45–47.5° (lit.[6] m.p. 47°), undepressed on admixture with an authentic sample.

Formation of solid byproducts in the reaction of phenylisocyanate with I. A mixture of 57.4 g. (0.482 mole) of phenyl isocyanate and 17.6 g. (0.241 mole) of I was heated at 160° for 13 hr. The reaction mixture was distilled to provide 3 g. of unchanged phenyl isocyanate and a 25% yield of the formamidine II. A considerable fraction of the reaction mixture remained as a solid residue in the distillation flask. This solid material was continuously extracted with ligroin (b.p. 66–75°) for 72 hr. at the end of which time 8.2 g. of impure 1,1-dimethyl-3-phenylurea had been extracted and was isolated as an insoluble solid in the extracting solvent, m.p. 118–126°. Repeated recrystallization from a benzene ligroin mixture raised the melting point to 132–135° (lit.[7] m.p. 134°), undepressed on admixture with an authentic sample prepared from the reaction of phenyl isocyanate with excess anhydrous dimethylamine.

The unextracted material remaining from the ligroin extraction was repeatedly recrystallized from a mixture of benzene and ligroin to yield 20.84 g. of a crystalline product (III), m.p. 227–228.5°, λ_{max} 5.73, 5.77, and 5.92 μ. Compound III, which was not further characterized, provided the following analysis.

Anal. Found: C, 72.28; H, 4.29; N, 12.52.

Acknowledgment. The author is indebted to D. L. Harms for the infrared spectral determinations.

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(7) R. Stolle, *J. prakt. Chem.*, **117**, 201 (1927).

Chemotherapeutic Nitrofurans. VI.[1] 3-(5-Nitrofurfurylideneamino)tetrahydro-2(1H)pyrimidinone

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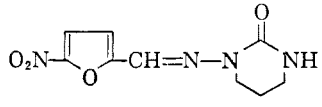
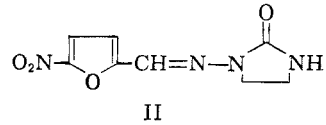
Interest in the chemotherapeutic activity of nitrofuran compounds has led to the preparation of 3-(5-nitrofurfurylideneamino)tetrahydro-2(1H)-pyrimidinone (I). A corresponding five-membered ring compound (II) has been reported.[2,3]



I



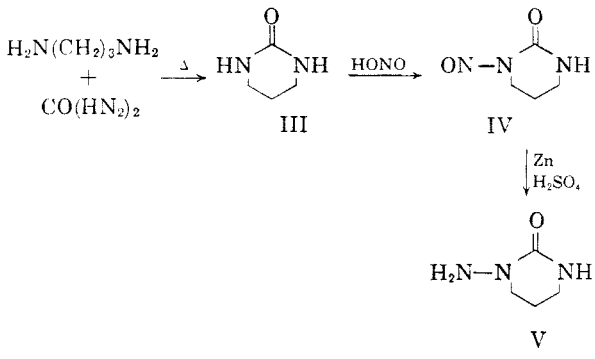
II

(1) For the previous paper in this series see Abstracts of Papers, 137th Meeting American Chemical Society, April 1960, p. 30N.

(2) J. G. Michels and G. Gever, *J. Am. Chem. Soc.*, **78**, 5349 (1956).

(3) G. Gever and J. G. Michels, U. S. Patent **2,746,960** (1956).

The method used for the synthesis of I is shown in the following scheme:



Tetrahydro-2-(1H)pyrimidinone (III) has been prepared by several methods[4–10] but none of these is particularly suited to large scale laboratory preparation. It was found most convenient to prepare III by heating a mixture of trimethylenediamine and urea. This general method of forming heterocyclic rings by heating urea with appropriately disubstituted aliphatic compounds has been used for the preparation of 2-oxazolidinones[11] and 2-thiazolidinone.[2]

The mononitrosation and reduction of III was carried out in the same manner described earlier for II.[2,3] Neither the intermediate nitroso compound IV nor the amino compound V was isolated. Treatment of the aqueous reduction solution containing the 3-aminotetrahydro-2(1H)pyrimidinone with an alcoholic solution of 5-nitrofurfural caused the direct precipitation of the desired product, I.

EXPERIMENTAL

Tetrahydro-2(1H)pyrimidinone. A mixture of 74 g. (1 mole) of trimethylenediamine, 43 g. (0.67 mole) of urea, and 18 ml. of water was heated under reflux (internal temperature 115°) for 4 hr. The water and excess amine were then distilled. The internal temperature rose slowly and after 2 hr. was 155°. During this heating period frothing occurred and a solid began to separate. After an additional 1.5 hr. heating, the solid was melted with a free flame, then allowed to cool. Recrystallization of the solid residue from 850 ml. of 95% alcohol using Darco gave 53 g. of the name compound, m.p. 258–262° (copper block; uncorr.). Evaporation of the alcoholic mother liquor and recrystallization of the residue from 450 ml. of 95% alcohol using Darco gave an additional 6 g. of product of the same melting point.

(4) E. Fischer and H. Koch, *Ann.*, **232**, 222 (1886).

(5) J. Tafel, *et al.*, *Ber.*, **33**, 3383 (1900); *Ber.*, **34**, 3286 (1901).

(6) A. P. N. Franchimont and H. Friedmann, *Rec. trav. chem.*, **26**, 218 (1907).

(7) Y. Iwakura, *Chem. High Polymers (Japan)*, **4**, 94 (1947); *Chem. Abstr.*, **45**, 2711g (1951).

(8) A. F. McKay, *et al.*, *J. Am. Chem. Soc.*, **71**, 766 (1949).

(9) C. W. Smith, U. S. Patent **2,662,080** (1953); *Chem. Abstr.*, **49**, 1110e (1955).

(10) J. J. Fox and D. Van Praag, *J. Am. Chem. Soc.*, **82**, 486 (1960).

(11) W. J. Close, *J. Am. Chem. Soc.*, **73**, 95 (1951).

The total yield was thus 59 g. (88%). The literature[4] reports a melting point of 260°.

3-(5-Nitrofurfurylideneamino)tetrahydro-2(1H)pyrimidinone (I). A solution of 59 g. (0.59 mole) of tetrahydro-2(1H)pyrimidinone in 1700 ml. of 2*N* sulfuric acid was cooled to 3°. During 8 min., 41 g. (0.59 mole) of sodium nitrite was added at a temperature of 3–5°. Stirring was continued at this temperature for 1.5 hr. Then, 85 g. (1.4 moles) of zinc dust was added in small portions during 40 min. at a temperature of 15–25°. After an additional 15 min. stirring, the excess zinc was filtered off and the clear filtrate treated with a solution of 79 g. (0.56 mole) of 5-nitrofurfural in 500 ml. of methanol. The orange precipitate which formed was filtered, washed with water, alcohol, and ether, and dried at 60°. The yield was 84 g. (63%) of I, m.p. 230–232° (copper block; uncorr.). Recrystallization from 1600 ml. of nitromethane using Darco gave an 83.5% recovery of purified product, m.p. 240–242° (copper block; uncorr.). The analytical sample melted at 242.5–244.5°, ϵ_{max} 17,600 at 286 mμ.

Anal.[12] Calcd. for $C_9H_{10}N_4O_4$: C, 45.4; H, 4.23; N, 23.5. Found: C, 45.2; H, 4.42; N, 23.35.

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(12) Microanalyses were performed by Mr. Gordon Ginther and associates of these Laboratories.

Synthesis of 17-Iso-19-nortestosterone

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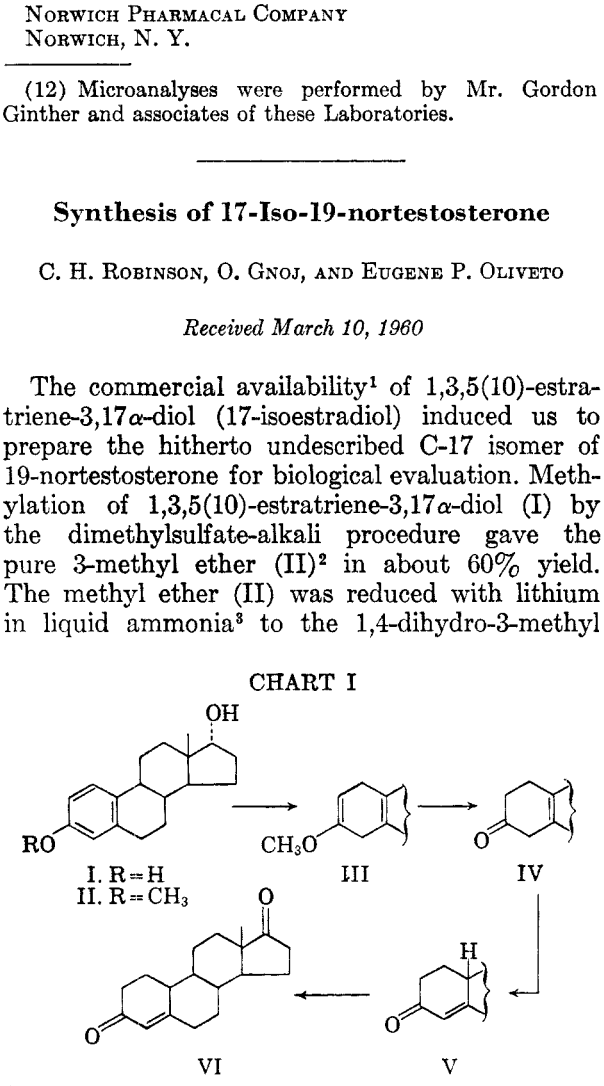
The commercial availability[1] of 1,3,5(10)-estratriene-3,17α-diol (17-isoestradiol) induced us to prepare the hitherto undescribed C-17 isomer of 19-nortestosterone for biological evaluation. Methylation of 1,3,5(10)-estratriene-3,17α-diol (I) by the dimethylsulfate-alkali procedure gave the pure 3-methyl ether (II)[2] in about 60% yield. The methyl ether (II) was reduced with lithium in liquid ammonia[3] to the 1,4-dihydro-3-methyl ether (III) which was isolated in 65% yield by direct crystallization and which showed no selective ultraviolet absorption in the 220–350 mμ region.

CHART I



The dihydromethyl ether (III) was then converted to 17-iso-19-nortestosterone (V) by refluxing methanolic hydrochloric acid. The β,γ-unsaturated ketone (IV) was obtained from III by the action of oxalic acid[3] in methanol at room temperature, and showed no selective ultraviolet absorption between 220 and 350 mμ, while exhibiting a saturated carbonyl band at 5.85 μ in the infrared spectrum. When subjected to the action of methanolic hydrochloric acid, IV was converted to the Δ⁴-3-ketone (V).

Oxidation of 17-iso-19-nortestosterone (V) with the chromium trioxide-sulfuric acid reagent[4] furnished the known[3] 19-norandrostene-3,17-dione (VI).

The molecular rotation differences between compounds II to V and the corresponding 17β-hydroxy analogs, together with figures for other pairs of 17-epimeric alcohols, are shown in the table. It is interesting to note that the Δ(17β-17α) values for the three pairs of 3-oxygenated-Δ⁴ compounds are distinctly higher (average Δ value +99°) than the Δ values for the other compounds cited (average Δ value +61°) which, with one exception (the etiocholane derivative), all share one common feature, namely a 5(10) double bond.

In view of the well known[5] biological activity of 19-nortestosterone, the properties of the 17-epimer (V) were of some interest. However V was found to be devoid of androgenic or myotrophic activity.[6]

EXPERIMENTAL[16]

1,3,5(10)-Estratriene-3,17α-diol 3-methyl ether (II). To a stirred solution of 1,3,5(10)-estratriene-3,17α-diol (3.0 g.)

(1) See British Patent No. 822,205 (1959).

(2) A. Butenandt and C. Groergens, *Z. physiol. Chem.*, 248, 129 (1937).

(3) A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, 75, 5366 (1953).

(4) *Cf.* R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 461 (1953).

(5)(a) L. G. Hershberger, E. G. Shipley, and R. K. Meyer, *Proc. Soc. Exptl. Biol. Med.*, 83, 175 (1953). (b) R. S. Stafford, B. J. Bowman, and K. J. Olsen, *Proc. Soc. Exptl. Biol. Med.*, 86, 322 (1954). (c) F. J. Saunders and V. A. Drill, *Endocrinology*, 58, 567 (1956).

(6) Personal communication from Dr. M. Eisler, Biochemistry Department, Schering Corp.

(7) The $[M]_D$ values are for ethanol, dioxan, or chloroform solutions, and are marked (E), (D), or (C) respectively.

(8) P. Wieland and K. Miescher, *Helv. Chim. Acta*, 32, 1768 (1949).

(9) M. Pesez, *Bull. soc. chim. France*, 911 (1947).

(10) A. Butenandt and A. Heusner, *Ber.*, 71, 198 (1938).

(11) H. Heusser, M. Feurer, K. Eichenberger, and V. Prelog, *Helv. Chim. Acta*, 33, 2243 (1950).

(12) Rotation, measured in dioxan, of a purified sample prepared according to the procedure of Wilds and Nelson, ref. (3).

(13) L. Ruzicka, M. W. Goldberg, and W. Bosshard, *Helv. Chim. Acta*, 20, 541 (1937).

(14) T. F. Gallagher and T. H. Kritchevsky, *J. Am. Chem. Soc.*, 72, 882 (1950).

(15) L. Velluz and A. Petit, *Bull. soc. chim. France*, 1113 (1948).