidine derivatives (Table IV). Preliminary pharmacological evaluation did not indicate any pronounced biological activity in the compounds that were studied.

EXPERIMENTAL[1]

α - {([2 - (5 - Ethyl - 2 - pyridyl)ethyl]methylamino)methyl}benzyl Alcohol (VI)—A mixture of 40 Gm. (0.3 mole) of 5-ethyl-2-vinylpyridine, 46 Gm. (0.3 mole) of *N*-methyl-β-hydroxyphenethylamine, 18 Gm. of glacial acetic acid, and 200 ml. of methanol was refluxed for 18 hr. The methanol was distilled *in vacuo*. The residual oil was added to ice and neutralized with 10% sodium hydroxide. An ether extract of the mixture was dried over anhydrous sodium sulfate. Evaporation of the ether and distillation of the oil gave product, n_D^{26} 1.5489.

1 - (4 - Chlorophenyl) - 3 - (2 - pyridyl) - 2 - propene-1-one (IX)—To 2 Gm. of piperidine cooled in an ice bath were added 2 Gm. of glacial acetic acid, 15 Gm. (0.1 mole) of 4′-chloroacetophenone, and 11 Gm. (0.1 mole) of picolinealdehyde, respectively. The resulting mixture was heated on a steam bath for 2 hr. and then cooled. An ether extract of the oily material was washed thoroughly with water and dried over anhydrous potassium carbonate. Evaporation of the solvent *in vacuo* left a dark brown oil which solidified on standing.

1,5 - Bis - (4 - chlorophenyl) - 3 - (2 - pyridyl)-pentane-1,5-dione (XII)—A solution of 4 Gm. (0.1 mole) of sodium hydroxide in 40 ml. of water and 20 ml. of ethyl alcohol was treated with 15.5 Gm. (0.1 mole) of 4′-chloroacetophenone. The mixture was cooled in an ice bath and treated with 10.7 Gm. (0.1 mole) of picolinealdehyde in one lot. The mixture was shaken intermittently during a 1-hr. period. The oil that separated solidified; it was removed by filtration, washed with methanol, and recrystallized.

1 - (4 - Nitrophenyl) - 3 - (2 - pyridyl) - 2 - propene-1-one (XI)—The procedure for the preparation of 1 - (4 - chlorophenyl) - 3 - (2 - pyridyl) - 2 - propene-1-one was followed using 16.5 Gm. (0.1 mole) of 4′-nitroacetophenone and 11 Gm. (0.1 mole) picolinealdehyde.

4′ - Chloro - 3 - (2 - pyridyl)propiophenone (X)—A solution of 44 Gm. (0.18 mole) of 1-(*p*-chlorophenyl)-3-(2-pyridyl)-2-propene-1-one in 200 ml. of warm methanol was hydrogenated at 52 p.s.i. in the presence of 1 Gm. of 5% Pd-C catalyst. Reduction was complete in 30 min. The catalyst was removed by filtration and the solvent was distilled under reduced pressure.

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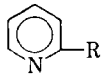
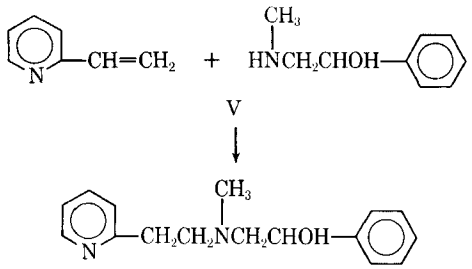
[1] All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected.

TABLE I—2-SUBSTITUTED PYRIDINES



No.	R	% Yield	B.p., °C. (mm.) M.p., °C.	Molecular Formula	Anal., % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VI	$C_6H_5CHOHCH_2N(CH_3)(CH_2)_2$—	29	178 (0.4 mm.)	$C_{18}H_{24}N_2O$[a]	76.0	8.51	...	76.3	8.70	...
IX	4-ClC_6H_4COCH=CH—	41	85–86[b]	$C_{14}H_{10}ClNO$[c]	69.0	4.14	5.75	69.3	3.95	5.75
X	4-$ClC_6H_4COCH_2CH_2$—	66	169–172 (1 mm.)	$C_{14}H_{12}ClNO$	68.4	4.92	...	68.7	5.17	...
XI	4-$NO_2C_6H_4COCH$=CH—	51	150–151[d]	$C_{14}H_{10}N_2O_3$	66.1	3.97	...	66.2	3.97	...
XII	$(4\text{-}ClC_6H_4COCH_2)_2CH$—	33	136–137[d]	$C_{22}H_{17}Cl_2NO_2$	66.3	4.30	3.51	66.4	4.39	3.63
XIII	3,4-di$CH_3OC_6H_3CH$=CH—	38	195–200 (0.2 mm.)	$C_{15}H_{15}NO_2$	74.7	6.27	5.81	74.5	6.01	6.05
XIV	3,4-di$CH_3OC_6H_3(CH_2)_2$—	90	152–155 (0.2 mm.)	$C_{15}H_{17}NO_2$	74.0	7.05	...	74.1	7.45	...

[a] Contains a 5-ethyl group in the pyridine ring. [b] Recrystallized from *n*-hexane. [c] *Reference 10.* [d] Recrystallized from methanol.

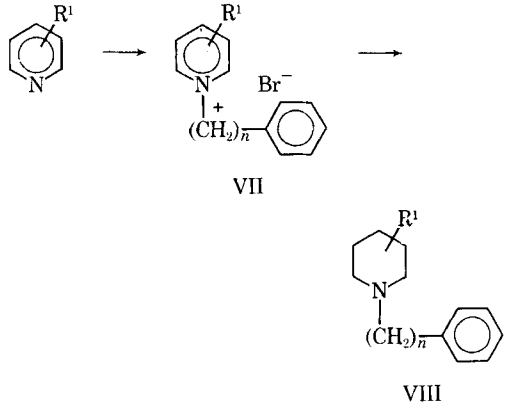


Scheme I

2-(3,4-Dimethoxystyryl)pyridine (XIII)—A solution of 93 Gm. (1 mole) of 2 picoline, 166 Gm. (1 mole) of veratric aldehyde in 204 Gm. (2 moles) of acetic anhydride was refluxed for 66 hr., cooled, and poured into ice water. The mixture was extracted with ether and dried over anhydrous sodium sulfate. Evaporation of the solvent and distillation of the residual oil gave product.

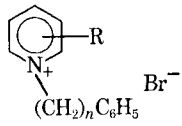
2-(3,4-Dimethoxyphenethyl)pyridine (XIV)—The procedure described for the preparation of X was followed using 93 Gm. (0.385 mole) of 2-(3,4-dimethoxystyryl)pyridine; reduction was complete after 18 hr.

Pyridinium Bromides (VII, Table II)—A solution of 0.2 mole of desired pyridine and 0.2 mole of phenylalkyl bromide in 100 ml. of acetonitrile was heated under reflux on a steam bath for 48 hr. and then cooled. The solid was removed by filtration, washed with cold acetone, and thereafter recrystallized from a suitable solvent. In some cases ether was added to the cooled acetonitrile solution to precipitate the pyridinium bromide.



Scheme II

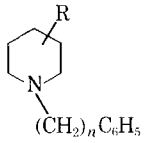
TABLE II—PYRIDINIUM BROMIDES



No.	R	n	% Yield	M.p., °C.	Molecular Formula	Anal., % Calcd. C	Calcd. H	Found C	Found H
VII*a*	3-HO	2	90	193–194[a]	$C_{13}H_{14}BrNO$	55.7	5.04	55.8	5.17
VII*b*	2-[4-$CH_3OC_6H_4(CH_2)_2$]	2	75	148–150[b]	$C_{22}H_{24}BrNO$	66.3	6.07	66.5	6.25
VII*c*	2-[3,4-di$CH_3OC_6H_3(CH_2)_2$]	2	57	[d]	$C_{23}H_{26}BrNO_2$	...	...	...	...
VII*d*	2-$C_6H_5CH_2$	2	66	164–166[a]	$C_{20}H_{20}BrNO$	67.8	5.69	68.0	5.45
VII*e*	4-[3-$HO(CH_2)_3$]	3	..	[c]	$C_{17}H_{22}BrN$	...	...	...	...
VII*f*	2-$C_6H_5CH_2$	3	76	85–90[d]	$C_{21}H_{22}BrN$	...	...	...	...
VII*g*	3-$HOCH_2$	2	85	144–145[a]	$C_{14}H_{16}BrNO$	57.2	5.48	57.2	5.55
VII*h*	4-CO_2CH_3	2	..	[c]	$C_{15}H_{16}BrNO_2$	...	...	...	...
VII*i*	3-$CO_2C_2H_5$	2	88	188–190	$C_{16}H_{18}BrNO_2$	57.1	5.40	57.2	5.44

[a] Recrystallized from acetonitrile. [b] Recrystallized from an acetonitrile–acetone solution. [c] Isolated as an oil and used in the preparation of the piperidine derivative (Table III). [d] Not purified, used in the preparation of the piperidine derivative (Table III).

TABLE III—PHENYLALKYLPIPERIDINES

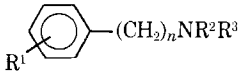


VIII

No.	R	n	Method	% Yield	B.p., °C. (mm.) M.p., °C.	Molecular Formula	Anal., % Calcd. C	Calcd. H	Found C	Found H
VIII*a*	3-ClCH$_2$	2	*D*	87	124–126 (0.3)	$C_{14}H_{20}ClN$	70.7	8.48	70.8	8.65
VIII*b*	3-HO	2	*A*	53	130 (0.5)	$C_{13}H_{19}NO$[a]	76.1	9.33	76.2	9.52
VIII*c*	2-(4-CH$_3$OC$_6$H$_4$CH$_2$CH$_2$)	2	*A*	87	138–139	$C_{22}H_{30}BrNO$[b]	65.3	7.48	65.5	7.67
VIII*d*	2-(3,4-diCH$_3$OC$_6$H$_3$CH$_2$CH$_2$)	2	*A*	89[c]	154–156	$C_{23}H_{32}BrNO_2$[b]	63.6	7.43	63.5	7.36
VIII*e*	2-C$_6$H$_5$CH$_2$	2	*A*	83[c]	166–168	$C_{20}H_{26}BrN$[b]	66.8	7.27	66.7	7.20
VIII*f*	4-(HOCH$_2$CH$_2$CH$_2$)	3	*B*	83[c]	172–175 (0.3)	$C_{17}H_{27}NO$	78.1	10.41	77.8	10.20
VIII*g*	2-C$_6$H$_5$CH$_2$	3	*C*	85[c]	160–161	$C_{21}H_{28}BrN$[b]	67.4	7.54	67.5	7.74
VIII*h*	4-CH$_3$OCO	2	*C*	54[c]	142 (0.3)	$C_{15}H_{21}NO_2$	72.8	8.56	73.0	8.45
VIII*i*	4-NH$_2$NHCO	2	*E*	70	154–155	$C_{14}H_{21}N_3O$	68.0	8.56	67.9	8.50
VIII*j*	3-C$_2$H$_5$OCO	2	*A*	81	137 (0.5)	$C_{16}H_{23}NO_2$	73.5	8.87	73.4	8.56

[a] Kralt, T., Asma, W. J., and Moed, H. D., *Rec. Trav. Chim.*, **80**, 330(1961). [b] Hydrobromide. [c] Yield is based on the tertiary amine used.

TABLE IV—PHENYLALKYLAMINES



No.	R^1	n	R^2	R^3	Recrystn. Solvent[a]	% Yield	B.P., °C. (mm.) M.p., °C.	Molecular Formula	Anal., % Calcd. C	Calcd. H	Found C	Found H
XV	3,4-diCH$_3$O	2	C$_9$H$_9$O[b]	H	M	71	126–127	$C_{19}H_{23}NO_3$	72.8	7.40	73.2	7.60
XVI	H	1	C$_{10}$H$_9$O[c]	H	M	53	192–193	$C_{17}H_{18}ClNO$[d]	71.0	6.30	71.3	6.60
XVII	2-HO-4-(1-indanyl)	1	CH$_3$	CH$_3$	M–W	40	63–64	$C_{18}H_{21}NO$	80.9	7.92	81.1	8.11
XVIII	2-HO-3-CH$_3$O	1	CH$_3$	H	B	96	90–91	$C_9H_{13}NO_2$	64.7	7.84	64.8	7.68
XIX	H	1	C$_{10}$H$_{11}$[e]	CH$_3$	...	79	152–156 (1 mm.)	$C_{18}H_{21}N$	...	...	...	...
XX	H	1	C$_{10}$H$_{11}$[e]	CH$_3$	MEK	90	193–194	$C_{18}N_{22}ClN$[d]	75.1	7.71	75.4	7.80

[a] M, Methanol; M–W, methanol–water; B, benzene; MEK, methyl ethyl ketone. [b] 2-Hydroxy-1-indanyl. [c] 1-Oxo-2-indanylmethyl. [d] Hydrochloride. [e] 2-Indanylmethyl.

Hydrogenation of Pyridines to Piperidines (Table III)—*Method A*—A solution of 0.1 mole of the desired 1-substituted pyridinium bromide in 200 ml. of water was hydrogenated at 50–60 p.s.i. at approximately 40–50° in the presence of 0.4 Gm. of platinum oxide catalyst until the theoretical amount of hydrogen was absorbed (5–18 hr.). The mixture was concentrated *in vacuo* on a water bath, treated with methanol, and thereafter filtered to remove the catalyst. The filtrate was concentrated *in vacuo* on a water bath and the residual material either was recrystallized from a suitable solvent or was converted to the base, isolated in the usual manner, and distilled.

Method B—A mixture of 0.2 mole of desired pyridine and 0.2 mole of phenylalkyl bromide was heated on a steam bath for 1 hr. The residual oil was dissolved in water and hydrogenated as described under *Method A*.

Method C—A solution of 0.2 mole of desired pyridine and 0.2 mole of phenylalkyl bromide in 100 ml. of acetonitrile was refluxed on a steam bath for 20–30 hr. and thereafter cooled and diluted with ether. The mixture was extracted with 200 ml. of water. The aqueous solution was warmed on a steam bath to expel any ether present and then hydrogenated as described under *Method A*.

1-Phenethyl-3-piperidylmethyl Chloride (VIIIa)—*Method D*—A solution of 28 Gm. (0.13 mole) of 1-phenethyl-3-piperidylcarbinol in 100 ml. of chloroform was added dropwise to a solution of 30 ml. of thionyl chloride in 100 ml. of chloroform. The solution was allowed to remain at room temperature for 18 hr. and then refluxed for 3 hr. The solvent and excess thionyl chloride were distilled *in vacuo*. The residual solid was dissolved in ice water, neutralized with 10% sodium hydroxide, extracted with chloroform, and dried over anhydrous potassium carbonate. Evaporation of the solvent and distillation of the residual oil gave product, n_D^{26} 1.5303.

1-Phenethylisonipecotohydrazide (VIIIi)—*Method E*—A solution of 10 Gm. (0.04 mole) of methyl 1-phenethylisonipecotate and 10 Gm. (0.2 mole) of hydrazine hydrate in 30 ml. of water was refluxed 3 hr. The solvent was distilled under reduced pressure and the residual solid was recrystallized.

α - {[2 - (5 - Ethyl - 2 piperidyl)ethyl]methylamino)methyl}benzyl Alcohol—The procedure described under *Method A* for the preparation of *N*-substituted piperidines (VIII) was followed. From 13 Gm. (0.05 mole) of the corresponding pyridine derivative (VI) there was obtained 12 Gm. (88%) of product, b.p. 178–180° (0.6 mm.), $n_D^{24.5}$ 1.5218.

1-(3,4-Dimethoxyphenethyl)-2-indanol (XV)—A mixture of 13.2 Gm. (0.1 mole) of indene oxide, 18.1

Gm. (0.1 mole) of 3,4-dimethoxyphenethyl amine, and 150 ml. of benzene was refluxed on a steam bath for 6 hr. The benzene was evaporated and thereafter the dark brown oily residue was heated on a steam bath for 6 hr. The residual material solidified on cooling.

2-Benzylaminomethyl-1-indanone (XVI)—To a mixture of 14 ml. of concentrated hydrochloric acid and 14 Gm. (0.13 mole) of benzylamine were added 18.5 Gm. (0.14 mole) of 1-indanone and 12 ml. (4.1 Gm., 0.14 mole) of 37% formaldehyde solution. The resulting mixture was heated on a steam bath for 40 min. and thereafter cooled and filtered. The residual material was washed with two 50-ml. portions of methanol to give 20 Gm. (53%) of white solid, m.p. 190–193° dec.

2 - Dimethylaminomethyl - 4 - (1 - indanyl)-phenol (XVII)—A solution of 21 Gm. (0.1 mole) of 4-(1-indanyl)phenol in 100 ml. of isopropanol was treated with 18 ml. of 25% aqueous dimethylamine solution and 10.5 ml. of a 37% formaldehyde solution and thereafter refluxed on a steam bath for 1.5 hr. The solvent was distilled *in vacuo*. The residue was treated with dilute hydrochloric acid and extracted with ether. The acid solution was neutralized with ammonium hydroxide and extracted with ether. The latter ether extract was dried over anhydrous magnesium sulfate and then evaporated to dryness. The residual material (10 Gm., 40%), which melted at 51–56°, was recrystallized.

2-Hydroxy-3-methoxybenzylmethylamine (XVIII)—The procedure for the preparation of X was followed using 31 Gm. (0.7 mole) of 2-hydroxy-3-methoxybenzalmethylamine. Reduction was complete after 18 hr.

N - Benzyl - N - (2 - indanylmethyl)methylamine (XIX)—A mixture of 10.6 Gm. (0.05 mole) of 2-bromomethylindan and 25 Gm. of *N*-benzylmethylamine was refluxed for 6 hr. Thereafter the mixture was cooled and extracted with dilute hydrochloric acid. The acid solution was neutralized and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and then distilled to give product.

A hydrochloride (XX) was prepared in the usual manner and recrystallized.

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Placebo Effect of Saline on Locomotor Activity in Several Strains of Mice

By W. M. DAVIS, W. T. KING, and M. BABBINI

The effect of intraperitoneal injection of 0.9 per cent saline solution upon locomotor activity of six strains of mice was observed in actometer cages. Whether tested singly or in groups of four, a depressant effect of saline upon activity was seen. The strains differed significantly in activity levels, but not in degree of effect of saline on activity. Group testing had differing degrees of effect on activity counts compared to single-mouse tests in the several strains.

A REDUCTION in the locomotor activity of mice which received an injection of physiological saline in comparison to the activity of uninjected mice has been reported by Schnitzer and Ross (1). They found that this effect was dependent upon more than the act of handling the mouse or handling plus intraperitoneal insertion of a hypodermic needle. Meier (2) confirmed their findings with 0.9% saline group compared to a sham-injected group even while using only one-half the volume (0.005 ml./Gm.) administered by the former workers. Schnitzer and Ross (3) later failed to observe an inhibitory effect of saline when they used younger mice than those of their first report; however, testing at a higher room temperature may have been responsible for the difference. Meier's confirmation was by means of younger mice than were used in either of the other reports.

Meier *et al.* again reported inhibition of locomotion by saline injection incidental to other observations involving four inbred strains of mice (4). They stated that the ranking of post-saline activities of the strains was significantly different from the ranking of activities in a previous noninjection test, but without presenting fully the data to describe this finding. Further evidence regarding the genetic factor as a possible variable in the "placebo effect" of saline in-

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