lization from ethanol or an ethanol–ether mixture; nmr spectrum of 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-4-imidazolin-2-one: δ 7.8–7.1 (aromatic protons, complex multiplet, 4 H), 6.62 and 6.42 (C-4 H and C-5 H, AB quartet, J_{AB} = 3 cps, 2 H), 3.73 ($CH_2NC{=}O$, triplet, J = 6 cps, 2 H), 2.60 (CH_2NMe_2, triplet, J = 6 cps, 2 H), 2.27 ($N(CH_3)_2$, singlet, 6 H).

Imidazolidinone Hydrochlorides (Table III). General Procedure D.—A mixture of 0.01 mole of the 1-aryl-3-(2-dimethylaminoethyl)-4-imidazolin-2-one hydrochloride, 100 ml of 85% ethanol, and 1 g of 10% Pd-C catalyst was shaken in a Parr hydrogenator under about 3.05 kg/cm² of hydrogen pressure for 1.5–3 hr. The reaction mixture was filtered and the mother liquor was concentrated to remove the solvents. The residue was triturated with acetone or ether until crystallization occurred. The crystals were filtered off and recrystallized from ethanol or an ethanol–ether mixture.

Procedure E. Reduction of 1-(*m*-Chlorophenyl)-3-(2-dimethylaminoethyl)-4-imidazolin-2-one Using Diborane.—A solution of 1 *M* borane in THF (3 ml, 0.003 mole) was added to a cooled mixture of 400 mg (0.0015 mole) of 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-4-imidazolin-2-one and 8 ml of diglyme. The solution was left at room temperature for 20 hr and then heated in an oil bath at 170–180° for 2 hr. The mixture was cooled, 3 ml of propionic acid was added, and the reaction mixture was again heated at 170–180° for 1 hr. The mixture was concentrated to remove the solvent, 5 ml of 5 *N* NaOH was added, and the product was extracted into ether. The ether layer was washed with salt solution and concentrated. The residue weighed 0.35 g, and vapor phase chromatography indicated that this was greater than 95% 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-2-imidazolidinone. The product was converted to the hydrochloride, mp 247–249° after recrystallization from ethanol, identical by mixture melting point and infrared spectra with the compound previously prepared by alkylation of 1-(*m*-chlorophenyl)-2-imidazolidinone;[5] nmr spectrum of 1-(*m*-chlorophenyl)-3-(2-dimethylaminoethyl)-2-imidazolidinone: δ 7.8–6.8 (aromatic protons, complex multiplet, 4 H), 3.9–3.4 (C-4 and C-5 CH_2, multiplet, 4 H), 3.35 ($CH_2NC{=}O$, triplet, J = 6 cps, 2 H), 2.47 (CH_2NMe_2, triplet, J = 6 cps, 2 H), 2.25 ($N(CH_3)_2$, singlet, 6 H).

Acknowledgment.—We wish to thank Mr. W. Fulmor and associates for the spectral data, Mr. L. Brancone and co-workers for the microanalyses, Mr. C. Pidacks and staff for the chromatography, and Dr. A. C. Osterberg and associates for the pharmacological results.

New Psychotropic Agents. VII.[1] 5H-Dibenzo[*a*,*d*]cycloheptenyl Sulfones

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Received April 30, 1966

5H-Dibenzo[*a*,*d*]cyclohepten-5-one and the 10,11-dihydro derivative were converted to their alkylene dithioketals which were oxidized to the corresponding tetroxides. Interaction of the ethylene thioketal tetroxides with amines gave 5-(5H-dibenzo[*a*,*d*]cycloheptenyl) 2-aminoethyl sulfones which may be considered as analogs of amitriptyline. Related benzhydryl sulfones were prepared employing hydrazine and 2-dimethylaminoethanol. The compounds possessed only slight biological activities.

Certain aminoalkyl benzhydryl sulfones have been reported to possess central nervous system activity. Thus Archer and Suter[2] have claimed anticonvulsant effect for a number of 2-(disubstituted amino)ethyl benzhydryl sulfones. The preparation of related compounds containing a 5H-dibenzo[*a*,*d*]cycloheptene nucleus in place of the benzhydryl group was of interest. These could be considered as analogs of the antidepressant drug amitriptyline (10,11-dihydro-*N*,*N*-dimethyl-5H-dibenzo[*a*,*d*]cycloheptene-$\Delta^{5,\gamma}$-propylamine) in which the methinyl carbon atom of the alkylidene side chain has been replaced by a sulfonyl group.

Several synthetic routes to the sulfones were considered. The benzhydryl compounds have been prepared[2,3] from the interaction of benzhydryl mercaptan with an alkylene chlorobromide followed by oxidation to the corresponding chloroalkyl sulfone and replacement of the chlorine atom by a secondary amino group; attempted oxidations of 2-piperidinoethyl benzhydryl sulfide were unsuccessful. A projected use of 10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene-5-thiol as a starting material for the tricyclic sulfones was not pursued in view of the report[4] that this thiol could not be obtained by the usual thiourea synthesis with the corresponding 5-chloro compound. An attempt was made to prepare a simple sulfone from this same 5-chloro compound through interaction with ethanethiol under alkaline conditions with subsequent oxidation of the resulting sulfide; none of the desired 5-ethylsulfonyl derivative was obtained. It was obvious that a quite different approach was required and this was found in a novel application of a known reaction, namely, the cleavage of 1,2-disulfones by nucleophilic reagents.[5] Thus Kuhn and Neugebauer[6] obtained 2-piperidinoethyl benzhydryl sulfone in 85% yield by heating 2,2-diphenyl-1,3-dithiolane 1,1,3,3-tetroxide (IV) with piperidine. The interaction of related spirodisulfones containing the dibenzocycloheptenyl nucleus (II) with secondary amines gave the desired basic sulfones (III) in generally good yields (see Tables I and II and Scheme I). The reactions were carried out by heating either with an excess of amine alone or in an appropriate solvent; the normeperidine derivative (IIIe) was prepared from one equivalent of the amine in boiling toluene containing pyridine. The products, best handled as the free bases, tended to retain solvent of crystallization and gave only fair analytical values.

The compounds could not be sublimed *in vacuo* without decomposition. The spectral data were, however, in accord with the proposed structures.

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(2) S. Archer and C. M. Suter, U. S. Patent 2,618,637 (1952).

(3) M. M. Kleok, C. M. Suter, and S. Archer, *J. Am. Chem. Soc.*, **70**, 3816 (1948).

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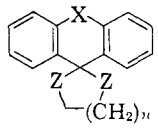
(5) (a) R. Otto and H. Dankobler, *J. Prakt. Chem.*, **30**, 171, 321 (1884); (b) E. P. Kohler and M. Reimer, *Am. Chem. J.*, **31**, 163 (1904).

(6) R. Kuhn and F. A. Neugebauer, *Chem. Ber.*, **94**, 2029 (1961).

TABLE I

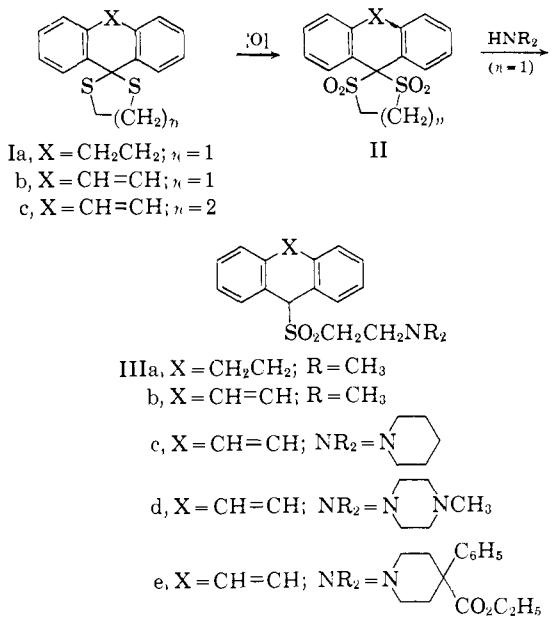
SPIRODITHIOLANES AND -DITHIANES



No.	X	Z	n	Mp, °C	Recrystn solvent	Yield, %	Ultraviolet spectra[k] λmax, mμ	ε	Formula	Calcd, % C	Calcd, % H	Calcd, % S	Found, % C	Found, % H	Found, % S
Ia	CH_2CH_2	S	1	104–105	*a*	53	265	1,430	$C_{17}H_{16}S_2$	71.80	5.67	22.55	72.03	5.72	22.62
Ib	CH=CH	S	1	206–207	*b*	82	214	30,600	$C_{17}H_{14}S_2$	72.35	4.99	22.70	72.06	4.77	22.56
							293	11,300							
Ic	CH=CH	S	2	212–213	*c, d*	44	217	38,500	$C_{18}H_{16}S_2$	73.00	5.44	21.61	72.31	5.81	22.17
							285	9,930							
IIa	CH_2CH_2	SO_2	1	204–205	*e, f*	86[i]	268[j]	1,517	$C_{17}H_{16}O_4S_2$	58.65	4.63	18.40	58.38	4.64	18.23
IIb	CH=CH	SO_2	1	215–216 dec	*e*	91[i]	223	37,600	$C_{17}H_{14}O_4S_2$	59.00	4.08	18.50	58.68	4.02	18.26
							293	9,700							
IIc	CH=CH	SO_2	2	167–168	*g, h*	85	297[j]	9,400	$C_{18}H_{16}O_4S_2$	60.00	4.48	17.76	59.51	4.16	16.61

[a] Ethyl acetate. [b] Toluene. [c] Chloroform. [d] Ether. [e] Nitromethane. [f] Solvent of crystallization removed by heating at 80° (0.01 mm). [g] Dimethylformamide. [h] The infrared spectrum showed the presence of solvent even after prolonged drying. [i] Using 3-chloroperbenzoic acid; also obtained with H_2O_2. [j] DMF added to dissolve. [k] In ethanol.

SCHEME I



The required disulfones were obtained from the corresponding sulfides (I) by oxidation with either hydrogen peroxide or, more conveniently, 3-chloroperbenzoic acid. A reaction time of from 24 to 48 hr was necessary for completion of the reaction. There was no evidence, based on ultraviolet spectral data, of oxidative attack at the 10,11 double bond of compounds Ib and Ic (see Table I). Rigaudy[7] has reported that 5H-dibenzo[*a,d*]cyclohepten-5-one was converted to the corresponding 10,11-epoxide on treatment with perphthalic acid for 1 week or longer. Further evidence for the stability of the double bond was seen from the inability to hydrogenate the disulfone IIb to its dihydro analog IIa using either palladium in dioxane at 80° or Adams' catalyst in acetic acid at room temperature, both reactions being carried out under 3 kg/cm² pressure. The dithioketal Ib was similarly unaffected by treatment with diimide[8] or diborane. The alkylene thioketals I were prepared from the appropriate tricyclic ketone and 1,2-ethanedithiol or 1,3-propanedithiol using boron trifluoride etherate as condensing agent.[9] Whereas the dithiols reacted smoothly, ethylene glycol failed to give the ethylene ketal of 5H-dibenzo[*a,d*]cyclohepten-5-one either by heating under reflux with *p*-toluenesulfonic acid or keeping in toluene with boron trifluoride etherate at room temperature. 2-Mercaptoethanol also failed to react with this ketone. It has been recently reported[10] that a related tricyclic ketone, 6,11(5H)-morphanthridinedione forms an 11-ethylene ketal under vigorous conditions.

Several related experiments were carried out with the benzhydryl disulfone (IV). Heating with hydrazine gave 2-hydrazinoethyl sulfone (V) as a somewhat unstable compound. Treatment with 2-dimethylaminoethanol containing sodium hydroxide gave the basic

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(9) L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).

(10) A. E. Drukker and C. I. Judd, *J. Heterocyclic Chem.*, **2**, 276 (1965).

Table II
Basic Sulfones

No.	X	NR2	Mp, °C	Recrystn solvent	Yield, %	Ultraviolet spectra[f] λmax, mμ	ε	Formula	Calcd, % C	H	N	S	Found, % C	H	N	S
IIIa	CH_2CH_2	$N(CH_3)_2$	117–119	*a*	66	268[g]	924	$C_{19}H_{23}NO_2S$	69.40	7.01	4.26	9.74	69.18	7.02	3.95	9.50
IIIb	CH=CH	$N(CH_3)_2$	148–150	*b*	63	291	11,400	$C_{19}H_{21}NO_2S$			4.28	9.80			4.15	9.56
IIIb·HCl	CH=CH	$N(CH_3)_2$	205–207 dec	*c, d*		284	14,070	$C_{19}H_{22}ClNO_2S$	9.77[h]		8.83		10.25[h]		8.39	
IIIc	CH=CH		181–183	*b*	55	303	11,800	$C_{21}H_{23}NO_2S$	71.90	6.86	3.82	8.74	71.60	6.62	3.74	8.57
IIId	CH=CH		185–186 dec	*e*	62	297	12,200	$C_{23}H_{28}N_2O_2S$			7.33	8.39			7.31	8.43
IIIe	CH=CH		130–131	*e*	78	298	11,300	$C_{31}H_{33}NO_4S$	72.30	6.46	2.72	6.22	70.38	6.45	2.76	6.38

[a] 2-Propanol. [b] Ethyl acetate. [c] Ethanol. [d] Solvated; treatment with aqueous sodium bicarbonate regenerated the base, mp 143–147°. The salt was used for the biological tests. [e] Acetonitrile. [f] In ethanol. [g] Center of fine structure. [h] Chlorine.

ether (VI); the corresponding methyl and ethyl ethers had been prepared in a similar manner from the disulfone and alkali dissolved in the appropriate alcohol.[5] When, however, the alkali was omitted, both sulfonyl groups were retained and a compound (VII) having the properties of a sulfinic acid was isolated. Possibly the amino alcohol was sufficiently basic to effect only the first step of the reaction. When the product was heated under reflux with alcoholic sodium hydroxide, only the sodium sulfinate was obtained. 2,2-Diphenyl-1,3-oxathiolane 3,3-dioxide (VIII) was recovered unchanged on heating with piperidine.

Pharmacological Activity.—Table III shows that the basic tricyclic (III) and benzhydryl (V–VII) sulfones were, in general, devoid of pronounced pharmacological activities in most tests. The experimental procedures have been described previously.[12] As can be seen, only the direct analog (IIIa) of amitriptyline had a spectrum of activity qualitatively similar to that of the parent drug. Unsaturation in the 10,11 position of the ring system led to a more toxic compound (IIIb), although it was ineffective in the other tests at one-quarter of the LD_{50}. The spirodisulfones (II) were also ineffective and relatively nontoxic (LD_{50} values >1200 mg/kg).

The effects of compounds IIIb, V, VI, and VII on the arterial blood pressure, intestinal tonus and motility, and respiratory movements were determined in cats which were anesthetized with chloralose–urethan. Intravenous administration of 5- to 10-mg/kg doses of IIIb, V, and VI caused a transient (<15 min) fall in blood pressure. The intestinal tonus and motility were increased by IIIb and V but decreased by VI. The frequency of respiration was increased by IIIb and VI. None of these parameters was affected by compound VII in doses up to 20 mg/kg.

In contrast to their lack of pronounced activity in the above-mentioned tests, most of the compounds possessed some antiparasitic activities. They showed trichomonacidal effects against *Trichomonas vaginalis* and *T. foetus* in concentrations ranging from $^1/_{50,000}$ to $^1/_{200,000}$. The basic sulfones III also had larvicidal activity against horse strongyles[12] when tested at 10^{-3} *M*. The piperidino sulfone (IIIe) exhibited a 56% kill in this assay.

Experimental Section

Melting points were read on a Thomas-Hoover Uni-Melt apparatus. 5H-Dibenzo[*a,d*]cycloheptan-5-one and its 10,11-dihydro analog were prepared according to known procedures;[13] 3-chloroperbenzoic acid was obtained from FMC Corp. and assayed before use by iodometric titration.

Spiro[10,11-dihydro-5H-dibenzo[*a,d*]cycloheptene-5,2′-(1′,3′-dithiolane)](Ia).—A solution of 10,11-dihydro-5H-dibenzo[*a,d*]cycloheptan-5-one (41.6 g, 0.2 mole) and 1,2-ethanedithiol (56.0 g, 0.6 mole) in glacial acetic acid (100 ml) was treated with boron trifluoride etherate (60 ml) and kept at room temperature. The addition of a few seed crystals after 1 week initiated the deposition of crystalline material; the reaction was completed by keeping it for a further 2 weeks. The precipitate was filtered off and dissolved in dichloromethane, and the solution was extracted with dilute NaOH solution and then water. Drying and evaporation of the solvent left 27.9 g, mp 103–105°. An addi-

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(12) N. D. Levine, *Trans. Illinois State Acad. Sci.*, **43**, 233 (1950).

(13) T. W. Campbell, R. Gingig, and H. Schmid, *Helv. Chim. Acta*, **36**, 1489 (1953).

TABLE III
PHARMACOLOGICAL RESULTS

Compd	LD_{50}[a] (mice), mg/kg	MES ED_{50} (mice), mg/kg	Ataxia ED_{50} (rats), mg/kg	Alcohol potentiation ED_{50} (mice), mg/kg	Mydriasis (mice), $^1/_4LD_{50}$	Local anesthesia[d] EC_{50}, % (w/v)
Amitriptyline	83	10	53	8	19	...
IIIa	640	90	140	90	15	...
IIIb	150	>40[c]	>40	>40	0	...
IIIc	43	>10	>10	18	0	...
IIId	25	>6	>6	16	0	...
IIIe	<200[b]	...	...	...	..	...
V	330	>80	>80	...	0	0.4
VI	215	>50	>50	29	4	0.75
VII	930	>250	>250	...	0	>2.0

[a] All compounds were injected intraperitoneally in each test except for local anesthesia; here they were administered subcutaneously at the base of the tail (mice). [b] No analgesia at 265 mg/kg ip. [c] No effect at this dose. [d] Method similar to one used for analgesic testing as described by F. Haffner, *Deut. Med. Wochsch.*, **55**, 731 (1929).

tional 2 g of product was obtained by dilution of the acetic acid filtrate with water (500 ml), extraction with dichloromethane, and washing of the latter with NaOH and water; the residue obtained on removal of the solvent was triturated with a little ethyl acetate. Recrystallization from ethyl acetate afforded white platelets, mp 104–105°.

When the reaction was carried out at 50° for 24 hr a yield of only 1.8% was obtained. The 10,11-dehydro analogs (Ib) and (Ic) were prepared in a manner similar to that described above except that the reaction times were decreased to 4 and 6 days, respectively.

Spiro[10,11-dihydro-5H-dibenzo[*a,d*]cycloheptene-5,2'-(1',3'-dithiolane)] 1',1',3',3'-Tetroxide (IIa). A.—To a solution of Ia (25.0 g, 0.09 mole) in dichloromethane (150 ml) was added in four equal portions a solution of 3-chloroperbenzoic acid (assay 85%; 75.0 g, 0.37 mole) in dichloromethane (1000 ml). The first 2 moles of oxidant were consumed at once; the third mole required about 5 hr and the last about 2 days for completion of the oxidation. The precipitate was filtered off and washed well with ether to remove 3-chlorobenzoic acid, leaving behind the insoluble disulfone. The dichloromethane filtrate was extracted successively with dilute $NaHSO_3$ and $NaHCO_3$ solutions and then with water. Removal of the solvent *in vacuo* gave an additional crop of product (total 27.7 g, mp 177–179°). Recrystallization from nitromethane afforded white needles, mp 204–205° dec. The infrared spectrum of this and the related disulfones (IIb and c) showed the two strong sulfone absorptions at 1350–1300 and 1160–1120 cm^{-1}; no sulfoxide band at 1070–1030 cm^{-1} was seen.[14]

The other disulfones were prepared in a similar manner; the consumption of the last 2 moles of oxidant was more rapid and the reactions were essentially complete after 24 hr.

B.—A solution of Ia (10.0 g, 0.035 mole) in acetic acid (100 ml) was treated with 30% H_2O_2 (20 g) and kept at 70°. After 4 hr another 20-g portion of peroxide was added and the heating was maintained for a further 4 hr. The mixture was cooled and diluted with water, and the precipitate was washed with ether. Recrystallization from nitromethane gave 7.7 g (63% yield), mp 203–205° dec.

2,2-Diphenyl-1,3-oxathiolane 3,3-Dioxide (VIII).—A solution of 2,2-diphenyl-1,3-oxathiolane[15] (2.0 g, 0.008 mole) in acetone (150 ml) was stirred for 48 hr with pulverized $KMnO_4$ (3 g). The mixture was filtered through Celite and the solvent was removed *in vacuo*. The residue was taken up in dichloromethane, the solutions were refiltered and then evaporated. Trituration of the residual oil with a little hexane removed the starting material and gave the product (0.9 g, 40% yield), mp 138–141°, unchanged on recrystallization from ethyl acetate–hexane; λ_{max}^{ether} 252, 258, 262, 269 mμ (ε 776, 804, 724, 466). Abnormal values were obtained when the spectrum was taken in ethanol.

Anal. Calcd for $C_{15}H_{14}O_3S$: C, 65.69; H, 5.15; O, 17.50; S, 11.66. Found: C, 65.60; H, 4.86; O, 17.68; S, 12.09.

Attempted preparations using hydrogen peroxide or 3-chloroperbenzoic acid were unsuccessful.

(14) W. Otting and F. A. Neugebauer, *Chem. Ber.*, **95**, 540 (1962).
(15) J. R. Marshall and H. A. Stevenson, *J. Chem. Soc.*, 2360 (1959).

5-(2-Dimethylaminoethylsulfonyl)-10,11-dihydro-5H-dibenzo-[*a,d*]cycloheptene (IIIa).—A suspension of disulfone IIa (7.7 g, 0.02 mole) in dry dioxane (50 ml) was saturated with dimethylamine and heated in an autoclave at 100° for 1 hr. The solvent was removed *in vacuo* to give a yellow oil which crystallized on trituration with water. The solid was taken up in dichloromethane, the solution was washed with water, then dried and evaporated leaving 5.6 g, mp 106–111°. Recrystallization from 2-propanol gave white plates, mp 117–119°.

5-[2-(4-Carbethoxy-4-phenylpiperidino)ethylsulfonyl]-5H-dibenzo[*a,d*]cycloheptene (IIIe).—A mixture of disulfone IIb (1.6 g, 0.005 mole), normeperidine (1.2 g, 0.005 mole), and dry pyridine (1 ml) in toluene (25 ml) was heated under reflux for 4.5 hr; gradual dissolution of the disulfone occurred. The cooled solution was diluted with ether (15 ml) and treated with CO_2, and a small amount of precipitate was filtered off. The filtrate was extracted with water, dried, and evaporated leaving an oil (1.6 g) which crystallized on trituration with ether, mp 121–129°. Recrystallization from ethanol afforded material, mp 130–131°, which gave variable and unsatisfactory analytical results for carbon (see Table II). The compound was homogeneous on thin layer chromatography and the spectral data supported the proposed structure.

The **oxalate** salt, mp 199–200°, also gave poor analytical values.

Anal. Calcd for $C_{33}H_{35}NO_8S$: C, 65.44; H, 5.83. Found: C, 63.33; H, 6.26.

2-Hydrazinoethyl Benzhydryl Sulfone (V).—A mixture of 2,2-diphenyl-1,3-dithiolane 1,1,3,3-tetroxide[6] (4.0 g, 0.012 mole) and anhydrous hydrazine (10 ml) was heated on the steam bath for 15 min; effervescence occurred and the reaction mixture became homogeneous. It was poured into cold water and the product was extracted into dichloromethane. The solvent was dried and removed *in vacuo* leaving an oil (2.5 g) which crystallized on trituration with hexane. Recrystallization from ethyl acetate gave a sample as white needles, mp 99–102°, which tended to decompose on standing.

Anal. Calcd for $C_{15}H_{18}N_2SO_2$: C, 62.00; H, 6.24; S, 11.03. Found: C, 61.16; H, 5.65; S, 10.88.

The **oxalate** salt formed white needles from aqueous ethanol; mp 165–167° dec; λ_{max}^{EtOH} 220, 258 mμ (ε 17,700, 799).

Anal. Calcd for $C_{17}H_{20}N_2SO_6$: N, 7.38; S, 8.44. Found: N, 7.21; S, 8.32.

2-(2-Dimethylaminoethoxy)ethyl Benzhydryl Sulfone (VI).—Sodium hydroxide (2.0 g, 0.05 mole) was pulverized and dissolved in 2-dimethylaminoethanol (15 ml) with heating. 2,2-Diphenyl-1,3-dithiolane 1,1,3,3-tetroxide (8.0 g, 0.025 mole) was added and the mixture was stirred for 3 hr on the steam bath. It was then cooled, diluted with water (70 ml), and extracted with dichloromethane. The organic layer was washed with water, dried, and evaporated, and the residue was recrystallized from ethyl acetate–hexane giving prisms (3.1 g, 36% yield): mp 104–105°; λ_{max}^{EtOH} 253, 259, 262, 269 mμ (ε 451, 581, 515, 355).

Anal. Calcd for $C_{19}H_{25}NSO_3$: C, 65.67; H, 7.25; N, 4.03; S, 9.23. Found: C, 65.34; H, 7.10; N, 3.86; S, 9.41.

2,2-Diphenyl-2-(2-dimethylaminoethoxy)ethylsulfonylmethanesulfinic Acid (VII).—The preceding reaction was repeated employing the disulfone (15.0 g, 0.05 mole) and basic alcohol

(20 ml) but omitting NaOH. Heating on the steam bath for 1 hr gave a clear solution which was cooled and diluted with dry ether (150 ml). The gummy precipitate crystallized on trituration with fresh ether giving 16.2 g, mp 141–145°. Recrystallization from ethanol gave a sample, mp 150–154°, which could not be completely purified: ν_{max}^{Nujol} 1132, 1302 (SO_2), 1083 (SO_2H), 3060–2760 (associated OH), 3440 (nonassociated OH), 1045 cm^{-1} (ether); λ_{max}^{EtOH} 253, 259, 269 (ε 410, 528, 293).

Anal. Calcd for $C_{19}H_{22}NO_5S_2 \cdot 2H_2O$: C, 50.99; H, 6.53; N, 3.13; S, 14.31. Found: C, 50.07; H, 6.04; N, 3.08; S, 14.12.

The material formed a sodium salt which was recrystallized from hot water: mp 235–237°.

Acknowledgment.—We wish to thank Dr. G. S. Myers and his group for furnishing the tricyclic ketones in quantity, Dr. D. Campbell for the results of antiparasitic testing, and Dr. H. Baker for the trichomonacidal testing. Spectral data were recorded and helpfully interpreted by Mr. M. Boulerice, and analyses were carried out by Mr. W. J. Turnbull.

The Preparation and Biological Activities of Some Azonino- and Azecinoindoles and Benzazecines

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Received May 5, 1966

Various 1,2,3,4,5,6,7,8-octahydro-3-methylazonino[5,4-*b*]indoles, 1,2,4,5,6,7,8,9-octahydro-3-methyl-3H-azecino[5,4-*b*]indoles, and 1,2,3,4,5,6,7,8-octahydro-3-methyl-3-benzazecines of types **1–3**, respectively, have been prepared by reduction (with lithium and 1-methoxy-2-propanol in liquid ammonia) of the corresponding 2,3,5,6,11,11b-hexahydro-4-methylindolo[3,2-*g*]-1H-indoliziniinm iodides, 1,2,3,4,6,7,12,12b-octahydro-5-methylindolo[2,3-*a*]quinoliziniinm iodides, and 1,2,3,4,6,7-hexahydro-5-methyl-11bH-benzo[*a*]quinoliziniinm iodides of types **4–6**, respectively. Evidence is presented that the reduction involves an initial addition of two electrons. Biological activities are given for various members of the series **1–3**.

This paper records initial findings in a program for the synthesis and biological testing of compounds containing the azonino- and azecinoindole and benzazecine nuclei **1–3**, respectively. Our interest in members of this series arose from their structural relationship to corresponding benz- and indolindolizines and -quinolizines, including a number of alkaloids, which have been shown to possess interesting biological activities. These include potent pharmacodynamic effects on the central nervous system[1] and hypotensive[2] and amebicidal[3] activity.

We proposed to make compounds with the nuclei **1–3** through the metal–ammonia reduction of quaternary salts containing the corresponding moieties **4–6**, since, although the respective cations may, theoretically, undergo carbon–nitrogen cleavage in four distinct ways, the bond involving the benzylic carbon in the benzene series and the benzylic-like carbon in the indole series is expected to be the most susceptible.[4,5] We believed that salt formation on the indolic nitrogen would not affect the postulated cleavage of the indole cations of types **4** and **5** (R^1 = H), since such a reaction did not interfere with the selective cleavage of the allylic carbon–nitrogen bonds in agroclavine and elymoclavine methiodides.[6] After the completion of our work on the azonino- and azecinoindoles **1** and **2** (R = CH_3; R^1 = H), respectively (below), Wenkert and his colleagues[7] independently disclosed the preparation of the former compound, and Dolby and Booth[8] obtained the 2-hydroxy derivative of the amine **2** (R = CH_3) by methods similar to those reported here.

Azonino- and Azecinoindoles.—The bases **1** and **2** (R = CH_3) were prepared by the metal-ammonia reduction of the salts **4** and **5** (R = CH_3). Wenkert, *et al.*,[7] who have already reported the preparation of the first compound by the reduction of the salt **4** (R = CH_3; X = I) with an undisclosed amount of lithium and ethanol in liquid ammonia, assigned the structure from the elemental analysis and nmr spectra. The nmr evidence (NCH_3 singlet; no CCH_3 signal) while demonstrating that cleavage of the C–N bridgehead bond had occurred, did not definitely exclude an olefinic structure formed through Hofmann elimination. However, we observed no vinylic proton signals in the nmr spectrum, thereby confirming structure **1**. The presence in the nmr spectra of an NCH_3 singlet and the absence of CCH_3 and vinylic proton signals were similarly used to assign structures to all of the azonino- and azecinoindoles described in this paper. In a detailed examination of the preparation of **1** (R = CH_3), we found that lithium gave better conversion to the azoninoindole than sodium, and inclusion of 1-methoxy-2-propanol in the reaction medium gave improved yields with either metal. The beneficial effect of the alcohol may be due to its buffering action upon the reaction medium which, by ensuring that alkoxide rather than the more basic amide anion is formed by protonation of the reaction intermediates,[4] could reduce the incidence of side reactions of the Hofmann elimination type. The results of a comparative study of the reductive cleavage of the salt **4** (R = CH_3; R^1 = H;

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