nearly a quantitative yield of which was suitable for subsequent reduction. Recrystallization from acetone, however, gave IIb (8.9 g), mp 168–169.5°, $[\alpha]^{25}D$ −75°.

Anal. Calcd for $C_{25}H_{42}N_2O_2$: C, 74.58; H, 10.52. Found: C, 74.63; H, 10.42.

N-Methyl-N-(3-dimethylamino)propyl-17β-aminoandrost-5-en-3α-ol (IIIb). General Method.—A solution of IIb (6.0 g) in purified dioxane (60 ml) was added with stirring to a refluxing slurry of $LiAlH_4$ (3.0 g) in purified dioxane (140 ml) over 0.5 hr. The reaction was refluxed for 18 hr, and the excess hydride was decomposed by the successive dropwise addition of aqueous dioxane (1:6, 20 ml), 20% NaOH solution (2.5 ml), and water (11 ml). The inorganic salts were removed by filtration and washed with additional dioxane (50 ml). Solvent removal *in vacuo* with heating gave an oily residue which solidified. Recrystallization from acetone gave IIIb (5.2 g), mp 119–121°, $[\alpha]^{25}D$ −62.5°.

N-Methyl-N-(3-dimethylamino)propyl-17β-aminoandrostane (IIIg).—A solution of the dihydrochloride in IIIh (1.25 g) in 95% ethyl alcohol (100 ml) was hydrogenated at atmospheric pressure (Parr shaker) and 25° using PtO_2 (100 mg) as catalyst. The catalyst was removed by filtration and washed with additional 95% ethyl alcohol. The solvent was removed *in vacuo* to leave a solid residue which was recrystallized from ethyl alcohol to give pure IIIg dihydrochloride (1.2 g), $[\alpha]^{25}D$ +11° (MeOH).

Anal. Calcd for $C_{25}H_{46}N_2 \cdot 2HCl$: N, 6.28. Found: N, 6.23.

A 10% aqueous solution of Na_2CO_3 (2.5 ml) was added with stirring to the dihydrochloride (0.5 g) in methanol (0.8 ml) and water (5 ml). The mixture was diluted with water (20 ml) and filtered to yield the free base IIIg (0.4 g), identical with that prepared by the Leuckart procedure described above.

N-Methyl-N-(3-dimethylamino)propyl-17β-aminoandrost-4-en-3-one (IV).—A solution of IIIa (4.0 g) and cyclohexanone (20 ml) in toluene (100 ml) was distilled until 20 ml had been collected. Aluminum isopropoxide (8.0 g) in toluene (75 ml) was added dropwise with stirring to the hot solution. Slow distillation of the reaction mixture was continued for 2 hr. After cooling to room temperature, a concentrated solution of Rochelle salts (120 ml) was added slowly with rapid stirring. The mixture was steam distilled for 1 hr. After cooling, the residual mixture was extracted with ether; the extract was treated with three 150-ml portions of 5% HCl. The aqueous acid fraction was washed with ether and made basic with 20% NaOH solution. The oily precipitate was extracted with ether, washed with water, and dried (Na_2SO_4 containing Darco); solvent removal *in vacuo* gave IV (3.5 g) as an oil ($[\alpha]^{20}D$ +70.5°), which solidified upon standing but resisted recrystallization from a variety of solvents. The ultraviolet spectrum displayed the characteristic absorption maximum for a 4-dehydro-3-keto system, at 240 mμ (log ε 4.19).

N-Methyl-N-(3-dimethylamino)propyl-17β-aminoandrost-4-en-3β-ol (V).—A solution of IV (1.7 g) in dry tetrahydrofuran (THF) (40 ml) was added with stirring dropwise to a suspension of $LiAlH_4$ (1.0 g) in THF (60 ml). The reaction mixture was refluxed for 3.5 hr. After cooling to room temperature, the excess hydride was decomposed by the successive dropwise addition of water (1 ml) in THF (20 ml), 20% NaOH (0.75 ml), and water (3.5 ml). The inorganic salts were removed by filtration and washed with additional THF (20 ml). The filtrate was concentrated to dryness *in vacuo* to give an oil which solidified upon standing. Recrystallization from acetone afforded V (1.3 g), mp 110–113°, $[\alpha]^{25}D$ +46°.

N-(Dimethylamino)propyl-1ξ-formamido-2ξ-methylcyclopentane (VII).—To a stirred solution of 2-methylcyclopentanone (50.0 g) in formic acid (330 ml, 98–100%) was added 3-dimethylaminopropylamine (250 g) dropwise over 20 min. The reaction was heated in a sealed container at 172–175° for 24 hr. The mixture was cooled and poured into a solution of NaOH (480 g) in water (2 l.). The resulting oily material was extracted with ether. The extract was washed repeatedly with water, until the aqueous portions were nearly neutral, and dried (Na_2SO_4). Solvent removal *in vacuo* gave VII as an oil which was distilled with the fraction boiling at 138–140° (9–10 mm) and collected (20.5 g), $n^{25}D$ 1.4688.

Anal. Calcd for $C_{12}H_{24}N_2O$: C, 67.88; H, 11.39. Found: C, 68.07; H, 11.39.

N-Methyl-N-(dimethylamino)propyl-1ξ-amino-2ξ-methylcyclopentane (VIII).—A solution of VII (14.0 g) in dioxane (100 ml) was added dropwise with stirring and heating to a slurry of $LiAlH_4$ (12.0 g) in dioxane (100 ml) over 0.5 hr. The mixture was refluxed for 16 hr and the excess hydride was decomposed by the successive dropwise addition of aqueous dioxane (1:3, 36 ml), 20% aqueous NaOH solution (9 ml), and water (41 ml). The salts were removed by filtration and washed with additional dioxane. The filtrate was concentrated *in vacuo* leaving a viscous oil. Distillation gave the product VIII (10.4 g), bp 84–85° (9–10 mm), $n^{25}D$ 1.4523, $[\alpha]^{25}D$ +0.5°.

Anal. Calcd for $C_{12}H_{26}N_2$: C, 72.66; H, 13.21. Found: C, 72.25; H, 12.83.

The **hydrochloride** salt of VIII gave the following analysis.

Anal. Calcd for $C_{12}H_{26}N_2 \cdot 2HCl$: N, 10.33. Found: N, 10.41.

Hydrochloride Salts.—The free base diamines were dissolved in a mixture of ether and acetone (1:1) and sufficient 7 *N* HCl in isopropyl alcohol was added dropwise with agitation. After stirring a few minutes, the dihydrochloride salts were collected by filtration and washed with acetone and ether. Recrystallization from ethanol or isopropyl alcohol gave the pure salts.

The Synthesis of Potential Anabolic Agents. Steroidal Oxadiazoles[1]

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The synthesis of several steroidal oxadiazoles and their N-oxide analogs, derived from cholesterol and 17α-methyltestosterone, is described and the results of their preliminary screening as anabolic agents are discussed. All the compounds tested showed some anabolic–androgenic activity. 17α-Methyl-5α-androstano[2,3-*c*][1′,2′,-5′]oxadiazol-17β-ol (**4**) is the most potent of those prepared, showing enhanced anabolic–myotropic activity and diminished androgenic response.

The incorporation of a heterocyclic ring fused onto ring A of selected steroids has been shown to lead to compounds therapeutically useful as anabolic agents.[2a] Clinton and co-workers,[2b] found that certain steroidal pyrazoles such as 17α-methyl-5α-androstano[3,2-*c*]-[1′,2′,5′]pyrazol-17β-ol (**1a**) represented a novel class of compounds with a high degree of separation of anabolic from androgenic activity. More recently, Manson

(1) Presented to the Division of Medicinal Chemistry at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965.

(2) (a) P. de Ruggieri, G. Gandolfi, U. Guzzi, D. Chiaramonti, and C. Ferrari, *Farmaco* (Pavia), *Ed. Sci.*, **20**, 280 (1965); (b) R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. P. Page, J. W. Dean, W. B. Dickinson, and C. Carabateas, *J. Am. Chem. Soc.*, **83**, 1478 (1961); (c) A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. P. Page, J. W. Dean, D. K. Philips, G. O. Potts, A. Arnold, A. L. Beyler, and R. O. Clinton, *J. Med. Chem.*, **6**, 1 (1963).

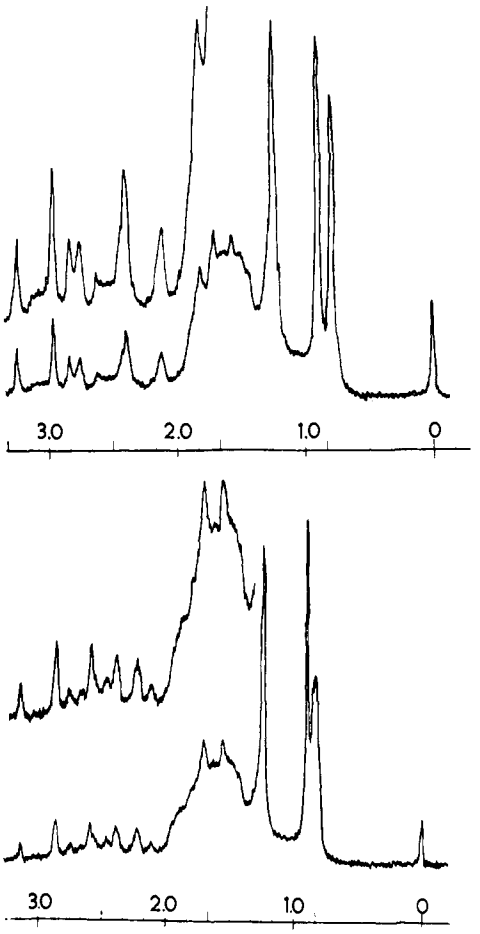
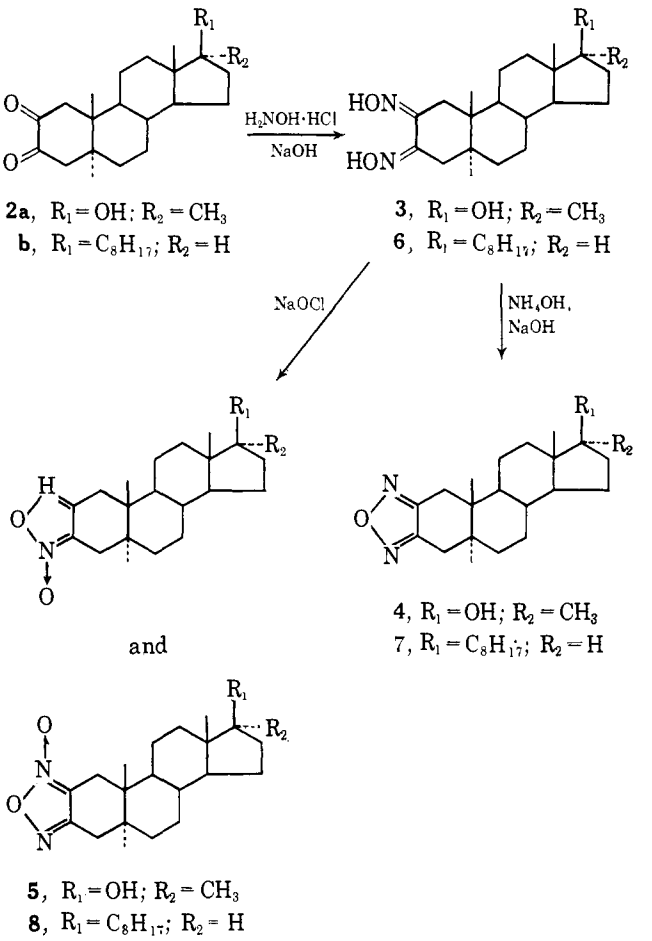
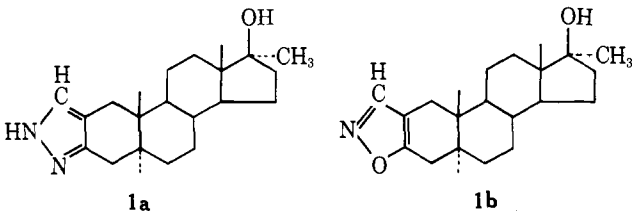


Figure 1.—Nmr spectra of compounds **4** (top) and **5** (bottom).

SCHEME I



and co-workers[2c] describe similar activity in certain steroidal isoxazoles such as 17α-methyl-5α-androstano-[2,3-*d*][1′,2′,3′]isoxazol-17β-ol (**1b**).



We wish to report the synthesis of isosteric steroidal oxadiazoles (**4** and **7**) and their N-oxide analogs (**5** and **8**). Subsequent to the completion of our synthesis program, compounds of the type **4** were reported to possess excellent oral anabolic activity with a favorable myotropic/androgenic ratio.[3]

Scheme I illustrates the synthesis route employed. 2,3-Dioximino-17α-methyl-5α-androstan-17β-ol (**3**) was prepared from 17α-methyl-5α-androstan-ol-17β-2,3-dione (**2a**)[4a] by treatment with hydroxylamine. Compound **3** was converted to 17α-methyl-5α-androstano-[2,3-*c*][1′,2′,5′]oxadiazol-17β-ol (**4**) by treatment with ammonium hydroxide and sodium hydroxide,[4b] or to 17α-methyl-5α-androstano[2,3-*c*][1′,2′,5′]oxadiazol-17β-ol N-oxide (**5**) by treatment with sodium hypochlorite.[4b]

Likewise, 2,3-dioximino-5α-cholestane (**6**) was prepared from 5α-cholestane-2,3-dione (**2b**). Analogously **6** was converted to 5α-cholestano[2,3-*c*][1′,2′,5′]-oxadiazole (**7**) by treatment with ammonium hydroxide and sodium hydroxide, or to 5α-cholestano-[2,3-*c*][1′,2′,5′]oxadiazole N-oxide (**8**) by treatment with sodium hypochlorite.

Nuclear magnetic resonance spectral analysis of the six compounds confirmed their structures.[5] As expected, the oxadiazole N-oxides were found to be approximately **1**:1 mixtures of the isomeric 2′- and 5′-N-oxides. Figure 1 illustrates the nmr spectra of 17α-methyl-5α-androstano[2,3-*c*][1′,2′,5′]oxadiazol-17β-ol (**4**) and 17α-methyl-5α-androstano[2,3-*c*][1′,2′,5′]oxadiazol-17β-ol N-oxide (**5**). Significantly, the C-19 methyl of the N-oxide appeared as a doublet of approximately equal intensities, the downfield peak at 50.5 cps representing the 2′-N-oxide interaction with the C-19 methyl group. The shifts observed for the C-1 and C-4 methylene protons likewise confirmed the isomeric N-oxide mixtures. A similar spectrum was obtained for compound **8** but it did not show the C-19 methyl splitting as the region around 50 cps was more complicated than for compound **5**.

Compounds **2**–**6** and **8** were tested for androgenic and anabolic activity according to Hershberger,

(3) G. Ohta, T. Takegoshi, T. Onodera, A. Kasahara, Y. Oshima, M. Shimizu, and K. Ueno, South African Patent 641,540 (April 1, 1964).

(4) (a) B. Camerino, B. Patelli, and R. Sciaky, U. S. Patent 3,068,229 (Dec 11, 1962); (b) J. H. Boyer in "Heterocyclic Compounds," Vol. 7, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p 462.

(5) We wish to thank Dr. Leonard R. Axelrod for obtaining these spectra and Mr. William H. Storey, Jr., for their interpretation.

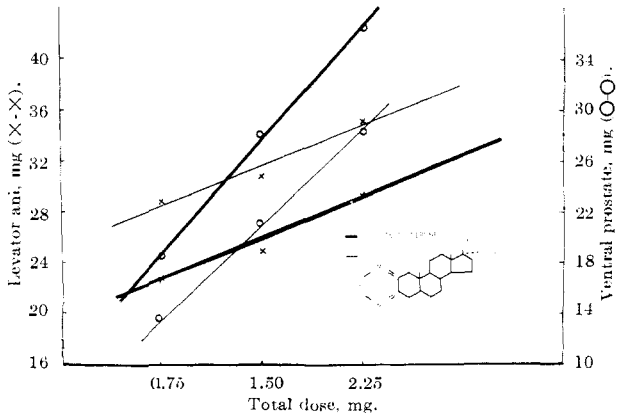


Figure 2.—Anabolic–androgenic activity of compound 4.

et al.[6] by subcutaneous administration to castrated 21-day-old male rats. The results obtained indicated that all the compounds possessed at least some anabolic–androgenic activity. Compound **4**, as shown in Figure 2 was the most potent of the series. As compared to testosterone, the anabolic–myotropic activity was substantially enhanced while the androgenic activity was appreciably lowered. Studies designed to determine the oral activity of these oxadiazoles are in progress and will be reported at a later date.

Experimental Section[7]

17α-Methyl-5α-androstan-17β-ol-2,3-dione (2a) was prepared in 60% yield by the method of Camerino, *et al.*, using 17α-methyl-5α-androstan-17β-ol-3-one, potassium *t*-butoxide, and oxygen in *t*-butyl alcohol; mp 202–203° (lit.[4] 183–184°); λ_{max} 2.78, 2.90, 5.75, 6.00, 6.10 μ; λ_{max}^{MeOH} 269 mμ; $FeCl_3$ test, positive.

2,3-Dioximino-17α-methyl-5α-androstan-17β-ol (3).—To a solution of 6.0 g (0.019 mole) of 17α-methyl-5α-androstan-17β-ol-2,3-dione in 200 ml of ethanol was added a twofold mole excess of $NH_2OH \cdot HCl$ and KOH. The solution was refluxed 30 min after which time 25 ml of water was added and reflux continued an additional 30 min. The turbid mixture was diluted with 1 l. of water and cooled, and the precipitate was collected. Recrystallization of the white solid from ethanol and water gave 6.1 g (0.0164 mole) of **3** which melted above 256° dec (lit.[3] mp 234–235°); λ_{max}^{KBr} 3.0, 3.19, 6.05–6.20 μ.

Anal. Calcd for $C_{20}H_{32}N_2O_3$: C, 68.93; H, 9.50; N, 8.00. Found: C, 68.95; H, 9.42; N, 8.08.

17α-Methyl-5α-androstano[2,3-*c*][1′,2′,5′]oxadiazol-17β-ol (4).—2,3-Dioximino-17α-methyl-5α-androstan-17β-ol (**3**, 9.0 g, 0.024 mole) was heated in an autoclave with 500 ml of concentrated NH_4OH and 20 g of NaOH for 12 hr at 160°. The product was collected by filtration and/or extraction with ether. Purification by crystallization from benzene–petroleum ether (bp 40–60°) gave 5.0 g (0.015 mole) of **4**: mp 152–154°;[3] λ_{max} 2.79, 3.42, 6.91, 7.15, 7.24, 7.37 μ.

Anal. Calcd for $C_{20}H_{31}N_2O_2$: C, 72.47; H, 9.43; N, 8.45. Found: C, 72.48; H, 9.32; N, 8.46.

17α-Methyl-5α-androstano[2,3-*c*][1′,2′,5′]oxadiazol-17β-ol N-Oxide (5).—2,3-Dioximino-17α-methyl-5α-androstan-17β-ol (**3**, 6.0 g, 0.016 mole) was dissolved in 400 ml of 4:1 ethanol–H_2O containing 40 g of NaOH. After cooling to 0°, 120 ml of 20% NaOH solution saturated with Cl_2 was added with rapid stirring. The bright yellow color of the NaOH–oxime solution was promptly discharged after the addition of 10–20 ml of the NaOCl solution. The mixture was allowed to stir for 1 hr after the addition was completed. After dilution with 1 l. of water, the solution was cooled and the precipitate was collected. Chromatography on neutral alumina followed by crystallization from acetone yielded 5.0 g of colorless granules: mp 175–178°; λ_{max} 2.18, 6.16, 6.83 μ. The nmr spectrum of the product indicated a mixture of the isomeric 2′- and 5′-N-oxides (Figure 1).

Anal. Calcd for $C_{20}H_{30}N_2O_3$: C, 69.13; H, 8.99; N, 8.06. Found: C, 69.48; H, 9.00; N, 8.16.

5α-Cholestane-2,3-dione (2b).—Two methods were employed to prepare **2b**. The method of Stiller and Rosenheim[8] using SeO_2 was inferior to the modified procedure of Camerino, *et al.*,[4] using potassium *t*-butoxide and oxygen. Compound **2b** (42% yield) melted at 137–150° (lit.[4] 137–138, 165–167°): λ_{max} 2.95, 6.01, 6.20 μ; λ_{max}^{MeOH} 270 mμ.

2,3-Dioximino-5α-cholestane (6).—5α-Cholestan-2,3-dione (3.0 g, 0.007 mole) was dissolved in 100 ml of ethanol and treated with a two-fold molar excess of hydroxylamine hydrochloride and KOH in 20 ml of water. The solution was heated on a steam bath for 1 hr, diluted with 230 ml of water, and cooled, and the white precipitate was collected. The solid was recrystallized from ethanol and water to yield 3.1 g (0.0066 mole); mp above 255° dec; λ_{max}^{KBr} 2.98, 3.18, 6.16 μ.

Anal. Calcd for $C_{27}H_{46}N_2O_2$: C, 76.60; H, 10.20; N, 6.16. Found: C, 74.99; H, 10.70; N, 5.67.

A satisfactory elemental analysis could not be obtained for the dioxime. However, a positive $FeCl_3$ test and the formation of the known quinoxaline derivative[4] by reaction of *o*-phenylenediamine with the 5α-cholestane-2,3-dione confirmed the identity of the dioxime.

5α-Cholestano[2,3-*c*][1′,2′,5′]oxadiazole (7).[9]—2,3-Dioximino-5α-cholestane (15 g, 0.03 mole) was placed in an autoclave with 10 g of NaOH and 500 ml of concentrated NH_4OH and heated to 160° for 12 hr. The steroidal material was extracted from the NH_4OH–NaOH aqueous mixture using $CHCl_3$. The $CHCl_3$ extract was washed with water and dried over Na_2SO_4. After the removal of the solvent the oil residue was chromatographed on Florisil. The material eluted with benzene was the desired product and was successfully crystallized from acetonitrile, mp 80–85°. Recrystallization from acetonitrile and ethyl acetate and drying gave 2.1 g (0.0051 mole); mp 100–102°; λ_{max} 6.82, 6.94, 7.15, 7.25 μ.

Anal. Calcd for $C_{27}H_{44}N_2O$: C, 78.59; H, 10.75; N, 6.79. Found: C, 78.81; H, 10.85; N, 6.90.

The remainder of the organic material remained as an uncrystallizable oil.

5α-Cholestano[2,3-*c*][1′,2′,5′]oxadiazole N-Oxide (8).—2,3-Dioximino-5α-cholestane (2.0 g, 0.0044 mole) was dissolved in 100 ml of 10% NaOH in 4:1 ethanol–H_2O. The solution was cooled to 0°, and 100 ml of 20% NaOH saturated with chlorine was added dropwise with rapid stirring. The yellow color of the oxime solution was rapidly discharged and a precipitate formed after 10–20 ml of NaOCl solution was added. On completion of the addition, 300 ml of water was added, and the mixture cooled. The white precipitate was recrystallized from ethanol to yield 1.7 g (0.004 mole) of **8**: mp 202–203°; λ_{max} 6.17, 6.81 μ.

The nmr spectrum of **8** indicates it is a mixture of the isomeric 2′- and 5′-N-oxides, although it does not have the split C-19 signal as seen in **5** (Figure 1).

Anal. Calcd for $C_{27}H_{44}N_2O_2$: C, 75.65; H, 10.35; N, 6.54. Found: C, 75.72; H, 10.12; N, 6.60.

(6) L. G. Hershberger, E. C. Shipley, and R. K. Meyer, *Proc. Soc. Exptl. Biol. Med.*, **83**, 175 (1953).

(7) Melting points were determined in a Thomas–Hoover capillary apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 21 spectrophotometer in chloroform solution (unless otherwise noted). Microanalyses were by Schwartzkopf Microanalytical Laboratory, Woodside 77, N. Y. The hormonal assays were carried out in cooperation with Hormone Assay Labs, Chicago, Ill.

(8) E. T. Stiller and O. Rosenheim, *J. Chem. Soc.*, 353 (1938).

(9) The synthesis of this compound in pure form was achieved only after completion of the preliminary screening program. Compound **7** has been included in the oral screening program.