action was allowed to proceed for an additional 13 min. at which time the solution was colorless. After addition of 7 ml. of methanol the NH_3 was evaporated using a water bath at a temperature of ~40°. The solution was then further concentrated *in vacuo*, and 50 ml. of water was added to the gummy residue to yield a powdery precipitate which was separated by filtration. Crystallization from petroleum ether and ether afforded 1.175 g. of I, m.p. 123–134°. Further recrystallization from the same solvents yielded a sample for analysis: m.p. 134–136°; α_D +46°; ultraviolet $\lambda_{max}^{dioxane}$ 269 mμ (ε 300), 276 mμ (ε 210).

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.06; H, 8.55.

TABLE I

Compd.	Oral gonadotrophin inhibition[a] (parabiotic rats)	Progestational activity[b]
17α-Chloroethynyl-4-estren-17β-ol-3-one[c]	1	1[d]
17α-Chloroethynyl-5(10)-estren-17β-ol-3-one[c]	1.2	0.03[d]
17α-Chloroethynyl-4,9(10)-estradien-17β-ol-3-one[c]	2.5	2[d]
III	0.2	0[e]
II	0[f]	0[g]

[a] J. A. Epstein, H. S. Kupperman, and A. Cutler, *Ann. N. Y. Acad. Sci.*, **71**, 560 (1958). [b] M. K. McPhail, *J. Physiol.*, **83**, 145 (1934). [c] Ref. 1. [d] Oral. [e] At 500 γ/kg. s.c. [f] At 400 γ s.c. [g] At 50 γ/kg. s.c.

3-Methoxy-2,5,7,9-estratetraen-17-one.—A solution consisting of 255 mg. of I (m.p. 129–136°), 306 mg. of freshly distilled aluminum isopropoxide, and 13 ml. of dry toluene was heated for 5 min. on the steam bath under an atmosphere of nitrogen. The solution was cooled in ice and 2.6 ml. of distilled cyclohexanone was added. The solution was again heated on the steam bath under nitrogen for 40 min. and cooled in ice. A saturated aqueous solution of Rochelle salts was added with vigorous shaking and the product separated with ether. After evaporation of the ether the remaining solution was steam distilled. The residue was extracted with ether, dried ($MgSO_4$), and concentrated to yield 210 mg. of the product, double m.p. 115–130°, 167–177°. Several crystallizations from methanol and finally from ether afforded a sample for analysis; m.p. 148–153; α_D +72°; ultraviolet λ_{max} 269 mμ (ε 300), 276 mμ (ε 230).

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.90; H, 7.61.

17α-Chloroethynyl-3-methoxy-2,5,7,9-estratetraen-17β-ol (II).—A solution of *cis*-1,2-dichloroethylene in 15 ml. of sodium-dried ether was added to a stirred solution consisting of 6.0 ml. of 1.30 *N* methyllithium in 15 ml. of sodium-dried ether maintained under an atmosphere of nitrogen and cooled by an ice bath. Stirring was continued for an additional 20 min. after removal of the ice bath, followed by the dropwise addition of 732 mg. of 3-methoxy-2,5,7,9-estratetraen-17-one in 80 ml. of sodium-dried ether over a 15-min. period. After an additional hour the reaction mixture was poured into ice water and ether. The ether layer was separated, washed with water, dried (K_2CO_3), and concentrated *in vacuo* to yield 620 mg. in two crops, m.p. 114–119° and 111–116°. A sample for analysis was crystallized three times from ether; m.p. 122–125° (sealed evacuated capillary); α_D −92°; ultraviolet λ_{max} 269 mμ (ε 450), 275 mμ (ε 400).

Anal. Calcd. or $C_{21}H_{23}ClO_2$: C, 73.57; H, 6.76; Cl, 10.34. Found: C, 73.27; H, 6.75; Cl, 10.28.

17α-Chloroethynyl-5,7,9-estratrien-17β-ol-3-one (III).—A solution consisting of 352 mg. of II, 35 mg. of *p*-toluenesulfonic acid, and 20 ml. of acetone was stirred at room temperature for 1 hr., diluted with ether, and washed with aqueous $NaHCO_3$ solution. The ether solution was dried (K_2CO_3) and concentrated to yield 251 mg. of III, m.p. 165–178° with slight decomposition. A sample for analysis was recrystallized three times from ether; m.p. 173–179°; α_D −102°; ultraviolet λ_{max} 270 mμ (ε 520), 307 mμ (ε 220).

Anal. Calcd. for $C_{20}H_{21}ClO_2$: C, 73.05; H, 6.44; Cl, 10.78. Found: C, 72.74; H, 6.43; Cl, 10.79.

A-Nor Oxa Steroids[1]

SEYMOUR D. LEVINE

The Squibb Institute for Medical Research, New Brunswick, New Jersey

Received February 1, 1965

Although the introduction of an oxygen atom into the steroid nucleus has attracted the attention of chemists for several decades,[2] it was only recently that the synthesis of 17-oxa-5α-androstan-3-one was reported.[3] This represents the first example of a steroid analog in which oxygen has been inserted into a five-membered ring. Since a ring A oxa steroid (17β-hydroxy-17α-methyl-2-oxa-5α-androstan-3-one)[4] has been demonstrated to be a potent anabolic agent, the synthesis of an A-nor steroid bearing an oxygen atom in ring A appeared an attractive target both from a chemical and biological view.

A-nortestosterone (I)[5] was hydroxylated with osmium tetroxide in pyridine to give A-norandrostan-2-one-3β,5β,17β-triol (II).[6] Periodic acid oxidation of glycol II gave a product whose infrared spectrum exhibited a single carbonyl band at 5.73 μ indicating that the lactol III and not a keto acid had been obtained. This lactol had been previously obtained in low yield by ozonation of 2-hydroxymethylenetestosterone.[7]

Sodium borohydride reduction of III gave 2,5-seco-3,4-bisnorandrostane-5β,17β-diol-2-oic acid (IV) as the major product. The assignment of configuration was based on the fact that sodium borohydride reduction of an unhindered ketone yields the equatorial isomer as the predominant product.[8] It is noteworthy that a similar reduction of a six-membered ring A steroidal lactol leads directly to the lactone *via* cyclization of the hydroxy acid.[9]

Efforts to prepare the γ-lactone by heating IV in refluxing hydrocarbon solvents (benzene, toluene, or *p*-cymene) were unsuccessful leading in each case to recovered starting material. Lactonization was ultimately achieved by treatment of IV with acetic anhydride containing sodium acetate to afford 3-oxa-5α-A-norandrostan-2-on-17β-ol acetate (V). The n.m.r. spectrum of V exhibited a quartet centered at τ 6.16 for the axial proton at C-5.[9b]

The reduction of lactone V with lithium aluminum hydride in ether gave 2,5-seco-3,4-bisnorandrostane-2,5β,-17β-triol (VI). Direct reduction of V to an ether using lithium aluminum hydride and boron trifluoride[10] was unsuccessful. The failure of a γ-lactone to be reduced to its corresponding ether under these conditions has been observed previously.[3]

(1) Presented at the 4th Annual Metropolitan Regional Meeting at Stevens Institute, Hoboken, N. J., Feb. 1, 1965.

(2) See L. Tokes in "Steroid Reactions," C. Djerassi, Ed., Holden Day, Inc., San Francisco, Calif., 1963, pp. 459–502, for references in this area.

(3) S. Rakhit and M. Gut, *J. Org. Chem.*, **29**, 229 (1964).

(4) R. Pappo and C. J. Jung, *Tetrahedron Letters*, **No. 9**, 365 (1962).

(5) F. L. Weisenborn and H. E. Applegate, *J. Am. Chem. Soc.*, **81**, 1960 (1959).

(6) S. D. Levine and P. A. Diassi, *J. Org. Chem.*, **30**, 1325 (1965).

(7) F. L. Weisenborn, D. C. Remy, and T. L. Jacobs, *J. Am. Chem. Soc.*, **76**, 555 (1954).

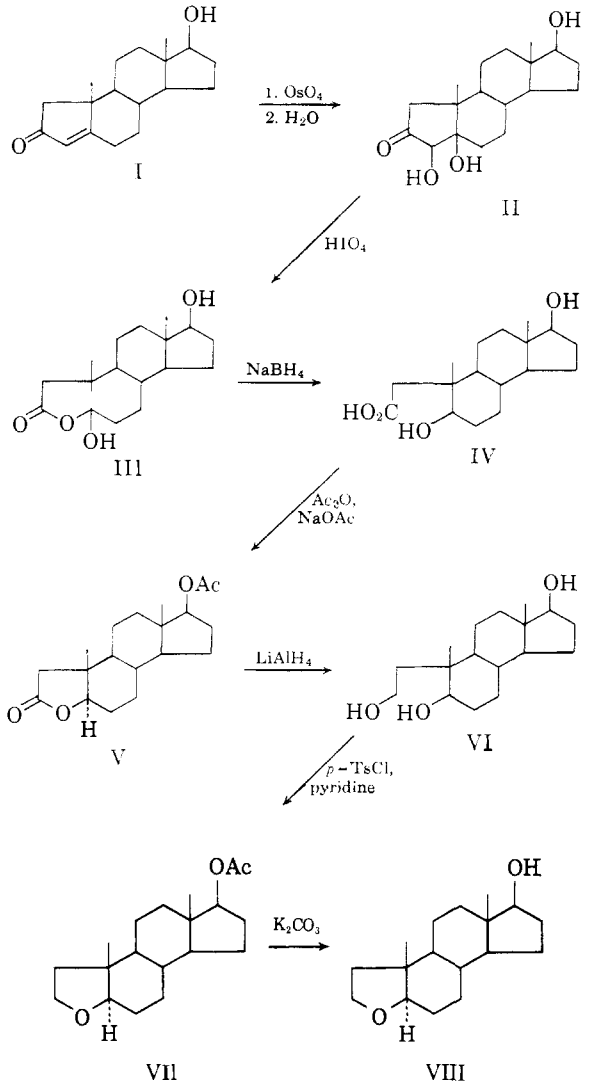
(8) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(9) (a) N. W. Atwater and J. W. Ralls, *J. Am. Chem. Soc.*, **82**, 2011 (1960); (b) E. Caspi, W. Schmid, and B. T. Khan, *J. Org. Chem.*, **26**, 3898 (1961).

(10) G. R. Petit and T. R. Kasturi, *ibid.*, **25**, 875 (1960).

The desired A-nor oxa steroid was obtained by treatment of triol VI with *p*-toluenesulfonyl chloride in pyridine and acetylation to provide 3-oxa-5α-A-norandrostan-17β-ol acetate (VII). Hydrolysis of VII with potassium carbonate in methanol gave 3-oxa-5α-A-norandrostan-17β-ol (VIII).

Biological Activity.[11]—When assayed in the immature castrate male rat, a daily subcutaneous dose of 1 mg./day/rat of VII was approximately as effective as a similar dose of A-norprogesterone in inhibiting the hypertrophy of sex accessory organs induced by testosterone propionate.[12] At this dose, VII was inactive as an androgen.



Experimental

Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Values of $[\alpha]D$ have been approximated to the nearest degree and were taken on a Perkin-Elmer 141 polarimeter in 95% ethanol. Infrared spectra were determined on a Perkin-Elmer 21 spectrometer in pressed potassium bromide pellets and n.m.r. spectra on a Varian A-60 spectrometer in $CDCl_3$ with $(CH_3)_4Si$ as internal standard.[13]

3-Oxa-A-norandrostane-5,17β-diol-2-one (III).—A solution of periodic acid (3.9 g.) in water (10 ml.) was added to a solution of A-norandrostan-2-one-3β,5β,17β-triol (II,[6] 1.93 g.) in pyridine (10 ml.) and methanol (80 ml.), and the reaction mixture was left at room temperature for 16.5 hr. The reaction mixture was evaporated *in vacuo* to near dryness, and the residue was diluted with water and extracted three times with $CHCl_3$. The chloroform extracts were extracted three times with a saturated $NaHCO_3$ solution. The aqueous phase was acidified and extracted four times with ethyl acetate. The ethyl acetate extracts were washed with an 8% salt solution, dried (Na_2SO_4), and evaporated *in vacuo*. Crystallization of the residue from ether–ethyl acetate gave III[7] (1.14 g.), m.p. 183–184°.

2,5-Seco-3,4-bisnorandrostane-5β,17β-diol-2-oic Acid (IV). A solution of 3-oxa-A-norandrostane-5,17β-diol-2-one (III) (2.46 g.) in 2 *N* NaOH solution (5 ml.) and methanol (175 ml.) was stirred with a solution of $NaBH_4$ (1.9 g.) in water (25 ml.) at room temperature for 4 hr. The reaction mixture was diluted with water and acidified with HCl. The precipitate was collected by filtration to give IV (2.09 g.), m.p. 199–201°. The filtrate was extracted twice with ethyl acetate. The ethyl acetate extracts were washed with an 8% salt solution, dried (Na_2SO_4), and evaporated to dryness *in vacuo*. Crystallization of the residue from methanol–isopropyl ether afforded additional IV (128 mg.), m.p. 202–203°. The analytical sample was prepared by recrystallization from methanol–isopropyl ether and had m.p. 203–204°; $[\alpha]^{23}D$ +32°; λ 3.03 (OH), 5.80 (sh), and 5.97 μ (CO_2H).

Anal. Calcd. for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.81; H, 9.54.

3-Oxa-5α-A-norandrostan-2-on-17β-ol Acetate (V).—A mixture of 2,5-seco-3,4-bisnorandrostane-5β,17β-diol-2-oic acid (IV) (400 mg.) and sodium acetate (100 mg.) in acetic anhydride (5 ml.) was refluxed for 4 hr. The reaction mixture was poured into ice–water and extracted three times with ethyl acetate. The ethyl acetate extracts were washed with an 8% salt solution, dried (Na_2SO_4), and evaporated to dryness *in vacuo*. Crystallization of the residue from isopropyl ether gave V (305 mg.), m.p. 166–168°. Recrystallization from isopropyl ether gave the analytical sample: m.p. 168–169°; $[\alpha]^{31}D$ +64°; λ 5.65 (lactone) and 5.80 μ (acetate); τ 9.19 (s, 18-Me), 9.01 (s, 19-Me), 7.96 (s, 17-acetate), and 6.16 (d,d, 4.3 c.p.s., 11.5 c.p.s., 5-H).

Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.41; H, 8.86.

2,5-Seco-3,4-bisnorandrostane-2,5β,17β-triol (VI).—A solution of 3-oxa-5α-A-norandrostan-2-on-17β-ol acetate (V) (300 mg.) in ether (20 ml.) was added to a stirred suspension of $LiAlH_4$ in ether (75 ml.) over a 10-min. period. The reaction mixture was then refluxed for 24 hr., diluted with ether (saturated with water), and treated with a 5% HCl solution. The aqueous phase was extracted four times with $CHCl_3$ and four times with ethyl acetate. The combined organic layers were washed with an 8% salt solution, dried (Na_2SO_4), and evaporated *in vacuo* to give VI (135 mg.), m.p. 250–253°. Recrystallization from methanol–isopropyl ether gave the analytical sample, m.p. 253–254°, $[\alpha]^{26}D$ +20°, λ 3.10 μ (OH).

Anal. Calcd. for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.42; H, 10.57.

3-Oxa-5α-A-norandrostan-17β-ol Acetate (VII).—A solution of 2,5-seco-3,4-bisnorandrostane-2,5β,17β-triol (VI) (1.11 g.) in pyridine (25 ml.) was treated with *p*-toluenesulfonyl chloride (1.4 g.) and left at room temperature for 20.5 hr., and then warmed on a steam bath for 3 hr. The reaction mixture was poured into ice–water and extracted three times with chloroform. The $CHCl_3$ extracts were washed with 2 *N* HCl, saturated $NaHCO_3$ solution, 8% salt solution, dried (Na_2SO_4), and evaporated *in vacuo* to give a 1.51-g. residue. Plate chromatography of the residue using Woelm neutral alumina (activity V) as adsorbent and $CHCl_3$ as the developing solvent gave a major band at *ca.* R_f 0.5, which was detectable by iodine vapor. Elution with ethyl acetate gave a 580-mg. residue which was acetylated in acetic anhydride (2.5 ml.) and pyridine (0.25 ml.) at room temperature for 15.5 hr., poured into ice–water, and extracted three times with ether. The ether extracts were washed with a saturated $NaHCO_3$ solution and 8% salt solution, dried (Na_2SO_4), and evaporated *in vacuo* to afford a 624-mg. residue. Plate chromatography of the residue as described above using hexane–chloroform (4:1) gave a major band at *ca.* R_f 0.5, which was eluted with ethyl acetate to afford a residue, which upon crystallization from petroleum ether (b.p. 30–75°) yielded VII (491 mg.), m.p. 118.5–119.5°. Recrystallization from petroleum ether gave the analytical sample: m.p. 118.5–119.5°; $[\alpha]^{25}D$ +15°; λ

(11) I wish to thank Dr. L. Lerner of our Endocrine Research Department for the biological results, which will be published in detail elsewhere.

(12) L. J. Lerner, A. Bianchi, and A. Borman, *Proc. Soc. Exptl. Biol. Med.*, **103**, 172 (1960).

(13) I wish to thank Dr. A. I. Cohen for the n.m.r. spectra.

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.

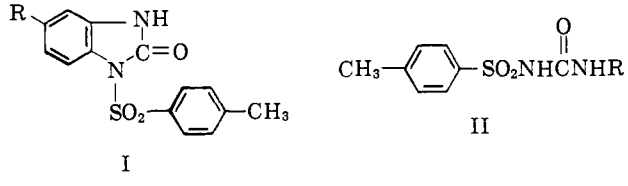
Synthesis of Potential Antidiabetic Agents. 1-*p*-Tolylsulfonyl-2-benzimidazolinones and 1-*p*-Tolylsulfonyl-2-benzimidazolinethiones

JOHN B. WRIGHT

Research Laboratories of The Upjohn Company, Kalamazoo, Michigan

Received November 11, 1964

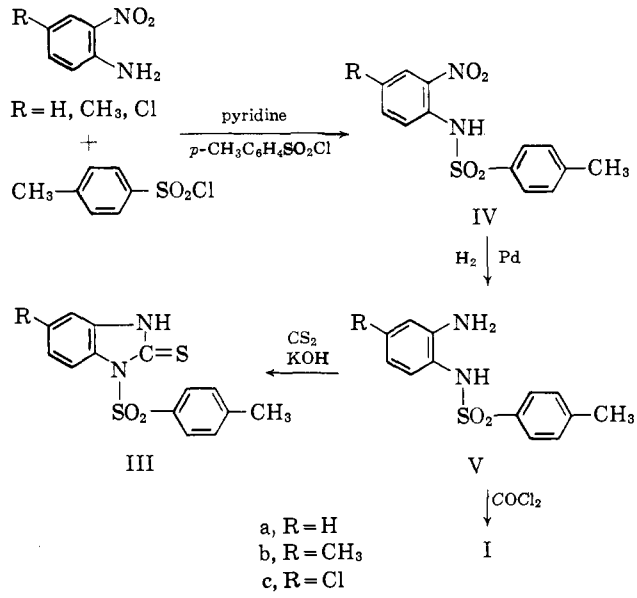
During the course of some continuing work[1] in these laboratories on antidiabetic compounds we were interested in investigating some *p*-tolylsulfonylbenzimidazolinones of the general type I. These may be looked upon as *p*-tolylsulfonylureas of the tolbutamide-type (II, R = n-C_4H_9) in which a phenyl 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).



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).