TABLE VIII

2-(3-ALKYLACYLAMINO-2,4,6-TRIIODOPHENYL)ALKANOIC ACIDS (VIII)

No.	R	R_1	R_2	Mp, °C[a]	Crystn solvent[b]	Yield, %	Formula[d]	Mouse toxicity LD_{50}, mg/kg p.o.	Mouse toxicity LD_{50}, mg/kg i.v.	I % excretion bile	I % excretion urine
27	H	CH_3	CH_3	197–198	A	84	$C_{11}H_{10}I_3NO_3$	2700	1100	13	72
28	H	CH_3	C_2H_5	131–133	A	74.5	$C_{12}H_{12}I_3NO_3$	2200	390	37	34
29	H	CH_3	C_3H_7	100–105	c	94	$C_{13}H_{14}I_3NO_3$	1250	210	35	33
30	H	CH_3	C_4H_9	100–105	c	91	$C_{14}H_{16}I_3NO_3$	1300	155	32	19
31	H	CH_3	CH_2–C_6H_5	167–168	B	84	$C_{17}H_{14}I_3NO_3$[e]	1550	235	34	28
32	H	C_3H_7	CH_3	164–166	A	76	$C_{13}H_{14}I_3NO_3$	880	180	20	20
33	H	C_3H_7	C_2H_5	188–189	C	76	$C_{14}H_{16}I_3NO_3$	880	100	15	35
34	H	C_3H_7	C_3H_7	139–140	A	70	$C_{15}H_{18}I_3NO_3$	365	49		
35	H	C_3H_7	C_4H_9	90–95	c	87	$C_{16}H_{20}I_3NO_3$	650	51	54	20
36	H	C_3H_7	CH_2–C_6H_5	95–102	c	95	$C_{19}H_{18}I_3NO_3$	770	74	34	12
37	CH_3	CH_3	CH_3	155–160	c	87	$C_{12}H_{12}I_3NO_3$[f]	2800	620	27	22
38	CH_3	CH_3	C_2H_5	125	c	72	$C_{13}H_{14}I_3NO_3$	1300	380	38	16
39	C_2H_5	CH_3	CH_3	115–120	c		$C_{13}H_{14}I_3NO_3$	700	600	33	9
40	C_2H_5	CH_3	C_2H_5	184–187	c	85	$C_{14}H_{16}I_3NO_3$	1260	420	31	8
41	C_3H_7	CH_3	CH_3	120	c	70	$C_{14}H_{16}I_3NO_3$	2800	550	17	10
42	C_3H_7	CH_3	C_2H_5	116	d	85	$C_{15}H_{18}I_3NO_3$	2800	170	28	15

[a] All these compounds sinter 20–30° before the melting point. [b] Final recrystallization: A, EtOAc; B, C_6H_6; C, Me_2CO. [c] Purification by reprecipitation. [d] *Anal.* C, H, I, equiv wt. [e] I: calcd, 57.10; found, 57.80. [f] I: calcd, 62.57; found, 63.40.

was poured into crushed ice (300 g), collected, washed (H_2O), and dissolved in 100 ml of 1 *N* NaOH at 70°. The solution was filtered and made acid with 1 *N* HCl. The precipitated acid was collected, dried, and recrystallized from a suitable solvent.

2-(3-Aminophenyl)alkanoic Acids (13–15, Table V).—A solution of 0.04 mol of 2-(3-nitrophenyl)alkanoic acid in 150 ml of EtOH was hydrogenated at room temperature and atmospheric pressure over Raney Ni catalyst. After consumption of the theoretical quantity of H_2 the catalyst was filtered off and the filtrate was evaporated to dryness. The crystalline residue was suspended in 80 ml of H_2O, collected, and recrystallized.

2-(3-Amino-2,4,6-triiodophenyl)alkanoic Acids (16–18, Table VI).—A solution of 0.09 mol of 1 *N* $KICl_2$[10] was added dropwise with vigorous stirring at 24° to 0.03 mol of 2-(3-aminophenyl)-alkanoic acid in 3000 ml of 0.01 *N* HCl. After a further 2-hr stirring the temperature was raised to 60° and another 0.03 mol of $KICl_2$ solution was added. The suspension was stirred at 60° for 15 hr, then cooled to room temperature, collected, and washed. The solid was dissolved in 300 ml of H_2O with 10 ml of 15% NaOH and the solution was treated with a trace of $Na_2S_2O_4$ and added dropwise to a mixture of 300 ml of H_2O, 12 ml of 18% HCl, and 0.3 g of $NaHSO_3$. The crude product was collected by filtration, washed (H_2O), dried, and recrystallized from EtOH.

2-(3-Acylamino-2,4,6-triiodophenyl)alkanoic Acids (19–26, Table VII).—2-(3-Amino-2,4,6-triiodophenyl)alkanoic acid (0.005 mol) was dissolved in 18 ml of $(Ac)_2O$ at 60°, 2 drops of concentrated H_2SO_4 were added and the temperature was raised to 90–95° for 3 hr. After evaporation to dryness, the residue was dissolved in 60 ml of H_2O with 2 ml of 15% NaOH. The pH was adjusted to 9 and the solution was heated for 2 hr at 90° at constant pH, then filtered and the product was precipitated with 15% HCl. Compounds **19**, **20**, **21**, **22**, **24**, and **25** were purified by reprecipitation, **23** was crystallized from EtOAc, and **26** from EtOH.

2-(3-Alkylacylamino-2,4,6-triiodophenyl)alkanoic Acids (27–42, Table VIII).[11]—A solution of 0.045 mol of alkyl iodide in 2.5 ml of Me_2CO was added during 0.5 hr to a solution of 0.03 mol of 2-(3-acylamino-2,4,6-triiodophenyl)alkanoic acid and 0.12 mol of KOH in 35 ml of H_2O. The mixture was stirred for 4 hr at 35° and then poured into 200 ml of ice–H_2O and extracted twice with Et_2O (30 ml). The crude product, obtained by precipitation with 18% HCl, was purified further by reprecipitation, extraction with boiling EtOAc, or recrystallization from a suitable solvent.

(10) A. A. Larsen, Ch. Moore, J. Sprague, B. Cloke, J. Moss, and J. O. Hoppe, *J. Amer. Chem. Soc.*, **78**, 3210 (1956).

(11) Intermediate 3-amino-2,4,6-triiodophenylacetic acid for compounds **27–36**, see ref 2a.

Chlorosulfonation of 17β-Acetoxy-3-methoxyestra-1,3,5(10)-triene

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The estrogenic potencies of 2- and 4-substituted estrones, among which were included Cl, O_2N, and H_2N derivatives, have been compared.[1b] These compounds, especially the 2-substituted and electronegatively substituted ones, all have very low estrogenic activities and this has been suggested to be one of the prerequisites for a practical lipodiatic, or antiatherogenic steroid in man.[2] The second, and effective, requirement may be a lowering of the cholesterol:lipid phosphorous (C:P) ratio.[3] This effect is shown as well by the 3-Me ethers which are considerably less estrogenic than the phenols, estrone methyl ether being 1% as estrogenic and 25% as lipodiatic, or lipid-shifting, as estrone.[2,4] A favorable change in the C:P ratio has been shown in the case of some simple estrogens to be related to an increase in serum phospholipid rather than a decrease in cholesterol[5] and this is regarded as corrective toward coronary atherogenesis[6] though without

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(2) (a) D. L. Cook, D. W. Calhoun, and R. A. Edgren, *ibid.*, **135**, 91 (1962); (b) D. L. Cook, R. A. Edgren, and F. J. Saunders, *Endocrinology*, **62**, 798 (1958); (c) R. A. Edgren and D. W. Calhoun, *Circulation*, 16, 505 (1957); (d) R. A. Edgren and D. W. Calhoun, *Proc. Soc. Exp. Biol. Med.*, **94**, 537 (1957).

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(6) R. Pick, J. Stamler, S. Rodbard, and L. N. Katz, *Circulation*, **4**, 468 (1951).

favorable influence on aortic atherogenesis.[6,7] The latter may more closely parallel an increase in β-lipoproteins and a decrease in α-lipoproteins in the serum, a condition which is brought about with a hypercholesterolemic diet,[5] rather than changes specifically in phospholipid or cholesterol levels. Estrone augments abnormal dietary changes in these levels, whereas equiline partially corrects the β:α ratio toward normal.[5]

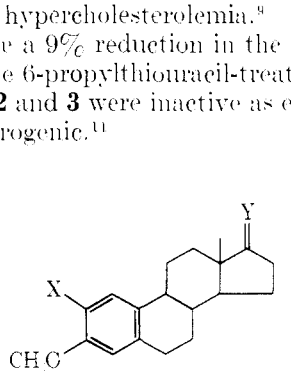
Of various aromatic substitution products of 3-oxygenated estratrienes, one type which has not been reported is that from sulfonyl substitution. Therefore, chlorosulfonation of 17β-acetoxy-3-methoxyestra-1,3,5(10)-triene was carried out in order to obtain representative compounds for antiatherogenic as well as anticancer and estrogen screening.

Using the two-phase procedure of Huntress and Carten,[8] the 17-acetate of estradiol 3-methyl ether was chlorosulfonated in good yield to give a crystalline sulfonyl chloride **1**. This, in turn, was converted into the sulfonamide **2**, to other sulfamyl derivatives (**3** and **4**), and into the 17-carbonyl and ethynyl derivatives **5** and **7**.

When the corresponding 17-ketone, estrone methyl ether, was sulfonated without the two-phase system, a crude sulfonyl halide was obtained which was converted into the dimethylsulfamyl derivative **6**. An attempt to chlorosulfonate the ketone at low temperatures in C_6H_6 prevented formation of the sulfonyl halide from the presumed intermediate sulfonic acid. On work-up, the ammonium salt **8** of the latter was isolated.

Biological Results.—In lipodiatic assays, **2** showed minimal activity (at 50 and 25, but not at 10 mpk) in lowering the serum cholesterol level in the rat with triton-induced hypercholesterolemia.[9] Compound **8**, at 10 mpk, gave a 9% reduction in the plasma cholesterol level in the 6-propylthiouracil-treated rat.[10]

Compounds **2** and **3** were inactive as estrogens and **3** was not antiestrogenic.[11]



1, X = $ClSO_2$; Y = OAc(β)
2, X = H_2NSO_2; Y = OAc(β)
3, X = H_2NSO_2; Y = HO(β)
4, X = $(CH_2)_5NSO_2$; Y = OAc(β)
5, X = H_2NSO_2; Y = =O
6, X = Me_2NSO_2; Y = =O
7, X = H_2NSO_2; Y = C≡CH,β-OH
8, X = $NH_4^+O_3S^-$; Y = =O

Compounds **2** and **4** showed no antileukemic[12] activity and **2** was also inactive against Walker carcinosarcoma.[12]

Experimental Section[13]

17β-Acetoxy-2-chlorosulfonyl-3-methoxyestra-1,3,5(10)-triene (1).—17β-Acetoxy-3-methoxyestra-1,3,5(10)-triene[14] (45 g) was dissolved in 225 ml of $CHCl_3$ (freshly washed with H_2O) to remove EtOH and dried (Na_2SO_4) in the cold overnight. The solution was cooled in an ice bath and 180 ml of $ClSO_3H$ was added over 70 min with moderate stirring (internal temperature maintained at 10 ± 2°). The reaction mixture was poured very cautiously onto ice, was diluted with H_2O, and the product was extracted with 2 portions of CCl_4. After drying (Na_2SO_4), the solvent was removed and the residue was recrystallized from C_6H_6–petroleum ether (bp 60–71°) to give 41.4 g of **1**, mp 196–199°; pmr as expected for angular, Ac and MeO methyls, and for isolated aromatic protons; ir also as expected. An analytical sample was crystallized from C_6H_6–C_6H_{14} and melted at 196–198.5°. *Anal.* C, H, Cl.

17β-Acetoxy-3-methoxy-2-sulfamylestra-1,3,5(10)-triene (2).—17β-Acetoxy-2-chlorosulfonyl-3-methoxyestra-1,3,5(10)-triene (**1**; 7.02 g) in 200 ml of THF was added over 10–15 min at room temperature with stirring to 300 ml of THF kept saturated with NH_3. Stirring and bubbling of NH_3 was continued for 3.5 hr. The reaction mixture was diluted to 1.5 l. with H_2O and cooled to give 6.55 g of **2**, mp 273–276.5° after drying at 55–60°. Ir as expected for acetoxy, amide, and sulfone functions. *Anal.* C, H, N.

17β-Hydroxy-3-methoxy-2-sulfamylestra-1,3,5(10)-triene (3).—The 17-acetate (**2**; 3.0 g), 50 ml of THF, 100 ml of EtOH, 30 ml of H_2O, and 10 ml of 8.5 *N* KOH were heated on the steam bath for 1.5 hr. The reaction mixture was cooled by addition of ice, and was clarified with Darco. The filtrate was acidified with 10% H_2SO_4 and diluted with H_2O and the precipitate was digested for 5–10 min on the steam bath. Cooling gave 2.12 g of **3**, mp 289–292.5°.

Recrystallization of 870 mg of this material from MeOH gave 540 mg mp 293–296°; ir as expected for OH, CONH, and SO_2 functions (no AcO). *Anal.* C, H, N.

2-Dimethylsulfamyl-3-methoxyestra-1,3,5(10)-trien-17-one (6).—Estrone methyl ether (10 g) was added portionwise over 5 min with stirring to 31 ml of cold (ice bath) $ClSO_3H$. The mixture was poured onto ice and diluted with H_2O to give 21.2 g of crude 2-chlorosulfonyl derivative as a (moist) solid, mp 101–140°. After air drying, 16 g of this material was triturated with $CHCl_3$ and the $CHCl_3$ was filtered. The filtrate was washed twice with 10% $NaHCO_3$, once with H_2O, dried, and the solvent was removed to give 5.3 g of a paste.

This material was triturated with 50 ml of 25% aqueous Me_2NH and evaporated to dryness. The residue was taken up in $CHCl_3$, washed twice with 0.85 *N* KOH and twice with H_2O. Drying and removal of solvent gave 4.0 g of material. Two recrystallizations from EtOH gave 800 mg of **6**, mp 189–194.5°; ir as expected. *Anal.* C, H, N.

17β-Acetoxy-3-methoxy-2-pentamethylenesulfamylestra-1,3,5(10)-triene (4).—17β-Acetoxy-2-chlorosulfonyl-3-methoxyestra-1,3,5(10)-triene (**1**; 7 g) in 100 ml of THF was treated with 20 ml of $C_5H_{11}N$ and let stand at room temperature for 3 hr. It was then diluted slowly with H_2O (the initial precipitate dissolves) and the product (8.4 g, mp 175–179.5°) was collected. It was recrystallized from MeOH to give 7.35 g, mp 207–211°, and again from CH_2Cl_2–MeOH to give 7.05 g of **4**, mp 206.5–209.5°; ir as expected; $\lambda_{max}^{CH_3OH}$ 291 (ε 4000), 296 (sh, 3800), 230-5 (sh, 9750); $[\alpha]^{CHCl_3}D$ 43.5°. *Anal.* C, H, N.

3-Methoxy-2-sulfamylestra-1,3,5(10)-trien-17-one (5).—17β-Hydroxy-3-methoxy-2-sulfamylestra-1,3,5(10)-triene (**3**; 5.86 g) was suspended in 100 ml of THF. The suspension was cooled

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(11) The author is indebted to Dr. R. E. Ranney and Dr. E. F. Nutting and their staff of the Biological Research Division of G. D. Searle & Co. for the cholesterol lowering and estrogen screening results, respectively.

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(13) The author wishes to thank Dr. R. T. Dillon and the staff of the Analytical Division of G. D. Searle & Co. for the analytical and spectral data. Where symbols for the elements are given, analyses were within ±0.4% of the theoretical values. Pmr was determined at 60 mHz. Ir was determined in either $CHCl_3$ or KBr.

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in an ice bath, 200 ml of Me_2CO was added and 4.5 ml (12% excess) of CrO_3 reagent (8 *N* in 8 *N* H_2SO_4)[15,16] was added with stirring. The reaction mixture was poured onto ice and diluted with H_2O to give 5.53 g of **5** mp 254.5–259.5°. *Anal.* C, H, N.

Ammonium 17-Keto-3-methoxyestra-1,3,5(10)-trien-2-yl-sulfonate (8).—Estrone methyl ether (10.5 g) was dissolved in 50 ml of boiling C_6H_6, 10 ml was distilled, and the solution was then cooled in an ice bath with stirring until precipitation began. Then 4.3 ml (2.4 equiv) of $ClSO_3H$ was added over *ca.* 10 min (addition after the first equiv was accompanied by formation of a solid). The reaction mixture was stirred for another 30 min, was poured onto 120 ml of concentrated NH_4OH and the mixture was triturated and evaporated to dryness. The solid was triturated and washed with H_2O, mp 290–300° dec. Samples which were dissolved in $NaHCO_3$ or NaOH did not reprecipitate on acidification. The solid was triturated with $CHCl_3$, filtered, and dried to give 12.2 g, mp >280° dec; ir identical with that of untriturated material. The solid was soluble in hot H_2O and its solution gave NH_3 (odor and moist alkacid paper) on addition of base; ir as expected. *Anal.* C, H, N, S.

17α-Ethynyl-3-methoxy-2-sulfamyl-estra-1,3,5(10)-trien-17β-ol (7).—3-Methoxy-2-sulfamylestra-1,3,5(10)-trien-17-one (4.56 g) in 100 ml of THF was added dropwise at 5–10° over 50 min under N_2 to a stirred suspension of 12 g of lithium acetylide ethylenediamine complex in 50 ml of THF. After 5.5 hr, H_2O was added dropwise to quench the reaction; it was further diluted and acidified with H_2SO_4. At this point an oil separated. The pH was adjusted to *ca.* 8 with 10% $NaHCO_3$ (200–300 ml) and the mixture was cooled overnight. The oil solidified and the solid was collected; 4.07 g, mp 207–217°. Attempted purification by recrystallization from MeOH gave 1.05 g, mp 218.5–247°, and dilution of the filtrate with H_2O gave 2.33 g, mp 194.5–208°. Both contained significant amounts of the ketone (ir); the solids were combined and chromatographed over silica gel in C_6H_6–EtOAc (10–100%). A peak eluted with 20% EtOAc was dissolved in *i*-PrOH and 25 ml of EtOH, 10 ml of HOAc, and 1.0 g of Girard's reagent T were added to remove unreacted ketone.[17] After boiling for 1 hr, the solution was poured onto ice, diluted with H_2O, and filtered to give 1.84 g, mp 210.5–220°. A further recrystallization from *i*-PrOH gave 560 mg of **7** after washing with Et_2O and drying; mp 219–228° (viscous melt); ir as expected; pmr as expected for methyls, ethynyl, isolated aromatic H, OH, and CONH (the last two eliminated by D_2O exchange). *Anal.* C, H, N.

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(17) The author wishes to thank Dr. R. M. Dodson for this suggestion and Dr. J. R. Deason for some preliminary editing and suggestions for the manuscript.

Thia Steroids. II. 2-Thia-A-nor-5α-pregnan-20-one[1]

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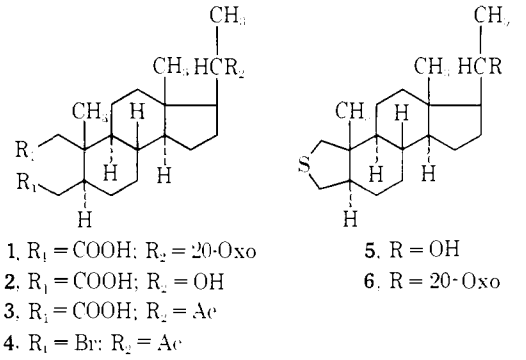
In view of the androgenic activity of 2-thia-A-nor-5α-androstan-17β-ol[2] the preparation of a progesterone analog was undertaken by a similar reaction sequence (**1**–**6**) as described in the Experimental Section. Compound **6** was inactive as a progestogen in the Clauberg-type test.[3]



1. R_1 = COOH; R_2 = 20-Oxo
2. R_1 = COOH; R_2 = OH
3. R_1 = COOH; R_2 = Ac
4. R_1 = Br; R_2 = Ac
5. R = OH
6. R = 20-Oxo

Experimental Section[4]

20-Oxo-2,3-seco-5α-pregnane-2,3-dioic Acid (1).—To a solution of 5 g of 5α-pregnan-3,20-dione[5] in 200 ml of glacial HOAc was added 5 g of CrO_3 at 24° and, the mixture was kept for 5 hr. H_2O was added and the pptd product was collected. It was purified by dissolving in Na_2CO_3 solution and extracting the nonacidic material with Et_2O. The alkaline layer was acidified with dil HCl and the pptd product was crystd from CH_3CN, mp 201–202°, M^+ = 364. *Anal.* ($C_{21}H_{32}O_5$) C, H.

20β-Hydroxy-2,3-seco-5α-pregnane-2,3-dioic Acid (2).—To a solution of 4 g of 1 in 250 ml of anhyd THF was added 8 g of LiAl(*t*-BuO)$_3$H and the mixture was heated under reflux for 1 hr. After removal of the solvent under vacuum, H_2O was added and the product was extd with Et_2O. The Et_2O layer was washed with H_2O, dried (Na_2SO_4), and evapd. Recrystn of the product from MeCN gave crystals, mp 273–275°; M^+ = 366. *Anal.* ($C_{21}H_{34}O_5$) C, H.

20β-Hydroxy-2,3-seco-5α-pregnane-2,3-dioic Acid Acetate (3).—A mixture of 10 ml of C_5H_5N, 8 ml of Ac_2O, and 1.2 g of **2** was kept at 24° for 18 hr. The product was isolated with $CHCl_3$ to afford 1.2 g of **3**; mp 184–185°, after several recrystns from hexane–Me_2CO. *Anal.* ($C_{23}H_{36}O_6$) C, H.

1,4-Dibromo-1,4-seco-2,3-bisnor-5α-pregnan-20β-ol Acetate (4).—To 1.2 g of **3** in 100 ml of stirred, refluxing CCl_4, there was added 1 g of red HgO. The reaction mixture was shielded from light, and 1 g of Br_2 was added dropwise. After 3 hr the reaction mixture was allowed to cool and the dark mixture was filtered. The filtrate was concd under vacuum and the residue was chromatographed on Al_2O_3 to give 0.6 g of pure **4**, mp 149–150° after recrystn from MeOH; M − 60 = 418. *Anal.* ($C_{21}H_{34}Br_2O_2$) C, H.

2-Thia-A-nor-5α-pregnan-20β-ol (5).—To a refluxing solution of 0.5 g of **4** in 80 ml of refluxing EtOH, there was added a tenfold excess of Na_2S dissolved in the minimum amount of H_2O. Heating was continued for 20 hr when tlc indicated complete conversion into **5**. The solvent was removed under vacuum and the residue was taken up in Et_2O, washed with dil HCl solution and then H_2O, dried (Na_2SO_4), and evapd to give 0.28 g of **5** as a white solid, which after recrystn from Me_2CO–hexane had mp 193–195°; M^+ = 308. *Anal.* ($C_{19}H_{32}OS$) C, H, S.

2-Thia-A-nor-5α-pregnan-20-one (6).—A solution of 0.15 g of **5** in 5 ml of cyclohexanone and 0.3 g of Al(*i*-PrO)$_3$ in 300 ml of PhMe was heated under reflux for 2 hr, cooled, and diluted with H_2O. Steam distn gave an aq suspension which was extd with Et_2O. Removal of the Et_2O under vacuum gave a residue which was adsorbed on silica gel. Elution with 2% EtOAc in C_6H_6 gave the product, which was recrystd from hexane–Me_2CO to give the analytical sample mp 158–159°; M^+ = 306. *Anal.* ($C_{19}H_{30}OS$) C, H.

(1) This investigation was supported in part by a Public Health Service Research Grant (AM-05016) from the National Institute of Arthritis and Metabolic Diseases, U.S. Public Health Service.

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(3) M. E. Wolff, W. Ho, and M. Honjoh, *ibid.*, **11**, 285 (1968).

(4) Melting points were determined with a Thomas–Hoover apparatus equipped with a corrected thermometer. Microanalyses were performed by the Microanalytical Department, University of California, Berkeley, Calif. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

(5) Purchased from Searle Chemicals, Inc., Lot V-4.