aminoacethydrazide in 10 ml of AcOH was stirred for 2 hr at 21–25°. Then 20% aq Na_2CO_3 was added to alkalinity. Some products pptd as solids, others sepd as thick oils which solidified on standing. The sepd solids were collected and crystd. The hydrochlorides were prepd by conventional procedures (see Tables I, II, and III).

1-Substituted-3,3-dimethylspiro[indoline-2,3′-thietane] 1′,1′-Dioxides Derived from 2-Methyleneindolines

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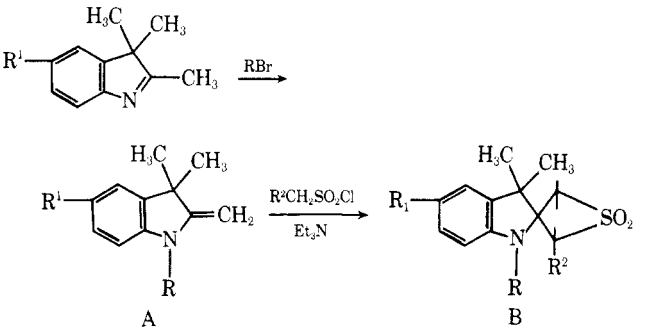
The enamine character of 2-methylene-1,3,3-trimethylindoline (A, R = Me; R¹ = H) was the subject of a review in 1949 by Coenen.[2] Stork and Borowitz[3] more recently reported a new class of amino-substituted, four-membered cyclic sulfones (thietane 1,1-dioxides) synthesized by reaction of enamines with $CH_2{=}{=}SO_2$, the intermediate sulfene generated *in situ* from MsCl upon treatment with Et_3N.[4] Cycloaddition of $CH_2{=}{=}SO_2$ and $PhCH{=}{=}SO_2$ to 1-substituted-2-methylene-3,3-dimethylindolines (A) under the Stork-Borowitz conditions has resulted in the new spiroindolinethietane ring system B as shown in the following reaction sequence.



No significant activity was observed under conditions of the test models in antiviral, antibacterial, antifungal, anthelmintic, hypotensive, and antiinflammatory, or reproductive physiology screening procedures.

Experimental Section

The following examples serve as general procedures for the preparation of compds A and B listed in Table I.

3,3-Dimethyl-1-hexyl-2-methyleneindoline (A-5).—A mixt of 68 ml (0.4 mole) of 2,3,3-trimethylindolenine (Fairmount Chemical Co.) and 65 g (0.4 mole) of *n*-$C_6H_{13}Br$ in 250 ml of PhMe was refluxed 24 hr with stirring.[5] The semisolid reaction mixt was treated with 100 ml of 30% KOH and stirred vigorously for 0.5 hr.[6] The PhMe layer was sepd and fractionally distd. After a forerun of unchanged *n*-$C_6H_{13}Br$, 30 ml of starting indolenine was recovered at 75–78° (0.25 mm). The desired product distd at 115–117° (0.82 mm) and amounted to 42 g of yellow oil that turned purple on exposure to air.

1-Hexyl-3,3-dimethylspiro[indoline-2,3′-thietane] 1′,1′-Dioxide (B-5).—To a stirred mixt of 32 g (0.2 mole) of the indoline A-5 and 40 ml of Et_3N in 200 ml of pure PhMe maintained at 5° was added dropwise 16.5 ml (0.2 mole) of MsCl in 30 ml of PhMe in 1 hr.[3] The mixt was stirred overnight at room temp then filtered, and the ppt was washed with 100 ml of PhMe. The product obtained by rotary evapn of the filtrate was recrystd from MeOH and washed with Et_2O to remove pink coloration.

TABLE I
1-SUBSTITUTED-3,3-DIMETHYLSPIRO[INDOLINE-2,3′-THIETANE] 1′,1′-DIOXIDES (B) AND THEIR INTERMEDIATE 2-METHYLENEINDOLINES (A)

	A					B			
	R	R¹	Bp (mm), °C	% yield	Formula (Analysis)[a]	R²	Mp (corr) °C (dec)	% yield	Formula (Analysis)[a]
1	CH_3	H	*b*			H	138–140	62	$C_{13}H_{17}NO_2S$
2	CH_3	H	*b*			Ph	130[c]	45	$C_{19}H_{21}NO_2S$
3	CH_3	H	*b*			CH_2CH_2Cl	129–30	25	$C_{15}H_{20}ClNO_2S$[d]
4	CH_3	Cl	*e*			H	200[c]	50	$C_{13}H_{16}ClNO_2S$
5	*n*-Hexyl	H	115–117 (0.28)	43	$C_{17}H_{25}N$	H	90–91	62	$C_{18}H_{27}NO_2S$
6	CH_2CO_2Et	H	111–113 (0.10)	29	$C_{15}H_{19}NO_2$[f]	H	143–144	57	$C_{16}H_{21}NO_4S$
7	Benzyl	H	130–132 (0.20)	48	$C_{18}H_{19}N$[g]	H	201[c]	41	$C_{19}H_{21}NO_2S$
8	2-Phenethyl	H	134–136 (0.25)	50	$C_{19}H_{21}N$	H	143–144	53	$C_{20}H_{23}NO_2S$
9	1-Naphthylmethyl	H	188–193 (0.20)	49	$C_{20}H_{21}N$[h]	H	190–192	20	$C_{23}H_{23}NO_2S$

[a] C, H, N (type A) and C, H, S (type B) analyses were within ±0.4% of calcd values unless indicated in this column. [b] Obtd from Aldrich Chemical Co., Inc. [c] Decomposes without melting. [d] S anal. not obtained; Cl and N values in good agreement with calcd. [e] Obtained from Gallard-Schlesinger Chemical Mfg. Corp. [f] Not analyzed as it decompd rapidly and required immediate use. [g] N anal. inadvertently omitted. [h] Used crude without anal.

The ir, uv, and nmr spectra, as well as elementary anal., were compatible with the structure proposed for B. For example, the nmr spectrum of B-1 (R = Me; R¹ = R² = H) showed chemical shifts as follows: δ 1.36 (singlet, 6 H, 3,3-Me_2); 2.95 (singlet, 3 H, NMe); 4.20, 4.25, 4.28, and 4.30 (singlets, each 1 H, 4 thietane ring H's); 6.3–7.3 (multiplet, 4 H, arom). Unexpectedly, these compds (B) were not sufficiently basic to form HCl salts.

Acknowledgments.—The author greatly appreciates the assistance of Dr. Alfred Richardson, Jr., of The Wm. S. Merrell Company, Cincinnati, Ohio, particularly in interpretation of nmr spectra. Acknowledgment is also made of the contributions of the biological divisions of The Wm. S. Merrell Company, The National Drug Company, and Hess and Clark

(1) Present address: 2167 Greensward Dr., N.E., Atlanta, Ga. 30345.

(2) M. Coenen, *Angew. Chem.*, **61**, 11 (1949).

(3) G. Stork and I. Borowitz, *J. Amer. Chem. Soc.*, **84**, 313 (1962); similar results were published almost simultaneously by G. Opitz and H. Adolph, *Angew. Chem., Int. Ed. Engl.*, **1**, 113 (1962).

(4) The existence of $CH_2{=}{=}SO_2$ and related sulfenes as intermediates generated *in situ* has been well documented since 1962; *cf.* the reviews by T. J. Wallace, *Quart. Rev.*, **20**, 67 (1966), and G. Opitz, *Angew. Chem., Int. Ed. Engl.*, **6**, 107 (1967). Opitz also reviews the cycloaddition of sulfenes to enamines.

(5) P. Lochon and O. O. Jamboo-Geoffroy, *Bull. Soc. Chim. Fr.*, 393 (1965), quarternarized with $Cl_2C{=}{=}CHCl$ as solvent.

(6) B. Robinson, *J. Chem. Soc.*, 586 (1963), reported this procedure.

for evaluating the B compounds in many of their screens. The research at Emory University was made possible by the support of Dr. R. A. Day, Jr., Chairman of the Department of Chemistry at the time, and a generous research grant from Richardson-Merrell Inc., both of which are gratefully acknowledged.

Synthesis of L-Dopa (3,4-Dihydroxyphenyl-L-alanine)

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N-Acetyl-3-(3,4-dimethoxyphenyl)-L-alanine (L-I) and *N*-acetyl-3-(3,4-methylenedioxyphenyl)-L-alanine (L-II) could be starting materials for the synthesis of L-dopa. A new chemical resolution method of *N*-acetyl-3-(3,4-dimethoxyphenyl)-DL-alanine (I) and *N*-acetyl-3-(3,4-methylenedioxyphenyl)-DL-alanine (II) by using *d*-ephedrine as a resolving reagent was adopted.

Experimental Section

***N*-Acetyl-3-(3,4-dimethoxyphenyl)-L-alanine-*d*-ephedrine Salt (*d*-Ephedrine-L-I Salt).**—*N*-Acetyl-3-(3,4-dimethoxyphenyl)-DL-alanine (DL-I) (53.4 g, 0.2 mole) and 33.0 g of *d*-ephedrine (0.2 mole) were dissd together in 130 ml of MeOH or in 200 ml of EtOH with warming at 55–60° for 1.0 hr, and the soln was kept in a refrigerator overnight. The colorless crystals that sepd were filtered off, washed with MeOH (*ca.* 30 ml), and dried, giving 37.9 g (87.8%) of the *d*-ephedrine-L-I salt: mp 147.5–149.5°, $[\alpha]^{20}D$ +49.8° (*c* 5, H_2O). After recrystn from 3 vol of MeOH, the mp and $[\alpha]D$ became constant: mp 152–153°; $[\alpha]^{20}D$ +54.5° (*c* 5, H_2O); yield, 28.4 g (68.1%). *Anal.* ($C_{23}H_{32}N_2O_6$) C, H, N.

***N*-Acetyl-3-(3,4-methylenedioxyphenyl)-L-alanine-*d*-ephedrine Salt (*d*-Ephedrine-L-II Salt).**—DL-II (90.4 g) and *d*-ephedrine (72.7 g were dissd in 600 ml of MeOH or 900 ml of EtOH at 55–60° with stirring for 1.0 hr, cooled, and kept in a refrigerator overnight. The colorless crystals that sepd were filtered off, washed with MeOH (*ca.* 30 ml), and dried, giving 66.5 g (89.1%) of the *d*-ephedrine-L-II salt: mp 150.2–152.5°; $[\alpha]^{20}D$ +48.2° (*c* 5, H_2O). Recrystn from 3 vol of MeOH gave 46.6 g (62.1%) of *d*-ephedrine-L-II: mp 156.3–158.6°; $[\alpha]^{20}D$ +55.6° (*c* 5, H_2O). *Anal.* ($C_{22}H_{28}N_2O_6$) C, H, N.

***N*-Acetyl-3-(3,4-dimethoxyphenyl)-L-alanine (L-I) from the *d*-Ephedrine-L-I Salt.**—*d*-Ephedrine-L-I (20 g was dissd in 50 ml of H_2O, then this soln was added dropwise with 30% HCl with cooling and stirring, giving colorless crystals. After standing in a refrigerator overnight they were filtered off, washed with H_2O (20 ml), and dried, affording 11.4 g (91.0%) of L-I: mp 149–150°; $[\alpha]^{20}D$ +46.2° (*c* 5, MeOH). *Anal.* ($C_{13}H_{17}NO_5$) C, H, N.

***N*-Acetyl-3-(3,4-dimethoxyphenyl)-L-alanine (L-I) from the *d*-Ephedrine-L-I Salt.**—*d*-Ephedrine-L-I (20 g) was dissd in 50 ml of H_2O, then this soln was added dropwise with 20% HCl with cooling and stirring, giving colorless crystals. After standing in a refrigerator overnight they were filtered off, washed with H_2O (20 ml), and dried, affording 11.4 g (91.0%) of L-I: mp 149–150°; $[\alpha]^{20}D$ +46.2° (*c* 5, MeOH). *Anal.* ($C_{13}H_{17}NO_5$) H, C, N. From the filtrate and washings of the acid (L-I), *d*-ephedrine·HCl was nearly quant recovered as colorless crystals; mp 217–218°; $[\alpha]^{20}D$ +34.1° (*c* 1, H_2O).

***N*-Acetyl-3-(3,4-methylenedioxyphenyl)-L-alanine (L-II) from the *d*-Ephedrine-L-II Salt.**—*d*-Ephedrine-L-II salt (58.8 g) was dissd in 150 ml of H_2O and added dropwise to 20% HCl under cooling and stirring, giving colorless crystals. After standing in a refrigerator overnight they were filtered off, washed with 50 ml of cold H_2O, and dried, affording 33.7 g (95.0%) of L-II based on the L-II of *d*-ephedrine-L-II used: mp 179.6–180.8°; $[\alpha]^{20}D$ +46.5° (*c* 5, MeOH). *Anal.* ($C_{12}H_{13}NO_5$) C, H, N.

L-Dopa (L-III) from L-I.—A mixt of 26.8 g (0.1 mole) of L-I, 69.8 ml (0.6 mole) of 47% HBr, and 28 ml (0.32 mole) of PhOH was heated under stirring and reflux for 6 hr, and the resulting slight brown soln was evapd to a reddish syrup. This was dissd in 30 ml of *n*-BuOAc and extd twice with 30 ml and 10 ml of H_2O. The 2 aq exts were combined and adjusted to pH 5.0 with 25% NH_4OH soln contg a little $NaHSO_3$, whereupon colorless crystals sepd. After standing in a refrigerator overnight the crystals were filtered off, washed with H_2O, and dried, giving 19.6 g (99.5%) of crude L-dopa: mp 266–269°; $[\alpha]^{15}D$ −11.6° (*c* 5, 1 *N* HCl). Recrystn from 800 ml of H_2O contg a little $NaHSO_3$ gave 15.6 g (79.5%) of L-dopa as colorless minute leaflets: mp 277–278° dec; $[\alpha]^{15}D$ −13.3° (*c* 5, N-HCl). *Anal.* ($C_9H_{11}NO_4$) C, H, N.

L-Dopa from L-II.—L-II (30 g) and PhOH (30 g) were heated in 300 ml of 20% HCl under reflux and stirring for 20.0 hr, and the resulting soln was evaporated to the reddish syrup. This was worked up as in the preceding expt: yield, 22.6 g (95.6%); mp 268–270°, $[\alpha]^{17}D$ −11.8° (*c* 5, N-HCl); after recrystn 16.4 g (82.0%) of L-dopa, mp 277.2–278.2° dec, $[\alpha]^{15}D$ −13.2° (*c* 5, 1 *N* HCl). *Anal.* ($C_9H_{11}NO_4$) C, H, N.

Evaluation of Carbazoles as Antifungal Agents

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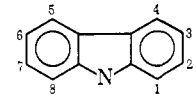
Some complex carbazole alkaloids have been reported to possess antifungal activity.[1] In a search for similar agents, a group of simple derivatives were prepared[2] and evaluated against *Candida albicans*.[3] None of the results are sufficiently high to recommend these compounds for further testing.

TABLE I
ANTI-*Candida* ACTIVITY



No.	Carbazole[a]	Concn, mg/ml	Activity zone size, mm[b]
1	1-OH	0.1	12
2	1-OH-3-Me	0.1	11
3	3-MeO-6-Me	0.1	12
4	1,3-$(MeO)_2$-6-Me	0.1	11
5	2,3-$(MeO)_2$-6-Me	0.1	11
6	2,4-$(MeO)_2$-6-Me	1.0	*c*
7	2,3-$(OH)_2$-6-Me	0.1	10
8	*N*-Me-2,3-$(MeO)_2$-6-Me	1.0	*c*
9	Glycozolidine[d]	1.0	*c*

[a] All new compds had satisfactory anal. (C, H, N) and spectral values. [b] In an agar diffusion cup-plate assay, where the cup diameter itself is 8 mm. [c] The zone was not larger than that produced by the diluent (ethylene glycol–EtOH, 4:1). [d] D. P. Chakraborty and B. P. Das, *Sci. Cult.*, **32**, 181 (1966).

Acknowledgment.—This investigation was supported by Public Health Service Grant No. UI 00697.

(1) K. C. Das, D. P. Chakraborty, and P. K. Bose, *Experientia*, **21**, 340 (1965).
(2) K. C. Das and B. Weinstein, unpublished data.
(3) We thank Dr. John W. Westley, Hoffman-LaRoche, Nutley, N. J., for furnishing the test report.