Synthesis and *in Vitro* Activity of Some Aryl Diaziridines as Potential Monoamine Oxidase Inhibitors[1a-c]

CHARLES J. PAGET[1d] AND CHARLES S. DAVIS

Department of Medicinal Chemistry, School of Pharmacy, Purdue University, Lafayette, Indiana

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A number of 3-benzyl- and 3-phenyldiaziridines, some having various alkyl and tertiary aminomethylene groups substituted on one or both ring nitrogens, have been synthesized. The compounds were screened *in vitro* for monoamine oxidase inhibition. The most active were the phenyldiaziridines.

The aryl diaziridine ring system has been investigated because it structurally resembles two classes of monoamine oxidase (MAO) inhibitors, the hydrazine and the cyclopropylamine inhibitors,[2] and also since, as yet, no investigation of its medicinal properties has been reported. Even conclusive proof for the synthesis of the diaziridine ring system was not given until 1959.[3,4] Diaziridines having structural features similar to known noncyclic hydrazine and amine MAO inhibitors have now been chosen for synthesis. The first ones were benzyldiaziridines since they contain a phenethyl chain and therefore resemble the inhibitor β-phenylisopropylhydrazine. Various alkyl and alkylamine functional groups were substituted on the nitrogens of the benzyldiaziridines. The phenyldiaziridines were synthesized in an effort to see what effect placing a phenyl ring adjacent to the diaziridine ring would have on the biological activity.

Synthesis.—3-Benzyl-3-methyldiaziridine was synthesized from *t*-butyl hypochlorite, phenylacetone, and excess ammonia by a method reported by Schmitz and Ohme.[5] This compound was allowed to react with aqueous dimethylamine and formaldehyde under typical Mannich reaction conditions[6] to yield 3-benzyl-1,2-bis(dimethylaminomethyl)-3-methyldiaziridine.

Phenylacetone and acetophenone were allowed to react with methylamine and hydroxylamine-O-sulfonic acid using a modification of a reported method[5] to give 3-benzyl-1,3-dimethyldiaziridine and 1,3-dimethyl-3-phenyldiaziridine.

Using the Mannich reaction,[6] 3-benzyl-1,3-dimethyldiaziridine was converted to 3-benzyl-1,3-dimethyl-2-piperidinomethyldiaziridine, 3-benzyl-1,3-dimethyl-2-morpholinomethyldiaziridine, and 3-benzyl-1,3-dimethyl-2-dimethylaminomethyldiaziridine in good yields.

3-Benzyl-3-methyldiazirine was obtained by the oxidation of 3-benzyl-3-methyldiaziridine with aqueous acid dichromate.[7] Propargylmagnesium bromide was added across the nitrogen–nitrogen double bond of 3-benzyl-3-methyldiazirine, using a high dilution technique to prevent allylic rearrangement of the Grignard reagent, to give 3-benzyl-3-methyl-1-propargyldiaziridine.

1-Methyl-3-phenyldiaziridine was prepared from benzal-N-methyl Schiff base by a modification of a reported method.[8,9]

Pharmacology.—The compounds were screened *in vitro* by the method of Ozaki, *et al.*[10] Briefly, this method involves incubation of the potential inhibitor with a rat liver homogenate, further incubation after the addition of serotonin, and the extraction and colorimetric assay of serotonin by the method of Udenfriend, *et al.*[11] The compounds were screened at a concentration of 10^{-3} *M* and the degree of inhibition compared to a 10^{-3} *M* iproniazid standard which was carried through each assay run. Compound blanks were also run through the assay to obviate any error in the colorimetric assay for serotonin. Compounds having less than 5% of the activity of iproniazid were considered inactive. The results are given in Table I.

The compounds were screened as the free base dissolved in ice-cold distilled water and used immediately. Three compounds which were not soluble in ice-cold water were dissolved with the aid of 1 equiv. of ice-cold 0.1 *N* HCl and the solutions were used immediately, before ring cleavage could occur.[12] These compounds were 3-benzyl-3-methyl-1-propargyldiaziridine, 3-benzyl-1,3-dimethyl-2-piperidinomethyldiaziridine, and 1,3-dimethyl-3-phenyldiaziridine.

3-Benzyl-3-methyldiaziridine, which is the cyclic analog of β-phenylisopropylhydrazine was screened *in vivo* on a limited basis. It has been found to be devoid of MAO inhibition *in vitro*, even at 10^{-2} *M*. Intravenous doses up to 10 mg./kg. did not appreciably affect rabbit or dog blood pressure. Tyramine and tryptamine pressor responses were not potentiated as might have been expected if the compound were converted *in vivo* to an active MAO inhibitor. Neither was the epinephrine nor norepinephrine pressor response blocked up to 1 hr. following the administration of the compound.[13]

Discussion

Zeller, *et al.*,[14] have postulated that the most suitable structure for a MAO substrate or inhibitor would be a

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(2) A. Pletscher, K. F. Gey, and P. Zeller in "Progress in Drug Research," Vol. II, E. Zucker, Ed., Interscience Publishers Inc., New York, N. Y., 1960, p. 117.

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(8) E. Schmitz, *Angew. Chem.*, **73**, 23 (1961).

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(10) M. Ozaki, H. Weissbach, A. Ozaki, B. Witkop, and S. Udenfriend, *J. Med. Pharm. Chem.*, **2**, 591 (1960).

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(13) G. Yim and C. Chambers, unpublished data.

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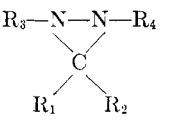
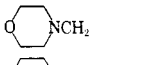
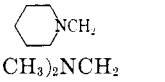
TABLE I
RESULTS OF *in Vitro* SCREENING FOR MAO INHIBITION USING RAT LIVER HOMOGENATES



Compd.	Inhibition at 10^{-3} *M* (Iproniazid = 1)	R_1	R_2	R_3	R_4
I	Inactive	$C_6H_5CH_2$	CH_3	H	H
II	Inactive	$C_6H_5CH_2$	CH_3	N=N	
III	0.53	$C_6H_5CH_2$	CH_3	$HC{\equiv}CCH_2$	H
IV	0.15	$C_6H_5CH_2$	CH_3	CH_3	H
V	0.13	$C_6H_5CH_2$	CH_3		CH_3
VI	0.22	$C_6H_5CH_2$	CH_3		CH_3
VII	Inactive	$C_6H_5CH_2$	CH_3	$(CH_3)_2NCH_2$	CH_3
VIII	Inactive	$C_6H_5CH_2$	CH_3	$(CH_3)_2NCH_2$	$(CH_3)_2NCH_2$
IX	0.99	C_6H_5	CH_3	CH_3	H
X	0.81	C_6H_5	H	CH_3	H

two-atom chain connecting an aryl ring and an amino group and that the atom α to the amine group should have a hydrogen atom attached. Biel, *et al.*,[15] have shown that the amine may be replaced by a hydrazine group, resulting in retention of activity and an increase in the MAO inhibition potency. Due to the general absence of activity in our benzyldiaziridines, Biel's finding apparently does not apply to diaziridines. This may be due to the lack of an α-hydrogen in the benzyldiaziridine series. Thus it would appear that the greater activity shown by the two phenyldiaziridines synthesized may be due to their close adherence to Zeller's requirements for an inhibitor.

Experimental

The melting points are corrected and were taken on a Fisher-Johns apparatus. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were taken on a Perkin-Elmer Model 21.

3-Benzyl-3-methyldiaziridine (I).—Phenylacetone (40.2 g., 0.3 mole) and liquid ammonia (104 ml.) were added with stirring to 200 ml. of methanol at −40°. The temperature was allowed to rise to −15°, and over a 15-min. period 48.8 g. (0.45 mole) of *t*-butyl hypochlorite in 50 ml. of *t*-butyl alcohol was added dropwise. The temperature was kept at −15° for 1 hr. and then allowed to rise to room temperature. After excess ammonia had boiled off, crushed ice was added, the reaction was acidified with 4 *N* H_2SO_4 and extracted twice with 100 ml. of ether, and the ether extracts were discarded. The aqueous portion was then basified with 4 *N* NaOH and extracted with ten 50-ml. portions of ether. The combined ether extracts were dried (Na_2SO_4), the ether was removed with a rotary evaporator, and the residual oil was recrystallized from petroleum ether (b.p. 30–60°). The total yield was 23 g. (52%), m.p. 73° after vacuum sublimation; infrared: (KBr) 3230 cm.$^{-1}$ strong (NH) (lit.[16] for diaziridines: 3175 to 3220 cm.$^{-1}$).

Anal. Calcd. for $C_9H_{12}N_2$: C, 72.94; H, 8.16. Found: C, 73.20; H, 8.20.

3-Benzyl-3-methyldiazirine (II).—Sodium dichromate (90 g., 0.3 mole) was added to 2.4 l. of 2 *N* H_2SO_4 in a 5-l. three-neck flask having a condenser and Dry Ice cooled receiver arranged for vacuum distillation. The pressure was reduced to 25 mm., and the flask was heated over a steam bath. Once boiling had begun, 59.2 g. (0.4 mole) of 3-benzyl-3-methyldiaziridine (I) in 200 ml. of water was added dropwise so as to get even distillation. Two liters of aqueous liquid was distilled, saturated with NaCl, and extracted eight times with 100 ml. of ether. The ether was dried (Na_2SO_4) and removed on a rotary evaporator and the oil remaining distilled at 39° (0.6 mm.), $n^{29}D$ 1.4943. The yield was 53.7 g. (92%); infrared: no band at 3230 cm.$^{-1}$ (NH) and appearance of strong band at 1600 cm.$^{-1}$ (—N=N—).

Anal. Calcd. for $C_9H_{10}N_2$: C, 73.94; H, 6.90; N, 19.16. Found: C, 74.14; H, 7.00; N, 19.24.

3-Benzyl-3-methyl-1-propargyldiaziridine (III).—A stirred solution of 14.6 g. (0.1 mole) of 3-benzyl-3-methyldiazirine (II) maintained at 5° in 50 ml. of ether was prepared. Into this flask was allowed to trickle, in a nitrogen atmosphere, the Grignard reagent prepared by allowing 23.6 g. (0.2 mole) of propargyl bromide in 450 ml. of ether to percolate through 24 g. of 1:1 magnesium amalgam packed in a Vigreux column. The rate of addition of bromide was adjusted to maintain a gentle reflux in the condenser during the 45-min. addition. The mixture turned a creamy buff color during the latter part of the addition. It was decomposed with ice, continuously extracted with ether for 24 hr., dried (Na_2SO_4), and then the ether was removed on a rotary evaporator. The remaining oil was vacuum distilled to yield 1.3 g. of starting diazirine, b.p. 44° (0.75 mm.), and 11.1 g. (60%) of product, b.p. 107° (0.75 mm.), $n^{29}D$ 1.5378; infrared: strong sharp band at 3300 cm.$^{-1}$ (≡CH) extending over to 3200 cm.$^{-1}$ (NH) and a weak band at 2125 cm.$^{-1}$ (C≡C).

Anal. Calcd. for $C_{12}H_{14}N_2$: C, 77.35; H, 7.58. Found: C, 77.26; H, 7.62.

3-Benzyl-1,3-dimethyldiaziridine (IV).—To 134 g. (1.0 mole) of phenylacetone was added 500 ml. of methanol–water 1:1, and at 0° 155 g. (5 moles) of monomethylamine was bubbled into the liquid. The ketone went into solution about halfway through the gas addition. The mixture was stirred for 30 min. and then at −10° 132 g. (1.1 moles) of 95% hydroxylamine-O-sulfonic acid was added slowly. About halfway through the addition the temperature began to rise and reached 15° before dropping back to −10°, from which it was slowly allowed to rise to room temperature after the completion of addition. Crushed ice was added and the mixture was acidified with 4 *N* H_2SO_4, extracted three times with 100 ml. of ether, and the ether extract was discarded. The aqueous portion was immediately basified with 4 *N* NaOH, extracted ten times with 100-ml. portions of ether, and the ether extract was dried (Na_2SO_4). The ether was removed with a rotary evaporator and the residual oil was vacuum distilled, b.p. 76° (0.75 mm.), yield 96.8 g. (60%), $n^{29}D$ 1.5232; infrared: band at 3230 cm.$^{-1}$ (NH) of medium intensity.

Anal. Calcd. for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70. Found: C, 74.22; H, 8.65.

1,3-Dimethyl-3-phenyldiaziridine (IX).—Using acetophenone in the preceding procedure, this compound was obtained in 54% yield, b.p. 67° (0.8 mm.), $n^{31}D$ 1.5774; infrared: band at 3300 cm.$^{-1}$ (NH) of medium intensity.

Anal. Calcd. for $C_9H_{12}N_2$: C, 72.94; H, 8.16. Found: C, 72.88; H, 7.90.

1- and 2-Substituted Methylene Dialkylated Amino Diaziridines (V–VIII).—The procedure for synthesis of these Mannich bases is essentially the method reported by Blicke.[6] An example of its use with diaziridines is the following.

3-Benzyl-1,3-dimethyl-2-morpholinomethyldiaziridine (V).—To 125 ml. of water was added 13 g. (0.15 mole) of morpholine and 16.2 g. (0.1 mole) of 3-benzyl-1,3-dimethyldiaziridine. The solution was cooled to 0°, and 12.2 ml. (0.15 mole) of 37% formaldehyde solution was added dropwise with stirring. The reaction was then refluxed on a steam bath for 30 min., cooled, saturated with NaCl, and extracted with three 100-ml. portions of ether. The ether extract was dried (Na_2SO_4), the ether was removed with a rotary evaporator, and the oil remaining was vacuum distilled at 132° (0.175 mm.) to yield 20.2 g. (77.4%) of product, $n^{26}D$ 1.5265.

Anal. Calcd. for $C_{15}H_{23}N_3O$: C, 68.93; H, 8.87. Found: C, 69.14; H, 9.02.

3-Benzyl-1,3-dimethyl-2-piperidinomethyldiaziridine (VI) had b.p. 115° (0.175 mm.), yield 46%, $n^{26}D$ 1.5203.

Anal. Calcd. for $C_{16}H_{25}N_3$: C, 74.08; H, 9.72. Found: C, 73.82; H, 9.57.

3-Benzyl-1,3-dimethyl-2-dimethylaminomethyldiaziridine (VII) had b.p 81° (0.3 mm.), yield 75%, $n^{29}D$ 1.5053.

Anal. Calcd. for $C_{13}H_{21}N_3$: C, 71.19; H, 9.65. Found: C, 71.02; H, 9.61.

3-Benzyl-1,2-bis(dimethylaminomethyl)-3-methyldiaziridine

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(16) E. Schmitz, *Chem. Ber.*, **95**, 688 (1962).

(**VIII**) was obtained from 3-benzyl-3-methyldiaziridine in 75% yield and had b.p. 110° (0.125 mm.), $n^{27}D$ 1.5033.

Anal. Calcd. for $C_{15}H_{26}N_4$: C, 68.66; H, 9.99; N, 21.35. Found: C, 68.65; H, 9.82; N, 21.39.

1-Methyl-3-phenyldiaziridine (X).—Benzal-N-methyl Schiff base[17] (47.6 g., 0.4 mole) was added to 200 ml. of 1:1 methanol–water. The mixture was cooled to 0° and 62 g. (2 moles) of monomethylamine was slowly bubbled into the solution. The reaction temperature was lowered to −10° and 52 g. (0.44 mole) of 95% hydroxylamine-O-sulfonic acid was added over a 5-min. period with stirring. The reaction temperature rose to 10° in spite of the Dry Ice–acetone bath and then returned to −10° at which it stirred for 30 min. and then was allowed to slowly rise to room temperature. 1,1-Dimethylhydrazine (60 g., 1 mole) was added slowly and the temperature rose from 35 to 45°. The mixture was cooled to 0° and extracted with six 100-ml. portions of ether and the ether extracts were dried (Na_2SO_4). The ether was removed with a rotary evaporator and the residual oil was distilled to yield 2 g. of benzonitrile, b.p. 45° (0.65 mm.) (identified by infrared) and 41.5 g. (77.5%) of product, b.p. 72–75° (0.4 mm.), $n^{26}D$ 1.6115; infrared: a strong band at 3370 cm.$^{-1}$ (NH).

Anal. Calcd. for $C_8H_{10}N_2$: C, 71.61; H, 7.51. Found: C, 71.56; H, 7.66.

(17) K. N. Campbell, A. H. Somers, and B. K. Campbell, *J. Am. Chem. Soc.*, **66**, 82 (1944).

Antidepressants.[1] II. Derivatives of Polynuclear Indoles

MEIER E. FREED, ELISABETH HERTZ, AND LEONARD M. RICE

Wyeth Laboratories, Inc., Research and Development Division, Radnor, Pennsylvania

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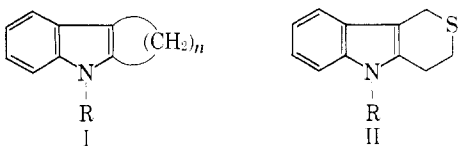
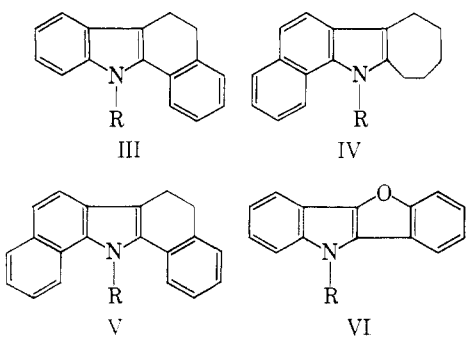
A series of N-substituted derivatives of polycyclic indole systems was prepared and examined for central nervous system activity. Examples of 1,3,4,5-tetrahydrothiopyrano[4,3-*b*]indoles, 5,6-dihydro-11H-benzo[*a*]-carbazole-2,3-pentamethylene-1H-benz[*g*]indole, 5,6-dihydro-13H-dibenzo[*a,i*]carbazole, and 10H-benzofuro-[3,2-*b*]indoles were included. The indole systems required were obtained *via* modifications of the Fischer indole synthesis and converted to N-substituted derivatives by varied methods. Some of the pharmacologic activities of the compounds are discussed.

The first paper[2] in this series described the synthesis and pharmacological behavior of a series of substituted 2,3-polymethyleneindoles (I). Because of the interesting pharmacological properties of certain members of this series, the investigation was extended to include a number of related types. The 1,3,4,5-tetrahydrothiopyrano[4,3-*b*]indoles (II, R = H) were selected



I II

because of an isosteric relationship with the 2,3-pentamethyleneindoles (I, n = 5) previously reported.[2] In an effort to investigate the effect on pharmacological activity of varying the size and shape of the aromatic moiety, analogous N-substituted derivatives of 5,6-dihydro-11H-benzo[*a*]carbazole[3] (III, R = H), 2,3-pentamethylene-1H-benz[*g*]indole (IV, R = H), 5,6-dihydro-13H-dibenzo[*a,i*]carbazole[4] (V, R = H), and 10H-benzofuro[3,2-*b*]indole[5] (VI, R = H), were prepared.



III IV

V VI

Penthian-4-one[6] was obtained from diethyl thiodipropionate by Dieckmann cyclization, followed by saponification and decarboxylation, and was converted directly to 1,3,4,5-tetrahydrothiopyrano[4,3-*b*]-indole[7] (II, R = H) by treatment with phenylhydrazine in glacial acetic acid.[3] In like manner, III, IV, and V were obtained, respectively, from phenylhydrazine and α-tetralone, α-naphthylhydrazine and cycloheptanone, and α-naphthylhydrazine and α-tetralone. 10H-Benzofuro[3,2-*b*]indole (VI, R = H) was prepared from phenylhydrazine and coumaranone as described by Cawley and Plant.[5]

The required dialkylaminoalkyl derivatives were obtained by treatment of an N-sodioindole (from the polycyclic indole and sodium hydride dispersion) with dialkylaminoalkyl chloride in dimethylformamide. After isolation, the products could be purified by distillation or converted directly to a suitable salt for testing. These compounds are shown in Tables I–III.[8]

The results of preliminary pharmacological screening were more promising in the tetrahydrothiopyrano[4,3-*b*]indole (II, R = H) and in the 5,6-dihydro-11H-benzo[*a*]carbazole (III, R = H) series than in the remainder (IV, V, and VI, R = H). Accordingly, II and III were investigated in considerable depth. In addition to a wide variety of dialkylaminoalkyl moieties, the N-(3-aminopropyl) and N-(3-methylaminopropyl)

(1) Paper II in this series.

(2) L. M. Rice, E. Hertz, and M. E. Freed, *J. Med. Chem.*, **7**, 313 1964.

(3) C. C. Rogers and B. B. Corson, *J. Am. Chem. Soc.*, **69**, 2910 (1947).

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(5) S. R. Cawley and S. G. P. Plant, *J. Chem. Soc.*, 1214 (1938).

(6) G. M. Bennett and L. V. D. Seorah, *ibid.*, 194 (1927).

(7) G. M. Bennett and W. B. Waddington, *ibid.*, 2829 (1929).

(8) In the course of this work, two lower homologs of 10-dimethylaminopropylbenzofuro[3,2-*b*]indole were reported by D. C. Schroeder, P. O. Corcoran, C. A. Holden, and M. C. Mulligan, *J. Org. Chem.*, **27**, 586 (1962).