and extracted with ethyl acetate. A small amount of chloroform was added and crystallization was induced by scratching. An analytical sample was not obtained.

The free acid III was decarboxylated by heating in several solvents, including methyl ethyl ketone, 2-propanol, acetonitrile and pyridine. The yield of crystalline acetyl β-methyltryptophan was always near 30%. Decarboxylation in water or toluene, which did not dissolve the acid III, led to red tar.

URBANA, ILL.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, RESEARCH DIVISION, LEDERLE LABORATORIES, AMERICAN CYANAMID COMPANY]

Vasodilator and Adrenergic Blocking Agents. I. 1,4-Disubstituted Piperazines and Related N-Phenylethylenediamine Derivatives

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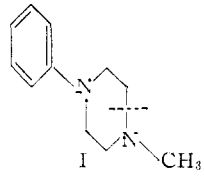
The syntheses and physiological properties of a series of 1,4-disubstituted piperazines and N-phenylethylenediamine derivatives are described. Also a discussion dealing with the importance of the phenyl and pyridylpiperazine nuclei in developing strong adrenergic blocking agents of this type is included.

In recent years a considerable number of compounds exhibiting strong vasodilator or adrenergic blocking action have been described in the literature.[1] However, because of undesirable side effects and poor oral activity, very few of these agents have found therapeutic application in the treatment of peripheral vascular disease. Two classes of compounds which have received considerable attention for their ability to inhibit responses to epinephrine are the β-diaralkylaminoethyl chlorides and the aralkylimidazolines. In our laboratories, pharmacological testing indicates that 1-methyl-4-phenylpiperazine (I) is also an effective vasodilator and adrenergic blocking agent.

To elucidate the structural requirements necessary for activity in this compound, we prepared a series of N-phenylethylenediamine derivatives. These diamines are related to products which would be formed by a scission of the piperazine ring of the active structure[2] I. The diamines were



I

synthesized by the interaction of one molecular equivalent of β-(N-ethyl-N-phenylamino)-ethyl chloride monohydrochloride with two molecular equivalents of the appropriate primary or secondary amine in a refluxing water–ethanol solution. Derivatives of a similar nature have been tested as antihistamines.[3,4] The fact that structural similarities exist between adrenergic blocking agents and compounds which antagonize spasmogenic substances, such as acetylcholine and histamine, has been discussed by Burger.[5] As shown in Table I, the simple isosteres derived from the parent compound I where one amino group is substituted by lower alkyls were relatively inactive[6] when compared to Priscoline[7] which was used as a standard. However, a marked increase in vasodilator activity was observed when these substituents were replaced by di-*n*-propyl or benzyl groups.

An extension of this work was the reconstitution of a piperazine ring to include one of the terminal N-atoms of the N-phenylethylenediamine structure. This led to the synthesis of a series of 1-[β-(N-ethyl-N-phenylamino)-ethyl]-4-substituted piperazines which are described in Table II. Preparation of these compounds involved a condensation between the β-(N-ethyl-N-phenylamino)-ethyl chloride monohydrochloride and 1-substituted piperazines in refluxing ethanol using sodium bicarbonate as an acid acceptor. The biphenylpiperazine analog was synthesized stepwise by condensing the appropriate haloalkylamine with diethanolamine to yield N-ethyl-N′,N′-di-(β-hydroxyethyl)-N-phenylethylenediamine. In the next step, reductive cyclization of the di-(β-hydroxyethyl)-amino portion of the molecule with 4-aminobiphenyl was accomplished in poor yield by subjecting a solution of the two reactants in dioxane over copper chromite to approximately 93 atmospheres of hydrogen for 7 hr. at 250°. An inspection of the activity ratings listed in Table II reveals a sharp change in biological response when the N-methyl, acetyl and carbethoxy groups in the piperazine moiety are replaced by phenyl, 2-pyridyl or 2-(6-methyl)-pyridyl radicals. Based on these findings a study of the scission products of I has by a circuitous route established the importance of not only the phenyl piperazine but also the pyridyl piperazine nucleus as a center of activity. It is also apparent that strong vasodilatation and adrenergic blocking action[8] are obtained when the simple alkyl substituent in I is replaced by a β-(N-ethyl-N-phenylamino)-ethyl chain II. Preliminary studies indicate that compound II is orally active in the test animal.

(1) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," 2nd Ed., The Macmillan Co., New York, N. Y., 1955, (Bibliography), pp. 592–595.

(2) W. T. Forsee and C. B. Pollard, THIS JOURNAL, **57**, 1788 (1935).

(3) A. M. Staub, *Ann. Inst. Pasteur*, **63**, 400, 420, 485 (1939).

(4) B. N. Halpern, *Arch. Intern. Pharmacodynamie*, **68**, 339 (1942).

(5) A. Burger, "Medicinal Chemistry," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1951, p. 359.

(6) See footnote (a), Table I, for explanation of vasodilator activity.

(7) 2-Benzyl-4,5-imidazoline monohydrochloride.

(8) See footntoes *b* and *c*, Table I, for explanation of adrenergic blocking action.

TABLE I

$C_6H_5N(C_2H_5)CH_2CH_2R$

R	Yield, %	M.p. or b.p., °C.	Mm.	Empirical formula	Analyses, % Calcd. C	H	N	Cl	Found C	H	N	Cl	Vasodilator[a] activity	Adrenergic blocking action I[b]	D[c]
$-NHCH_3$[h]	48	179–181[d]		$C_{11}H_{20}Cl_2N_2$	52.6	8.0	11.2	28.3	52.4	8.1	11.0	27.9	1+	0	0
$-N(CH_3)_2$[e,h]	60	199–200[d]		$C_{12}H_{22}Cl_2N_2$	54.3	8.3	10.6	26.8	54.5	8.5	10.6	26.2	2+	0	0
$-N(CH_2CH_2OH)_2$[f,h]	58	195–200	1.5	$C_{14}H_{24}N_2O_2$	66.7	9.5	11.1		66.3	10.0	10.8		1+	1+	>1+[g]
$-N(n\text{-}C_3H_7)_2$[f]	28	121–122	0.5	$C_{16}H_{28}N_2$	77.5	11.3	11.3		76.9	11.1	11.7		4+	0	0
$-NHCH_2C_6H_5$	31	157–162	0.5	$C_{17}H_{22}N_2$	80.3	8.7	11.0		80.6	9.0	11.1				
	52	185–188		$C_{17}H_{24}Cl_2N_2$[i]	62.3	7.7	8.6	21.7	62.2	7.7	8.9	21.5	4+	1+	1+

[a] Vasodilator activity was determined in the isolated perfused rabbit ear (all compounds tested as hydrochlorides in 0.1% solution using buffered, perfusion fluid as diluent). The vessels of the ear were constricted by the addition of epinephrine to the perfusion fluid and the increase of venous effluent measured by a drop recorder was the index of vasodilator or adrenergic blocking action. Ratings of 0, 1, 2, 3 or 4+ were assigned to compounds which showed, respectively, 0–5, 6–69, 70–120, 121–170 or >170% of Priscoline activity. [b] When a compound showed strong vasodilator activity in initial screening, the possibility of adrenergic blocking activity was investigated in the anesthetized dog. I represents intensity of adrenergic blockade measured in % inhibition or reversal of intravenous epinephrine pressor response. A rating of 0, 1 or 2+ was assigned to 0–19, 20–50 or 51–100% inhibition. Partial reversal and complete reversal were rated 3+ and 4+, respectively. [c] D represents duration of adrenergic blockade. A rating of 1, 2, 3 or 4+ was assigned to durations of <2, 2–3, 3–4 or >4 hours. [d] Melts with sintering and evolution of gas. [e] Tested as an antihistamine, ref. 4. [f] Compounds submitted for testing as dihydrochlorides in 1.0% aqueous solution. [g] The sign > was used when an experiment was discontinued before duration of action ended. [h] See Experimental. [i] Dihydrochloride prepared by passing hydrogen chloride through ethereal solution of basic material.

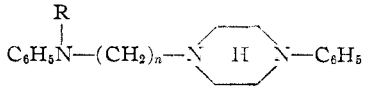
TABLE II

$C_6H_5N(C_2H_5)CH_2CH_2N$ (H) $N-R$

R	Yield, %	M.p. or b.p., °C.	Mm.	Empirical formula	Analyses, % Calcd. C	H	N	Cl	Found C	H	N	Cl	Vasodilator activity[a]	Adrenergic blocking action I[b]	D[c]
$-CH_3$[d]	25	138–142	0.5	$C_{16}H_{28}N_6$[e]	73.0	10.1	17.0		72.7	10.3	16.8		2+	1+	2+
$-COCH_3$	26	192–197	.5	$C_{18}H_{26}N_2O$	69.8	9.1	15.3		69.8	9.4	15.2				
	95[f]	214–216		$C_{18}H_{26}ClN_3O$	61.7	8.1	13.5	11.4	61.7	8.3	13.6	11.4	2+	1+	>1+
$-COOC_2H_5$	49	186–189	.5	$C_{17}H_{27}N_3O_2$	66.9	8.9	13.8		66.6	9.2	13.7				
		200–202		$C_{17}H_{28}Cl_2N_3O_2$	54.0	7.7	11.1	18.8	53.6	8.3	11.5	18.7	2+	0	0
$-C_6H_5$[g]	51	205–210	.2	$C_{20}H_{27}N_3$	77.7	8.7	13.6		77.9	9.1	13.5				
		223–224		$C_{20}H_{28}ClN_3$	69.7	8.1	12.2	10.1	69.4	7.8	12.4	10.2	4+	4+	4+
$-p\text{-}C_6H_4Cl$[g]	59	225–227	.5	$C_{20}H_{27}ClN_3$	69.5	7.8	12.2	10.3	69.8	7.8	12.4	10.2			
		225–228		$C_{20}H_{26}Cl_2N_3$	63.0	7.3	11.0	18.6	62.7	7.3	11.4	18.3	4+	4+	>1+
$-m\text{-}C_6H_4Cl$[h]	39	218–220	.5	$C_{20}H_{27}ClN_3$	69.5	7.8	12.2	10.3	69.6	7.8	12.4	10.6			
		220–222		$C_{20}H_{26}Cl_2N_3$	63.0	7.4	11.0	18.7	62.9	7.1	11.4	18.5	..[q]	1+	>1+
$-p\text{-}C_6H_4OCH_3$[i]	62	235–240	.5	$C_{21}H_{29}N_3O$	74.3	8.6	12.4		74.4	8.8	12.2				
		214–216		$C_{21}H_{30}ClN_3O$	67.2	8.0	11.2	9.7	67.0	8.3	11.0	9.4	4+	1+	>1+
$-C_{12}H_9$[j,g]	3	115–118		$C_{26}H_{31}N_3$	81.0	8.1	10.9		80.8	8.4	11.2				
	14	221–224		$C_{26}H_{32}ClN_3$			10.0	8.4			10.0	8.8	..[k]		
$-C_5H_4N$[l,m]	35	210–215	.5	$C_{19}H_{26}N_4$	73.6	8.4	18.1		73.3	8.4	18.3				
		213–215		$C_{19}H_{27}ClN_4$	65.8	7.8	16.2	10.2	66.0	8.0	16.0	10.4	4+	1+	1+
$-C_6H_6N$[n,g]	63	205–210	.1	$C_{20}H_{28}N_4$	74.1	8.6	17.3		74.1	8.7	17.0				
		212–214		$C_{20}H_{29}ClN_4$	66.6	8.3	15.5	9.8	66.4	8.2	15.8	9.8	4+	2+	>3+
$-C_4H_3N_2$[o,m]	31	225–230	2.0	$C_{18}H_{26}N_6$	69.1	8.6	22.4		69.2	8.3	22.4				
				$C_{18}H_{27}ClN_6$	61.8	8.0	20.0	10.3	61.6	7.6	20.4	10.0	3+	1+	>1+
$-C_3H_2NS$[p,m]	29	216–218	0.5	$C_{16}H_{22}N_4S$[r]	63.5	7.3	18.5		64.1	7.1	18.2				
		221–224		$C_{16}H_{23}ClN_4S$[s]	56.8	6.8	16.5	10.5	56.6	7.0	16.7	10.8	2+	1+	>2+
$-(CH_2)_2NC_6H_5$ (C_2H_5)	38	200–204		$C_{24}H_{40}Cl_4N_4$			10.7	26.7			10.7	26.2	4+	1+	>2+

[a,b,c] See Table I. [d] A general method for preparing these compounds is given in Experimental section. [e] Basic material was acidified with one molar equivalent of hydrochloric acid and submitted for testing in a 1.0% aqueous solution. [f] All hydrochlorides recrystallized from warm ethanol in yields of 90% or better unless otherwise indicated. [g] See Experimental. [h] Intermediate 1-*p*(and *m*)-chlorophenylpiperazine prepared as described by C. B. Pollard and T. H. Wicker, Jr., THIS JOURNAL, **76**, 1853 (1954). [i] Intermediate 1-*p*-methoxyphenylpiperazine prepared as described by E. Cerkovnikov and P. Stern, *Arhiv. Kem.*, **18**, 12 (1936). [j] 4-Biphenyl. [k] Hydrochloride too insoluble for testing. [l] 2-Pyridyl. [m] 1-Heterocyclic piperazine intermediates prepared according to procedure of M. E. Hultquist and K. L. Howard, U. S. Patent 2,606,906 (August 12, 1952). [n] 2-(6-Methyl)-pyridyl. [o] 2-Pyrimidyl. [p] 2-Thiazolyl. [q] Vasodilator activity data not available. [r] *Anal.* calcd. S, 10.6; found S, 10.6. [s] *Anal.* calcd. S, 9.8; found S, 9.3.

Compounds in Table III were derived from II by keeping the phenylpiperazine portion of the

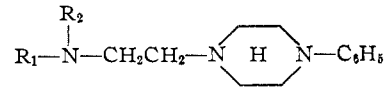


II, R = $-C_2H_5$; $n = 2$
III, R = $-H$; $n = 2$
IV, R = $-C_2H_5$; $n = 3$

molecule intact while substituents on the terminal N-atom of the β-aminoethyl moiety were varied. Compound III[9] offered a convenient starting point for direct acylation and alkylation as described in the Experimental section. In order to incorporate some of the structural features of Dibenamine[10] in one of these congeners, we condensed the appropriate β-chloroethyldiaralkylamine with 1-phenylpiperazine. This derivative was rated[6] 4+ as a vasodilator but was not considered a strong adrenergic blocking agent.

(9) J. van Alphen, *Rec. trav. chim.*, **56**, 1009 (1937).
(10) β-Dibenzylaminoethyl chloride monohydrochloride.

TABLE III



R_1	R_2	Yield, %	M.p. or b.p., °C.	Mm.	Empirical formula	Analyses, % Calcd. C	H	N	Cl	Found C	H	N	Cl	Vasodilator activity[a]	Adrenergic blocking action I[b]	D[c]
-H	$-C_6H_5$[d,e]	85	175–180	0.5	$C_{16}H_{22}N_2$	76.9	8.2	14.9		76.7	8.1	15.3		4+	4+	2+
$-CH_3$	$-C_6H_5$[f]	90[g]	220–222		$C_{13}H_{23}ClN_2$	68.8	7.8	12.7	10.7	68.4	7.4	13.2	10.6	4+	4+	>1+
$-C_7H_{15}$	$-C_6H_5$	31	235–240	.5	$C_{26}H_{42}N_2$	79.3	9.8	11.1		79.2	10.1	11.2				
			186–188		$C_{26}H_{43}BrN_2$[h]	65.3	8.3	9.1		64.9	8.5	9.1		0	1+	>2+
$-CH_2C_6H_5$	$-CH_3$	49	190–195	.5	$C_{28}H_{27}N_3$	77.7	8.7	13.6		77.4	8.7	13.6				
			243–245		$C_{21}H_{29}Cl_2N_3$	62.8	7.6	11.0	18.6	62.7	7.9	11.1	18.3	3+	1+	2+
$-CH_3C_6H_5$	$-CH_2C_6H_5$	92	88–91		$C_{28}H_{31}N_3$	81.2	8.1	10.9		81.4	7.8	10.7				
			210–212		$C_{28}H_{33}Cl_2N_3$	68.1	7.2	9.2	15.5	68.4	7.1	9.3	15.1	4+	1+	>2+
$-COCH_3$	$-C_6H_5$	80	245–252	.1	$C_{19}H_{24}N_2O$	73.4	8.9	12.9		73.7	8.6	12.6				
		30	168–171		$C_{20}H_{25}ClN_2O$	66.8	7.2	11.7	9.9	66.8	7.2	11.6	9.8	..[i]	4+	>1+
$-COC_6H_4I$[k]	$-C_6H_5$	80	209–211		$C_{25}H_{27}ClIN_3O$[j]	54.8	4.9	7.7	6.5	54.8	5.2	7.8	6.5	4+	2+	>1+
$-(CH_2)_2-N\langle NH\rangle N-C_6H_5$	-H	32	195–198		$C_{24}H_{26}ClN_5$	67.1	8.4	16.3		67.3	8.6	16.0		1+	0	0

[a,b,c] See Table I. [d] See ref. 9. [e] See Table II. [f] Preparation of compounds in this table included in the Experimental. [g] See Table II, footnote *f*. [h] *Anal.* calcd. Br, 17.4; found, Br, 18.0. [i] See Table II, footnote *q*. [j] *Anal.* calcd. I, 23.2; found I, 23.2. [k] *o*-Iodobenzoyl.

Several miscellaneous compounds were synthesized to determine the pharmacodynamic effect of chain lengthening IV and piperazine ring substitution. None of these structural changes resulted in activity comparable to II.

Pharmacology.—The authors are grateful to Dr. W. D. Gray and his staff of this Laboratory for their evaluation of these compounds. A pharmacological interpretation of the results obtained in this program will be published elsewhere.

Acknowledgment.—We wish to thank L. Brancone and staff for the analyses contained within.

Experimental[11]

1-Substituted Piperazines.—References for the preparation of these intermediates are given in the footnotes of Table II.

β-Disubstituted Aminoethyl Chloride Monohydrochlorides.—The following preparation of β-(N-ethyl-N-phenylamino)-ethyl chloride monohydrochloride is similar to the procedure described by Dehnert.[12] Forty grams (0.24 mole) of N-ethyl-N-(β-hydroxyethyl)-aniline was dissolved in 150 ml. of chloroform, cooled to 0° and treated with thionyl chloride (20 ml.) which was added dropwise with stirring. The reaction mixture was allowed to warm to room temperature and then refluxed for 4 hr. After this time the solvent was removed and the crystalline mass was triturated with dry ether; 48.0 g. (90%). The material obtained in this manner (crude m.p. 125–128°) was suitable for use as an intermediate.

This procedure was also used in the preparation of β-(N-methyl-N-phenylamino)-ethyl chloride monohydrochloride (crude m.p. 100–105°) and β-(N-benzyl-N-methylamino)-ethyl chloride monohydrochloride (crude m.p. 135–138°).

N-Ethyl-N'-methyl-N-phenylethylenediamine Dihydrochloride.—Twenty-six grams (0.117 mole) of β-(N-ethyl-N-phenylamino)-ethyl chloride hydrochloride was warmed at the steam-cone with 100 ml. of methylamine in water (25%) for 3 hr. after which time an oily layer separated. Ethanol was added until a clear solution was obtained and the mixture was refluxed an additional 3 hr. The residual oil remaining after concentration was extracted with ether, dried over anhydrous magnesium sulfate and distilled, b.p. 148–150° (20 mm.). The dihydrochloride was formed by adding 10 ml. of concentrated hydrochloric acid in 100 ml. of ethanol to 9.0 g. (0.05 mole) of the basic material. Recrystallization from an ethyl acetate–ethanol solution yielded the pure product.

N,N-Dimethyl-N'-ethyl-N'-phenylethylenediamine Dihydrochloride.—This compound was prepared as described above without distilling the basic product. The residual oil from the reaction was acidified with an excess of concentrated hydrochloric acid and the resulting salt was recrystallized from an ethyl acetate–ethanol solution.

N-Ethyl-N',N'-di-(β-hydroxyethyl)-N-phenyl-ethylenediamine.—Preparation of the remaining ethylenediamine derivatives in Table I is illustrated by the following procedure. β-(N-Ethyl-N-phenylamino)-ethyl chloride monohydrochloride (13.0 g., 0.058 mole) was refluxed with 6.09 g. (0.058 mole) of diethanolamine and 16.8 g. (0.20 mole) of sodium bicarbonate in 100 ml. of ethanol for 15 hr. After removing the solvent the semi-crystalline residue was made strongly alkaline with 5.0 ml. of concentrated potassium hydroxide solution and extracted with two 50-ml. portions of warm chloroform. The combined extracts were decolorized with Norit and concentrated to a residual oil which was fractionated *in vacuo* to yield 8.0 g. of pure product.

1-[β-(N-Ethyl-N-phenylamino)-ethyl]-4-phenylpiperazine (II).—The preparation of the 1,4-disubstituted piperazines and their salts (Table II) is illustrated by the following example. To a solution of 1-phenylpiperazine (17.8 g., 0.11 mole) in 150 ml. of ethanol was added 20.0 g. (0.11 mole) of β-(N-ethyl-N-phenylamino)-ethyl chloride monohydrochloride and 27.7 g. (0.33 mole) of sodium bicarbonate. After a reflux period of approximately 15 hr., the reaction mixture was concentrated to a semi-crystalline mass and then treated as described in the above procedure. The pure product boiled at 205–210° (0.2 mm.), 15.7 g. (51%). On standing this material solidified and could be recrystallized from ether; m.p. 64–66°.

The monohydrochloride was prepared by treating 30.9 g. (0.10 mole) of the basic material with 33.5 ml. (0.099 mole) of 2.98 *N* hydrochloric acid. The salt was then dissolved in 150 ml. of warm water, decolorized with Norit, filtered and concentrated to dryness; 32.0 g. (92%). A pure sample of this product was obtained after two recrystallizations from warm ethanol.

1-[β-(N-Ethyl-N-phenylamino)-ethyl]-4-(4-biphenyl)-piperazine.—A suspension consisting of 25.0 g. (0.10 mole) of N-ethyl-N',N'-di-(β-hydroxyethyl)-N-phenylethylenediamine, 16.9 g. (0.10 mole) of 4-aminobiphenyl and 5.0 g. of copper chromite catalyst in 75 ml. of dry dioxane was placed in a steel bomb and autoclaved at 250° under 93 atmospheres of hydrogen for 7 hr. After this period of time the dioxane was removed under reduced pressure at 90–100°, leaving a residual oil. This residue was distilled *in vacuo* until a distillate boiling at 190° (0.3 mm.) was obtained. Distillation was then discontinued and the pot residue (2.0 g.) was taken up in 25 ml. of ethanol, decolorized with Norit and filtered. When the filtrate was concentrated to three-quarters of the original volume and allowed to cool, a tan, granular precipitate was deposited. This material (0.329 g.) was collected and air-dried; m.p. 115–118°.

(11) The melting and boiling points are uncorrected.

(12) H. Dehnert, German Patent 650,259.

A monohydrochloride of this material was formed by treating 0.329 g. of the base with a calculated amount of 2.98 *N* hydrochloric acid in 20 ml. of ethanol. The salt was collected as fine, white needles, m.p. 221–224°.

1-[β-(N-Ethyl-N-phenylamino)-ethyl]-4-[2-(6-methyl)-pyridyl]-piperazine.—Following a procedure developed by Hultquist,[13] a solution consisting of 200.0 g. (1.16 moles) of 1-bromo-6-methylpyridine, 244.8 g. (2.84 moles) of anhydrous piperazine and 171 g. (2.20 moles) of pyridine was heated 6 hr. at 155° in a rocking autoclave. After cooling the autoclave, the brown reaction mass was taken up in water, the aqueous solution made strongly alkaline (1.0 l. of 10 *N* sodium hydroxide) and extracted with ether. The ethereal extracts were combined, dried over anhydrous magnesium sulfate, concentrated and the residual oil was fractionated. The desired product was a yellow oil boiling at 125–127° (1.5 mm.); 133.0 g. (65%).

A suspension of 15.0 g. (0.085 mole) of 1-[2-(6-methyl)-pyridyl]-piperazine, 18.7 g. (0.085 mole) of β-(N-ethyl-N-phenylamino)-ethyl chloride monohydrochloride and 21.4 g. (0.255 mole) of sodium bicarbonate in 100 ml. of ethanol was refluxed 15 hr. The desired basic material and monohydrochloride were obtained using the procedure described for the preparation of II.

1,4-Bis-[β-(N-Ethyl-N-phenylamino)-ethyl]-piperazine Tetrahydrochloride.—A solution consisting of 1.82 g. (0.021 mole) of anhydrous piperazine and 9.35 g. (0.043 mole) of β-(N-ethyl-N-phenylamino)-ethyl chloride monohydrochloride in 75 ml. of absolute ethanol was refluxed 7 hr. The solvent was then removed and the crystalline mass triturated with two 50-ml. portions of acetone to yield 6.0 g. (52%) of the tetrahydrochloride, m.p. 200–204°.

1-β-(N-Phenylamino)-ethyl-4-phenylpiperazine (III).—This substance was prepared by refluxing a mixture of aniline and tri-(β-chloroethyl)-amine hydrochloride for 3 hr. according to process described by van Alphen.[9]

1-[β-(N-Phenyl-N-methylamino)-ethyl]-4-phenylpiperazine.—This derivative was prepared according to the procedure described for II. β-(N-Phenyl-N-methylamino)-ethyl chloride monohydrochloride (11.2 g., 0.066 mole), 10.7 g. (0.066 mole) of 1-phenylpiperazine and 11.0 g. (0.132 mole) of sodium bicarbonate were refluxed in 150 ml. of ethanol for 15 hr. The basic material boiled at 203–208° (0.5 mm.) and was characterized as a monohydrochloride, m.p. 220–222°.

1-[β-(N-Benzyl-N-methylamino)-ethyl]-4-phenylpiperazine.—This substance was prepared as described above from β-(N-benzyl-N-methylamino)-ethyl chloride and 1-phenylpiperazine. The basic material was characterized as a dihydrochloride, m.p. 243–245°.

1-(β-Dibenzylaminoethyl)-4-phenylpiperazine.—β-Dibenzylaminoethyl chloride monohydrochloride (32.3 g., 0.109 mole) was added to 17.6 g. (0.109 mole) of 1-phenylpiperazine, 18.4 g. (0.218 mole) of sodium bicarbonate in 50 ml. of water and 50 ml. of ethanol. The reaction mixture was refluxed 12 hr. and then concentrated to a heavy brown oil which was dissolved in chloroform and decolorized with Norit. Concentration of the chloroform solution yielded a dark-yellow oil which solidified on standing. This waxy material was triturated with water until release of the white, crystalline product was complete; 38.5 g. (92%). An analytical sample was obtained after two recrystallizations from warm ethanol; m.p. 88–91°.

The dihydrochloride was formed by dissolving 4.50 g. (0.012 mole) of the base in 30 ml. of warm ethanol and 2.0 ml. of 11.7 *N* hydrochloric acid. On standing the solution deposited a crystalline material melting at 210–212°.

1-[β-(N-*n*-Heptyl-N-phenylamino)-ethyl]-4-phenylpiperazine.—A suspension consisting of 15.0 g. (0.05 mole) of III and 5.0 g. (0.12 mole) of sodamide in 100 ml. of dry toluene was refluxed 7 hr. At the end of this period of reflux, 9.0 g. (0.05 mole) of *n*-heptyl bromide was added and the mixture refluxed an additional 15 hr. The suspension was filtered hot, the filtrate decolorized with Norit and then concentrated to a heavy, brown oil. Fractionation yielded 6.2 g. (31%) of the crude product, b.p. 220–240° (0.3–0.5 mm.). A pure sample was obtained by refractionation; b.p. 235–240° (0.5 mm.).

A solid monohydrobromide salt of this substance was prepared by treating one molar equivalent of the base with one molar equivalent of hydrobromic acid in ethanol; m.p. 186–188°.

1-[β-(N-Acetyl-N-phenylamino)-ethyl]-4-phenylpiperazine.—Acetic anhydride (16.2 g., 0.159 mole) and 16.9 g. (0.06 mole) of III were mixed in a distilling flask and fractionated *in vacuo*. The acetylated derivative was collected as a viscous, yellow oil boiling at 247–252° (0.1 mm.); 15.7 g. (80%).

A calculated amount of hydrochloric acid was added to 1.69 g. of the base, and the acidic solution was concentrated to a gummy residue. A crystalline material was isolated by taking the residue up in ethanol, treating the solution with decolorizing charcoal, filtering and adding petroleum ether (90–100°) to the filtrate until turbidity. The crystalline precipitate weighed 1.6 g. (93%); m.p. 168–171°.

1-[β-(N-*o*-Iodobenzoyl-N-phenylamino)-ethyl]-4-phenylpiperazine Monohydrochloride.—Eight grams (0.029 mole) of III, 7.6 g. (0.029 mole) of *o*-iodobenzoyl chloride and 100 ml. of toluene were refluxed 2 hr. On cooling the solution deposited a crystalline precipitate which was collected and dried in an evacuated desiccator over solid potassium hydroxide. The salt obtained in this manner weighed 12.5 g. (80%); m.p. 208–210°. Two recrystallizations from warm ethanol yielded a pure salt, m.p. 209–211°.

Di-{β-[1-(4-Phenyl)-piperazinyl]-ethyl}-amine Monohydrochloride.—A suspension consisting of 4.05 g. (0.025 mole) of 1-phenylpiperazine and 4.46 g. (0.025 mole) of di-(β-chloroethyl)-amine hydrochloride was refluxed overnight in 50 ml. of absolute ethanol. The reaction mixture was then diluted with 10 ml. of water and the insoluble, quasi-crystalline material which separated was collected and triturated with two 25-ml. portions of acetone. The platelets obtained after trituration melted at 195–196° with decomposition; 1.5 g. (14%).

The more soluble trihydrochloride was prepared by adding two additional molecular equivalents of hydrochloric acid to the monohydrochloride in ethanol.

Anal. Calcd. for $C_{24}H_{33}N_5Cl_3$: N, 14.0. Found: N, 14.0.

1-(γ-Chloropropyl)-4-phenylpiperazine.—To 70.9 g. (0.340 mole) of phosphorus pentachloride in 200 ml. of chloroform was added portionwise 50.0 g. (0.227 mole) of 1-(γ-hydroxypropyl)-4-phenylpiperazine. During this addition the reaction temperature was maintained at 10–20°. The resulting dark-brown, solution was refluxed for 1 hr. at 95° and then poured on 300.0 g. of ice. The chloroform layer was separated, concentrated to a semi-crystalline mass and the residual material dissolved in warm water. The combined aqueous, acidic solutions were then treated with decolorizing charcoal and evaporated to dryness. When the residue was triturated with acetone 54.1 g. of the crude hydrochloride remained.

Twenty-seven grams (0.983 mole) of the crude salt, dissolved in 50 ml. of water, was then neutralized in the cold with 25% potassium hydroxide solution. Two 50-ml. portions of chloroform were used to extract the organic base which was isolated as a yellow oil after removing the solvent. A pure product was obtained by fractionating the oil and collecting the portion boiling at 146–150° (0.1 mm.).

Anal. Calcd. for $C_{13}H_{19}ClN_2$: C, 65.3; H, 8.0; N, 11.7; Cl, 14.9. Found: C, 65.2; H, 8.2; N, 11.9; Cl, 14.9.

1-[γ-(N-Ethyl-N-phenylamino)-propyl]-4-phenylpiperazine (IV).—Ethylaniline (3.3 g., 0.03 mole) was refluxed with 1.1 g. (0.03 mole) of sodamide in 75 ml. of dry toluene for 15 hr. After this time 6.5 g. (0.03 mole) of 1-(γ-chloropropyl)-4-phenylpiperazine was added and refluxing continued an additional 7 hr. The reaction mixture was then cooled, filtered and concentrated to a brown oil. Fractional distillation *in vacuo* yielded a pure product boiling at 198–205° (0.1 mm.).

Anal. Calcd. for $C_{21}H_{29}N_3$: N, 13.0. Found: N, 12.8.

The monohydrochloride of this material melted at 205–207°.

Anal. Calcd. for $C_{21}H_{30}ClN_3$: C, 70.0; H, 8.3; N, 11.7; Cl, 9.9. Found: C, 69.5; H, 8.3; N, 11.5; Cl, 9.7.

3,5-Dimethyl-1-[β-(N-ethyl-N-phenylamino)-ethyl]-4-phenylpiperazine.—The 2,6-dimethyl-1-phenylpiperazine used as an intermediate was prepared according to a procedure described by Pollard and Wicker.[14] This involved dis-

(13) See Table II, footnote *m*

(14) C. B. Pollard and T. H. Wicker, Jr., THIS JOURNAL, **76**, 1853 (1954).

tilling water from a mixture of diisopropanolamine and aniline which had been made slightly acidic with concentrated hydrochloric acid. The crude piperazine derivative boiling at 120–125° (1.0 mm.) was used in the next step without further purification.

A suspension consisting of 9.0 g. (0.047 mole) of 2,6-dimethyl-1-phenyl-piperazine, 8.7 g. (0.047 mole) of β-(N-ethyl-N-phenylamino)-ethyl chloride monohydrochloride and 10.9 g. (0.13 mole) of sodium bicarbonate in 100 ml. of ethanol was refluxed for 12 hr. The basic derivative was isolated following the procedure used in synthesizing the compounds reported in Table II. This substance boiled at 215–220° (0.4 mm.); 3.9 g. (25%).

Anal. Calcd. for $C_{22}H_{31}N_3$: C, 78.4; H, 9.2; N, 12.5. Found: C, 78.1; H, 9.4; N, 12.2.

The base was not characterized as a hydrochloride because of the hygroscopicity of the salt.

2-Hydroxymethyl-piperazine Dihydrobromide.—This intermediate was prepared by the interaction of 2,3-dibromopropanol-1 and the disodio derivative of N,N′-di-*p*-tosylethylenediamine in refluxing ethanol following the procedure previously described by Bach, Kushner and Williams,[1] m.p. 254–260° dec.

Anal. Calcd. for $C_5H_{14}Br_2N_2O$: C, 21.6; H, 5.0; Br, 57.6; N, 10.1. Found: C, 22.1; H, 5.3; Br, 58.0; N, 9.8.

1,4-Di-[β-(N-Ethyl-N-phenylamino)-ethyl]-2-hydroxymethylpiperazine.—A suspension consisting of 11.8 g. (0.0425 mole) of 2-hydroxymethylpiperazine dihydrobromide, 15.7 g. (0.085 mole) of β-(N-ethyl-N-phenylamino)-ethyl chloride monohydrochloride and 42.0 g. (0.50 mole) of sodium bicarbonate in 100 ml. of ethanol was refluxed for 15 hr. After this period of time the reaction mixture was concentrated to a semi-crystalline residue and the desired product was obtained following the procedure outlined for the isolation of compounds described in Table II. This derivative was an oil distilling at 245–250° (1.5 mm.); 4.5 g. (25%).

Anal. Calcd. for $C_{25}H_{38}N_4O$: N, 13.7. Found: N, 13.6.

The dihydrochloride of this material was extremely hygroscopic.

(15) F. L. Bach, Jr., S. Kushner and J. H. Williams, THIS JOURNAL, **77**, 6049 (1955).

PEARL RIVER, NEW YORK

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Reactions with Substituted Xanthones. III. Reactions with Hydroxy-9-xanthenones

BY AHMED MUSTAFA AND ORKEDE HASSAN HISHMAT[1]

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1-Hydroxy-9-xanthenone (Ia) condenses with the acyl and arylsulfonyl chlorides in the presence of aluminum chloride to give 2-acylated-1-hydroxy-9-xanthenones (Table II). The acyl, aroyl and benzenesulfonyl derivatives of Ia and of 1-hydroxy-3-methyl-9-xanthenone (Ii) undergo Fries migration of the acyl group under the influence of aluminum chloride to give the corresponding 2-acyl derivatives (Table II). 1-(β-Naphthoyloxy)-4-benzoyloxy-9-xanthenone and 4-benzoyloxy-1-methyl-10-thiaxanthenone undergo elimination reaction when treated with aluminum chloride under the Fries reaction conditions, yielding the corresponding hydroxy-9-xanthenone and hydroxy-10-thiaxanthenone derivatives, respectively, together with, *e.g.*, β-naphthoic in the case of the naphthoyl ester. Benzoyl esters of 2-hydroxy-3-methyl- and of 2-hydroxy-4-methyl-10-thiaxanthenones proved to be stable toward the action of aluminum chloride under similar conditions. Nencki's reaction offers a convenient method for the preparation of the new 1-hydroxybenzo[b]xanthene-12-one (IIIa), using resorcinol and 2-hydroxy-3-naphthoic acid. The same reaction, using salicylic acid and resacetophenone and/or 2,4-dihydroxybenzophenone, resulted in the formation of Ia in each case together with the removal of the acetyl- and/or the benzoyl group.

Previous work[2] on the study of reactions of substituted xanthenones now has been continued. Hydroxyxanthones, *e.g.*, 1-hydroxy-9-xanthenone (Ia), show the typical reactions of phenols[3] and it should be expected that they undergo the Friedel–Crafts as well as the Fries rearrangement, resulting in the formation of acylated derivatives of hydroxy-9-xanthenones which so far as we are aware[4] have not been synthesized and, meanwhile, constitute important intermediates for the syntheses of naturally occurring substances. Thus, when Ia is treated with acetyl chloride in the presence of aluminum chloride (2.5 moles), using anhydrous nitrobenzene as a solvent, on a steam-bath for three hours and kept aside at room temperature overnight, 2-acetyl-1-hydroxy-9-xanthenone (IIa) is obtained in *ca.* 50% yield. IIa forms a benzoyl derivative with benzoyl chloride in pyridine.

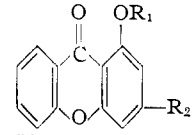
(1) Abstracted from a portion of the dissertation to be submitted by Orkede H. Hishmat in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) A. Mustafa, W. Asker and M. E. E. Sobhy, THIS JOURNAL, **77**, 5121 (1955).

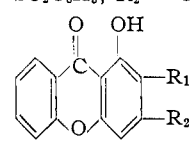
(3) *Cf.* R. C. Elderfield, "Heterocyclic Compounds," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 439.

(4) A perusal of the literature revealed that hardly any work has been done on the migration of esters of condensed heterocyclic ring system phenols, though migration has been reported recently in the case of 1-acetoxy-9-xanthenone (*cf.* ref. 8).

Although substitution may occur in more than one way, we have only been able to isolate one



Ia, R_1 = H; R_2 = H
b, R_1 = $COCH_3$; R_2 = H
c, R_1 = COC_6H_5; R_2 = H
d, R_1 = $COC_6H_4NO_2$-*p*; R_2 = H
e, R_1 = $SO_2C_6H_5$; R_2 = H
f, R_1 = $COC_{10}H_7(\beta)$; R_2 = H
g, R_1 = CH_3; R_2 = H
h, R_1 = $CH_2{\cdot}CH{:}CH_2$; R_2 = H
i, R_1 = H; R_2 = CH_3
j, R_1 = COC_6H_5; R_2 = CH_3
k, R_1 = $COC_6H_4NO_2$-*p*; R_2 = CH_3
l, R_1 = $SO_2C_6H_5$; R_2 = CH_3



IIa, R_1 = $COCH_3$; R_2 = H
b, R_1 = COC_6H_5; R_2 = H
c, R_1 = $COC_6H_4NO_2$-*p*; R_2 = H
d, R_1 = $SO_2C_6H_5$; R_2 = H
e, R_1 = COC_6H_5; R_2 = CH_3
f, R_1 = $SO_2C_6H_5$; R_2 = CH_3