precipitation of I. The product was dissolved in 10% sodium hydroxide solution and the acidification to pH 5 was repeated. Then the filtrate from the precipitated impurities was again acidified to pH 2, giving a purer material; yield, 15.8 g. (60%); m.p. 255°. By recrystallization from glacial acetic acid yellow needles were obtained, m.p. 279°.

Anal. Calcd. for $C_9H_5BrO_3$: C, 44.85; H, 2.09. Found: C, 84.48; H, 1.89.

4-Hydroxy-6,7-benzocoumarin (III).—Methyl 3-acetoxy-2-naphthoate (97 g.) was suspended in liquid paraffin (600 ml.). The suspension was heated to 200° with stirring. At that temperature sodium (16 g.) was added in small amounts. The reaction mixture was heated to 220–230° and kept at this temperature for 2 hr. After cooling the extracted dark brown mass was separated by filtration from liquid paraffin and washed with ether and petroleum ether. After drying, the mass was powdered in a mortar and dissolved in 1.5 l. of water. The water solution was boiled with activated charcoal and filtered. The mass was then acidified with 2 *N* HCl to pH 2. III precipitated as yellow microcrystals. After recrystallization from water and ethanol 40.5 g. (48%) of a product with m.p. 225–230° was obtained. III is soluble in ethanol and acetic acid but insoluble in water. It is very soluble in alkali. The alcohol solution of this alkali salt gives a green color with $FeCl_3$.

Because III could be isolated in a pure state, we determined its composition by preparing its acetyl derivative and other derivatives, which could be isolated pure. The analysis of acetyl derivative was:

Anal. Calcd. for $C_{15}H_{10}O_4$: C, 70.88; H, 3.97. Found: C, 70.64; H, 3.94.

Condensation Products of Aldehydes with 4-Hydroxycoumarin, 6-Bromo-4-hydroxycoumarin (II, V) and 4-Hydroxy-6,7-benzocoumarin (IV, VI).—By boiling 4-hydroxycoumarin or its derivatives (0.2 mole) with the corresponding aldehyde (0.1 mole) in ethanol under reflux, 3,3'-alkylidene- or 3,3'-arylidene-bis-4-hydroxycoumarin, -bis-6-bromo-4-hydroxycoumarin, or -bis-4-hydroxy 6,7-benzocoumarin was obtained. An excess of aldehyde (up to 2% above the theoretical amount) was used in the experiments reported here. The duration of this reaction was from 30 min. to 3 hr., whereas for the majority of compounds the reaction time was 1 hr. The reaction times are listed in Tables I and II. After cooling, the crystals were collected by filtration. Those soluble were recrystallized from glacial acetic acid; the insoluble ones were treated as shown in Tables I and II.

3-Acyl-6-bromo-4-hydroxycoumarins (VII).—6-Bromo-4-hydroxycoumarin (0.5 g.) was dissolved in 2 ml. of the corresponding acid, 0.5 ml. of phosphorus oxychloride was added, and the mixture refluxed for 35 min. The reaction mixture was kept for several hours at room temperature, and the separated crystals were removed by filtration. The compounds were recrystallized from ethanol with the aid of activated charcoal.

Derivatives of 4-Hydroxycoumarin with Oxalic (VIII) and Malonic Acids (IX).—The reactants for the preparation of derivatives of oxalic and malonic acid were used at a weight ratio of 1:1, except that 2–3 parts of phosphorus oxychloride had to be added. This reaction had to be carried out very carefully on a water bath in order to avoid pronounced resinification. The reaction mixture was refluxed for 2 hr. and evolved HCl. After that, the reaction mixture was kept for several hours at room temperature and carefully added to 5 volumes of cold water. After boiling, the substance was extracted 3 times from the dark mixture with warm ethanol. On adding water to the ethanolic extract, orange crystals of the new compound precipitated. Pure substances suitable for the analysis were obtained by repeated fractional recrystallization from ethanol and water.

4-Acetoxy-3-acetyl-6,7-benzocoumarin (X).—4-Hydroxy-6,7-benzocoumarin (0.6 g.) was dissolved in a mixture of 6 ml. of acetic anhydride and 2 ml. of pyridine and heated to boiling for 10 min. After standing for several hr., yellow crystals of 4-acetoxy-6,7-benzocoumarin separated. This compound (0.3 g.) was dissolved in 2 ml. of acetic acid and 0.8 ml. of phosphorus oxychloride was added. The mixture was kept for several hours at room temperature. The separated crystals were recrystallized from glacial acetic acid.

Acknowledgment.—The authors are very grateful to Prof. Dr. S. Hukovič for pharmacological results and to Dr. K. Dursun-Grom for performing the microanalyses.

β-Hydroxyphenethylamino Derivatives of Various Nitrogen Heterocycles

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β-Hydroxyphenethylamino derivatives of pyridazine, pyrazine, triazine, thiazole, and triazole have been prepared for purposes of pharmacological comparison with their pyridine and pyrimidine analogs. Pharmacological properties ranging from analgesic and interneuronal blocking to antiinflammatory (on mustard-induced rat paw edema) have been observed and are discussed in the context of the relative basicities of the compounds. Optically active (−)-2-(β-hydroxyphenethylamino)pyridine has been synthesized and found to be equipotent to the racemate as an analgesic. In connection with this work a number of the corresponding mandelamido derivatives have been prepared. The physical properties, in particular the acidity of these secondary amides and the positions of their carbonyl stretching bands in the infrared, are discussed.

Continued interest in the analgesic and muscle relaxant (interneuronal blocking) properties of 2-(β-hydroxyphenethylamino)pyridine[1,2] and in the more potent muscle relaxant and sedative–hypnotic properties of the corresponding pyrimidine derivative, 2-(β-hydroxyphenethylamino)pyrimidine,[3,4] has encouraged further study of the effects of structural modification on pharmacological actions. A number of facets of this problem have been explored. This paper is concerned with one aspect which, in view of the striking shift in spectrum of biological effects in going from pyridine to pyrimidine derivative, seemed potentially most instructive, *viz.*, the pharmacological consequences of altering, particularly isosterically, the heterocyclic system attached to the nitrogen of the β-hydroxyphenethylamine moiety. To this end derivatives incorporating a variety of heterocyclic nuclei have been examined; many of these are described here.

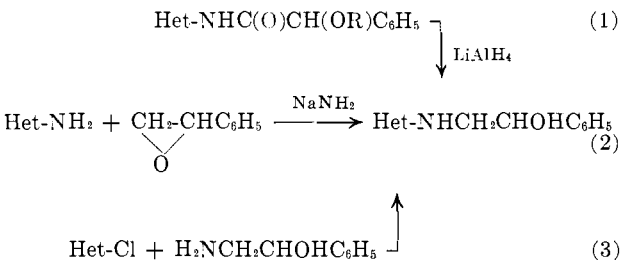
(1) (a) A. P. Gray and D. E. Heitmeier, *J. Am. Chem. Soc.*, **81**, 4347 (1959); (b) A. P. Gray, D. E. Heitmeier, and E. E. Spinner, *ibid.*, **81**, 4351 (1959).

(2) T. B. O'Dell, L. R. Wilson, M. D. Napoli, H. D. White, and J. H. Mirsky, *J. Pharmacol. Exptl. Therap.*, **128**, 65 (1960); generically phenyramidol.

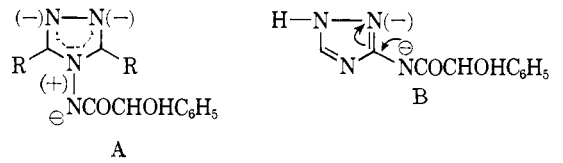
(3) D. E. Heitmeier, E. E. Spinner, and A. P. Gray, *J. Org. Chem.*, **26**, 4419 (1961).

(4) T. B. O'Dell, M. D. Napoli, and J. H. Mirsky, *Arch. Intern. Pharmacodyn.*, **141**, 83 (1963).

Synthetic approaches to the N-(β-hydroxyphenethylamino)heterocycles listed in Table III generally paralleled those employed earlier.[1,3] Most of the compounds were prepared by one of the following methods: (1) lithium aluminum hydride reduction of the corresponding N-substituted mandelamide (VIII, XI, XII, and XX); (2) reaction of an aminoheterocycle with styrene oxide (IX, XXI); or (3) aminolysis of the appropriate chloroheterocycle with β-hydroxyphenethylamine (X, XIII, XIV, XV, XVII, and XIX).



The N-substituted mandelamides (Table II) were obtained in 36 (V, VI) to 71% (IV) yield by acylation of an aminoheterocycle with (±)-mandelic acid in refluxing xylene with azeotropic removal of water, or under milder conditions and in better yield (83–92%; I, II, III, and VII) by reaction with (±)-O-acetylmandelyl chloride in ether (or tetrahydrofuran)–triethylamine, or in cold pyridine. 4-Mandelamido-1,2,4-triazole (V) and 4-mandelamido-3,5-dimethyl-1,2,4-triazole (VI), were fairly strong acids as shown by their pK_a' values (Table II) and by their ready solubility in dilute sodium bicarbonate. In contrast, 3-mandelamido-1,2,4-triazole (IV) was insoluble in bicarbonate but soluble in dilute sodium hydroxide. The stronger acidity of V and VI in comparison with IV reflects the powerful inductive influence of the nitrogen in the 4-position of the electronegative 1,2,4-triazole ring in stabilizing the anionic charge (compare A and B). [It should be noted that it has not actually been established that in the formation of the anion of IV the amide nitrogen loses a proton (to give B) rather than a ring nitrogen.] The higher frequency of the



amide carbonyl stretching absorption in the infrared spectrum of V in comparison with that of IV (Table I) also indicates the relative effects of these electron withdrawing ring systems.[5] The structural assignment of IV as 3-mandelamido- rather than a ring N-substituted mandelyltriazole derivative is based on the conditions of amide formation (refluxing xylene), the position of the carbonyl absorption in the infrared and the stability of the compound to hydrolysis.[6]

The structures assigned to 2-mandelamidothiazole (III) and 2-mandelamido-1,3,4-thiadiazole (VII) follow from the known behavior of the parent amines in providing thermodynamically more stable products acylated on the exocyclic nitrogen under basic conditions.[7,8] Lithium aluminum hydride reduction of III to give 2-(β-hydroxyphenethylamino)thiazole (XX) in 70% yield confirms the structural assignment. The amide VII appeared to be a stronger acid (soluble in dilute potassium carbonate) than III (soluble *only* in dilute sodium hydroxide) and showed a higher frequency carbonyl band in the infrared (Table I). This accords with the

TABLE I

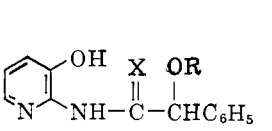
CARBONYL STRETCHING FREQUENCIES, INFRARED[a]

	ν_{max} cm.$^{-1}$	
	Ester	Amide
I[b]	1720	1700
II	1755	1685
IV	...	1685
V	...	1715
III	1743	1698
III[c]	1750	1700
VII[c]	1740	1710

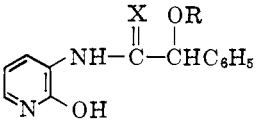
[a] Spectra were measured on the solids in KBr disks with a Beckman IR-5 infrared spectrophotometer. [b] Hydrochloride salt. [c] Compound in chloroform.

more electronegative character of the heterocyclic ring of VII owing to the presence of the additional nitrogen. In general, increases in acidity of the secondary N-substituted mandelamides paralleled increases in carbonyl stretching frequency (see Table I), both of which properties may be useful indices of the electron-withdrawing power of the N-attached heterocyclic ring.

That the acylation of 2-amino-3-hydroxypyridine and of 3-amino-2-hydroxypyridine by (±)-O-acetylmandelyl chloride gave the amides I and II rather than the isomeric esters was shown by their ready solubility in cold dilute aqueous sodium hydroxide, their amide absorption in the infrared (Table I), and by their reduction to substituted amines.



I, X = O; R = −COCH$_3$
XII, X = H$_2$; R = H



II, X = O; R = −COCH$_3$
XI, X = H$_2$; R = H

Lithium aluminum hydride reduction of these amides gave the corresponding hydroxyamino derivatives XII and XI in poor yield accompanied by large amounts of dark by-products that appeared to form during work-up of the reactions and may have arisen from air oxidation of the *o*-hydroxyamine products.

(−)-2-(β-Hydroxyphenethylamino)pyridine (VIII) was obtained by the reaction of 2-aminopyridine with (+)-O-acetylmandelyl chloride in ether–triethylamine followed by reduction of the resultant optically active 2-(O-acetylmandelamido)pyridine with lithium aluminum hydride in ether.

(5) See H. A. Staab, *Angew. Chem. Intern. Ed. Engl.*, **1**, 351 (1962), and A. P. Katritzky and A. P. Ambler, in "Physical Methods in Heterocyclic Chemistry," Vol. II, A. P. Katritzky, Ed., Academic Press, Inc., New York, N. Y., 1963, pp. 308–309, 327–329.

(6) *Cf.* H. A. Staab and G. Seel, *Chem. Ber.*, **92**, 1302 (1959).

(7) I. A. Kaye and C. L. Parris, *J. Org. Chem.*, **16**, 1761 (1951); I. Ya. Posotovskiĭ and I. B. Lundina, *Zh. Obshch. Khim.*, **29**, 608 (1959); *Chem. Abstr.*, **54**, 1499 (1960).

(8) E. Testa, G. G. Gallo, and F. Faya, *Gazz. Chim. Ital.*, **88**, 1272 (1958); *Chem. Abstr.*, **53**, 21904 (1959); F. Ueda, T. Ueda, and S. Toyoshima, *Yakugaku Zasshi*, **79**, 920 (1959); *Chem. Abstr.*, **53**, 21888 (1959).

TABLE II

N-SUBSTITUTED MANDELAMIDES, Het-NHC(O)CH(OR)C_6H_5

	Het	R	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Neut. equiv. Calcd.	Neut. equiv. Found
I	3-Hydroxy-2-pyridyl	Acetyl	148–150	$C_{15}H_{14}N_2O_4$					4.89	4.71		
	b		184–187	$C_{15}H_{15}ClN_2O_4$	55.83	55.55	4.69	5.22	10.98	10.30[c]		
II	2-Hydroxy-3-pyridyl	Acetyl	186–187	$C_{15}H_{14}N_2O_4$	62.90	63.29	4.93	4.88			286.3	287.0[d]
III	2-Thiazolyl	Acetyl	148–149	$C_{13}H_{12}N_2O_3S$	56.51	56.68	4.38	4.26	11.60	11.51[e]		
IV	3-(1,2,4-Triazolyl)	H	216–217	$C_{10}H_{10}N_4O_2$	55.02	55.04	4.62	4.81	6.42	6.39[f]		
V	4-(1,2,4-Triazolyl)	H	183–185	$C_{10}H_{10}N_4O_2$	55.02	55.17	4.62	4.49	6.42	6.25	218.2	215.4[g]
VI	3,5-Dimethyl-4-(1,2,4-triazolyl)	H	211–212	$C_{12}H_{14}N_4O_2$	58.51	58.86	5.73	5.69	5.68	5.60	246.3	244.2[h]
VII	2-(1,3,4-Thiadiazolyl)	Acetyl	179–180	$C_{12}H_{11}N_3O_3S$	51.96	52.14	4.00	4.17	11.55	11.60[e]		

[a] Basic nitrogen by acetous–perchloric titration. [b] Hydrochloride salt of I; melts with decomposition. [c] Potentiometric determination of ionic chlorine. [d] By titration with lithium methoxide in dimethylformamide; nitrogen would not titrate with acetous–perchloric acid. [e] Schöniger determination of sulfur; nitrogen would not titrate with acetous–perchloric acid. [f] Valid determination potentiometrically but not colorimetrically. [g] By potentiometric titration in 80% Methyl Cellosolve with 0.1*N* NaOH; $pK_a' = 7.54$. [h] See footnote *g*; $pK_a' = 8.47$.

3-(β-Hydroxyphenethylamino)pyridine (IX) was prepared in 67% yield and 4-(β-hydroxyphenethylamino)-1,2,4-triazole (XXI) in low (19%) yield by the reaction of styrene oxide with the respective parent aminoheterocycle in the presence of sodamide, a reaction that was found useful in preparing the 2-isomer[1b] of IX.

The most generally applicable method for preparing the N-substitued β-hydroxyphenethylamines listed in Table III was the aminolysis of a chloroheterocycle with β-hydroxyphenethylamine. The more reactive halides, 2,5-dichloropyrimidine, 2-chloro-4-methoxypyrimidine, and 2,4-diamino-6-chlorotriazine, reacted smoothly with β-hydroxyphenethylamine at steam bath temperature or better in boiling toluene to give 54 to 80% yields of the derivatives XIII, XIV, and XIX. The chloroheterocycles of less reactivity, 6-chloronicotinamide, 3,6-dichloropyridazine, and 2-chloro-3-methylpyrazine, required temperatures of 150–170°, affording X, XV, and XVII in approximately 30% yields.

The palladium-on-carbon–hydrazine promoted hydrogenolysis of the 6-chloro derivative (XV) gave 3-(β-hydroxyphenethylamino)pyridazine (XVI) in good yield. The compound 3-(β-hydroxyphenethylamino)-*s*-triazine (XVIII) was prepared by reaction of *s*-triazine with β-hydroxyphenethylguanidine hydrobromide.[9]

Pharmacological Properties.[2,4,10]—As noted earlier, it is considered that by limiting to isosteric systems we can minimize (but not eliminate) variations in any agent–receptor interactions and thereby attempt to concentrate on the modification of properties which will mainly affect distribution of the agent in the animal organism. Table IV lists relative pharmacological activity data for β-hydroxyphenethylamino derivatives of some selected (largely isosteric) heterocyclic systems, in conjunction with published dissocation constants of the parent aminoheterocycles (measured in water). pK_a data for the parent bases were used as a matter of convenience and were considered entirely adequate for purposes of internal comparison in this discussion. Introduction of the constant β-hydroxyphenethyl substituent involves a minor shift in basicity compared to the large changes produced by alteration of the heterocyclic nucleus, and, in any event, would not change the relative order of basicity.[1b,3,11] Inspection of the data indicates that the simple, unidimensional relationship between a ratio of interneuronal blocking to analgesic activity and basicity, tentatively advanced on the basis of an admittedly limited series,[3] will not stand up, in a quantitative sense, on extension. Nevertheless a rough correlation of pharmacological activities with basicity can still be discerned.

For significant analgesic activity in this series it certainly appears necessary, but not sufficient [note the diaminotriazine (XIX) and thiazole (XX) derivatives], for the compound to have a pK_a above 5. The inactivity of XIX can be rationalized on the basis of an extremely low lipophilic to hydrophilic balance, but the low order of activity of XX cannot be explained away so simply. The analgesic activity of the 3-pyridine analog (IX), since resonance interaction in the monocation of this compound would not partially distribute the charge to the amino nitrogen, indicates that such charge distribution is not essential to activity.[1b] This conclusion is borne out by the finding of analgesic agents among 2-(phenylalkyl)-, optimally 2-(phenylpropyl)-, pyridine derivatives,[12] *i.e.*, replacement of –NH– by $–CH_2–$ is not deleterious. The finding that the (–) isomer of 2-(β-hydroxyphenethylamino)pyridine is equal to the racemate in potency is particularly noteworthy since it implies that a stereospecific interaction is not involved.

Interneuronal blocking activity is in evidence over the entire pK_a range under discussion[13] but the most potent compounds have pK_a values of the order of 3–3.5. The low order of activity of XIX can be explained as already indicated, but the lack of activity of the 3-pyridazine derivative XVI is certainly perplexing. It is interesting that XVI ($pK_a = 5.19$) appears more to resemble the aminopyridine in its pharmacological profile whereas the 3-methyl-2-pyrazine analog (XVII, $pK_a = 3.14+$) follows a pattern more reminiscent of the aminopyrimidine. This is in accord with previous observations.[3] It is of particular note that the pyrimidine derivative seems to stand alone in being (at higher doses) an effective general depressant of the central nervous system as well as a powerful interneuronal blocking agent.

(9) See F. C. Schaefer and G. A. Peters, *J. Am. Chem. Soc.*, **81**, 1470 (1959).

(10) We thank Dr. T. B. O'Dell and associates for permission to use unpublished data.

(11) It should be noted that previous discussions have been based on apparent dissociation data obtained on the derivatives in 60% aqueous dimethylformamide.

(12) A. P. Gray and T. B. O'Dell, U. S. Patent 3,063,902 (1962).

(13) It was shown previously that this property is lost in more strongly basic analogs (see ref. 3).

TABLE III

N-SUBSTITUTED β-HYDROXYPHENETHYLAMINES, Het-$NHCH_2CHOHC_6H_5$

	Het	Salt	M.p., °C.[c]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, %[a] Calcd.	Nitrogen, %[a] Found	Chlorine, %[b] Calcd.	Chlorine, %[b] Found
VIII	2-Pyridyl[d]		102–105	$C_{13}H_{14}N_2O$					6.54	6.49		
		HCl	124–126	$C_{13}H_{15}ClN_2O$	62.27	62.89	6.03	6.19			14.14	14.10
IX	3-Pyridyl		87–89	$C_{13}H_{14}N_2O$					6.54	6.56		
		HCl	125–126	$C_{13}H_{15}ClN_2O$	62.27	62.45	6.03	5.90			14.14	14.15
X	5-Carbamyl-2-pyridyl		188–190	$C_{14}H_{15}N_3O_2$					5.44	5.27		
		HCl[e]	90–95	$C_{15}H_{19}ClN_3O_{2.5}$	56.87	56.86	6.05	6.27			11.20	10.78
XI	2-Hydroxy-3-pyridyl		167–168	$C_{13}H_{14}N_2O_2$					6.08	5.82		
		HCl	160–162	$C_{13}H_{15}ClN_2O_2$	58.54	58.39	5.67	5.54			13.30	13.27
XII	3-Hydroxy-2-pyridyl	HCl	198–199	$C_{13}H_{15}ClN_2O_2$	58.54	59.04	5.67	5.75			13.30	12.94
XIII	5-Chloro-2-pyrimidyl		123–124	$C_{12}H_{12}ClN_3O$					5.62	5.11	14.20	14.18[f]
		HCl	178–179	$C_{12}H_{13}Cl_2N_3O$	50.35	50.42	4.58	4.63			12.38	12.21
XIV	4-Methoxy-2-pyrimidyl	HCl	130–132	$C_{13}H_{16}ClN_3O_2$	55.43	56.12	5.72	6.20			12.58	12.37
XV	6-Chloro-3-pyridazyl		149–150	$C_{12}H_{12}ClN_3O$					5.62	5.51		
		HCl	185–186	$C_{12}H_{13}Cl_2N_3O$	50.35	50.67	4.58	4.65			12.39	12.37
XVI	3-Pyridazyl		141–142	$C_{12}H_{13}N_3O$					6.51	6.50		
		HCl	122–124	$C_{12}H_{14}ClN_3O$	57.25	57.53	5.60	5.50			14.09	14.08
XVII	3-Methyl-2-pyrazyl		[g]	$C_{13}H_{15}N_3O$					6.11	6.06		
		HCl	111–113[h]	$C_{14.5}H_{20}ClN_3O_{1.5}$	58.80	59.22	6.82	6.77			12.00	12.36
XVIII	2-(*s*-Triazyl)		211–212	$C_{11}H_{12}N_4O$	61.10	61.46	5.60	5.88	6.48	6.45		
XIX	4,6-Diamino-2-(*s*-triazyl)		176–178	$C_{11}H_{14}N_6O$	53.64	54.00	5.73	5.83	5.69	5.60		
		HCl	231–232	$C_{11}H_{15}ClN_6O$							12.54	12.49
XX	2-Thiazolyl		96–97	$C_{11}H_{12}N_2OS$					6.36	6.32		
		HCl	161–162	$C_{11}H_{13}ClN_2OS$	51.43	52.18	5.10	5.35			13.80	13.74
XXI	4-(1,2,4-Triazolyl)		137–141	$C_{10}H_{17}N_4O$	58.82	58.84	5.93	6.05	6.86	6.80		

[a] Basic nitrogen by acetous-perchloric titration. [b] Potentiometric determination of ionic chlorine. [c] Hydrochloride salts melt with decomposition. [d] (−) Isomer; hydrochloride salt showed $[\alpha]D^{25}$ −64.8° (*c* 2.0, ethanol). [e] Formulated as hemiethanolate on the basis of analysis. [f] Total chlorine by Schöniger method. [g] Base was an oil, b.p. 195–201° (0.5 mm.). [h] Loses hydrogen chloride when dried *in vacuo* at higher than room temperature; formulated as hemiisopropyl alcoholate.

TABLE IV

RELATIVE PHARMACOLOGICAL ACTIVITIES OF SELECTED N-SUBSTITUTED β-HYDROXYPHENETHYLAMINES

	N-Substituent	pK_a[a]	Analgesic[b]	Interneuronal blocking[c]	General central depression[d]	Anti-inflammatory[e]
	2-Pyridyl[f]	6.86	3+	2+	0	0
VIII	2-Pyridyl[k]		3+			
IX	3-Pyridyl	5.98	1+	1+	0	
	2-Pyrimidyl[g]	3.54	1±	4+	4+	2+
XVI	3-Pyridazyl	5.19	1+	0	1+	
XVII	3-Methyl-2-pyrazyl	3.14[h]	1±	4+	±	
XVIII	2-(*s*-Triazyl)	2.9[i]	0	2+	0	1+
XIX	4,6-Diamino-2-(*s*-Triazyl)	5.0[j]	0	±	0	4+
XX	2-Thiazolyl	5.39	±	2+	0	

[a] The listed dissociation constants are of the parent aminoheterocycle measured in water as reported by A. Albert, R. Goldacre, and J. Phillips [*J. Chem. Soc.*, 2240 (1948)]. [b] In mice, see ref. 1b–3. [c] In dogs, see ref. 1b–4. [d] An over-all evaluation used by the Pharmacology Section of these laboratories; based on a spectrum of tests including the effect of the compound on voluntary and amphetamine-stimulated motor activity of mice (mouse run), and on the behavior of unanesthetized dogs; see also ref. 2 and 4. [e] Based on % reduction in mustard-induced edema of the rat's paw effected by the compound administered subcutaneously; on this scale cortisone is rated 4+. [f] See ref. 1. [g] See ref. 3. [h] This value is for the desmethyl base. The pK_a of the methyl derivative could be up to 0.5 units higher; see ref. 1b. [i] Determined spectrophotometrically [R. C. Hirt, R. G. Schmitt, H. L. Strauss, and J. G. Koren, *J. Chem. Eng. Data*, **6**, 610 (1961). [j] J. K. Dixon, N. T. Woodberry, and G. W. Costa, *J. Am. Chem. Soc.*, **69**, 599 (1947). [k] (−) Isomer.

Antiinflammatory activity, as measured by the per cent reduction in the mustard-induced edema of the rat's paw, appears to require a pK_a about 5 or below. This is supported by the fact that the mandelanidopyridine derivatives reported earlier (pK_a values *ca.* 3)[1b] are, almost without exception, effective anti-inflammatory agents. In fact, this property is evidenced quite generally by the amide relatives of the present compounds as well. The exceptional efficacy of XIX, however, could well be more complexly dependent on its additional amino substituents.

Basicity has been exploited in this discussion as a conveniently measured parameter but certainly other, not independent, factors are involved. As basicity is reduced the proportion of the agent in free base form increases and thereby the lipoid solubility and ability to penetrate biological membranes. At a pK_a of 5 or below, however, essentially all of the compound is in the form of free base at physiological pH values and further reduction in basicity by the insertion of additional heteroatoms can only serve to have the counter effect of *reducing* lipoid solubility. On this basis (and in this series) interneuronal blocking properties might be inferred to be associated optimally with weakly basic (or nonbasic) compounds with a moderately high lipophilic to hydrophilic balance. Only analgesic activity may require that a significant amount of the protonated cation of the agent be present.[14]

Experimental[15]

Intermediates.—2,4-Dichloropyrimidine,[3] (±)-O-acetylmandelyl chloride,[1] 2,5-dichloropyrimidine,[16] m.p. 54–56°, 2-chloro-4-

(14) See also A. P. Gray, Program of the Eighth National Medicinal Chemistry Symposium of the American Chemical Society, University of Colorado, June, 1962, p. 11a.

(15) Microanalyses were performed by the Clark Microanalytical Laboratories, Urbana, Ill., the Micro-Tech. Laboratories, Skokie, Ill., and the Galbraith Laboratories, Knoxville, Tenn. Melting points are corrected and were determined with a modified Hershberg melting point apparatus using M.C.A. thermometers.

methoxypyrimidine,[17] 3,6-dichloropyridazine,[18] m.p. 67–69°, 3-hydroxypyridine N-oxide,[19] m.p. 186–188°, 3-hydroxy-2-nitropyridine N-oxide,[20] m.p. 200–203°, 3-amino-2-hydroxypyridine,[21] m.p. 124–126°, 4-amino-1,2,4-triazole,[22] m.p. 82–83°, 4-amino-3,5-dimethyl-1,2,4-triazole,[22] m.p. 197–200°, 2-amino-1,3,4-thiadiazole,[23] m.p. 190–192°, and *s*-triazine,[24] m.p. 80–81°, were prepared by published procedures. A sample of 2-chloro-3-methylpyrazine was kindly supplied by Wyandotte Chemical Co. (−)-Mandelic acid, m.p. 130–132°, $[\alpha]^{25}D$ −146.5° (*c* 2.0, water), was obtained as described by Roger[25] and was judged to be at least 95% pure based on a value of $[\alpha]^{20}D$ −157.5° (water) reported for pure (−)-mandelic acid.[26] (+)-O-Acetylmandelyl chloride, b.p. 124° (2 mm.), $n^{25}D$ 1.5105, $[\alpha]^{25}D$ +63.6° (neat) was prepared in 45% yield from (−)-mandelic acid essentially according to the procedure of Berlingozzi, *et al.*[27] Other intermediates were available commercially.

2-Amino-3-hydroxypyridine.—To a suspension of 18.0 g. (0.11 mole) of 3-hydroxy-2-nitropyridine N-oxide in 200 ml. of dioxane–methanol (1:1) was added 7 teaspoonsful of Raney nickel catalyst (W-2) and the mixture was shaken in a Parr apparatus at an initial hydrogen pressure of 3.5 kg./cm.^{2}. After 3 moles of hydrogen had been absorbed, the mixture was heated at 60° and the shaking was continued for 2 hr. longer.[28] The catalyst was removed and the filtrate concentrated to a dark oil that crystallized from isopropyl alcohol to yield 6.2 g. (51%) of product, m.p. 163–165°; picrate, recrystallized from ethanol–methanol, melted at 247–249° (lit.[19] m.p. 166–168°, picrate m.p. 246–248°).

Reaction of 2-Aminopyridine with (+) O-Acetylmandelyl Chloride.—To a cold solution of 9.2 g. (0.1 mole) of 2-aminopyridine and 10 g. (0.1 mole) of triethylamine in 150 ml. of dry ether was added, dropwise, a solution of 20.8 g. (0.1 mole) of (±)-O-acetylmandelyl chloride in 30 ml. of dry ether. The reaction mixture was stirred for 2 hr., the precipitated triethylamine hydrochloride (13.4 g., m.p. 255–256°) was filtered and the filtrate concentrated to yield 28.4 g. of optically active 2-(O-acetylmandelamido)-pyridine as an intractable yellow oil.

(−)-2-(β-Hydroxyphenethylamino)pyridine (VIII).—A solution of 21.0 g. (0.08 mole) of optically active 2-(O-acetylmandelamido)pyridine in 300 ml. of dry ether was reduced with 11.5 g. (0.3 mole) of lithium aluminum hydride, essentially as described for the racemic compound,[1] to give 8.2 g. of solid, m.p. 93–100°. This was recrystallized twice more from isopropyl alcohol to give 5.0 g. (30% yield) of VIII, m.p. 102–105°.

The **hydrochloride salt of VIII,** recrystallized from isopropyl alcohol, had m.p. 124–126°.

Preparation of N-Substituted Mandelamides. 4-Mandelamido-1,2,4-triazole (V).—A stirred mixture of 37.5 g. (0.45 mole) of 4-amino-1,2,4-triazole and 69.0 g. (0.45 mole) of (±)-mandelic acid was heated at reflux in xylene for 5 hr. with azeotropic removal of water. The reaction mixture was diluted with 150 ml. of ethyl acetate. On standing an oily solid precipitated. The crude solid was recrystallized 3 times from isopropyl alcohol to give 35 g. (36%) of product, m.p. 183–185°. Work-up of the xylene–ethyl acetate filtrate gave only uncharacterizable, oily material.

3-(O-Acetylmandelamido)-2-pyridinol (II).—To a stirred, ice-cooled solution of 50.0 g. (0.45 mole) of 2-hydroxy-3-aminopyridine and 70 ml. of triethylamine in 800 ml. of tetrahydrofuran was added, during 45 min., a solution of 85.0 g. (0.4 mole) of (±)-O-acetylmandelyl chloride in 100 ml. of tetrahydrofuran. After being stirred for 1 hr. in the cold the mixture was allowed to warm to room temperature over an additional 3 hr. period. The precipitated triethylamine hydrochloride (51 g., m.p. 253–254°) was filtered and the tetrahydrofuran filtrate was concentrated to a gray solid that was washed with water and crystallized from methanol to give 105.4 g. (92% yield) of II, m.p. 186–187°.

Preparation of N-Substituted β-Hydroxyphenethylamines. 3-(β-Hydroxyphenethylamino)-2-pyridinol (XI).—To a stirred slurry of 31.5 g. (0.82 mole) of lithium aluminum hydride in 700 ml. of tetrahydrofuran was added, portionwise, 88.2 g. (0.31 mole) of II. The mixture was heated at reflux for 6 hr. and then cautiously treated with 50 ml. of ethyl acetate followed by 100 ml. of water. During the hydrolysis additional tetrahydrofuran had to be added to aid in stirring. The precipitate was filtered and the light yellow filtrate was dried over sodium sulfate. On standing overnight the tetrahydrofuran solution became very dark. The solution was filtered and concentrated to a dark green oily residue which was crystallized from ethanol–water to give 19.0 g. of light green solid melting at 160–162°. This was dissolved in cold dilute hydrochloric acid and the solution was neutralized with sodium bicarbonate to precipitate a cream colored solid, m.p. 160–162°, that crystallized from acetonitrile to give 12.5 g. of colorless crystals, m.p. 167–168°.

The **hydrochloride salt of XI** was recrystallized from ethanol–ethyl acetate, m.p. 160–162°.

3-(β-Hydroxyphenethylamino)pyridine (IX).—A slurry of 22.5 g. (0.55 mole) of sodium amide and 47.0 g. (0.5 mole) of 3-aminopyridine in 400 ml. of liquid ammonia was treated with 54.0 g. (0.45 mole) of styrene oxide and worked up essentially as described for the 2-isomer[1] to yield an oil that was vacuum distilled to give a yellow glass, b. p. 195–202° (0.3 mm.). Crystallization of the crude product from ether–hexane gave 54.8 g. (67% yield) of IX, m.p. 87–89°.

The **hydrochloride salt of IX** was crystallized from isopropyl alcohol–ethyl acetate, m.p. 125–126°.

4-(β-Hydroxyphenethylamino)-1,2,4-triazole (XXI).—To 10.2 g. (0.26 mole) of sodium amide in 200 ml. of liquid ammonia was added, in small portions with stirring, 20.2 g. (0.24 mole) of 4-amino-1,2,4-triazole. After the addition was complete, the mixture was stirred for 30 min. and then 29.0 g. (0.24 mole) of styrene oxide was added. As the ammonia evaporated it was replaced with ethylene glycol dimethyl ether. In about 3 hr. the reaction mixture clumped into a gummy mass that could not be stirred. The solvent was decanted, the residue was dissolved in dilute hydrochloric acid, and the solution washed with ether. The cold, aqueous acid solution was made basic with 20% sodium hydroxide and saturated with potassium carbonate. The precipitated brown solid was washed with a small amount of ice–water and crystallized from isopropyl alcohol to give 9.3 g. (19%) of colorless crystals, m.p. 137–141°.

2-(β-Hydroxyphenethylamino)-5-carbamoylpyridine (X).—A stirred mixture of 25.0 g. (0.16 mole) of 6-chloronicotinamide, 23.2 g. (0.17 mole) of β-hydroxyphenethylamine,[3] 23.5 g. (0.17 mole) of potassium carbonate, and 1 g. of copper powder was heated for 6 hr. in an oil bath at 170°. The cooled reaction mixture was dissolved in a mixture of ethanol and methanol, filtered, and the filtrate concentrated to give 22 g. of residue which was dissolved in dilute hydrochloric acid. The aqueous acid solution was washed with ether, cooled, and made basic with ammonium hydroxide to precipitate an oil that solidified on standing. The crude solid was crystallized from ethanol to yield 12.1 g. (30%) of X, m.p. 188–190°.

The **hydrochloride salt of X** was prepared in ethanol and recrystallized from ethanol and analyzed as a hemiethanolate, m.p. 90–95°.

2-(β-Hydroxyphenethylamino)-5-chloropyrimidine (XIII).—A solution of 18.0 g. (0.13 mole) of β-hydroxyphenethylamine and 20 ml. of triethylamine in 60 ml. of toluene was treated with 20.0 g. (0.13 mole) of 2,5-dichloropyrimidine, essentially as with 2-chloropyrimidine,[3] to give crude product that was crystallized from isopropyl alcohol to yield 26 g. (80%) of XIII, m.p. 123–124°.

The **hydrochloride salt** was crystallized from ethanol to give colorless crystals, m.p. 178–179°.

3-(β-Hydroxyphenethylamino)-6-chloropyridazine (XV).—A solution of 38.0 g. (0.25 mole) of 3,6-dichloropyridazine, 36 g. (0.26 mole) of β-hydroxyphenethylamine, and 27.5 g. (0.27 mole) of triethylamine in 200 ml. of ethanol was heated in an autoclave at 150° for 10 hr. The ethanol solution was concentrated *in vacuo* and the residue was triturated with water and recrystallized from isopropyl alcohol to give 23.3 g. (37%) of colorless crystals, m.p. 149–150°.

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The **hydrochloride salt** was recrystallized from ethanol, m.p. 185–186°.

3-(β-Hydroxyphenethylamino)pyridazine (XVI).—A stirred mixture of 15.0 g. (0.06 mole) of XV, 2 g. of 10% palladium-on-carbon, 25 ml. of 64% hydrazine, and 200 ml. of ethanol was boiled on the steam bath for 1.5 hr. The cooled mixture was filtered and the filtrate concentrated to a tan solid residue that was washed with water and crystallized from isopropyl alcohol–water to yield 8.8 g. (68%) of XVI, m.p. 141–142°.

The **hydrochloride salt of XVI,** crystallized from isopropyl alcohol, melted at 122–124°.

2-(β-Hydroxyphenethylamino)-3-methylpyrazine (XVII).—A mixture of 18.0 g. (0.14 mole) of 2-chloro-3-methylpyrazine, 18.0 g. (0.13 mole) of β-hydroxyphenethylamine, 23.2 g. (0.14 mole) of potassium carbonate, and 0.5 g. of copper powder was heated in an oil bath maintained at 160° for 7 hr. The mixture was triturated with benzene and the solution filtered and concentrated to a dark oil that was vacuum distilled to yield 8.3 g. (28%) of product, b.p. 195–201° (0.5 mm.).

The **hydrochloride** salt was crystallized from isopropyl alcohol–ethyl acetate to give tan crystals, m.p. 111–113°.

2-(β-Hydroxyphenethylamino)-s-triazine (XVIII).—A solution of 13.8 g. (0.05 mole) of β-hydroxyphenethylguanidine hydrobromide[3] and 4.2 g. (0.05 mole) of *s*-triazine in 25 ml. of dry ethanol was heated on the steam bath for 20 hr. The precipitated solid was collected and crystallized from methanol to give 4.3 g. (40% yield) of XVIII, m.p. 211–212°.

2-(β-Hydroxyphenethylamino)-4,6-diamino-s-triazine (XIX).—To a slurry of 72.8 g. (0.5 mole) of 2,4-diamino-6-chloro-*s*-triazine and 71.3 g. (0.52 mole) of β-hydroxyphenethylamine in 500 ml. of water was added, dropwise at steam-bath temperature, a solution of 74.4 g. (0.6 mole) of sodium carbonate monohydrate in 160 ml. of warm water. The addition required approximately 1 hr. after which the mixture was heated for an additional 3 hr. and then cooled and filtered. The water-washed precipitate was recrystallized from ethanol to yield 66.7 g. (54%) of white crystals, m.p. 176–178°.

2-(β-Hydroxyphenethylamino)-4,6-diamino-s-triazine hydrochloride, recrystallized from ethanol, showed m.p. 231–232°.

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Synthesis and Antitussive Activity of a New Heterocyclic Ring System. Some 1,2-Diazabicyclo[2.2.2]octanes

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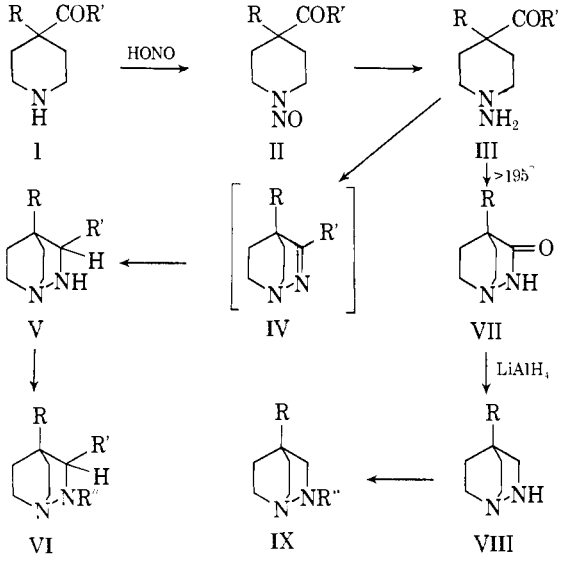
Two routes to the previously unknown 1,2-diazabicyclo[2.2.2]octane ring system have been developed. The parent heterocycle, 1,2-diazabicyclo[2.2.2]octane, as well as a number of substituted derivatives, has been synthesized. The most effective compound is similar to codeine in antitussive potency and is devoid of analgesic activity.

The use of 4-acyl-4-phenylpiperidines for the preparation of the corresponding 1-alkyl derivatives has been reported previously.[2] The same intermediates are suitable starting materials for the synthesis of the previously unknown[3] 1,2-diazabicyclo[2.2.2]octane ring system. The preparation of the parent compound, 1,2-diazabicyclo[2.2.2]octane, as well as a series of 2- and 3-substituted derivatives has now been accomplished.

SCHEME I



The 3-alkyl-4-phenyl-1,2-diazabicyclo[2.2.2]octanes (V) listed in Table II were prepared as shown in Scheme I. Addition of a slight excess of aqueous sodium nitrite to aqueous solutions of the hydrochlorides of the amino ketones (I) gave very good yields of the corresponding 1-nitrosopiperidines (II). These are listed in Table I. In all cases, the products as obtained from the reaction mixture were analytically pure and were used directly in the next step. Any attempts at recrystallization or distillation resulted in partial decomposition. Reduction of the nitroso ketones (II) with zinc dust and acetic acid at 15–20° gave basic materials which proved to be the 3-alkyl-4-phenyl-1,2-diazabicyclo[2.2.2]octanes (V). No other products could be isolated. Apparently, cyclization of the 1-amino derivatives (III) occurs to yield what are probably the cyclic hydrazones (IV). Under the conditions of the reaction, these are further reduced to the saturated heterocycle (V).

The method of synthesis, elemental analyses, and the infrared and n.m.r. spectra of representative compounds are all consistent with the bicyclic structure assigned for the products (V). The infrared spectrum of 4-phenyl-3-propyl-1,2-diazabicyclo[2.2.2]octane (V, R = C_6H_5; R′ = C_3H_7) hydrochloride, a typical compound in this series, shows a broad absorption band at 4.20–4.32 μ, which is indicative of a disubstituted >NH+ function. The carbonyl band at 5.92 μ

(1) This paper is taken in part from the thesis of Philip M. Carabateas, submitted to Rensselaer Polytechnic Institute, Troy, N. Y., in partial fulfillment of the requirements for the Ph.D. degree.

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