water acidified with a few drops of glacial acetic acid. The mixture was set aside at room temperature with intermittent agitation for 2 hr. and filtered, and the filtrate was evaporated to dryness. The crude aminoguanidine sulfate (3.2 g.) so obtained was dissolved in water, filtered from a trace of insoluble material, acidified (H_2SO_4), and, to the resultant solution, benzaldehyde (1.59 g., 0.015 mole) dissolved in ethanol was added. A white solid precipitated which was separated and recrystallized from isopropyl alcohol and finally twice from water to yield the product (1.5 g., 29%) as the monohydrate, m.p. 184.5–186°.

1-Benzyl-3-benzylideneaminoguanidine (19).—In a similar manner 1-amino-3-benzylguanidine hydriodide (20.0 g., 0.069 mole) was converted to the sulfate and treated with benzaldehyde. The benzylideneaminoguanidine sulfate so obtained was converted to the free base by the addition of 40% NaOH. Recrystallization from benzene–petroleum ether (60–80°) yielded pure product (7.3 g., 42%), m.p. 115–119°. The picrate had m.p. 209–212° (lit.[23] m.p. 215–216°).

1-Benzylideneamino-3-(2-chlorobenzyl)guanidine (20).—In a similar manner 1-amino-3-(2-chlorobenzyl)guanidine hydriodide (15.0 g., 0.046 mole) was converted to **20**, and the free base was purified by three recrystallizations from benzene–petroleum ether; yield 4.3 g. (33%), m.p. 115.5–118.5.°

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3-Amino-4-[2-(2,6-xylyloxyethyl)]-1,2,4-triazole (14).—A suspension of 1-amino-3-[2-(2,6-xylyloxy)ethyl]guanidine hydriodide (5.0 g., 0.014 mole) in formic acid (15 ml.) was boiled under reflux for 2 hr., evaporated to low bulk, diluted with water, and basified with NaOH solution. Solid separated on standing, which was filtered off, washed with water, and recrystallized from *n*-butyl alcohol, affording the triazole (1.9 g., 59%), m.p. 248–250°.

3-Amino-4-benzyl-1,2,4-triazole (25) and 3-Benzylamino-1,2,4-triazole.—A suspension of 1-amino-3-benzylguanidine hydriodide (80.0 g., 0.275 mole) in formic acid (16 ml.) was heated on the steam bath for 1 hr., cooled, diluted with water, and neutralized with $NaHCO_3$ solution. After standing overnight, the precipitated solid was separated, washed with boiling water, and recrystallized from *n*-butyl alcohol affording **25** (22.7 g.) as colorless plates, m.p. 213–215°. From the mother liquors, more of this compound was obtained (6.7 g., m.p. 212–215°) and also 3-benzylamino-1,2,4-triazole[24] (2.2 g.), m.p. 161–163° (lit.[24] m.p. 164–165°).

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Totally Synthetic Steroid Hormones. V.[1] (±)-2,3-Dimethoxyestra-1,3,5(10)-trien-17β-ol and Some Congeners

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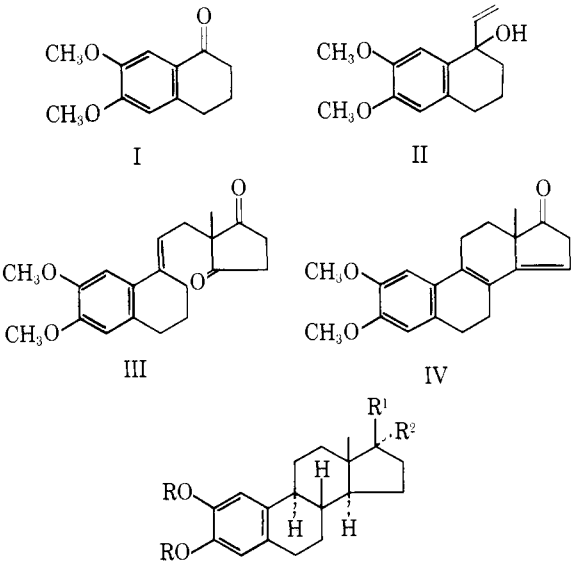
(±)-2,3-Dimethoxy-1,3,5(10)-estratrien-17-one and -17β-ol have been totally synthesized from 6,7-dimethoxy-1-tetralone. Their estrogenic and blood cholesterol lowering properties are recorded.

We[2] have demonstrated the flexibility of our recently described total syntheses of estrone[3] by their extension to a variety of related 13β-alkylgonanes. This paper describes a further application to compounds of the (±)-2,3-dimethoxyestra-1,3,5(10)-triene series which were required for biological evaluation. The project seemed worthwhile in view of the occurrence of 2-methoxyestrone as a metabolite of estradiol in man.[4]

The 6,7-dimethoxy-1-tetralone (I) required as starting material was made, following Haworth and Martin,[5] by cyclodehydrating 4-(3,4-dimethoxyphenyl)butyric acid which was obtained in two stages from veratrole by a modification of the published method,[5] or from 3,4-dimethoxycinnamic acid in five stages, by way of 3-(3,4-dimethoxyphenyl)propyl bromide. Both routes are described in the Experimental Section. The former is the more efficient.

The tetralone (I) was converted into compounds of the (±)-2,3-dimethoxyestra-1,3,5(10)-triene series by the general methods developed earlier.[2,3] Briefly, initial reaction with vinylmagnesium chloride in tetrahydrofuran gave the alcohol II which was condensed with 2-methylcyclopentane-1,3-dione to give the seco steroid III and transformed thence by acid cyclodehydration to the pentaene IV.[6] Catalytic hydrogenation of the



I II III IV

V, Δ^8; R = CH_3; R^1,R^2 = O
VI, Δ^8; R = CH_3; R^1 = OH; R^2 = H
VII, R = CH_3; R^1 = OH; R^2 = H
VIII, R = CH_3; R^1,R^2 = O
IX, $\Delta^{9(11)}$; R = CH_3; R^1,R^2 = O
X, R = H; R^1,R^2 = O

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latter over palladized calcium carbonate in benzene gave the tetraene V which was reduced, first with sodium borohydride to the alcohol VI, and then with lithium in liquid ammonia–aniline to the trienol VII, which, on oxidation by chromic acid, gave the trienone VIII. An alternative route to this ketone involved rearrangement of the tetraene V with alcoholic HCl and catalytic hydrogenation of the resultant isomer IX. Demethylation of the trienone VIII with molten pyridine hydrochloride gave (±)-2-hydroxyestrone (X). The stereo structures of compounds V–X are assigned by analogy with the stereochemical course demonstrated for corresponding syntheses in the 3-hydroxy- and -methoxyestratriene series.[3]

Biological Activities.—Compounds IV, VII, and VIII had, respectively, <0.01, 0.03, and 0.6% of the activity of estrone by subcutaneous administration in a 3-day mouse uterine-weight assay.[7] By the same route of administration the three compounds had approximately 16, 100, and 100% of the activity of estrone in a 9-day rat blood cholesterol lowering test.[8] Considering the differing biological test procedures used, the results with compounds VII and VIII are consistent with the estrogenic and hypocholesterolemic activities recorded by Gordon, *et al.*,[9] for the corresponding (+)-enantiomorphs. Compound V had approximately 11% of the antilipemic activity of estrone in a 4-day assay using cholesterol-fed cockerels.[9]

Experimental Section

Melting points were determined in a Thomas–Hoover capillary melting point apparatus and are uncorrected. Proton n.m.r. spectra were measured at 60 Mc. on the Varian A-60 spectrometer using 5–10% solutions in $CDCl_3$ containing tetramethylsilane (TMS) as an internal reference standard. Chemical shifts are expressed in τ units measured downfield from the reference (τ 0).

3-(3,4-Dimethoxyphenyl)propyl Bromide.—3,4-Dimethoxycinnamic acid[10] (226 g.) in acetic acid (2 l.) containing 10% palladized charcoal (10 g.) was shaken with hydrogen at atmospheric pressure until 27 l. had been absorbed. Filtration and evaporation of the filtrate gave 3-(3,4-dimethoxyphenyl)propionic acid (226 g.), m.p. 98° (lit.[11] 98°). The acid (297 g.) was reduced with $LiAlH_4$ (43 g.) in ether (2 l.) to give 3-(3,4-dimethoxyphenyl)propyl alcohol (150 g.), b.p. 131–145° (0.15 mm.). Phosphorus tribromide (16.5 g.) was added dropwise with stirring to the alcohol (25.9 g.) in benzene (33.5 ml.) at 0°, and the mixture was kept at 65° for 3 hr., cooled, poured onto ice, and extracted with ether. Distillation of the product gave the bromide (18 g.), b.p. 115–140° (0.2 mm.), $n^{25}D$ 1.5535.

Anal. Calcd. for $C_{11}H_{15}BrO_2$: C, 51.0; H, 5.8; Br, 30.8. Found: C, 50.7; H, 5.8; Br, 30.9.

6,7-Dimethoxy-1-tetralone (I). A.—3-(3,4-Dimethoxybenzoyl)propionic acid (156 g., prepared using Fieser and Hershberg's procedure[12]) was reduced by Huang-Minlon's method[13] to give 4-(3,4-dimethoxyphenyl)butyric acid (125 g.), m.p. 135–136° (lit.[5] 135–136°). The acid (110 g.) was heated on the steam bath for 45 min. with P_2O_5 (120 g.) in 80% H_3PO_4 (300 ml.), and the cooled mixture was poured onto crushed ice. The product was isolated with chloroform and recrystallized from methylcyclohexane to give the tetralone (80.6 g.), m.p. 96–100° (lit.[5] 99–100°).

B.—The foregoing bromide (18 g.) was refluxed for 3 hr. with magnesium turnings (2 g.) in ether–tetrahydrofuran (150:100 ml.). The cooled mixture was added to solid CO_2, the product was extracted with ether, and the ethereal layer extracted with 10%, aqueous NaOH. Acidification gave crude 4-(3,4-dimethoxyphenyl)butyric acid (7.3 g.) which was converted as in A to 6,7-dimethoxy-1-tetralone.

2,3-Dimethoxy-8,14-secoestra-1,3,5(10),9(11)-tetraene-14,17-dione (III).—6,7-Dimethoxy-1-tetralone (6.1 g.) was stirred for 3 hr. at room temperature with vinylmagnesium chloride (6.5 g.) in tetrahydrofuran (90 ml.). The mixture was added to saturated aqueous NH_4Cl and then extracted with ether. The crude alcohol II, obtained after removing the ether, was refluxed for 3 hr. with 2-methylcyclopentane-1,3-dione (4 g.) in methanol (35 ml.) containing a trace of KOH. Recrystallization of the product from methanol gave the dione (5.45 g.), m.p. 104–106°, λ_{max} 257 and 310 mμ (ε 13,900 and 8200).

Anal. Calcd. for $C_{26}H_{28}O_4$: C, 73.1; H, 7.4. Found: C, 73.4; H, 7.1.

(±)-2,3-Dimethoxyestra-1,3,5(10),8,14-pentaen-17-one (IV).—Hydrochloric acid (10 *N*) was added dropwise to the dione III (60 g.) in refluxing methanol (750 ml.) until the solution just became turbid. The solution was clarified with tetrahydrofuran and allowed to cool. The next day the product was filtered off and recrystallized from ethanol to give the pentaenone (38 g.), m.p. 137–140°, λ_{max} 243 and 328 mμ (ε 15,300 and 22,900).

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.3; H, 7.1. Found: C, 77.2; H, 7.1.

The **ethylene ketal** had m.p. 113–117° (from methanol), λ_{max} 243 and 326 mμ (ε 15,100 and 23,600).

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.4. Found: C, 74.55; H, 7.4.

(±)-2,3-Dimethoxyestra-1,3,5(10),8-tetraen-17-one (V).—Catalytic hydrogenation at atmospheric pressure of the pentaenone IV (2 g.) in benzene (55 ml.) containing 2% palladized calcium carbonate (0.5 g.) gave the tetraenone (1.1 g.): m.p. 158–162° (from ethanol); λ_{max} 224, 287, and 306 mμ (ε 20,400, 10,000, and 9400).

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.9; H, 7.7. Found: C, 76.6; H, 7.7.

(±)-2,3-Dimethoxyestra-1,3,5(10),9(11)-tetraen-17-one (IX).—Hydrochloric acid (10 *N*, 1 ml.) was added to the tetraene V (0.2 g.) in refluxing methanol–tetrahydrofuran (25:6 ml.). The solution was refluxed for 15 min. and added, while hot, to saturated aqueous $NaHCO_3$ (250 ml.), and the mixture was extracted with ether. Recrystallization of the product from methanol gave the tetraenone (0.15 g.): m.p. 158–162°; λ_{max} 265, 271, and 306 mμ (ε 13,800, 12,700, and 7100); n.m.r. C-11 H (0.9 proton) as a multiplet, τ 3.89.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.9; H, 7.7. Found: C, 77.2; H, 7.7.

(±)-2,3-Dimethoxyestra-1,3,5(10),8-tetraen-17β-ol (VI).—Sodium borohydride (2.5 g.) was added with stirring to the tetraene V (10 g.) in methanol (400 ml.). After stirring for 1 hr. acetic acid was added and the mixture was extracted with ether. Recrystallization of the product from methanol gave the tetraenol (9.0 g.), m.p. 178–181°, λ_{max} 282 and 305 mμ (ε 10,800 and 9200).

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.4; H, 8.3. Found: C, 76.2; H, 8.1.

(±)-2,3-Dimethoxyestra-1,3,5(10)-trien-17β-ol (VII).—Lithium (0.2 g.) was added with stirring to the preceding tetraenol (2 g.) in liquid ammonia–aniline (250:12 ml.). After stirring for 1 hr. the blue color was discharged by adding a few drops of acetone and the product was worked up in the usual manner and recrystallized from methanol to give the trienol (1.1 g.), m.p. 154–158°, λ_{max} 287 mμ (ε 3800).

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.9; H, 8.9. Found: C, 75.7; H, 9.0.

(±)-2,3-Dimethoxyestra-1,3,5(10)-trien-17-one (VIII).—Chromic acid[14] (8 *N*, 1 ml.) was added dropwise to the trienol VII (1 g.) in acetone (500 ml.). After 10 min. isopropyl alcohol (5 ml.) was added and the mixture was evaporated to dryness. The residue, in ether, was washed with aqueous $NaHCO_3$ and

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water, and dried. Recrystallization of the product from methanol gave the trienone (0.5 g.), m.p. 140–144°, λ_{max} 282–289 mμ (ε 3250).

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.4; H, 8.3. Found: C, 76.2; H, 8.1.

The same trienone was obtained by hydrogenation over 10% palladized charcoal in ethanol of the tetraenone IX.

(±)-2,3-Dihydroxyestra-1,3,5(10)-trien-17-one (X).—The trienone VIII (0.3 g.) was stirred for 30 min. under nitrogen in molten pyridine hydrochloride at 185–195°. The cooled melt was added to 3 *N* HCl and the mixture was extracted with ether. Recrystallization of the product from ether gave the trienone, m.p. 220–230°, λ_{max} 290 mμ (ε 4100).

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.3; H, 7.7. Found: C, 75.1; H, 7.5.

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Derivatives of Imidazole. II. Synthesis and Reactions of Imidazo[1,2-*a*]pyrimidines and Other Bi- and Tricyclic Imidazo Derivatives with Analgesic, Antiinflammatory, Antipyretic, and Anticonvulsant Activity

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The synthesis and pharmacological properties of some derivatives of imidazo[1,2-*a*]pyrimidine, 1H-imidazo[1,2-*d*]tetrazole, imidazo[2,1-*b*]thiazole, 1H-imidazo[1,2-*b*]-*s*-triazole, and imidazo[1,2-*b*]pyridazine are described. The results have been compared with those obtained under the same conditions with acetylsalicylic acid, aminopyrine, phenylbutazone, and chlortenoxazine. Some members of the series display activities in one or more of the pharmacological tests; the most interesting compounds are 2-(*p*-methylthiophenyl)-3-(morpholinomethyl)imidazo[1,2-*a*]pyrimidine (**7**), 2-(*p*-methylthiophenyl)-3-[4-(2-hydroxyethyl)-1-piperazinylmethyl]-imidazo[1,2-*a*]pyrimidine (**8**), and 2-(*p*-methylsulfonylphenyl)-5,6,7,8-tetrahydroimidazo[2,1-*b*]benzothiazole hydrochloride (**17**).

The first paper in this series[2] described the synthesis of a series of substituted imidazo[1,2-*a*]pyridines examined for analgesic, antiinflammatory, antipyretic, and anticonvulsant (muscle-relaxant) activity. The most active compounds were 2-(*p*-methylsulfonylphenyl)imidazo[1,2-*a*]pyridine hydrochloride and its dimethylaminomethyl Mannich base.

In order to study whether modification in the heterocyclic ring might result in a different spectrum or order of pharmacological activity, we synthesized a series of new imidazo[1,2-*a*]pyrimidines (Table I) which are closely related to the compounds described in the first paper. Other heterocyclic derivatives of imidazole were also synthesized (Table II) in order to extend the pharmacological screening to imidazo derivatives with an atom of nitrogen in angular position. Since earlier studies[2] have shown that substitution in R with a methylsulfonyl group seemed to be necessary for a broad spectrum of activity, this group was kept constant in these compounds.

Substituted 2-arylimidazo[1,2-*a*]pyrimidines (**1–5**) were prepared by condensation of 2-aminopyrimidine and 2-amino-5-methoxypyrimidine[3] with ω-bromoacetophenones, substituted in the *para* or *ortho* position with a methylthio, methylsulfoxy, or methylsulfonyl group.[2] Mannich bases **6–13** were obtained in acetic acid as previously described for imidazo[1,2-*a*]pyridines.[2]

2-(*p*-Methylsulfonylphenyl)-1H-imidazo[1,2-*d*]tetrazole (**14**) was obtained from 5-amino-1H-tetrazole and ω-bromo-*p*-methylsulfonylacetophenone. Other products reported in Table II (**15–22**) were prepared by the same method, starting from 2-aminothiazole, 2-amino-4,5,6,7-tetrahydrobenzothiazole,[4] 2-amino-5,6-dihydro-4H-cyclopentathiazole,[4] 3-amino-1,2,4-triazole, 3-aminopyridazine, 3-amino-6-chloropyridazine, and 3-amino-6-methoxypyridazine, respectively.

The rings of imidazo[1,2-*b*]pyridazine,[5] 1H-imidazo[1,2-*b*]-*s*-triazole, and 6,7-dihydro-5H-imidazo[2,1-*b*]-cyclopentathiazole are not recorded in "The Ring Index."[6]

Pharmacological Studies.—LD_{50} values in mice were determined, and analgesic, antiinflammatory, antipyretic, and anticonvulsant activities were investigated in several basic screening procedures as previously described.[2] The pharmacological results are presented in Table III as are the results of the standard drugs (acetylsalicylic acid, aminopyrine, phenylbutazone, and chlortenoxazine) and the most active compound of the earlier series (2-(*p*-methylsulfonylphenyl)imidazo[1,2-*a*]pyridine hydrochloride) for comparison.

Analgesic Activity.—Among the 22 compounds examined, significant analgesic activity was displayed only by the 2-phenylimidazo[1,2-*a*]pyrimidine analogs. Although several compounds of this series showed analgesic properties in one or more of the tests employed, this effect was accentuated in those substances where R = *o*-SO_2CH_3 (**1**) and *p*-$SOCH_3$ (**3**). Introduction of a

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