0.90 g (27%) of yellow crystals, an analytical sample of which melted at 190–192°; ir ($CHCl_3$) 3000, 1650, 1520, 1455, 1285, 1172 cm^{-1}. *Anal.* ($C_{13}H_{10}N_2O_2$) C, H, N.

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Potential Antifertility Agents. 2. Tetrazole Derivatives of Nonsteriodal Estrogens[1]

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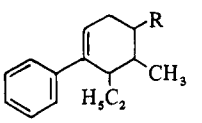
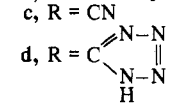
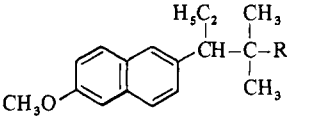
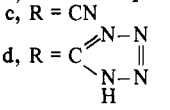
Replacement of the carboxyl group in biologically active compounds with the comparably acidic 5-tetrazoyl group has often resulted in retention of biological activity.[2] Work from these laboratories has shown that tetrazoles have retained activities of known carboxyl counterparts in the anti-inflammatory,[2,3] hypocholesterolemic,[4] and antiinfective[5] areas. We now report the tetrazole analogs (**1d** and **2d**) of the potent nonsteroidal estrogens **1a**[6,†] and **2a**.[‡] We hoped that the tetrazole derivatives might show a favorable dissociation of antifertility and estrogenic activities or a wide separation between feminizing and hypocholesterolemic properties of estrogens.

Chemistry. A sample of the acid **1a** was prepared from phenylmagnesium bromide and 2-methyl-3-ethyl-4-keto-



1a, R = CO_2H
b, R = $CONH_2$
c, R = CN
d, R = 



2a, R = CO_2H
b, R = $CONH_2$
c, R = CN
d, R = 

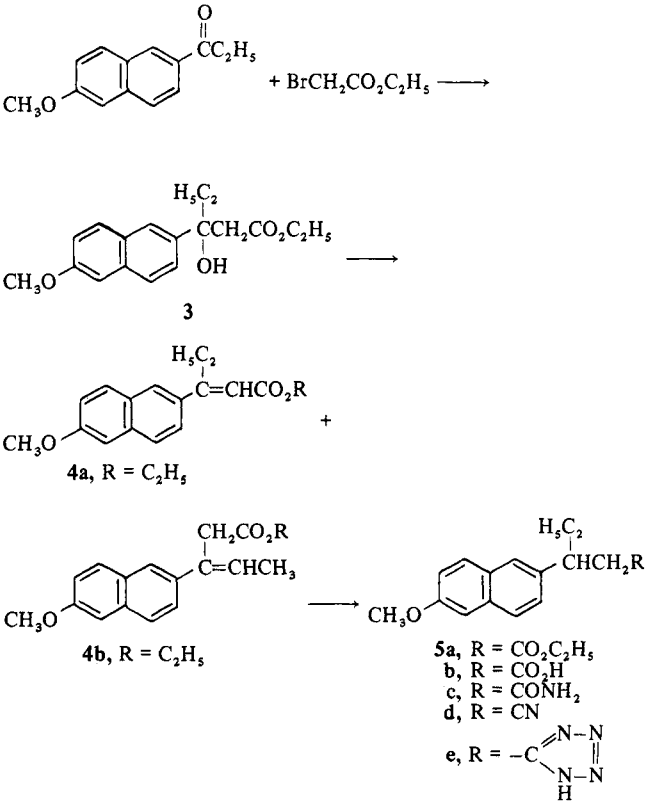
cyclohexanecarboxylic acid as described by Mebane.[6] The reported procedure was followed exactly in order to produce the same presumed mixture of diastereoisomers obtained by Mebane. Vpc analysis confirmed that **1a** (assayed as the methyl ester) is a mixture of diastereoisomers. Standard procedures were used to convert **1a**, *via* the amide (**1b**) and nitrile (**1c**), to the desired tetrazole (**1d**). The broad melting range of **1d** is suggestive of an isomeric mixture, but we have no additional evidence to confirm this. Nmr spectra confirmed that **1a–d** were the pure Δ^4 isomers with no detectable Δ^3 double bond isomer present.

A commercial sample of **2a** was similarly converted to the nitrile **2c**. The nitrile **2c** was resistant to treatment with NH_4N_3 under conditions employed with **1c**, but reaction with AlN_3 in diglyme produced the desired tetrazole **2d** in satisfactory yield.

In other series of tetrazoyl derivatives of biologically active acids, optimal activities were seen with tetrazoles which were less highly substituted than the standard drug after which they were modeled.[3,4] Because of this, we prepared the tetrazole **5e** (Scheme I) which is devoid of the crowding effect of the geminal dimethyl groups present in **2d**.

Oral Biological Activities. Methodology for assays reported herein has been previously described.[1] Compound **1d** was not contraceptive in mice in doses as high as 50 mg/kg,

Scheme I



3

4a, R = C_2H_5

4b, R = C_2H_5

5a, R = $CO_2C_2H_5$
b, R = CO_2H
c, R = $CONH_2$
d, R = CN
e, R =

†Derivatives of **1a** bearing a *p*-methoxyl group on the aromatic ring were first reported as potent estrogens by Nathan and Hogg, *cf.* ref 7.

‡Vallestril; obtained from Searle Chemicals, Inc.

whereas **1a** was active at 0.1 mg/kg. In the rat, estrogenicity of **1d** was only approximately 0.04% that of **1a**. In the normal rat hypocholesterolemic assay **1d** was inactive at 10 mg/kg, whereas **1a** at 0.02 mg/kg produced cholesterol depression of 50–60%. Although at 10 mg/kg compound **1d** was not hypocholesterolemic, it did produce marginal lowering of the weights of the testes, ventral prostate, and the seminal vesicles.

Compound **2d** was not contraceptive in mice (50 mg/kg) and was only weakly uterotropic in mice. In rats, its estrogenicity was likewise very weak in comparison with **2a**. A dose of 250 μg/rat of **2d** increased the uterine weight in immature rats to the same level as 0.2 μg/rat of **2a**. However, a tenfold increase in dosage of **2d** produced only a small additional increment in uterine weight, whereas 2 μg of **2a** resulted in a uterine weight nearly twice that produced by 0.2 μg of **2a**. Compound **2d** had hypocholesterolemic activity at 50 mg/kg (−60%) and at the same dose reduced the weights of sexual end points. As with **1d**, **2d** at 10 mg/kg produced nonsignificant lowering of serum cholesterol but gave a marginal depression of sexual end points. Compound **5e** was inactive in all of the above-mentioned assays.

Thus, substitution of the 5-tetrazoyl group for carboxyl in the potent estrogenic acids **1a** and **2a** resulted in nearly complete loss of biological activity in all of the assays described. The lack of activity may result from failure of the tetrazole group to bind to estrogenic receptors, failure of the tetrazole derivatives to reach receptor sites, or inability of the tetrazoles to undergo metabolic conversion to biologically active forms analogous to those required for **1a**[8] and **2a**.[9]

Experimental Section

Melting points are capillary and are uncorrected. All compounds had ir and nmr spectra consistent with assigned structures. Where elemental analyses are indicated by symbols of the elements, analytical results were within ±0.4% of the theoretical values.

3-Ethyl-2-methyl-4-phenyl-Δ⁴-cyclohexenecarboxamide (1b). A 3.40-g sample of the acid **1a** (mp 157–161°, reported[6] 158–163°) was treated with $SOCl_2$ in CH_2Cl_2 to produce the acid chloride.§ The crude acid chloride was stirred with cold concd NH_4OH to yield the amide **1b**: 3.15 g (93%); mp 144–150° (MeCN). *Anal.* ($C_{16}H_{21}NO$) C, H, N.

5-(3-Ethyl-2-methyl-4-phenyl-Δ⁴-cyclohexenyl)tetrazole (1d). Triethylamine (2.07 g, 0.02 mole) was added to a soln of the amide **1b** (2.45 g, 0.01 mole) in $POCl_3$ (15 ml), and the soln was heated under reflux for 1.75 hr. Excess $POCl_3$ was removed at 15 mm. A $CHCl_3$ soln of the residue was washed with H_2O and aqueous NH_4OH. Evapn of the dried $CHCl_3$ soln left the nitrile **1c** as an oil (2.06 g, 91%). The crude nitrile (2.02 g, 0.009 mole) in DMF (20 ml) contg NaN_3 (0.62 g, 0.01 mole) and NH_4Cl (0.51 g, 0.01 mole) was heated at 118° for 18 hr. The DMF was removed under reduced pressure, and the residue was partitioned between aqueous 1 *N* NaOH and Et_2O. The aqueous basic layer was acidified and extd with fresh Et_2O. Evapn of the dried Et_2O soln yielded **1d** (0.57 g, 24%); recrystd (aqueous EtOH) to a hydrated cryst form of **1d**, mp 105–120°. The analytical sample was dried at 100° (0.1 mm) over P_2O_5 to a glass. *Anal.* ($C_{16}H_{20}N_4$) C, H, N.

3-(6-Methoxy-2-naphthyl)-2,2-dimethylvaleramide (2b). A commercial sample‡ of the acid **2a** was converted to the amide **2b** by the procedure described for **1b**: yield, 75%; mp 144–145.5° (MeCN). *Anal.* ($C_{18}H_{23}NO_2$) C, H, N.

3-(6-Methoxy-2-naphthyl)-2,2-dimethylvaleronitrile (2c) was prepd from the amide **2b** (3.00 g) using the procedure described for **1c**: yield of **2c**, 2.45 g (87%); mp 111–113° (EtOH). *Anal.* ($C_{18}H_{21}NO$) C, H, N.

5-[2-(6-Methoxy-2-naphthyl)-1,1-dimethylbutyl]tetrazole (2d). A mixt of $AlCl_3$ (5.70 g, 0.043 mole) and NaN_3 (8.25 g, 0.127 mole) in diglyme (73 ml) was warmed to 75°, and then a soln of the nitrile **2c** (8.15 g, 0.031 mole) in diglyme (37 ml) was added. The mixt was stirred under reflux for 16 hr. Most of the solvent was removed at reduced pressure, and the residue was acidified with 6 *N* aqueous HCl. An ether ext of the product was washed with aqueous 1 *N* NaOH. Acidification of the basic extracts yielded **2d** (1.81 g, 19%): mp 168–170°. Recrystn (aqueous EtOH) gave mp 171–173°. *Anal.* ($C_{18}H_{22}N_4$) C, H, N.

3-(6-Methoxy-2-naphthyl)valeric Acid (5b). 6-Methoxy-2-propionaphthone[10] and ethyl bromoacetate were condensed according to a general procedure[11] to yield the hydroxyester **3** (67%): mp 72.5–73.5° (*i*-PrOH). *Anal.* ($C_{18}H_{22}O_4$) C, H.

Dehydration of **3** by heating under reflux in AcOH contg *p*-TsOH gave a mixt of the ene esters **4a**:**4b** in approximately a 2:3 ratio (nmr): bp 161–165° (0.1 mm) (82% yield). *Anal.* ($C_{18}H_{20}O_3$) C, H.

Hydrogenation of **4** in abs EtOH contg 5% Pd/C gave **5a** (90%): bp 143–146° (0.04 mm). *Anal.* ($C_{18}H_{22}O_3$) C, H.

Hydrolysis of the ester **5a** (23.32 g) by heating under reflux for 18 hr in 80% EtOH (120 ml) contg KOH (6.13 g) yielded, after acidification, the acid **5b** (20.52 g, 97%): mp 92–94.5° (aqueous EtOH). *Anal.* ($C_{16}H_{18}O_3$) C, H.

5-[2-(6-Methoxy-2-naphthyl)butyl]tetrazole (5e). Following the general procedure described above, the acid **5b** was converted to the amide **5c** (89%): mp 112.5–113.5° (toluene). *Anal.* ($C_{16}H_{19}NO_2$) C, H, N. Dehydration of **5c** using the procedure described above gave the nitrile **5d** (84%): mp 58.5–61°. *Anal.* ($C_{16}H_{17}NO$) C, H, N.

The nitrile **5d** was treated with NaN_3–NH_4Cl as described in the procedure for **1d** to produce the tetrazole **5e** (30%): mp 138–139.5° (MeCN). *Anal.* ($C_{16}H_{18}N_4O$) C, H, N.

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§ An aliquot of the acid chloride was dissolved in MeOH. Vpc analysis of the resultant methyl ester indicated the same isomeric ratio as the starting acid 1a.

Adamantyl Analogs of 2′-(3-Dimethylaminopropylthio)cinnamanilide†

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Several recent reports have described the synthesis and biological activity of a variety of adamantane derivatives.[1-10] This note describes the syntheses and immunosuppressive activity of representative adamantyl analogs (**2–9**) of 2′-(3-dimethylaminopropylthio)cinnamanilide [cinanserin (**1**)], which had been developed in our laboratories by Krapcho, *et al.*[11-14]

Chemistry. 1-Adamantanecarboxylic acid‡ (**10**), 1-ada-

†Cinanserin is the approved generic name for 2′-(3-dimethylaminopropylthio)cinnamilide (1).

‡Aldrich Chemical Co., Milwaukee, Wisconsin.