N-Carboxymethyldiketopiperazine. Hydrazinolysis under standard conditions[12] was not successful, but could be accomplished in the following way. A mixture of 2.303 g. (0.01 mole) of phthalylglycyliminodiacetic acid, 10 ml. of ethanol, 10 ml. of 1*N* piperidine in ethanol (0.01 mole), and 10 ml. of 1*N* hydrazine hydrate in ethanol was heated in a pressure tube at 100° for 40 min. with occasional shaking. After the removal of the solvent, the residue was treated with 18.81 ml. of 0.5315*N* hydrochloric acid (0.01 mole) and 50 ml. of water. The phthalhydrazide was filtered, the filtrate evaporated *in vacuo* and the residue crystallized from water, giving 1.326 g. (70% yield) of product, m.p. 165–171°. After four recrystallizations from water the melting point was 174.5–175.5° dec.

Anal. Calcd. for $C_6H_8N_2O_4$: C, 41.86; H, 4.68; N, 16.27. Found: C, 41.96; H, 4.79; N, 16.34.

Carbobenzoxyglycine di-n-propylamide. A mixture of 2.02 g. (0.02 mole) of di-*n*-propylamine, 2.09 g. (0.01 mole) of carbobenzoxyglycine,[8] 2.04 g. (0.01 mole) of dicyclohexylcarbodiimide,[9] and 5.7 ml. of acetonitrile was shaken for 36 hr. After removal of the precipitate, the filtrate was evaporated, taken up in ethyl acetate and washed with acid, water, bicarbonate, and water. The yield of product from the organic layer was 1.46 g. (50%). After recrystallization from ethyl acetate the substance melted at 146–147°.

Anal. Calcd. for $C_{16}H_{24}N_2O_3$: N, 10.42. Found: N, 10.13.

Phthalylglycine di-n-propylamide. The reaction of phthalylglycylchloride and di-*n*-propylamine in pyridine gave a 71% yield of product melting at 104–105° after recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.61; H, 7.04; N, 9.88.

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Pyridylethylated *d*-α-Methylphenethylamines

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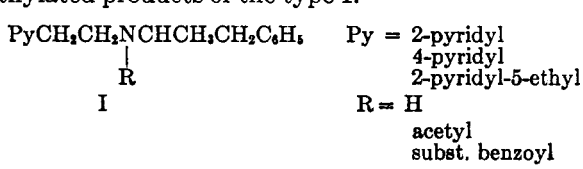
Our explorations[1,2] of derivatives of *d*-α-methylphenethylamine are herein extended to pyridylethylated products of the type I.



Other work[3,4] has shown that the pyridylethyl substituent, particularly the 4-pyridylethyl group, promotes central nervous system depression. It was therefore of interest to assess the effect of this radical on the analeptic activity of *d*-α-methylphenethylamine. Conversion of this amine to a secondary amine (*N*-methyl)[5] or to a tertiary amine (*N*-methyl, *N*-benzyl)[6] has been associated with significant retention of analeptic properties.

The examination of I as acyl- and arylamides[1] was suggested by "reverse" chelidamic acid[7] structures.

Pyridylethylation of *d*-α-methylphenethylamine[8] proceeded readily[9] in acetic acid following the method of Levine,[10] to give compounds 1, 7, and 9.[11] In the preparation of compound 9, some *N*-*d*-α-methylphenethylacetamide was obtained as a side product.

The amino nitrogen of I R = H, although hindered to a large degree, was readily acylated or arylated. In an effort to obtain the corresponding *N*-methylpiperidylethyl analogs of I, preliminary trials of hydrogenation of compound 3 failed. This work, however, is being pursued further.

Pharmacology. Using the reduction of motor activity as an indicator of effect on the central nervous system,[12] the analeptic activity of the *d*-α-methylphenethylamine was retained with compound 1, and depressant effects were observed with compounds 7 and 9. Compounds 4 and 5 also gave depressant effects. Other significant activity was 3+ hypotension[13] and anesthesia (ED_{50} = 9.7 mg./ml.)[14] with compound 4, and potentiation of adrenalin[14] with compounds 3 and 7.

EXPERIMENTAL[15]

N-d-α-Methylphenethyl-2-(5-ethyl-2-pyridyl)ethylamine (Compound 9). A mixture of one-third mole each of *d*-α-methylphenethylamine, 2-vinyl-5-ethylpyridine, and acetic acid in 80 ml. of methanol was heated under reflux for 8 hr. and distilled. After removal of low boiling fractions, a forerun was collected at 128–140° (0.3 mm.), and the product

(1) S. L. Shapiro, I. M. Rose, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 6065 (1958).

(2) S. L. Shapiro, I. M. Rose, F. C. Testa, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 5646 (1959).

(3)(a) S. L. Shapiro, I. M. Rose, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 1648 (1958); (b) S. L. Shapiro, I. M. Rose, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 386 (1959).

(4) B. Elpern, L. N. Gardner, and L. Grumbach, *J. Am. Chem. Soc.*, **79**, 1951 (1957).

(5)(a) L. S. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics*, 2nd Ed., The Macmillan Co., New York, 1955, p. 532; (b) K. Soehring and G. Ergenzinger, *Arzneimittel-Forsch.*, **5**, 478 (1955).

(6)(a) B. Simkin and L. Wallace, *Current Therap. Research*, **2**, 33 (1960); (b) Y. Matsushima, *Nippon Yakurigaku Zasshi*, **53**, 926 (1957) [*Chem. Abstr.*, **52**, 20638c (1958)].

(7) D. G. Markees, *J. Org. Chem.*, **23**, 1030 (1958).

(8) Under somewhat similar conditions, 4-vinylpyridine did not react with isopropylamine. E. Profft, *J. prakt. Chem.*, **4**, 19 (1956).

(9) For possible mechanism of reaction, see L. S. Luskin, M. J. Culver, C. E. Gantert, W. E. Craig, and R. S. Cook, *J. Am. Chem. Soc.*, **78**, 4042 (1956).

(10) H. E. Reich and R. Levine, *J. Am. Chem. Soc.*, **77**, 5434 (1955).

(11) For pyridine analogs of α-methylphenethylamine, see A. Burger, M. L. Stein, and J. B. Clements, *J. Org. Chem.*, **22**, 143 (1957).

(12) See ref. (1) and (3a) for method used. Noted significant activity is reported as compound no./LD_{min} mg./kg./test dose, mg./kg., s.c./% reduction (or increase) in activity: Increase, 1/75/10/166. Decrease, 4/1000/100/22; 5/>1000/100/26; 7/100/10/28; 9/75/10/30.

(13) For method of testing, see S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 2743 (1958).

(14) For method of testing, see S. L. Shapiro, H. Soloway, E. Chodos, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 203 (1959).

(15) Descriptive data shown in the table are not herein reproduced.

TABLE I

$PyCH_2CH_2—N(R)—CH(CH_3)CH_2C_6H_5$[a]

No.	R	M.P.[b,c] or B.P., (Mm.)	Yield,[d] %	Formula	Carbon,[e] % Calcd.	Carbon,[e] % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	120 (0.05)	66[g]	$C_{16}H_{20}N_2$	80.0	80.1	8.4	8.2	11.7	12.0
2	CH_3CO—	170–179 (0.16)	87	$C_{18}H_{22}N_2O$					9.9	10.1
3	[f]	151–152[c1]	85	$C_{19}H_{25}IN_2O$	53.8	54.0	5.9	6.0	6.6	6.8
4	*p*-$CH_3OC_6H_4CO$—	238–242 (0.03)	39	$C_{24}H_{26}N_2O_2$	77.0	77.0	7.0	6.7	7.5	7.0
5	*o*-$C_2H_5OC_6H_4CO$—	226–229 (0.03)	47	$C_{25}H_{28}N_2O_2$					7.2	6.8
6	TMB[h]	117–118[c2]	58	$C_{26}H_{30}N_2O_4$	71.9	71.7	7.0	7.2	6.5	6.0
7[a1]	H	128–134 (0.08)	53[g]	$C_{16}H_{20}N_2$	80.0	79.5	8.4	8.4	11.7	11.7
8[a1]	*o*-$C_2H_5OC_6H_4CO$—	103–106[c2]	57	$C_{25}H_{28}N_2O_2$	77.3	77.4	7.3	7.1	7.2	6.9
9[a2]	H	148–150 (0.4)	46[g]	$C_{18}H_{24}N_2$	80.6	80.7	9.0	9.1	10.4	9.8

[a] Py = 2-pyridyl unless otherwise indicated; [a1] Py = 4-pyridyl; [a2] Py = 5-ethyl-2-pyridyl. [b] Melting points are not corrected and were established on a Fisher-Johns melting point block. [c] Recrystallizing solvent; [c1] ethyl acetate; [c2] hexane-benzene. [d] Yields are expressed as recrystallized or distilled product. [e] Analyses are by Weiler and Strauss, Oxford, England. [f] Compound is methiodide of compound 2. [g] $[\alpha]_D^{20}$ in methanol: compound 1, +21.40; compound 7, +24.30; compound 9, +22.30. [h] TMB = 3,4,5-trimethoxybenzoyl.

(41.5 g.) was obtained, b.p. 148–150° (0.4 mm). The forerun, upon trituration with hexane, gave 2.4 g. (4.1%), m.p. 126–127°, not depressing the melting point of authentic *d*-α-methylphenethylacetamide.[16]

Compounds 1 and 7 were similarly prepared.

Acetamide of compound 1 (Compound 2). A mixture of 9.6 g. (0.04 mole) of compound 1 and 10 ml. of acetic anhydride was heated under reflux for 1 hr. When cool, after addition of 100 ml. of water, and treatment with base, the formed oil was extracted with 100 ml. of benzene and the product was obtained by distillation, 9.77 g. (87%), b.p. 170–179° (0.16 mm.).

A solution of 2.8 g. (0.01 mole) of this compound in 25 ml. of acetonitrile and 2 ml. of methyl iodide was refluxed for 2 hr., and upon cooling, yielded 3.6 g. (85%) of the methiodide (compound 3). Attempted hydrogenation[17] with rhodium on carbon afforded only unconverted reactant.

3,4,5-Trimethoxybenzamide of compound 1 (Compound 6). A solution of 9.6 g. (0.04 mole) of compound 1 in 35 ml. of benzene was added dropwise under stirring over 1 hr. to a solution of 4.6 g. (0.02 mole) of 3,4,5-trimethoxybenzoyl chloride in 65 ml. of benzene while maintaining the temperature at 25–30°. When addition was complete, the reaction mixture was heated under reflux for 1 hr. and then stored at 20° for 24 hr. After extraction with dilute hydrochloric acid, and treatment with base, 8.6 g. (98%) of product was separated and recrystallized.

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(16) Ref. (1) reports m.p. 123–125°.

(17) S. L. Shapiro, K. Weinberg, T. Bazga, and L. Freedman, *J. Am. Chem. Soc.*, 81, 5146 (1959).

Thiete Sulfone[1]

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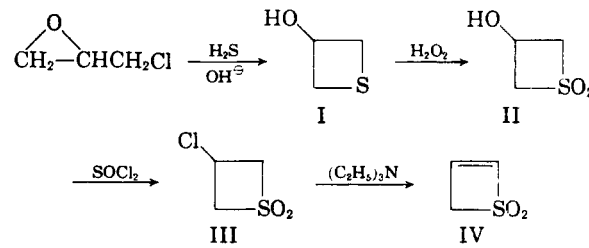
The synthesis and properties of five- and six-membered cyclic unsaturated sulfones have been described[2,3] but the four-membered cyclic unsaturated sulfones have been unreported.

The most simple four-membered cyclic unsaturated sulfone, thiete sulfone (thiete 1,1-dioxide), has been prepared according to the following reaction sequence:



Starting material, 3-thiethanol, (I),[4] was obtained by the addition of epichlorohydrin to a barium hydroxide solution saturated with hydrogen sulfide.[5] Oxidation of I in glacial acetic acid at room temperature gave the sulfone II in 56% yield. If the oxidation is carried out at 90–100°, the product is dimethyl sulfone which also is obtained by oxidation of I with potassium permanganate in acetone at 0°. The dimethyl sulfone probably arises from methylsulfonylacetic acid which is known to decarboxylate readily.[6]

(1) Presented at the 137th Meeting, American Chemical Society, Cleveland, Ohio, April, 1960.

(2) For a brief review see A. Schöberl and A. Wagner, *Methoden der Organischen Chemie*, Vol. IX, Schwefel-, Selen-, Tellur-Verbindungen, E. Müller, ed., Georg Thieme, Stuttgart, 4th Ed., 1955, p. 236.

(3) L. Bateman and R. W. Glazebrook, *J. Chem. Soc.*, 2834 (1958); R. C. Krug, G. R. Tichelaar, and F. E. Didot, *J. Org. Chem.*, 23, 212 (1958); R. C. Krug and T. Yen, *J. Org. Chem.*, 21, 1441 (1956); E. A. Fehnel and P. A. Lackey, *J. Am. Chem. Soc.*, 73, 2473 (1951); R. F. Naylor, *J. Chem. Soc.*, 2749 (1949).

(4) B. Sjöberg, *Svensk. Kem. Tid.*, 50, 250 (1938).

(5) Modification of the method of B. Sjöberg, *Ber.*, 75, 13 (1941).

(6) E. Baumann and G. Walter, *Ber.*, 26, 1131 (1893).