led to an amido acid **5** whose structure was confirmed through its nmr spectrum. Catalytic hydrogenation of **5** gave the saturated amido acid **6**. Hydrolysis with hydroiodic acid converted **6** to 3,5-diisopropylthyronine (**7**) which showed color reactions with ninhydrin (amino acid) and with MBTH[8] (phenol). The structure of **7** was confirmed through its nmr spectrum. Iodination of **7** in alkaline medium easily led to **8** in excellent yield.

3,5-Diisopropyl-3′-iodo-DL-thyronine (**8**) was tested for antigoitrogenic activity by Professor Kenkichi Tomita, Faculty of Pharmaceutical Science, Kyoto University, but it showed practically no activity.

### Experimental Section

Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values.

**3,5-Diisopropyl-4-hydroxybenzaldehyde** (**1**) was prepared according to the method of Nikiforov, *et al.*;[9] mp 106–108°, lit.[9] 119–120°; nmr ($CDCl_3$), δ 9.87 (s, 1, $CHO$), 7.60 (s, 2, aromatic protons), 6.90 (s, 1, $OH$), 3.30 (septet, 2, $J$ = 6 Hz, $2CH(CH_3)_2$), 1.30 (d, 12, $J$ = 6 Hz, $2CH(CH_3)_2$).

**Ethylene Acetal of 3,5-Diisopropyl-4-hydroxybenzaldehyde** (**2**).—A solution of 10 g (0.048 mole) of aldehyde **1**, 20 ml (0.35 mole) of ethylene glycol, and 5 g of $NH_4Cl$ in 250 ml of dry $C_6H_6$ was saturated with dry HCl gas. The mixture was refluxed and $H_2O$ generated in the course of the reaction was removed by azeotropic distillation. After 30 hr no more $H_2O$ was formed. The reaction mixture, after neutralization with 15 g of $Na_2CO_3$, was evaporated *in vacuo* to dryness. The residue was taken up with ether and water. The ether layer was washed ($H_2O$), dried, and evaporated to give a crystalline residue. Recrystallization from cyclohexane gave 10.6 g (88%) of **2** as colorless prisms, mp 132–134°. This substance shows no carbonyl band in its ir spectrum.

**3,5-Diisopropyl-4-(4-methoxyphenoxy)benzaldehyde** (**3**).—To a solution of 10 g (0.04 mole) of **2** in 150 ml of DMF, dried over BaO, was added 1.56 g (0.04 g-atom) of K. To the green solution was added 21.1 g (0.05 mole) of dianisyliodonium bromide[7] and 1 g of active powder.[10] The mixture was heated on an oil bath of 150–180° for 6 hr with stirring and under exclusion of moisture. The reaction mixture was cooled to room temperature, then taken up with ether and water. The ether layer was washed (dilute NaOH, $H_2O$) and evaporated. The residue was dissolved in 150 ml of EtOH containing *ca.* 4 ml of concentrated HCl, then heated for 30 min. The reaction mixture was evaporated *in vacuo* to dryness and the residue was taken up with ether and water. The ether layer was washed ($H_2O$), dried, and evaporated *in vacuo* to dryness. The residue (11.1 g) was chromatographed on a column of 200 g of silica gel (Mallinckrodt 100 mesh). Elution with $C_6H_6$ gave 2.05 g (16.5%) of **3**, which was recrystallized from benzene–isooctane to give colorless needles: mp 87–88°; ir (Nujol), 1700 $cm^{-1}$ (C=O); nmr ($CDCl_3$), δ 1.16 (d, 12, $J$ = 6.1 Hz, $2CH(CH_3)_2$), 3.11 (septet, 2, $J$ = 6.1 Hz, $2CH(CH_3)_2$), 3.77 (s, 3, $OCH_3$), 6.68 (d (incompletely resolved), 4, *para*-disubstituted $C_6H_4$), 7.66 (s, 2, aromatic protons adjacent to formyl group), and 9.89 (s, 1, $CHO$). *Anal.* ($C_{20}H_{24}O_3$).

**2-Phenyl-4-[3,5-diisopropyl-4-(4-methoxyphenoxy)benzal]-5-oxazolone** (**4**).—A mixture of 1.0 g (0.0032 mole) of **3**, 0.69 g (0.0038 mole) of hippuric acid, 0.316 g (0.0038 mole) of anhydrous NaOAc, and 4 ml (0.039 mole) of $Ac_2O$ was heated at 100° for 5 hr. The reaction mixture was kept overnight at 2° to give a semisolid material which was pressed on a suction filter and washed (cold $H_2O$, hot $H_2O$), yielding 1.13 g of yellow crystals. Recrystallization from MeOH gave 0.87 g (73.5%) of yellow needles: mp 149–152°; uv, $\lambda_{max}$ (95% $C_2H_5OH$) 360 mμ (ε 41,300), 372 (39,200), and 388 (43,600); ir (Nujol), 1795, 1770, 1655, and 1560 $cm^{-1}$. *Anal.* ($C_{29}H_{29}NO_4$) C, H, N.

**α-Benzamido-3,5-diisopropyl-4-(4-methoxyphenoxy)cinnamic Acid** (**5**).—A solution of 4.2 g (0.0092 mole) of azlactone **4** in 300 ml of EtOH and 100 ml of 2 *N* NaOH was warmed at 60° for 30 min. The reaction mixture, after cooling, was acidified with chilled dilute HCl and concentrated *in vacuo* at room temperature to yield a brown solid residue. Crystallization from $C_6H_6$–isooctane gave 2.5 g (57%) of acid **5** as colorless needles: mp 200–202°; uv, $\lambda_{max}$ 223 mμ (ε 35,800) and 292 (24,100); ir (Nujol), 2700–2500 (COOH), 1673, and 1623 $cm^{-1}$; nmr ($CDCl_3$), δ 1.02 (d, 12, $J$ = 6.1 Hz, $2CH(CH_3)_2$), 3.02 (septet, 2, $J$ = 6.1 Hz, $2CH(CH_3)_2$), 3.72 (s, 3, $OCH_3$), 6.68 (incompletely resolved doublet, 4, aromatic H), 7.65 (s, 2, aromatic H), 7.20–7.90 (m, 5, aromatic H), and 10.00 (s, 1, $COOH$). *Anal.* ($C_{30}H_{33}NO_5$) C, H, N.

**3,5-Diisopropyl-DL-thyronine** (**7**).—A solution of 0.93 g (0.002 mole) of **6**[11] prepared by catalytic hydrogenation (Pd, MeOH, 1 mole of $H_2$ uptake) of **5** in 24 ml of HI (sp gr 1.7) and 40 ml of AcOH was refluxed for 5 hr under $N_2$. The reaction mixture was evaporated *in vacuo*, and AcOH was completely removed by repeated additions and evaporations of $H_2O$ *in vacuo*. The residue was dissolved in dilute NaOH, and the solution was decolorized with Norit and then neutralized (pH 7.2) with dilute AcOH. Fine crystals of 3,5-diisorpopyl-DL-thyronine (0.51 g, 73%) were obtained which were collected by centrifugation, washed ($H_2O$), and dried. Paper chromatography (1-BuOH–concentrated $NH_4OH$–$H_2O$, 5:1:2) ($R_f$ 0.71) showed a single spot: mp 227°; nmr ($CD_3OD$), δ 1.10 (d, 12, $J$ = 6.1 Hz, $2CH(CH_3)_2$), 3.00 (septet, 2, $J$ = 6.1 Hz, $2CH(CH_3)_2$), and 6.45–6.98 (two broad singlets, 6, aromatic H). A sample for elemental analysis was prepared by reprecipitation with $H_2O$ from a solution in MeOH. *Anal.* ($C_{21}H_{27}NO_4 \cdot 0.5H_2O$) C, H, N.

**3,5-Diisopropyl-3′-iodo-DL-thyronine** (**8**).—To a stirred, ice-cooled solution of 71.4 mg (0.2 mmole) of 3,5-diisopropylthyronine (**7**) in 2 ml of 0.2 *N* NaOH and 2 ml of 0.1 *M* $Na_2CO_3$ was added dropwise 2 ml (0.2 mmole) of 0.1 *M* $KI_3$ solution. After the addition was completed, a small amount of $NaHSO_3$ solution was added and the mixture was neutralized (pH 6.5) with dilute AcOH to yield 870 mg (90%) of colorless microcrystals which were collected by centrifugation, washed ($H_2O$), and dried: mp 187° dec. *Anal.* ($C_{21}H_{26}O_4NI \cdot 0.5H_2O$) C, H, N.

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(11) This compound could not be obtained in crystalline form but as a glassy material which was used without further purification in the next step.

## Synthesis and Pharmacology of Some Indanamines. Dialkylaminoethylindans

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In view of the potent hypoglycemic activity shown by hexahydroindeno[1,2-*c*]pyrroles and their possible degradation products indanamines,[2-4] a series of dialkylaminoethylindans (**1, 2**) were prepared. Syntheses and a brief pharmacology of these compounds are reported. A few of these compounds showed slight

(8) Methylbenzothiazolone hydrazone; E. Kamada, *Nippon Kagaku Zasshi*, **87**, 380 (1965).

(9) G. A. Nikiforov, K. M. Dyumaev, A. A. Vold'Kin, and V. V. Ershov, *Izv. Akad. Nauk SSR, Otd. Khim. Nauk*, 1836 (1962); *Chem. Abstr.*, **58**, 7856*f* (1963).

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(1) To whom inquiries regarding this paper should be sent.

(2) S. C. Lahiri and B. Pathak, *J. Med. Chem.*, **8**, 131 (1965).

(3) S. C. Lahiri and B. Pathak, Indian Patent Application 105,586 (June 4, 1966).

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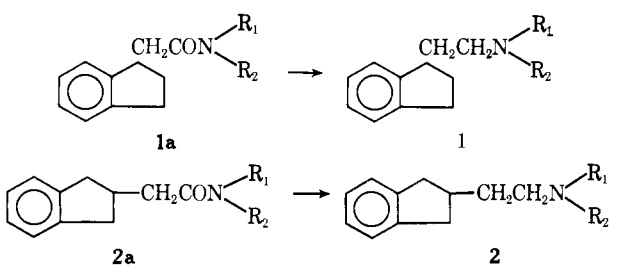
TABLE I

| Compd | $R_1$ | $R_2$ | Bp, °C (mm) | $n^{25}D$ | Formula[c] | HCl mp, °C[a] | Av % ↓ blood sugar[b] |
|---|---|---|---|---|---|---|---|
| 1a | Me | Me | 170–172 (2.5) | 1.523 | $C_{13}H_{17}NO$ | | |
| | Et | Et | 175–180 (1.5) | 1.532 | $C_{15}H_{21}NO$ | | |
| | *n*-Pr | *n*-Pr | 160–170 (0.2) | 1.525 | $C_{17}H_{25}NO$ | | |
| | *n*-Bu | *n*-Bu | 130–140 (0.2) | 1.527 | $C_{19}H_{29}NO$ | | |
| | *n*-Pr | H | 141–145 (0.5) | 1.553 | $C_{14}H_{19}NO$ | | |
| | *n*-Bu | H | 156–159 (0.35) | 1.543 | $C_{15}H_{21}NO$ | | |
| 2a | Me | Me | 138–142 (0.6) | 1.535 | $C_{13}H_{17}NO$ | | |
| | Et | Et | 146–150 (0.4) | 1.515 | $C_{15}H_{21}NO$ | | |
| | *n*-Pr | *n*-Pr | 161–163 (0.8) | 1.542 | $C_{17}H_{25}NO$ | | |
| | *n*-Bu | *n*-Bu | 156–157 (0.4) | 1.555 | $C_{19}H_{29}NO$ | | |
| | *n*-Pr | H | 151–153 (0.45) | 1.544 | $C_{14}H_{19}NO$ | | |
| | *n*-Bu | H | 166–168 (0.9) | 1.505 | $C_{15}H_{21}NO$ | | |
| 1 | Me | Me | 120–122 (3.0) | 1.526 | $C_{13}H_{19}N$ | 153–155 | 6.5 ± 1.2 |
| | Et | Et | 126–130 (2.5) | 1.536 | $C_{15}H_{23}N$ | 120–122 | 10.2 ± 1.7 |
| | *n*-Pr | *n*-Pr | 154–160 (0.2) | 1.524 | $C_{17}H_{27}N$ | 126–128 | 12.5 ± 2.1 |
| | *n*-Bu | *n*-Bu | 115–120 (0.3) | 1.573 | $C_{19}H_{31}N$ | 134–136 | 7.8 ± 1.5 |
| | *n*-Pr | Me | 149–153 (0.2) | 1.534 | $C_{15}H_{23}N$ | 156–158 | 14.0 ± 2.2 |
| | *n*-Bu | Me | 120–126 (1.0) | 1.508 | $C_{16}H_{25}N$ | 162–164 | 12.1 ± 2.7 |
| | *n*-Pr | H | 125–127 (1.0) | 1.525 | $C_{14}H_{21}N$ | 133–134 | 9.1 ± 2.3 |
| | *n*-Bu | H | 140–142 (1.1) | 1.527 | $C_{15}H_{23}N$ | 145–146 | 10.3 ± 1.5 |
| 2 | Me | Me | 96–100 (0.8) | 1.423 | $C_{13}H_{19}N$ | 189–191 | ... |
| | Et | Et | 108–110 (0.5) | 1.475 | $C_{15}H_{23}N$ | 128–130 | 8.0 ± 1.2 |
| | *n*-Pr | *n*-Pr | 126–128 (0.55) | 1.486 | $C_{17}H_{27}N$ | 119–121 | 11.3 ± 1.2 |
| | *n*-Bu | *n*-Bu | 141–143 (0.5) | 1.492 | $C_{19}H_{31}N$ | 134–136 | 7.5 ± 1.7 |
| | *n*-Pr | Me | 159–161 (0.6) | 1.466 | $C_{15}H_{23}N$ | 146–149 | 11.0 ± 2.2 |
| | *n*-Bu | Me | 159–162 (0.8) | 1.444 | $C_{16}H_{25}N$ | 168–169 | 10.0 ± 1.6 |
| | *n*-Pr | H | 143–145 (1.4) | 1.521 | $C_{14}H_{21}N$ | 140–141 | 7.7 + 1.8 |
| | *n*-Bu | H | 130–132 (0.8) | 1.532 | $C_{15}H_{23}N$ | 146–148 | 9.1 + 2.1 |
| Tolbutamide | | | ... | ... | ... | ... | 22.5 ± 2.5 |

[a] Crystallized from EtOAc and EtOH. [b] Data on eight rabbits given a 25-mg/kg dose. [c] All compounds showed a correct analyses for C, H, N.

to moderate hypoglycemic and slight hypotensive and muscle relaxant activities.




All of the compounds reported in Table I were prepared by a method similar to that described earlier by the present author[2] as described in the Experimental Section.

The compounds were primarily screened for hypoglycemic activity on normal, healthy, male rabbits at a dose level of 25 mg/kg of body weight by the oral route. Blood glucose determinations were made at different intervals up to 12 hr following dosing, following a procedure of Hagedorn and Jensen.[5] No significant activity was observed compared to tolbutamide (Table I).[6] A few of these compounds, however, showed slight muscle relaxant and hypotensive activity.

(5) H. C. Hagedorn and B. N. Jensen, *Biochem. Z.*, **135** 46 (1923); **137**, 92 (1923).

(6) Hypoglycemic screening of some of these compounds were also carried out by Bristol Laboratories, Syracuse, N. Y., on fasting adrenalectomized and alloxan-diabetic rats at 50 mg/kg along with insulin and tolbutamide. Blood glucose determinations were made employing the Technicon autoAnalyzer microglucose method. None of these compounds showed significant activity.

### Experimental Section[7]

**1- and 2-Indanacetic Acids.**—3-Oxoindan-1-acetic acid[8] and 1-oxoindan-2-acetic acid[9,10] were subjected to Clemmensen reduction and the acids were crystallized from dilute alcohol. 2-Indanacetic acid[9] melts at 91–92°. *Anal.* ($C_{11}H_{12}O_2$) C, H. 1-Indanacetic acid[11] melts at 56–57°. *Anal.* ($C_{11}H_{12}O_2$) C, H.

**1- and 2-Indanacetyl Chloride.**—A mixture of 1- or 2-indanacetic acid and $SOCl_2$ (1.2 moles) was refluxed for 1 hr. The 1-indanacetyl chloride boiled[11,12] at 120° (1.5 mm). *Anal.* ($C_{11}H_{11}ClO$) C, H, Cl. 2-Indanacetyl chloride boiled at 110–115° (0.8 mm). *Anal.* ($C_{11}H_{11}ClO$) C, H, Cl.

**1- and 2-N,N-Dialkylacetamidoindans (1a, 2a).**—The appropriate acid chloride (1 mole) was added dropwise to a mixture of an appropriate amine (1.5 moles) and NaOH solution (10%, 1 mole) cooled in an ice bath. The amides were extracted with a suitable solvent and either distilled under reduced pressure or crystallized from a suitable solvent.

**1- and 2-Dialkylaminoethylindans (1, 2).**—The amides were reduced with $LiAlH_4$ (1.2 moles) in absolute ether under reflux for 8–12 hr and the amines were isolated and extracted with ether. In some cases, the secondary amines were methylated by heating a mixture of amines, $HCO_2H$ (98–100%), and $H_2CO$ (40%) on an oil bath for 6–8 hr at 95–100°.[13] The bases were characterized as hydrochlorides. The physical properties and analyses of the amides and amines were listed in Table I.

**Acknowledgment.**—The authors are grateful to Dr. B. Pathak, Calcutta University, for encouragement in

(7) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. All melting points are corrected and were determined in Gallenkamp apparatus. Boiling points are uncorrected.

(8) R. H. Manske, *J. Am. Chem. Soc.*, **53**, 1104 (1931).

(9) L. H. Groves and G. A. Swan, *J. Chem. Soc.*, 867 (1951).

(10) B. P. Sen, A. Chatterjee, S. K. Gupta, and B. K. Bhattacherjee, *J. Indian Chem. Soc.*, **35**, 751 (1958).

(11) A. G. Anderson, Jr., and R. H. Wade, *J. Am. Chem. Soc.*, **74**, 2274 (1952).

(12) J. von Braun, E. Danzier, and Z. Koehler, *Ber.*, **50**, 56 (1917).

(13) W. E. Bachmann, *Org. Syn.*, **25**, 89 (1945).

this investigation and to Dr. Fritz. A. Bader and coworkers of Bristol Laboratories for the biological evaluation of some of these compounds. One of the authors (N. C. D.) is thankful to C.S.I.R. Government of India for awarding him a fellowship.

## 5-Aryl-2-furanacetic Acids

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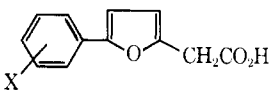
A series of 5-aryl-2-furanacetic acids (Table I), active as antiinflammatory agents as measured by the anti-uv erythema test,[1] have been prepared by the route outlined in Scheme I.

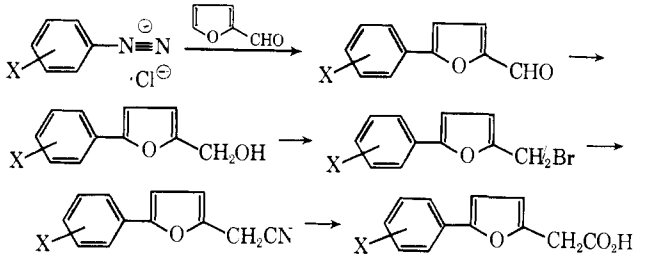
TABLE I
5-ARYL-2-FURANACETIC ACIDS



| X | Rel act.[a] | Mp,[b] °C | Recrystn solvent[c] | $\tau$[d] | Formula | Analyses[e] |
|---|---|---|---|---|---|---|
| H | 0.9 | 126–128 | B | 6.15 | $C_{12}H_{10}O_3$ | C, H |
| 4-Cl | 1.7 | 147.5–149 | A | 6.22 | $C_{12}H_9ClO_3$ | C, H, Cl |
| 3-Cl | 0.4 | 109–110 | B | 6.20 | $C_{12}H_9ClO_3$ | C, H, Cl |
| 2-Cl | 0.1 | 98–99.5 | A | 6.20 | $C_{12}H_9ClO_3$ | C, H, Cl |
| 4-Br | 0.4 | 162–164 | A | 6.22 | $C_{12}H_9BrO_3$ | C, H, Br |
| 4-F | 0.2 | 116–117.5 | A | 6.23 | $C_{12}H_9FO_3$ | C, H, F |
| 4-$CH_3$ | 0.4 | 143–144 | B | 6.23 | $C_{13}H_{12}O_3$ | C, H |
| 4-$CH_3O$ | 0.9 | 143–145.5 | B | 6.25 | $C_{13}H_{12}O_4$ | C, H |

[a] Preliminary estimates; phenylbutazone = 1. [b] Melting points were taken on a Thomas–Hoover melting point apparatus in open capillaries and are uncorrected. [c] A = $C_6H_6$, B = $C_6H_6$–hexane. [d] The $\tau$ values are for the $-CH_2-$ grouping and were determined on a Varian A-60 in $CDCl_3$. [e] Analyses for the elements indicated were within ±0.3% of the theoretical values.

SCHEME I



### Experimental Section

**5-Aryl-2-furfurals.**[2]—A mixture of 0.5 mole of the arylamine in $H_2O$ (50 ml) and 135 ml of concentrated HCl was diazotized by the dropwise addition of 36.2 g (0.525 mole) of $NaNO_2$ in 100 ml of $H_2O$ keeping the temperature below 10° by the addition of ice. After stirring at 10° for 10 min, the solution was filtered and added all at once to a solution of 61.5 g (0.64 mole) of furfural in $H_2O$ (200 ml), followed by 23 g of $CuCl_2 \cdot 2H_2O$ in $H_2O$ (100 ml). The mixture was kept at 50–65° for 4 hr, then left standing at room temperature overnight. Volatiles were steam distilled and the black residue was taken up in ether and washed (twice with 5% NaOH, $H_2O$ until neutral). Drying ($Na_2SO_4$), treatment with charcoal, and removal of the solvent under reduced pressure gave the crude product which could be partially purified by crystallization from EtOH, or by distillation for those compounds which were oils. Yields were in the range of 10–55%.

**5-Aryl-2-hydroxymethylfurans.**—Reduction of the 5-aryl-2-furfurals with $LiAlH_4$ in 1:1 $Et_2O$–THF gave the crude products which were converted to the bromo derivatives without further purification.

**5-Aryl-2-bromomethylfurans.**—A solution of 0.0282 mole of the 5-aryl-2-hydroxymethylfuran in 65 ml of $Et_2O$ was cooled in an ice bath. To this was added dropwise a solution of 2.8 g (0.0103 mole) of $PBr_3$ in $Et_2O$ (20 ml). After the addition was complete, the mixture was allowed to stir at room temperature for 1 hr. The ether was then decanted and the gummy residue was washed ($Et_2O$). The combined ether extracts were swirled with cold 50% NaOH, decanted, and dried (solid KOH). The solvent was removed under reduced pressure at *room temperature*. The unstable nature of the bromomethyl compounds necessitate their immediate conversion to the nitriles.

**5-Aryl-2-cyanomethylfurans.**—The crude 5-aryl-2-bromomethylfuran from 0.0282 mole of the hydroxymethyl compound was dissolved in 50 ml of acetone and treated with 1.5 g (0.03 mole) of NaCN in 10 ml of $H_2O$ and the solution was heated at reflux for 3 hr. Work-up of the dark reaction mixture in the usual manner gave the crude nitrile as a dark, viscous oil.

**5-Aryl-2-furanacetic Acids.**—The crude nitrile (5 g) in EtOH (100 ml) was treated with 5 g of KOH in 25 ml of $H_2O$ and the resulting solution was heated at reflux for 6 hr. Work-up in the usual manner gave the crude acid as an oil which was chromatographed on silica gel. After elution of some colored material with benzene, the product was eluted with 10% ether in benzene. Recrystallization gave the pure 5-aryl-2-furanacetic acids.

**Acknowledgments.**—The authors thank Dr. C. V. Winder and associates of these laboratories for the antiinflammatory testing, and Mr. C. E. Childs and coworkers for the microanalyses.

## The Preparation and Pharmacology of Some 11β-Hydroxy-4-methylestratrienes

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Recently we reported that 17α-ethynyl-1,4-dimethylestra-1,3,5(10)-trien-17β-ol (IIIa) and its acetate IIIb showed antiinflammatory properties in the carrageenin-induced foot edema rat assay and that both of these substances also reduced the plasma cholesterol concentration of rats made hypercholesterolemic with propylthiouracil.[1] Earlier, Goldkamp, *et al.*, observed that estra-1,3,5(10)-trien-17-ones and 17α-ethynylestra-1,3,5(10)-trien-17β-ols with a methyl group attached to ring A had a favorable lipodiatic–estrogenic ratio.[2] These findings prompted us to determine whether estratriene derivatives with an oxygen function at C-11, but not in ring A, also possess antiinflammatory and antiatherogenic effects.

11-Oxygenated corticosteroids are systemically active

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