Anal. Calcd for $C_{21}H_{39}NO$: C, 78.44; H, 12.23; N, 4.36. Found: C, 77.88; H, 12.15; N, 4.35.

Reduction product a was converted into a maleate salt (**13**) and addition product b was converted into a monocitrate salt (**10**). Analyses of both salts are recorded in Table I.

The above synthesis generalizes the concomitant formation of addition and reduction products when the Grignard reagent contains a β-hydrogen atom. This applies to compounds **9**–**14** in Table I.

5-Phenyl-2,2-dimethyl-1-dimethylamino-5-pentanone (15).—Phenylmagnesium bromide (0.05 mole) was prepared by treating 1.28 g of magnesium with 8.24 g of bromobenzene in 25 ml of anhydrous ether. Ethyl 4,4-dimethyl-5-dimethylaminovalerate[4] (3 g, 0.015 mole) in 15 ml of ether was added dropwise to the phenyl Grignard reagent. The mixture was then refluxed for 4 hr, cooled, poured into NH_4Cl solution (large excess), and extracted with ether. HCl was used to extract this ether layer. The combined aqueous–acidic solution was made basic and extracted with ether. The ethereal solution was dried (Na_2SO_4) and filtered, and the ether was evaporated. A preliminary distillation indicated the presence of a small amount of starting ester in the ketone fractions. The mixture was hydrolyzed with acid, made alkaline, then extracted with ether (1-g recovery). The residue was distilled at 107–108° (0.05 mm); yield 0.5 g; ν_{max}^{smear} 3060 w, 2820 m, 2775 m, 1689 s, 1600 m, 1387 w, 1365 m, 1045 s, 847 m, 743 m, 695 s cm^{-1}.

1,5-Diphenyl-2,2-dimethyl-1-dimethylaminopentane Hydrochloride (16).—A mixture of 8.6 g of 1, 8.6 g of KOH pellets, and 20 ml of 85% hydrazine hydrate in 80 ml of diethylene glycol was refluxed for 30 min (Dean–Stark trap), while 2 ml of water was collected and removed.[12] The mixture was cooled, and an additional 50 ml each of hydrazine hydrate and diethylene glycol were added. After an additional 2-hr reflux, 50 ml of distillate was removed. The mixture was refluxed 2 hr more, and another 20 ml of distillate was removed. The reaction mixture, a homogeneous solution at this point, was cooled and poured into water. The mixture was extracted with ether, and the ether layer was extracted with 2 *N* HCl. The acid extract was made basic with solid $NaHCO_3$ and brought to pH 10 with 5 *N* NaOH. The mixture was extracted with ether, dried (Na_2SO_4), and filtered, and the ether was evaporated *in vacuo*. The residue of 6.8 g was distilled to give 6 g of 1,5-diphenyl-2,2-dimethyl-1-dimethylaminopentane: bp 153–154° (0.3 mm); ν_{max}^{smear} 3084 m, 3060 m, 3021 s, 2820 s, 2780 s, 1605 s, 1583 s, 1495 s, 1385 w, 1364 w, 1018 s, 752 s, 702 s cm^{-1}. The amine was converted into its HCl salt (**16**), mp 118–119°. This procedure serves as a model for preparation of **17**.

1,5,5-Triphenyl-2,2-dimethyl-1-dimethylamino-5-pentanol (18).—A number of attempts were made to prepare **18** by treatment of 1 with phenylmagnesium bromide both in ether and tetrahydrofuran. There were never any OH-stretching bands observed in the infrared spectra, and only starting material (1) could be recovered. Phenyllithium (0.22 mole) was prepared from 0.44 g-atom of lithium and 0.22 mole of bromobenzene in 200 ml of ether. A solution of 62.0 g (0.2 mole) of 1 in 170 ml of anhydrous ether was added dropwise over 45 min to the organolithium reagent. Anhydrous benzene (370 ml) was added to the mixture, and ether was allowed to evaporate through the condenser upon heating. The mixture was refluxed for 8 hr after removing the ether and poured onto ice and 40 ml of concentrated HCl. A tan precipitate appeared (hydrochloride salt, only slightly water soluble). This salt (83.5 g) was dissolved in 700 ml of boiling water and the cooled solution was adjusted to pH 10 with 5 *N* NaOH. This resulted in the separation of a viscous oil which was extracted with ether and dried (Na_2SO_4). After evaporation of the ether the glassy mass was distilled, bp 231° (0.5 mm), to give 51 g (66%) of the alcohol (**18**); $\nu_{max}^{CCl_4}$ 3600 w (sharp), 3080 m, 3060 m, 3020 m, 2820 m, 2780 m, 1600 m, 1582 w, 1505 w, 1390 m, 1365 m, 705 s cm^{-1}.

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(12) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

Substituted 2,3-Dihydro-1,5-benzothiazepin-4(5H)-one and Related Compounds. II. A New Class of Antidepressants[1]

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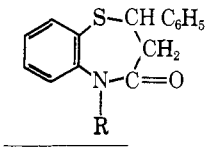
The syntheses of 2-aryl-2,3-dihydro-1,5-benzothiazepin-4(5H)-ones, 2,3,4,5-tetrahydro-2-phenyl-1,5-benzothiazepine, 2-phenyl-1,5-benzothiazepin-4(5H)-one, 2,3-dihydro-2-phenyl-1,5-benzoxazepin-4(5H)-one, 1,3,4,5-tetrahydro-4-phenyl-2H-1-benzazepin-2-one, and 4-phenyl-1H-1,4-benzodiazepine-2,5(3H,4H)-dione and their alkylation with basically substituted alkyl halides are described. Of the thirty-three basically substituted derivatives reported, four were found to be effective in calming rats with lesions in the septal area of the brain.

We have recently reported[2] the preparation of a number of substituted 2,3-dihydro-1,5-benzothiazepin-4(5H)-ones. Three of these compounds, Ia,[3] b, and c, were active in calming rats with lesions in the septal area of the brain. These compounds were unique in that they caused no ataxia at their effective dose; in contrast, the effective dose of chlordiazepoxide is accompanied by considerable ataxia.[4] Although Ib was about twice as active as Ia and Ic in the septal rat by the intraperitoneal route, Ia was selected for further study because of its more predictable adsorption by the oral route. Subsequent studies in the cat showed that Ia depressed only the amygdala of the cat's brain, whereas chlordiazepoxide depressed the amygdala, hippocampus, and septal areas.[4] In the initial clinical study, Ia caused moderate to marked



HCl

Ia, R = $(CH_2)_2N(CH_3)_2$[3]
b, R = $(CH_2)_2N(C_2H_5)_2$
c, R = $(CH_2)_3N(CH_3)_2$

(1) Presented in part before the Division of Medicinal Chemistry, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964.

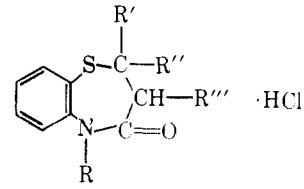
(2) J. Krapcho, E. R. Spitzmiller, and C. F. Turk, *J. Med. Chem.*, **6**, 544 (1963).

(3) Thiazesim is the approved generic name for 5-(2-dimethylaminoethyl)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one.

(4) Z. P. Horovitz, A. R. Furgiuele, L. J. Brannick, J. C. Burke, and B. N. Craver, *Nature*, **200**, 369 (1963).

TABLE I

BASICALLY 5-SUBSTITUTED ALKYL-2-ARYL-2,3-DIHYDRO-1,5-BENZOTHIAZEPIN-4(5H)-ONES AND RELATED COMPOUNDS

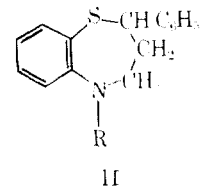


No.		R	R′	R″	R‴	Mp, °C[a]	Yield, %[b]	Formula	Chlorine, % Calcd	Chlorine, % Found	Nitrogen, % Calcd	Nitrogen, % Found
1[c]		$(CH_3)_2NHCH_3$	H	C_6H_5	H	193-195	57	$C_{18}H_{21}BrN_2OS$	20.31	20.14[d]	7.12	7.30
2		$(CH_2)_2N(CH_3)C_2H_5$	H	C_6H_5	H	191-193	65	$C_{20}H_{25}ClN_2OS$	9.41	9.42	7.43	7.36
3[e]		$CH(CH_3)CH_2N(CH_3)_2$	H	C_6H_5	H	176-178	5	$C_{20}H_{25}ClN_2OS$	9.41	9.23	7.43	7.55
4[e]		$CH_2CH(CH_3)N(CH_3)_2$	H	C_6H_5	H	239-241	7	$C_{20}H_{25}ClN_2OS$	9.41	9.56	7.43	7.14
5		$(CH_2)_2NC_5H_{10}$[f]	H	C_6H_5	H	198-200	17	$C_{22}H_{27}ClN_2OS$	8.80	8.98	6.95	7.02
6[g]		$(CH_2)_2NC_4H_8O$[f]	H	C_6H_5	H	225-227	5	$C_{21}H_{25}ClN_2O_2S$	8.76	8.74	6.92	6.99
7		$(CH_2)_2N_2C_5H_{10}$	H	C_6H_5	H	245-247	47	$C_{23}H_{29}Cl_2N_3OS$[h]	15.60	15.44	9.25	8.90
8		$(CH_2)_3N_2C_5H_{10}$[f]	H	C_6H_5	H	234-236	52	$C_{23}H_{31}Cl_2N_3OS$[h]	15.14	15.04	8.97	8.93
9		$(CH_2)_3N(C_2H_5)_2$	H	C_6H_5	H	163-165	49	$C_{22}H_{29}ClN_2OS$	8.75	8.62	6.92	7.04
10		$CH_2CH(CH_3)CH_2N(CH_3)_2$	H	C_6H_5	H	183-185	29	$C_{21}H_{27}ClN_2OS$	9.07	8.87	7.17	7.36
11		$(CH_2)_2N(CH_3)_2$	CH_3	C_6H_5	H	182-184	32	$C_{20}H_{25}ClN_2OS$	9.41	9.28	7.43	7.25
12		$(CH_2)_2N(CH_3)_2$	H	C_6H_5	C_6H_5	269-271	35	$C_{25}H_{27}ClN_2OS \cdot 0.5H_2O$[i]	7.91	8.19	6.25	6.02
13		$(CH_2)_2N(CH_3)_2$	H	2-Pyridyl	H	184-186	32	$C_{18}H_{22}ClN_3OS$	9.74	9.63	11.55	11.65
14		$(CH_2)_2N(CH_3)_2$	H	3-Pyridyl	H	194-196	13	$C_{18}H_{22}ClN_3OS$	9.74	9.99	11.55	11.55
15		$(CH_2)_2N(CH_3)_2$	H	4-Pyridyl	H	195-197	30	$C_{18}H_{22}ClN_3OS$	9.71	9.60	11.55	11.56
16		$(CH_2)_4N(CH_3)_2$	H	4-Pyridyl	H	160-162	26	$C_{19}H_{24}ClN_3OS$	9.38	9.43	11.12	11.25
17		$(CH_2)_2N(CH_3)_2$	H	2-Thienyl	H	201-203	36	$C_{17}H_{21}ClN_2OS_2$	9.61	9.80	7.59	7.48
	Class											
18[j]	II	$(CH_2)_2N(CH_3)_2$				217-219	28	$C_{19}H_{26}ClN_2S$	10.16	10.20	8.03	7.99
19[k]	II	$(CH_2)_3N(CH_3)_2$				155-157	33	$C_{20}H_{27}ClN_2S$	9.76	10.10	7.71	7.68
20	III	$CH_2N(CH_3)_2$				240-242	24	$C_{19}H_{23}ClN_2OS$	9.77	9.43	7.72	7.99
21	III	$CH_2N(C_2H_5)_2$				215-217	53	$C_{21}H_{27}ClN_2OS$	9.07	9.04	7.17	7.33
22	III	$(CH_2)_2N(CH_3)_2$				187-189	60	$C_{20}H_{25}ClN_2OS$	9.41	9.59	7.43	7.42
23	IV	$(CH_2)_2N(CH_3)_2$				224-226	69	$C_{19}H_{21}ClN_2OS$	9.82	9.68	7.76	7.77
24	IV	$(CH_2)_3N(CH_3)_2$				165-167	72	$C_{20}H_{23}ClN_2OS$	9.47	9.66	7.64	7.48
25	IV	$(CH_2)_3N_2C_5H_{10}$[f]				245-247	81	$C_{23}H_{29}Cl_2N_3OS$[h]	15.20	15.06	9.01	8.97
26	V	$(CH_2)_2N(CH_3)_2$				186-188	30	$C_{19}H_{23}ClN_2O_2$	10.22	10.15	8.08	8.20
27	V	$(CH_2)_3N(CH_3)_2$				206-208	52	$C_{20}H_{25}ClN_2O_2$	9.83	9.82	7.77	7.96
28	V	$(CH_2)_3N_2C_5H_{10}$[f]				238-240	39	$C_{23}H_{31}Cl_2N_3O_2$[h]	15.67	15.74	9.29	9.13
29	VI	$(CH_2)_2N(CH_3)_2$				227-229	54	$C_{20}H_{25}ClN_2O$	10.28	10.26	8.12	7.94
30	VI	$(CH_2)_3N(CH_3)_2$				197-199	51	$C_{21}H_{27}ClN_2O$	9.88	9.92	7.81	7.59
31[l]	VII	$(CH_2)_2N(CH_3)_2$				191-193	10	$C_{19}H_{23}ClN_2O$	10.31	10.38	12.22	12.22
32	VIII	$(CH_2)_2N(CH_3)_2$				207-208	43	$C_{19}H_{22}ClN_3O_2$	9.85	9.85	11.68	11.68
33	VIII	$(CH_2)_3N(CH_3)_2$				209-211	48	$C_{20}H_{24}ClN_3O_2$	9.48	9.64	11.24	11.29

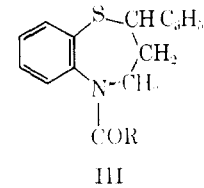
[a] These salts were crystallized from acetonitrile except **1**, **3–8**, **14**, **29**, and **30** (isopropyl alcohol); **11** (ethyl acetate); **19** (benzene); **21** ($CHCl_3$–ether); **25** (EtOH); **32** (MeOH); and **33** (isopropyl alcohol–ether). Several of these compounds were purified prior to conversion to the hydrochlorides by crystallization of the bases, usually from hexane: **3**, mp 106–108°; **8**, 91–93°; **10**, 123–125°; **12**, 152–154°; **17**, 104–106°; **20**, 103–105°; **21**, 105–106°; **28**, 92–94°; and **32**, 151–153° (from toluene). [b] These yields are the result of a single experiment. [c] The alkylations were usually carried out in toluene using sodamide and the basically substituted alkyl bromides (**2–4** and **7–17** at room temperature for 20 hr; **25** at 60–65° for 3 hr; and **28–30** at 110° for 5 hr) or the corresponding chlorides (**5**, **23**, and **24** at 60–70° for 4 hr; **26** and **27** at 80–85° for 6 hr; **19**, **31**, and **32** at 110° for 2 hr; and **33** at 110° for 5 hr). In the case of **12–16**, the sodium salts were prepared from NaH in dimethylformamide. [d] Obtained by treatment of I, where R = 2-(N-benzyl-N-methylamino)ethyl[2] with ethyl chloroformate in benzene, followed by hydrolysis of the intermediate 2-(N-carbethoxy-N-methylamino)-ethyl derivative (mp 97–98°, from cyclohexane) with 32% HBr in acetic acid at room temperature. Prepared by E. R. Spitzmiller. [e] Bromide analysis. [f] **3** and **4** were obtained from the same reaction mixture and were separated as oxalic acid salts. This salt of **3** (mp 185–187°) was purified by crystallization from EtOH, converted to the base (mp 106–108° from hexane) and then to the hydrochloride. Concentration of the above ethanol mother liquor gave the oxalate salt of **4** and the latter was then converted to the hydrochloride. Structural assignment to these isomers was based on the nmr spectra. [g] NC_5H_{10} = piperidino, NC_4H_8O = morpholino, and $N_2C_5H_{10}$ = 4-methylpiperazino. [h] The alkylating agent in this experiment was N-(2-iodoethyl)morpholine. The major product of the reaction (67% yield) was **2′-(2-morpholinoethylthio)cinnamanilide hydrochloride**), mp 194–196° (from acetonitrile). *Anal.* Calcd for $C_{21}H_{25}ClN_2O_2S$: Cl, 8.76; N, 6.92. Found: Cl, 8.86; N, 6.96. [i] Dihydrochloride salt. [j] *Anal.* Calcd: C, 67.02; H, 6.30. Found: C, 67.39; H, 6.09. [k] Prepared by addition of an ethereal solution of the free base of Ia to a suspension of $LiAlH_4$ in ether; bp 188–190° (0.4 mm). [l] Free base purified by distillation; bp 180–183° (0.1 mm). Compound was prepared by E. R. Spitzmiller. [m] The precursor (VII, R = H) of this material was obtained from the reaction of *o*-phenylenediamine with ethyl benzoylacetate according to the procedure of N. Reid and P. Stahlhofen, *Ber.*, **90**, 831 (1957). This intermediate and **31** were prepared by J. Williams.

mood elevation in severely depressed patients within 1 hr after administration of a 75–300-mg dose by the oral route.[5] This compound is under extensive clinical investigation.

In order to establish a structure–activity relationship in this class of compounds, the structures shown below were prepared by a variety of synthetic approaches and the specific compounds are tabulated in Table I. Products of type I represent further modification of the substituent in the 5 position and in some cases the 2 or 3 position. Compounds of type II contain a methylene group in place of the carbonyl group of I; III differs from I in that the carbonyl linkage is exo-



II

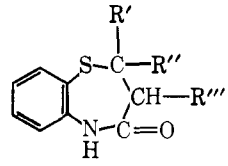


III

(5) Y. I. J. Mapp, R. Dykyj, C. K. Gorby, and J. H. Nodine, *Pharmacologist*, **5**, 234 (1963).

TABLE II

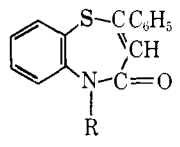
2-ARYL-2,3-DIHYDRO-1,5-BENZOTHIAZEPIN-4(5H)-ONES



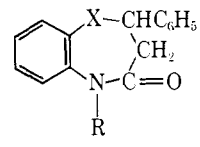
No.	R′	R″	R‴	Mp, °C[a]	Yield, %[b]	Formula	Nitrogen, % Caled	Nitrogen, % Found	Sulfur, % Caled	Sulfur, % Found
A	CH_3	C_6H_5	H	149–151	43	$C_{16}H_{15}NOS$	5.20	5.08	11.90	11.85
B	H	C_6H_5	C_6H_5	285–287	35	$C_{21}H_{17}NOS$	4.23	4.45	9.67	9.41
C	H	2-Pyridyl	H	161–163	53	$C_{14}H_{12}N_2OS$	10.93	10.85	12.51	12.55
D	H	3-Pyridyl	H	152–154	44	$C_{14}H_{12}N_2OS$	10.93	11.17	12.51	12.64
E	H	4-Pyridyl	H	202–204	56	$C_{14}H_{12}N_2OS$	10.93	10.77	12.51	12.51
F	H	2-Thienyl	H	166–168	24	$C_{13}H_{11}NOS_2$	5.36	5.58	24.53	24.37

[a] Recrystallized from acetonitrile except B (dimethylformamide–acetonitrile) and E (methanol). [b] These yields are the result of single experiments in which 2-aminobenzenethiol and the appropriate acrylic acid were heated in an oil bath at 180–200° (A and B for 90 min; C, D, and F for 45 min) or at 250–260° (E for 45 min). In the preparation of A, a small quantity of dimethylformamide was added to the reaction mixture.

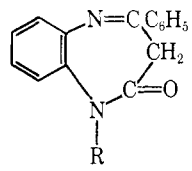
cyclic. Type IV contains a double bond at the 2–3 position; V–VII represent the oxa, methylene, and aza analogs of I; and VIII represents a related heterocyclic system.



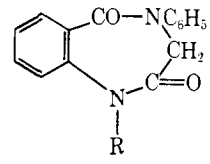
IV



V, X = O
VI, X = CH_2



VII



VIII

Most of the compounds of Table I were obtained by treatment of the intermediates of I–VIII (R = H) with sodamide and the appropriate basically substituted alkyl halide. The precursors (R = H) for the compounds were obtained in the following manner: I, by reaction of 2-aminobenzenethiol with the appropriate acrylic acid (several new analogs of I are listed in Table II); II, by reduction of I with lithium aluminum hydride; IV, by reaction of 2-aminobenzenethiol with phenylpropiolic acid; V and VI, by treatment of flavanone and 3-phenyl-1-tetralone with hydrazoic acid; VII, by reaction of *o*-phenylenediamine with ethyl benzoylacetate; and VIII, by thermal cyclization of the ethyl ester of *o*-amino-N-phenylhippuric acid or by reductive cyclization of *o*-nitro-N-phenylhippuric acid. The products of III were prepared by treatment of II (R = H) with the corresponding chloro-substituted acid chlorides, followed by reaction of the intermediate chloro compound with a dialkylamine.

In our previous publication,[2] we reported the susceptibility of I (R = H) to ring cleavage by sodamide during the course of alkylation with basically substituted alkyl chlorides at elevated temperatures. By utilizing the corresponding bromides and allowing the reaction to proceed at room temperature overnight, improved yields of product were obtained. The treatment of I (R = H) with 2-dimethylaminoethyl bromide resulted in an 80% yield of Ia. In our previous preparation of this compound using the corresponding chloride a 33% yield of Ia was obtained. Compound Ia, labeled with C^{14}, was prepared by alkylation with 2-dimethylaminoethyl-1,2-C^{14} bromide. Metabolic studies on this material are now in progress and will be reported elsewhere. The syntheses of several new basically substituted alkyl bromides and the preparation of compounds of Table I are outlined in the Experimental Section.

All of the compounds of Table I were evaluated for their ability to calm rats with lesions in the septal area of the brain. The most active materials, 8, **23**, **27**, and **30**, had essentially the same potency as Ia in this test procedure. One of these compounds, 8, was also tested for specific actions on the limbic system of the cat; it showed an amygdaloid suppressant action equal to Ia and also increased the duration of the after-discharge evoked from the hippocampus,[6] an activity not shown by Ia. Further studies on 8 and Ia demonstrated that these compounds did not inhibit monoamine oxidase (MAO) and had little antireserpine activity[6] indicating that the mechanism of antidepressant action of Ia differs from that of tranylcypromine and imipramine.

Experimental Section

Melting points are corrected. Infrared spectra were recorded on a Perkin–Elmer Model 21 spectrometer.

5-(2-Dimethylaminoethyl)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one Hydrochloride (1).—A suspension of 78.0 g (2.0 moles) of sodamide in 5 l. of toluene was cooled to 20° and treated with 510 g (2.0 moles) of 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one.[2] The temperature of the mixture rose to 30° during a period of 5 min to give a solution. The latter was cooled to 20° and treated with a cold solution of 2.3 moles of 2-dimethylaminoethyl bromide in 1.5 l. of toluene [prepared by treatment of a slurry of 700 g (3.0 moles) of the hydrobromide salt in 200 ml of water with a cooled suspension of 420 g of K_2CO_3 in 400 ml of water, extraction by three portions of toluene, and drying the combined toluene extracts ($MgSO_4$)]. A precipi-

(6) Z. P. Horovitz, A. R. Furgiuele, E. Uczen, and P. W. Ragozzino, *Federation Proc.*, **24**, 134 (1965).

tate began to separate from the mixture in about 30 min. After stirring for 20 hr at room temperature, the resulting heavy slurry was treated with 1.4 l. of cold water. The organic phase was washed with 600 ml of water and then added to 2.0 l. of 1.5 *N* HCl. The aqueous phase was cooled and treated with 600 ml of 7.5 *N* NaOH solution, and the mixture was extracted three times with 1-l. portions of ether. After drying ($MgSO_4$), the ether was evaporated to give 623 g of residue. This material was dissolved in 2 l. of ether and filtered from the insoluble material, and the solvent was evaporated to yield 573 g (89%) of the free base. A solution of this material in 1 l. of ethanol was treated with an equivalent quantity of HCl in 400 ml of ethanol to give a solution from which the hydrochloride salt rapidly crystallized. Dilution of the mixture with 1.2 l. of ether gave 623 g (86%) of colorless solid, mp 224–226°. After crystallization from 3.2 l. of ethanol, the material weighed 583 g (80%), mp 225–227°. Material prepared from 2-dimethylaminoethyl chloride and crystallized from acetonitrile melted at 222–224°.[2]

The free base was crystallized from hexane; mp 78–80°.

Preparation of Basically Substituted Alkyl Bromide Hydrobromides.—The reaction of 48% HBr with the appropriate basically substituted alkanol according to the general procedure[7] gave the following new compounds in 80–87% yield.

2-(Ethylmethylamino)ethyl bromide hydrobromide, mp 171–173° (from butanone). *Anal.* Calcd for $C_5H_{12}BrN \cdot HBr$: Br, 64.71; N, 5.67. Found: Br, 64.83; N, 5.57.

1-(2-Bromoethyl)-4-methylpiperazine dihydrobromide, mp 310–312° (methanol). *Anal.* Calcd for $C_7H_{15}BrN_2 \cdot 2HBr$: Br, 64.98; N, 7.59. Found: Br, 64.08; N, 8.16. Analysis indicated contamination by a small quantity of the hydrobromide salt of the starting alcohol.

1-(3-Bromopropyl)-4-methylpiperazine dihydrobromide, mp 258–260° (methanol). *Anal.* Calcd for $C_8H_{17}BrN_2 \cdot 2HBr$: Br, 62.60; N, 7.32. Found: Br, 62.80; N, 7.53.

3-Dimethylaminopropyl bromide hydrobromide, mp 107–109° (methanol). *Anal.* Calcd for $C_5H_{12}BrN \cdot HBr$: Br, 64.71; N, 5.67. Found: Br, 64.86; N, 5.84.

3-Dimethylamino-2-methylpropyl bromide hydrobromide, mp 152–154° (ethanol). *Anal.* Calcd for $C_6H_{14}BrN \cdot HBr$: Br, 61.24; N, 5.37. Found: Br, 61.26; N, 5.54. The preparation of the hydrobromide salts of 2-dimethylaminoethyl bromide,[7] 3-diethylaminopropyl bromide,[8] and 2-bromo-N,N-dimethylpropylamine[9] has been reported.

2,3,4,5-Tetrahydro-2-phenyl-1,5-benzothiazepine (II, R = H).—To a stirred mixture of 24.0 g (0.63 mole) of $LiAlH_4$ in 1 l. of dry tetrahydrofuran was added 140 g (0.55 mole) of the amide (I, R = H).[2] After stirring for 2 hr at room temperature, the mixture was refluxed for 3 hr, cooled, and treated dropwise with 30 ml of water, followed by 100 ml of 16% NaOH solution. The slurry was filtered and the inorganic salts were washed with ether. After the filtrate was dried ($MgSO_4$), the solvent was evaporated and the residue was fractionated to give 118.5 g (90%) of a pale yellow product, bp 179–181° (0.2 mm). The distillate slowly solidified, mp 62–64°. Crystallization from diisopropyl ether gave a colorless product, mp 65–67°, λ_{max}^{Nujol} 2.95 μ.

Anal. Calcd for $C_{15}H_{15}NS$: N, 5.80. Found: N, 5.99.

By addition of a benzene solution of this material, containing an equivalent quantity of triethylamine, to a solution of the appropriate chloroacetyl or 2-chloropropionyl chloride in benzene there was obtained **III (R = CH_2Cl)** in 46% yield from benzene, mp 151–153°, λ_{max}^{Nujol} 6.0 μ (*Anal.* Calcd for $C_{17}H_{16}ClNOS$: Cl, 11.16; N, 4.41. Found: Cl, 11.28; N, 4.31.); and **III (R = CH_2CH_2Cl)** in 75% yield from acetonitrile, mp 103–105°, λ_{max}^{Nujol} 6.05 μ (*Anal.* Calcd for $C_{18}H_{18}ClNOS$: Cl, 10.68; N, 4.22; S, 9.66. Found: Cl, 9.31; N, 4.16; S, 9.94.).

2-Phenyl-1,5-benzothiazepin-4(5H)-one (IV, R = H).—A mixture of 79.0 g (0.54 mole) of phenylpropiolic acid and 68.0 g (0.54 mole) of 2-aminobenzenethiol was cooled to control the initial exothermic reaction and then heated at 160–180° for 1 hr. After cooling to 100°, the semisolid mass was added to 250 ml of hot acetonitrile and then cooled to give 40.0 g (29%) of pale yellow product, mp 216–219°. The analytical sample was recrystallized from dimethylformamide; mp 220–222°; λ_{max}^{Nujol} 3.18, 6.00, 6.31 μ.

Anal. Calcd for $C_{15}H_{11}NOS$: N, 5.53; S, 12.66. Found: N, 5.58; S, 12.41.

2,3-Dihydro-2-phenyl-1,5-benzoxazepin-4(5H)-one (V, R = H).—A suspension of 10.0 g. (0.045 mole) of flavanone[10] and 4.0 g (0.062 mole) of NaN_3 in 33 ml of glacial acetic acid was stirred, cooled in an ice bath, and treated with 6.6 ml of concentrated H_2SO_4. Effervescence occurred and the temperature rose to about 45°. After the exothermic reaction subsided, the mixture was maintained at 45–50° for 45 min, cooled, and poured onto 350 ml of cold 10% Na_2CO_3. The oily product was extracted into ether. Evaporation of the ether solution (dried, $MgSO_4$) gave 11.6 g of residue. The latter was dissolved in 500 ml of hot hexane and cooled to give 4.8 g of product, mp 122–124°. After recrystallization from 25 ml of acetonitrile, the colorless product weighed 4.1 g (38%); mp 123–125°; λ_{max}^{Nujol} 3.15, 3.27, 6.03 μ.[11]

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.17; H, 5.48; N, 5.77.

1,3,4,5-Tetrahydro-4-phenyl-2H-1-benzazepin-2-one.—Interaction of 12.0 g (0.054 mole) of 3-phenyl-1-tetralone[12] with hydrazoic acid in the above manner gave 9.7 g of product, mp 137–139°. After recrystallization from 45 ml of acetonitrile, the colorless material weighed 7.8 g (61%); mp 140–142°; λ_{max}^{Nujol} 3.15, 6.01 μ.[11]

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.88; H, 6.40; N, 6.09.

***o*-Nitro-N-phenylhippuric Acid Ethyl Ester**—A suspension of 94.0 g (0.56 mole) of *o*-nitrobenzoic acid in 400 ml of chloroform was treated with 80 ml of $SOCl_2$, and the mixture was refluxed for 1 hr. The solvent and excess $SOCl_2$ were removed under reduced pressure. The residual *o*-nitrobenzoyl chloride was dissolved in 500 ml of chloroform, cooled, and maintained at 10–15° during the dropwise addition of a solution of 100 g (0.56 mole) of N-phenylglycine ethyl ester, 56.5 g (0.56 mole) of triethylamine, and 300 ml of $CHCl_3$. The mixture was stirred for 1 hr at room temperature, refluxed for 2 hr, cooled, and washed twice with 100-ml portions of water followed by 100 ml of 5% $NaHCO_3$ solution. The organic phase was dried ($MgSO_4$), treated with Darco, and filtered. Evaporation of the solvent at reduced pressure yielded a yellow-brown solid. The latter was triturated with 250 ml of hexane and filtered to give 171.7 g of product, mp 90–95°. After crystallization from 200 ml of 95% ethanol, the pale yellow material weighed 161.7 g (84%); mp 98–100°; λ_{max}^{Nujol} 5.75, 6.03, 6.55 μ.

Anal. Calcd for $C_{17}H_{16}N_2O_5$: N, 8.53. Found: N, 8.45.

***o*-Amino-N-phenylhippuric Acid Ethyl Ester.**—A warm solution of 33.0 g (0.1 mole) of the above nitro compound in 300 ml of ethanol was treated with 5 g of 5% palladium on carbon, and the mixture was placed on a Parr apparatus under 3 atm of hydrogen at room temperature. The theoretial quantity of hydrogen was consumed in 5 min. The mixture was diluted with 300 ml of ethanol, heated to dissolve the crystallized product, and filtered. The filtrate was cooled to give 25.2 g (84%) of colorless product; mp 138–140°; λ_{max}^{Nujol} 2.89, 2.95, 5.76, 6.08 μ.

Anal. Calcd for $C_{17}H_{18}N_2O_3$: N, 9.39. Found: N, 9.57.

4-Phenyl-1H-1,4-benzodiazepine-2,5(3H,4H)-dione (VIII, R = H). A. Thermal Cyclization.—A flask containing 40.0 g (0.13 mole) of the amino ester was placed in an oil bath and heated at 230–240° for 1 hr (5.5 g of ethanol was collected during this period). After cooling, the solid was crystallized from 350 ml of acetonitrile to give 29.7 g (88%) of colorless product; mp 199–200°; λ_{max}^{Nujol} 3.10, 5.83, 6.13 μ.

Anal. Calcd for $C_{15}H_{12}N_2O_2$: N, 11.11. Found: N, 11.04.

B. Hydrolysis. Reductive Cyclization.—A warm solution of 32.8 g (0.1 mole) of the above nitro ester in 70 ml of acetic acid was treated with 100 ml of concentrated HCl and 50 ml of water. This solution was refluxed for 3 hr, diluted with 250 ml of water, and cooled to give 30.5 g of the acid, mp 103–105° (melting point varied with degree of hydration). Catalytic reduction of this material according to the procedure used above, followed by

(7) F. Cortese, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 91.

(8) C. S. Marvel, W. H. Zartman, and O. D. Bluthardt, *J. Am. Chem. Soc.*, **49**, 2299 (1927).

(9) Y. Sanno, *Yakugaku Zasshi*, **77**, 622 (1957); *Chem. Abstr.*, **51**, 16431 (1957).

(10) H. Ryan and G. Cruess-Callaghan, *Proc. Roy. Irish Acad.*, **39B**, 136 (1929); *Chem. Abstr.*, **24**, 4037 (1930). In one preparation, the 2'-hydroxychalcone was cyclized by heating in a mixture of orthophosphoric acid and glacial acetic acid.

(11) The nmr spectrum confirmed the assigned structure.

(12) F. S. Spring, *J. Chem. Soc.*, 1333 (1945).

concentration of the filtrate to 100 ml, gave 16.9 g (67%) of colorless product, mp 199–200°.

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Aziridine Derivatives as Potential Monoamine Oxidase Inhibitors[1]

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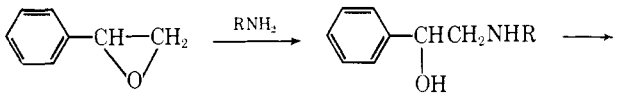
A series of 1-substituted phenylaziridines has been prepared and tested for *in vitro* MAO-inhibition activity. The most active compounds were studied to assure that a hydrolysis product of the aziridine ring was not responsible for MAO inhibition.

Zeller, *et al.*,[2] postulated that the most suitable inhibitors of monoamine oxidase (MAO) contained a two-carbon chain between an aromatic ring and an amino group. Work by Paget and Davis indicated that the high π-electron density, presumably present in heterocyclic systems analogous to cyclopropane, may give rise to MAO inhibition.[3] The latter work also showed that, in the diaziridine series, a free amino group was not necessary for MAO inhibition.

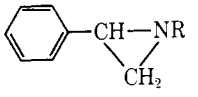
In this paper the preparation and *in vitro* MAO-inhibition activity of 1-substituted derivatives of 2-phenylaziridine are reported. These derivatives are essentially phenethylamine structures with the amine incorporated in a three-membered ring. Such a configuration offers a unique advantage of increasing the π-electron density between the two carbon atoms of the alkyl chain. The MAO activity of 2-phenylaziridine has been demonstrated.[4] Our interest was to determine the effect of increased electron density in the aziridine ring and also the effect of bulk in the 1-position on MAO-inhibition activity.

Treatment of styrene oxide with alkyl or aralkyl primary amines gave the desired 2-amino-1-phenylethanol derivatives (I).[5] Compound IIa was prepared by the method of Brois[6] using 70% sulfuric acid to prepare the O-sulfate ester. Compounds IIb, c, and d were prepared according to the method of Taguchi and Kojimi.[7]



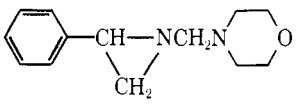
I

a, R = CH_3 c, R = $CH(CH_3)_2$
b, R = C_2H_5 d, R = $CH_2CH_2C_6H_5$



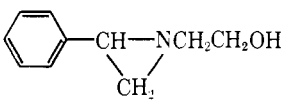
II

The hydrogen on the aziridine nitrogen was reactive enough to undergo aminomethylation.[8] Reaction between 2-phenylaziridine, formaldehyde, and morpholine gave 1-morpholinomethyl-2-phenylaziridine (III).

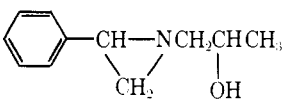


III

The method used for the preparation of 1-(2-hydroxylalkyl)-2-phenylaziridines (IV and V) was a slight modification of that reported by Funke and Benoit[9] in which 2 equiv of the appropriate epoxide was treated with 1 equiv of 2-phenylaziridine.



IV



V

A convenient preparation of 2-[(2-phenethyl)amino]-ethanol consisted of refluxing 2-phenyl-1-bromoethane with an excess of 2-aminoethanol. 2-[(2-Phenethyl)-amino]ethanol was converted to 1-(2-phenethyl)-aziridine (VI).[7] Compound VII, 2-[(2-phenethyl)-amino]-2-phenylethanol, was prepared by refluxing 2-phenyl-1-bromoethane with a large excess of 2-amino-2-phenylethanol.

In Vitro **Studies.**—Inhibition of monoamine oxidase *in vitro* was assessed by the method of Wurtman and Axelrod[10] which consists of incubating the potential MAO inhibitor and the substrate, 2-C^{14}-tryptamine, with rat liver homogenate. After a suitable length of time the deaminated product (C^{14}-indoleacetic acid) was extracted and counted for its radioactive content. The compounds here were screened at 5×10^{-4} *M* concentration as the free base, which was dissolved in phosphate buffer (pH 7.4) containing not more than 4% *p*-dioxane. The degree of inhibition was compared to a 5×10^{-4} *M* iproniazid standard. The results are given in Table I.

(1) From the Ph.D. Thesis of Ajit V. Shirodkar, Purdue University.
(2) E. A. Zeller, S. Sarkar, R. Banerjee, and M. S. Ise, *Helv. Chim. Acta*, **43**, 439 (1960).
(3) C. J. Paget and C. S. Davis, *J. Med. Chem.*, **7**, 626 (1964).
(4) J. F. Moran, Dissertation, University of Ottawa, Ottawa, Canada, 1962.
(5) W. S. Emerson, *J. Am. Chem. Soc.*, **67**, 516 (1945).
(6) S. J. Brois, *J. Org. Chem.*, **27**, 3532 (1962).
(7) T. Taguchi and M. Kojimi, *Chem. Pharm. Bull.* (Tokyo), **7**, 103 (1959).
(8) F. F. Blicke, *Org. Reactions*, **1**, 303 (1942).
(9) A. Funke and G. Benoit, *Bull. Soc. Chim. France*, 1021 (1953).
(10) R. J. Wurtman and J. Axelrod, *Biochem. Pharmacol.*, **12**, 1439 (1963).