5.77 μ (acetate); τ 9.18, 9.17 (s,s, C-18 Me or C-19 Me), 7.96 (s, 17-acetate), 6.94 (d,d, 3.5 c.p.s., 12 c.p.s., 5-H), and 5.39 (m, 17-H).

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.46; H, 9.84.

3-Oxa-5α-A-norandrostan-17β-ol (VIII).—A solution of 3-oxa-5α-A-norandrostan-17β-ol acetate (VII) (200 mg.) in methanol (20 ml.) was treated with a 10% K_2CO_3 solution (2 ml.) and stirred at room temperature for 1 day. The reaction mixture was concentrated on a steam bath and diluted with water, and the precipitate was collected by filtration and dried *in vacuo* at 60° for 1.5 hr. to give VIII (170 mg.), m.p. 138–141°. Recrystallization from hexane gave the analytical sample, m.p. 143.5–145.5°, $[\alpha]^{22}D$ +25°, λ 3.04 μ (OH).

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.19; H, 10.68.

Synthesis of Potential Antidiabetic Agents. 1-*p*-Tolylsulfonyl-2-benzimidazolinones and 1-*p*-Tolylsulfonyl-2-benzimidazolinethiones

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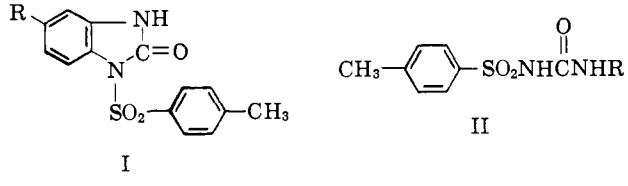
Received November 11, 1964

During the course of some continuing work[1] in these laboratories on antidiabetic compounds we were interested in investigating some *p*-tolylsulfonylbenzimidazolinones of the general type I. These may be looked upon as *p*-tolylsulfonylureas of the tolbutamide-type (II, R = n-C_4H_9) in which a phenyl ring is fused to the N-1 and N-2 urea nitrogens. Compounds of this type were prepared as outlined below.

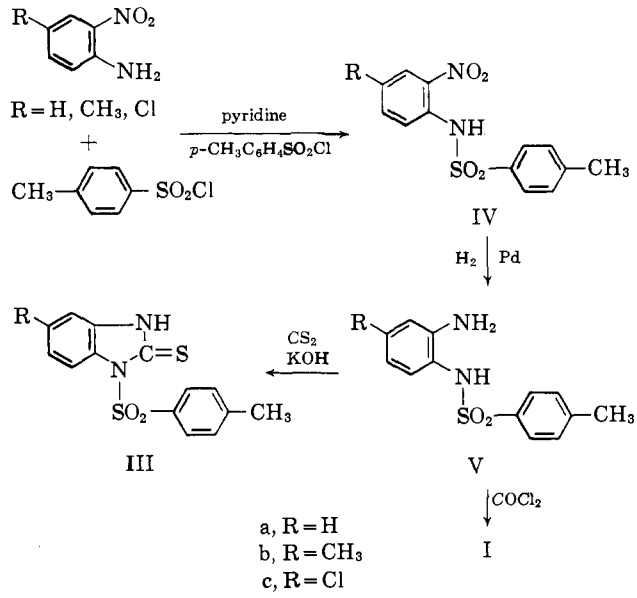


I

II

R = H, CH_3, Cl

Treatment of the requisite *o*-nitroanilines with *p*-toluenesulfonyl chloride in refluxing pyridine gave the sulfonamides (IV) in excellent yields. Reduction of the nitrosulfonamides (IV) to the *o*-aminosulfonamides (V) was effected in good yield with hydrogen and palladium-on-charcoal catalyst in alkaline or ammoniacal solution. The N-*o*-aminophenylsulfonamides (V) were converted to their hydrochlorides in aqueous dioxane by the addition of an equivalent amount of hydrochloric acid. The resulting solution upon saturation with phosgene gave the desired 1-*p*-tolylsulfonylbenzimidazolinones (I) in good yield. Treatment of the aminosulfonamides (V) with carbon disulfide in ethanolic potassium hydroxide solution gave the corresponding 1-*p*-tolylsulfonylbenzimidazolinethiones (III).



a, R = H
b, R = CH_3
c, R = Cl

When tested in glucose-primed intact rats the benzimidazolinones (I) and benzimidazolinethiones (III) showed practically no blood sugar lowering activity.[2]

TABLE I

PROPERTIES OF COMPOUNDS PREPARED

No.	Method of prepn.	Yield, %	Recrystn. solvent[a]	M.p., °C.	Formula	Calcd., % C	H	N	S	Found, % C	H	N	S
Vb	A	66	F	135–137	$C_{14}H_{16}N_2O_2S$	60.85	5.84	10.14	11.60	60.56	5.88	9.86	11.26
Ib	B	78	E	263–265	$C_{15}H_{14}N_2O_3S$	59.59	4.67	9.27	...	59.38	4.34	9.27	...
IIIb	C	62	E	148.5–150	$C_{15}H_{14}N_2O_2S_2$	56.58	4.43	8.80	20.14	56.48	4.75	8.81	19.92
IVc	D	81	G	107.5–109.0	$C_{13}H_{11}ClN_2O_4S$	47.78	3.39	...[b]	9.81	47.79	3.17	...[b]	10.10
Vc	A	19[c]	H	129.5–131	$C_{13}H_{13}ClN_2O_2S$	52.61	4.42	9.49	10.80[d]	53.06	4.53	9.21	10.80[d]
Ic	B	60	E	252–253	$C_{14}H_{11}ClN_2O_3S$	52.10	3.44	8.68	9.93[e]	52.35	3.21	8.43	9.74[e]
IIIc	C	59	J	142.5–143.5	$C_{14}H_{11}ClN_2O_2S_2$	...	...	8.29	18.92	...	...	7.98	18.88

[a] F = 90% ethanol, E = ethanol, G = 2-propanol, H = benzene, J = 20% ethanol. [b] Calcd.: Cl, 10.85. Found: Cl, 10.55. [c] A 1.5 *N* NH_4OH solution was used instead of 5% NaOH solution. [d] Calcd.: Cl, 11.95. Found: Cl, 11.56. [e] Calcd.: Cl, 10.98. Found: Cl, 10.58.

Experimental[3,4]

N-*p*-Tolylsulfonyl-*o*-phenylenediamine (Va). Method A.—A mixture of 14.6 g. (0.05 mole) of N-*p*-tolylsulfonyl-*o*-nitroaniline[5] and 300 ml. of 5% NaOH solution was hydrogenated at 3.1 kg./cm.^{2} using 1 g. of 10% palladium-on-charcoal catalyst. The catalyst was removed by filtration and washed with a 5% NaOH solution. The filtrate was acidified with acetic acid and the precipitate was filtered and recrystallized from benzene. There was obtained 6.24 g. (48%) of tan needles melting at 141–142°.

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68; S, 12.22. Found: C, 59.68; H, 5.00; N, 10.32; S, 12.23.

1-*p*-Tolylsulfonyl-2-benzimidazolinone (Ia). Method B.—To 3.94 g. (0.015 mole) of N-*p*-tolylsulfonyl-*o*-phenylenediamine

(1) J. B. Wright and R. E. Willette, *J. Med. Pharm. Chem.*, **5**, 815 (1962).

(2) For these biological results we are indebted to Dr. William E. Dulin and co-workers of these laboratories.

(3) All of the melting points reported are uncorrected for stem exposure.

(4) We are indebted to Dr. Robert Rinehart and co-workers for the microanalytical data and for infrared and ultraviolet spectral studies. We are especially indebted to Mr. Albert Lallinger for technical assistance.

(5) F. Bell and P. H. Robinson, *J. Chem. Soc.*, 1127 (1927).

was added 15 ml. of 1 *N* HCl, 50 ml. of water, and 30 ml. of dioxane. The resulting solution was cooled to 10° and saturated with phosgene. The mixture was filtered, washed with water, and recrystallized from ethanol. There was obtained 2.50 g. (59%) of red-tan prisms melting at 211–215°.

Anal. Calcd. for $C_{14}H_{12}N_2O_3S$: C, 58.32; H, 4.20; N, 9.72; S, 11.12. Found: C, 58.32; H, 4.07; N, 9.67; S, 11.11.

1-*p*-Tolylsulfonyl-2-benzimidazolinethione (IIIa). Method C.—A mixture of 4.33 g. (0.0165 mole) of *N*-*p*-tolylsulfonyl-*o*-phenylenediamine, 0.93 g. (0.0165 mole) of KOH, 1.30 g. (0.017 mole) of carbon disulfide, 20 ml. of ethanol, and 2.25 ml. of water was heated under reflux for 3 hr. The mixture was diluted with about 20 ml. of water and acidified with acetic acid. The solid was removed by filtration and washed with water; yield, 3.84 g. Recrystallization from ethanol gave light tan needles melting at 153°. The melting point appeared to vary depending upon the rate of heating.

Anal. Calcd. for $C_{14}H_{12}N_2O_2S_2$: C, 55.26; H, 3.98; N, 9.21; S, 21.03. Found: C, 55.25; H, 4.04; N, 9.38; S, 21.24.

N-*p*-Tolylsulfonyl-4-methyl-2-nitroaniline (IVb). Method D.—A solution of 95.32 g. (0.5 mole) of *p*-toluenesulfonyl chloride and 76.07 g. (0.5 mole) of 4-methyl-2-nitroaniline in 200 ml. of pyridine was heated under reflux for 1 hr. The pyridine was removed *in vacuo* at 50°. The residue was diluted with water. The precipitate was removed by filtration and recrystallized from 2-propanol. There was obtained 142.9 g. (93%) of yellow rosettes melting at 100–101°.

Anal. Calcd. for $C_{14}H_{14}N_2O_4S$: C, 54.89; H, 4.61; S, 10.47. Found: C, 55.06; H, 4.62; S, 10.60.

Hexahydropyrimidines. VI. Some 2-{4-[N,N-Bis(2-chloroethyl)amino]aryl}-1,3-bis(aralkyl)hexahydropyrimidines[1]

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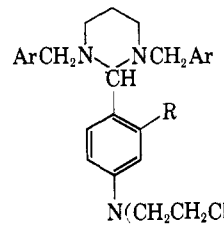
Received February 24, 1965

In a previous publication[2] the syntheses of some



Ia, R = CH_3

b, R = H

compounds of type I were described. The degree of activity of those compounds against Walker carcinoma 256 appeared to be related to the electron-donating ability of the substituents on the nitrogens of the hexahydropyrimidine ring. Two additional compounds of type Ia have been prepared, as indicated in Table I. Compound II was synthesized by condensing *o*-tolualdehyde nitrogen mustard with N,N′-bis(*p*-dimethylaminobenzyl)-1,3-diaminopropane, and III was obtained in a similar manner from *o*-tolualdehyde nitrogen mustard and N,N′-bis(*o*-methoxybenzyl)-1,3-diaminopropane.

Biological Results.—Compounds II and III indicated some inhibitory activity against Walker carcinoma 256.[3]

TABLE I

2-{4-[N,N-BIS(2-CHLOROETHYL)AMINO]ARYL}-1,3-BIS-(ARALKYL)HEXAHYDROPYRIMIDINES[a]

No.	Ar	R	Yield, % (pure)	M.p., °C. (cor.)	Nitrogen, % Calcd.	Found
II	*p*-Dimethylaminophenyl[c]	CH_3	32	117–118	12.01	12.09
III	*o*-Methoxyphenyl[c]	CH_3	50	127.5–129	7.55	7.26

[a] See compound I for general structure. [b] Microanalyses were performed by Midwest Microlab, Indianapolis, Ind. [c] Recrystallized from acetonitrile.

TABLE II

INHIBITION OF WALKER CARCINOMA 256[a]

Ar	R	Dose, mg./kg.	% inhibition	Animal deaths
p-Methoxyphenyl[2]	CH_3	100	100	None
o-Methoxyphenyl	CH_3	100	95	None
p-Dimethylaminophenyl	CH_3	100	77	None
p-Chlorophenyl[2]	CH_3	100	71	None
2,4-Dichlorophenyl[2]	CH_3	100	22	None
3,4-Dichlorophenyl[2]	CH_3	100	57	None

[a] See ref. 3; see compound I for general structure.

Both have an electron-releasing group on the phenyl ring of the substituent Ar, and the results followed the general structure–activity relationship previously suggested.[2] A comparison of the antitumor activity of II and III with other compounds of type Ia is given in Table II.

If electron release by Ar is indeed a factor in inhibitory activity, then the possibility of some loss of activity through *in vivo* protonation of the dimethylamino nitrogens should be considered.

Experimental

The preparation of N,N′-bis(*p*-dimethylaminobenzyl)-1,3-diaminopropane has been described.[4]

N,N′-Bis(*o*-methoxybenzyl)-1,3-diaminopropane.—Equimolar quantities of *o*-methoxybenzaldehyde and 1,3-diaminopropane were well mixed and then warmed with an oil bath at 100° for 30 min. The water which formed was removed by adding benzene and distilling the azeotrope. All of the benzene was removed under vacuum and absolute ethanol was added to the crude N,N′-bis(*o*-methoxybenzylidene)-1,3-diaminopropane. This di-Schiff base was hydrogenated to produce the corresponding diamine using PtO_2 and a hydrogen pressure of 2–3 atm. The catalyst was removed by filtration and the ethanol was removed under vacuum using a rotary evaporator. The crude diamine oil was used in the preparation of III. A small sample of the diamine dihydrochloride was prepared by passing dry HCl through a solution of the diamine in benzene. This dihydrochloride was recrystallized from an ethanol–acetone mixture to give a sample with m.p. 184.5° dec.

Anal. Calcd. for $C_{19}H_{26}N_2O_2 \cdot 2HCl$: Cl, 18.32; N, 7.24. Found: Cl, 18.67; N, 7.31.

2-{4-[N,N-Bis(2-chloroethyl)amino]aryl}-1,3-bis(aralkyl)hexahydropyrimidines (Table I).—These compounds were prepared by the method reported in ref. 2. The *o*-tolualdehyde nitrogen mustard was obtained commercially.[5]

Acknowledgment.—The authors thank Mr. John Sherman for his assistance in preparing some of the intermediate compounds. We wish to acknowledge Drs. H. W. Bond, R. B. Ross, and J. Leiter of the Cancer Chemotherapy National Service Center for their cooperation in obtaining the screening data. Thanks are also due the Union Carbide Chemicals Company for the 1,3-diaminopropane they supplied.

(1) This investigation was supported by a Public Health Service Research Grant No. CA-08888-01 from the National Cancer Institute.

(2) Part IV: J. H. Billman and J. L. Meisenheimer, *J. Med. Chem.*, **7**, 115 (1964).

(3) Screening data were obtained by the Cancer Chemotherapy National Service Center, Bethesda, Md.

(4) J. H. Billman and L. C. Dorman, *J. Pharm. Sci.*, **51**, 1071 (1962).

(5) Frinton Laboratories, South Vineland, N. J.