solved in petroleum ether (b.p. 30–60°). The petroleum ether solution was decanted from insoluble impurities, treated with decolorizing charcoal and filtered. The solvent was removed *in vacuo*, the residue treated with an excess of ethanolic hydrogen chloride and the mixture evaporated to dryness *in vacuo* on the steam bath. The residue was pulverized and dried *in vacuo* at 45° for 18 hr.; yield, 13 g. (46%), m.p. indefinite, foaming at 100°.

Anal. Calcd. for $C_{44}H_{76}N_6O_2 \cdot 6HCl$: C, 56.22; H, 8.79. Found: C, 56.64; H, 8.65.

6,6′-Diallyl-α,α′-bis[bis(3-diethylaminopropyl)amino]-4,4′-bi-*o*-cresol Hexahydrochloride (Vb).—A mixture of 15.3 g. (0.063 mole) of 3,3′-bis(diethylamino)dipropylamine and 1.9 g. (0.063 mole) of paraformaldehyde in 100 ml. of 95% ethanol was warmed until a clear solution was obtained. The cooled solution was subsequently added to a solution of 8.0 g. (0.03 mole) of 2,2′-diallyl-*p,p*′-biphenol in 100 ml. of 95% ethanol, and the mixture boiled under reflux on the steam bath for 2 hr. The ethanol was allowed to evaporate, the residue was dissolved in ether, and the ether extracts were washed several times with 10% sodium hydroxide solution and water. The ether solution was then extracted thoroughly with *N* acetic acid solution, the acetic acid extracts were made strongly alkaline by the addition of sodium hydroxide, and the base was extracted with ether. The ether solution was treated with excess concd. hydrochloric acid, allowed to stand for several hr., made strongly alkaline with ammonium hydroxide and the base again extracted with ether. The ether extracts were washed with water, treated with decolorizing charcoal, and dried over anhydrous potassium carbonate. The drying agent was collected by filtration, and the ether filtrate treated with anhydrous hydrogen chloride. The sticky mass which separated was dissolved in methanol, treated with ethanolic hydrogen chloride, and the solvent removed *in vacuo* at room temperature. The hygroscopic white powder thus obtained weighed 19.5 g. (64%), m.p. 110°.

Anal. Calcd. for $C_{48}H_{84}N_6O_2 \cdot 6HCl \cdot H_2O$: C, 56.85; H, 9.14; N, 8.28. Found: C, 57.02; H, 8.95; N, 8.15.

Preparation of Amidines by Catalytic Reduction of Amidoximes

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Received January 9, 1962

Recently[1] several large-membered heterocyclic compounds possessing side chains with terminal amidoxime or guanidine groups were prepared and found to manifest antihypertensive activity. Similar compounds with respect to the heterocyclic moiety of the molecule, but with an amidine instead of the amidoxime or guanidine group are

(1) R. P. Mull, P. Schmidt, M. R. Dapero, J. Higgins, and M. J. Weisbach, *J. Am. Chem. Soc.*, **80**, 3769 (1958); R. P. Mull, M. E. Egbert, and M. R. Dapero, *J. Org. Chem.*, **25**, 1953 (1960).

not known in the literature; we were prompted therefore to undertake the preparation of these new compounds.

Since the amidoximes previously described were obtained readily as stable crystalline compounds, their conversion to amidines by catalytic reduction seemed preferable to the less satisfactory but more commonly employed method of Pinner.[2] References to the former method[3] are few and pertain exclusively to the reduction of aromatic amidoximes at elevated temperature and pressure in the presence of a Raney nickel catalyst. A variety of amidoximes were employed in the present study and thus served to establish the general applicability of the method. The reduction was found to occur under relatively mild conditions when rhodium-on-alumina was used as the catalyst; although somewhat slower acting, palladium-on-charcoal also was found to be satisfactory. The hydrobromide salts of the amidines were found to be particularly advantageous for isolation and purification purposes. Under the experimental conditions employed, *o*-chlorophenylacetamidoxime was dehalogenated to give phenylacetamidine.

Pharmacological evaluation of these compounds revealed that some of the large-membered heterocyclic compounds had activities which were the same as those exhibited by the amidoxime[4] and guanidine[5] compounds. The compounds were most easily tested by administering 15 to 30 mg./kg. of each intravenously to dogs. Active compounds produced the following effects which were graded for their intensity: (1) relaxation of the nictitating membranes, (2) bradycardia, (3) blockade of carotid occlusion reflex pressor responses and (4) suppression of the pressor response to intravenously administered amphetamine. The hexahydro-1-azepinyl and octahydro-1-azocinyl-propionamidines were most potent.

Experimental[6]

Amidoximes.—The general method employed for the preparation of the amidoxime hydrochlorides has been described.[1] These salts were converted to crystalline bases by treatment with alkali, extraction with chloroform and concentration

(2) A. Pinner, "Die Imidoäther und ihre Derivate," Robert Oppenheim (Gustav Schmidt), Berlin, Germany, 1892.

(3) H. J. Barber and A. D. H. Self, U. S. Patent 2,375,611 (1945); H. C. Carrington, *J. Chem. Soc.*, 2527 (1955).

(4) R. A. Maxwell, S. D. Ross, and A. J. Plummer, *J. Pharmacol. Exptl. Therap.*, **123**, 128 (1958).

(5) R. A. Maxwell, A. J. Plummer, F. Schneider, H. Povalski, and A. 1. Daniels, *ibid.*, **128**, 22 (1960).

(6) We are indebted to Mr. Louis Dorfman and his associates for the microanalyses; all melting points are uncorrected.

TABLE I

PHYSICAL PROPERTIES OF THE AMIDINES R—$(CH_2)_n$—C(=NH)—NH_2

R	n	M.p., °C.[a]	Formula[c]	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Phenyl	1	119–120[b]	$C_8H_{11}BrN_2$[d]	44.69	5.15	13.03	45.02	5.22	13.29
Cyclopropyl	0	142–145	$C_4H_9BrN_2$	29.12	5.50	16.98	28.93	5.59	17.03
1-Piperidyl	2	169–170	$C_8H_{19}Br_2N_3$	30.31	6.04	13.26	30.22	5.92	13.14
Hexahydro-1-azepinyl	1	186–188	$C_8H_{19}Br_2N_3$	30.31	6.04	13.26	30.86	6.13	12.81
Hexahydro-1-azepinyl	2	164–166	$C_9H_{21}Br_2N_3$[e]	32.66	6.40	12.70	32.63	6.17	12.52
Hexahydro-1-azepinyl	3	142–144	$C_{10}H_{23}Br_2N_3$	34.81	6.72	12.18	34.84	6.92	12.04
Octahydro-1-azocinyl	2	176–178	$C_{10}H_{23}Br_2N_3$	34.81	6.72	12.18	34.57	6.71	11.80
4-Methylpiperazinyl	2	183–184	$C_8H_{20}Br_2N_4$[f]	28.94	6.07		29.12	6.05	

[a] The recrystallizations were from ethanol–hexane.

[b] P. E. Fanta and A. A. Hedman, *J. Am. Chem. Soc.*, **78,** 1434 (1956), reported m.p. 151–153° for the hydrochloride.

[c] Melting point and analyses are of mono- or dihydrobromides.

[d] Bromine: calcd. 37.17; found 36.87.

[e] Bromine: calcd. 48.29; found 48.22.

[f] Bromine: calcd. 48.14; found 48.07.

in vacuo. The free bases were employed for the reduction to amidines after recrystallization from xylene or toluene.

Amidines.—In a typical experiment 18.5 g. (0.1 mole) of hexahydro-1-azepinylpropionamidoxime was dissolved in 100 ml. of anhydrous ethanol, charged with 5 g. of 5% rhodium-on-alumina catalyst and shaken in a Parr hydrogenator under about 3.1 kg./cm.^{2} of hydrogen pressure until the theoretical amount of hydrogen was absorbed. Filtration directly into cold ethanol previously saturated with hydrogen bromide gave the crystalline hexahydro-1-azepinylpropionamidine dihydrobromide. Recrystallization from ethanol–hexane gave 13.2 g. (40%) of product, m. p. 164–166°. The other amidines listed in Table I were likewise obtained in yields of 40–45%.

COMMUNICATIONS TO THE EDITOR

Non-classical Antimetabolites. VII.[1,2] The Bridge Principle of Specificity with Exo-alkylating Irreversible Inhibitors

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Received February 5, 1962

Recently, we presented[3] strong experimental evidence to support the concept[4] of a new class of irreversible inhibitors that operate by exo-alkylation. A properly designed compound, such as I, can complex reversibly with an enzyme, then become irreversibly bound within the complex adjacent to the active site. In the detailed version of this experimental evidence,[2] the bridge hypothesis of specificity was proposed. Compared to a reversible inhibitor, the exo-alkylating type of irreversible inhibitor can have an extra dimension of specificity; this extra specificity is dependent upon the ability of the reversibly-bound inhibitor to bridge to and alkylate a nucleophilic group on the enzyme surface and upon the nucleophilicity of the enzymic group being alkylated.

This paper presents experimental evidence for the bridge hypothesis of specificity that warrants raising its status from hypothesis to principle.

It is not surprising that enzymes performing similar reactions—such as dehydrogenation of anionic substrates—would be reversibly

(1) This work was generously supported by Grant CY-5869 of the National Cancer Institute. U. S. Public Health Service.

(2) B. R. Baker, W. W. Lee and E. Tong, Paper VI of this series in press, *J. Theor. Biol.*

(3) B. R. Baker, W. W. Lee, E. Tong, and L. O. Ross, *J. Am. Chem. Soc.*, **83**, 3713 (1961).

(4) B. R. Baker, Cancer Chemotherapy Reports, No. 4, 1 (1959), published by the National Cancer Institute, Paper I of this series.