(5) R. Wiechert and E. Kaspar, *Chem. Ber.*, **93**, 1710 (1960).
(6) G. W. Krakower and H. A. Van Dine, *J. Org. Chem.*, **31**, 3467 (1966).
(7) H. van Kamp, private communication.
(8) H. van Kamp, P. Nissen, and E. van Vliet, *Tetrahedron Lett.*, 1457 (1967).
(9) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, 84, 867 (1962); 87, 1353 (1965).
(10) (a) T. L. Popper, J. N. Gardner, R. Neri, and H. L. Herzog, *J. Med. Chem.*, 12, 393 (1969); (b) G. W. Moersch, D. E. Evans, and G. S. Lewis, *ibid.*, **10**, 254 (1967); (c) N. H. Dyson, J. A. Edwards, and J. H. Fried, *Tetrahedron Lett.*, 1841 (1966); (d) H. G. Lehmann, *Angew. Chem., Int. Ed. Engl.*, 4, 783 (1965).
(11) Searle and Company, British Patent 871.487; *Chem. Abstr.*, **54**, 22732*i* (1960).
(12) (a) G. W. Duncan, S. C. Lyster, J. W. Hendrix, J. J. Clark, and H. D. Webster, *Fert. Steril.*, **15**, 419 (1964); (b) J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes, and W. E. Dublin, *J. Amer. Chem. Soc.*, **80**, 2904 (1958); (c) H. J. Ringold, E. Batres, and G. Rosenkranz, *J. Org. Chem.*, 22, 99 (1957).
(13) S. Liisberg, W. O. Godtfredsen, and S. Vangedal, *Tetrahedron Lett.*, 9, 149 (1960).
(14) H. van Kamp and S. J. Halkes, *Recl. Trav. Chim. Pays-Bas*, 84, 904 (1965).
(15) R. Wiechert, *Experientia*, 24, 767 (1968).
(16) A. Boris, L. Demartino, and T. Trmal, *Acta Endrocrinol.*, **63**, 476 (1970).
(17) R. W. Kierstead, J. Blount, K. E. Fahrenholtz, A. Faraone, R. A. LeMahieu, and P. Rosen, *J. Org. Chem.*, **35**, 4141 (1970).
(18) N. Sugimoto, T. Fujita, N. Shigematsu, and A. Ayada, *Chem. Pharm. Bull.*, **10**, 427 (1962).
(19) Syntex Corporation, U. S. Patent 3076823; *Chem. Abstr.*, **59**, 12880*e* (1963).
(20) J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.*, **75**, 2273 (1953).
(21) G. Rosenkranz, O. Mancera, and F. Sondheimer, *ibid.*, **76**, 2227 (1954).
(22) J. Fried and E. F. Sabo, *ibid.*, 79, 1130 (1957).
(23) H. R. Nace, *ibid.*, 81, 5428 (1959).
(24) (a) Z. Čekan, M. Seda, J. Mikulaskova, and K. Syhora, *Steroids*, 4, 415 (1964); (b) 8, 205 (1966).
(25) H. J. Ringold, E. Batres, A. Bowers, J. Edwards, and J. Zderic, *J. Amer. Chem. Soc.*, 81, 3485 (1959).
(26) E. L. Shapiro, T. L. Popper, L. Weber, R. Neri, and H. L. Herzog, *J. Med. Chem.*, 12, 631 (1969).
(27) F. A. Kincl, *Endokrinologie*, **40**, 257 (1961).
(28) R. van Strik, "Quantitative Methods in Pharmacology," H. de Jonge, Ed., North Holland Publishing Co., Amsterdam, 1961, p 88.
(29) J. Hartog, J. I. G. M. Wittelaar, L. Morsink, and A. M. de Wachter, *J. Med. Chem.*, 15, 1292 (1972).
(30) Handbuch der experimentelle Pharmakologie, Band XXI, Teil 1 Die Gestagene, K. Junkmann-Springer Verlag, Berlin, 1968, p 870.

Investigations on Sterols. 39.[1] Synthesis and Progestational Activities of Some 16-Methylene-17α-acetoxy-9β,10α-pregna-4,6-diene-3,20-dione Derivatives

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The syntheses and progestational activities of some 16-methylene-9β,10α-steroids are reported. Introduction of a 16-methylene group leads to compounds with orally high progestational activity in rabbits, in particular introduction into **16c** resulted in a very potent progestational agent (**8d**). Comparison of structure-activity relationships reveals a striking difference between the natural (9α,10β) and the retro (9β,10α) series as far as substitution at position 6 is concerned.

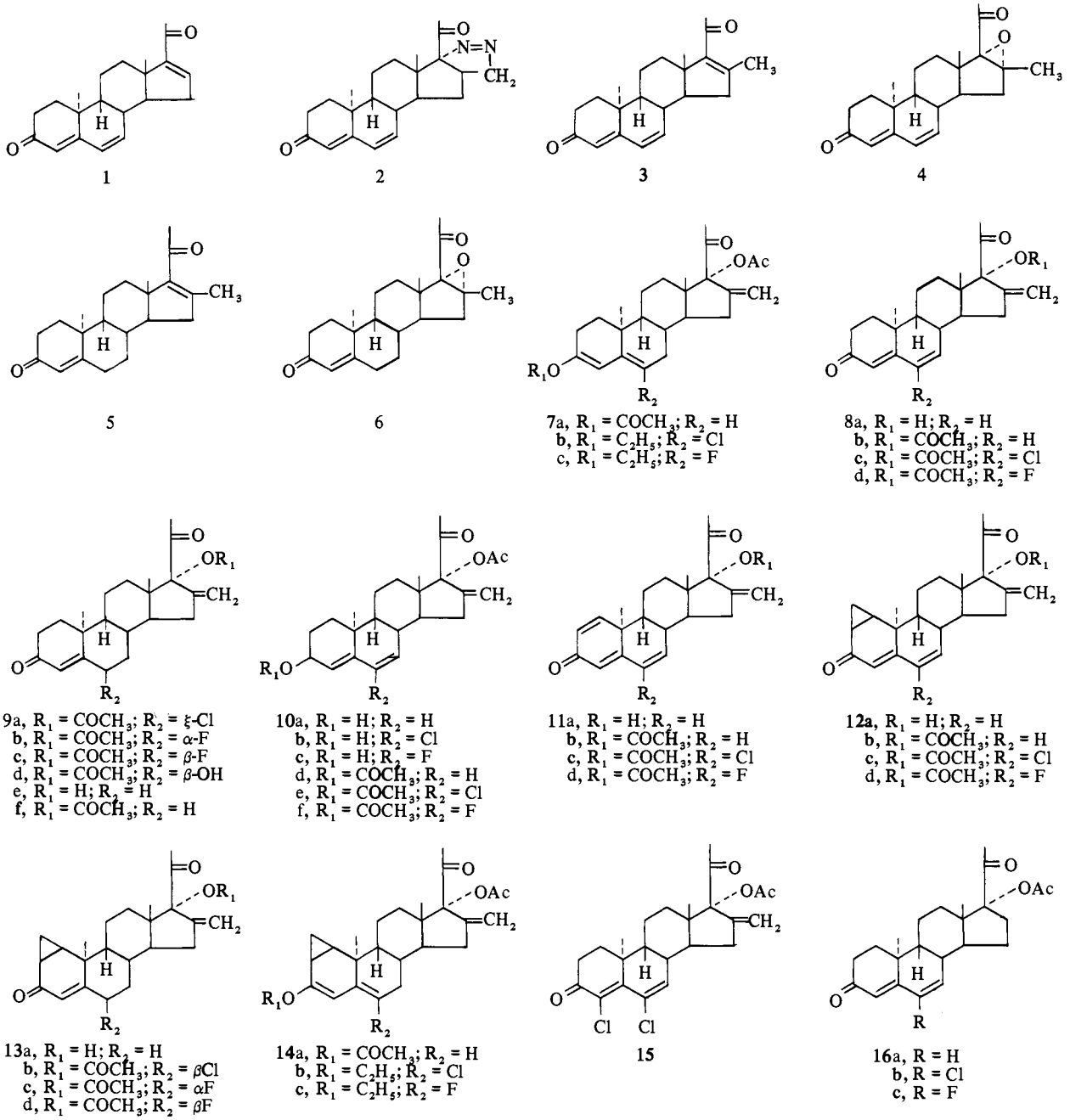
Introduction of a 16-methylene group into 17α-acetoxypregnanes leads to an enhancement of progestational activity.[2] Furthermore our own studies[3] of steroids having an unnatural configuration showed that 9β,10α-pregnanes possessed interesting hormonal properties. This prompted us to investigate a number of 16-methylene- and 1,2β;16-bis(methylene)-17α-acetoxy-9β,10α-pregnanes.[1] The synthesis and the remarkable progestational properties of this new class of retrosteroids form the subject of this paper.

Chemistry. The introduction of the 17α-hydroxy-16-methylene moiety has been accomplished by the following method (Chart I). The 16-en-20-one system in compound **1**[4] was converted into the 16α,17α-pyrazolino structure **2** with CH_2N_2.[5] Thermolysis[5] at 190° in paraffin oil yielded the 16-methyl-16-en-20-one derivative **3**. Epoxidation of **3** with *m*-Cl-$C_6H_4CO_3H$ afforded as a major product the 16,17α-epoxy-16-methyl compound **4**. The corresponding 4-en-3-one **6** was prepared by Pd-$CaCO_3$ catalyzed hydrogenation of the 4,6-dien-3-one **3**, followed by similar epoxidation of the 16-en-20-one system. Isomerization of **4** and **6** with TsOH[6] in boiling $PhCH_3$ gave the 17α-hydroxy-16-methylene compounds **8a** and **9e**, which on treatment with Ac_2O, AcOH, and TsOH afforded the 17α-acetoxy-16-methylene derivatives **8b** and **9f**. The TsOH-catalyzed treatment of **6** with boiling $PhCH_3$ in the presence of Ac_2O[7] resulted in a high yield of the diacetate **7a**. Fluorination of **7a** with perchloryl fluoride ($FClO_3$)[3b] in Me_2CO-EtOH solution furnished, in addition to the 6α- and 6β-fluoro-4-en-3-ones **9b** and **9c**, a small amount of the 6β-hydroxy-4-en-3-one **9d**. The 6β-chloro compound **9a** could be obtained by treatment of **7a** with Cl_2[3b] in Et_2O-AcOH. The final dehydrogenation of **9a**, **9b**, and **9c** was performed by treatment of the 3-enol ethers **7b** and **7c** with MnO_2 in AcOH,[3a,8] resulting in the 6-halo-4,6-dien-3-ones **8c** and **8d**.

The introduction of the 1,2β-methylene substituent was carried out as reported before.[1] For this purpose the 1-dehydro derivative **11a** was prepared by dehydrogenation of **8a** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dioxane.[3a] The 1,4,6-trien-3-one **11a** was converted into the 1,2β-methylene compound **12a** with the Corey ylide reagent.[1,9] Acetylation of **12a** with AcOH, Ac_2O, and TsOH afforded the 17-acetate **12b**. The syntheses of respectively the 6-chloro and 6-fluoro derivatives **12c** and **12d** were realized as outlined before and as described in ref 1.

In the natural series, introduction of a 6-methyl[10] or a 4-chloro[11] substituent, as well as conversion of the 4,6-dien-3-one system into a 3-acetoxy-4,6-diene[12] moiety, results in enhanced biological activity. For that reason some of the

Chart I



corresponding 16-methylene-9β,10α isomers were synthetized. The 6-methyl analog **20** was prepared as outlined in Scheme I. The 3,5-dien-3-amine **17** (obtained by reaction of **9f** with pyrrolidine in boiling MeOH) was converted into the 6-hydroxymethyl compound **18** with aqueous formaldehyde.[13] Dehydration to the 6-methylene derivative **19** was performed in a dioxane-HCl solution. This compound (**19**) was isomerized with Pd/C, cyclohexene, and CH_3CO_2Na in EtOH[14] to 17α-acetoxy-6-methyl-16-methylene-9β,10α-pregna-4,6-diene-3,20-dione (**20**).

Chlorination of **8c** with Cl_2 in $C_2H_5CO_2H$[11] gave the 4,6-dichloro compound **15** in low yield.

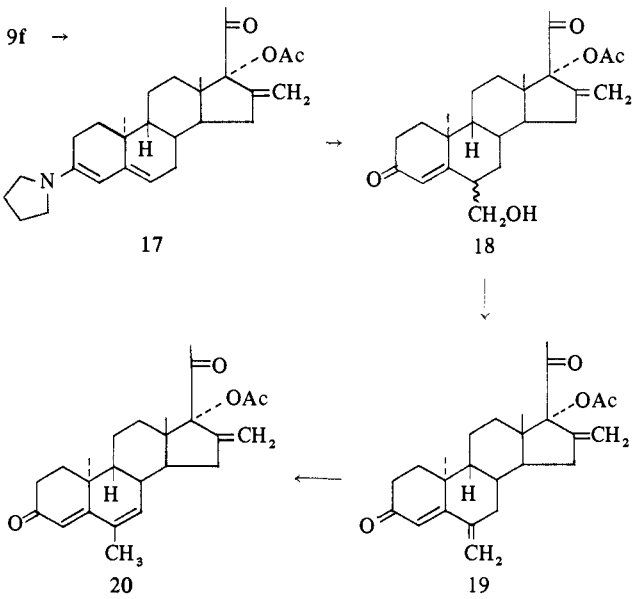
Reduction with LiAlH(O-*tert*-Bu)$_3$ of **8b**, 8c, and 8d, followed by acetylation with Ac_2O-pyridine, resulted in the 3α-acetoxy-4,6-dienes **10d**, **10e**, and **10f**, respectively.

Biological Activity. Most of the 9β,10α-steroids described in this paper were examined for their progestational activity. The oral progestational activities were determined in a Clauberg assay in rabbits (see Experimental Section). The potency of each compound as shown in Table I, column 2, was estimated directly, in the same test, against the reference dydrogesterone† (9β,10α-pregna-4,6-diene-3,20-dione). The tests fulfilled all statistical criteria of the standard six-point assay,[19] if not otherwise indicated. For fuller information the 95% confidence limits are included in column 2.

For comparative purposes the data of column 2 have been recalculated on the basis of contemporary potency determinations of the reference (dydrogesterone or) against progesterone sc. The average value of three experiments (0.07, 0.06, and 0.1 times progesterone sc) has been used (Table I, column 3). Column 4 (Table I) shows some published data concerning related compounds in the natural series. Most of these values were measured orally with progesterone sc as a standard; otherwise the published values have been recalculated on this basis.

†Generic name. Registered Trademark name: Duphaston.

Scheme I



From the data summarized in Table I it can be concluded that the introduction of a 16-methylene substituent in the 17α-acetoxy-6-dehydro-9β,10α-progesterones[3a] (**16a**, **16b**, and **16c**) leads to a considerable increase in activity (**8b**, **8c**, and **8d**). A similarly enhanced progestational activity has been reported in the natural series,[2a,b,12,15] but the absolute levels of activity in the 9β,10α series proved to be much higher. This difference in activity is not caused by differences in test conditions as can be concluded from a comparison of the data obtained with chlormadinone acetate in our own laboratory (column 4, footnote *i*) and those published in the literature (column 4, footnotes *c–e*). In fact, as far as we know, compound **8d** is about 20 times as active as chlormadinone acetate and the most active oral progestational agent hitherto described in the literature (see also ref 1).

Looking at the influence of 6-substitution in both the 9α,10β- and the 9β,10α-16-methylene series on the progestational activity, we note two striking points. First, the order of substituents, if arranged according to a decreasing influence, differs completely in the natural (Cl > F > CH_3 > H) from that in the retro (F > Cl > H > CH_3) series. Second, the magnitude of the effect of substitution is quite different: whereas in the retro series the extremes (6-F and 6-CH_3) differ by a factor of 40, in the normal series this difference amounts to only a factor of 6 (6-Cl and 6-H).

The favorable effect of a 1,2β-methylene group on the progestational activity in the retro series[1] is in this class of compounds found only in the 6-unsubstituted 1,2β;16-bis(methylene) compound **12b**. The 6-chloro and 6-fluoro compounds (**12c** and **12d**) show a decrease in activity when compared with the 1,2-unsubstituted analogs **8c** and **8d**.

The introduction of a 1,2 double bond into compounds **8c** and **8d** also resulted in a decrease in activity (**11c** and **11d**), in contrast to the findings in the natural series, where equal activities have been reported for the 16-methylene-chlormadinone acetate and its 1,2-dehydro analog.[2c]

The activities could not be enhanced by changing the 3-oxo group in **8b**, **8c**, and **8d** into an esterified hydroxyl function (**10d**, **10e**, and **10f**).

The favorable influence of 4-chloro substitution in the natural series[11] is not observed with the 17α-acetoxy-16-methylene-9β,10α-compound **15**. The activity of the 4,6-dichloro derivative **15** proved to be comparable to that of the monochloro compound **8c**.

The compounds described in this paper, and, in particular, the compounds **8c** and **8d**, show in addition to the already mentioned remarkable progestational Clauberg activity in rabbits, a high activity in the maintenance of pregnancy test, and they also show very interesting ovulation inhibitory and antioestrogenic properties. A more detailed endocrinological profile of the compounds will be published elsewhere.

Experimental Section‡

Pyrazolino[17α,16α-*c*]-9β,10α-pregna-4,6-diene-3,20-dione (2). Into a soln of 9β,10α-pregna-4,6,16-triene-3,20-dione (**1**) (30 g) in CH_2Cl_2 (50 ml) and Et_2O (1500 ml), CH_2N_2 (generated from *p*-tolylsulfonylmethylnitrosamide (75 g))[20] was introduced at 0°. The reaction mixt was kept at 0° for 5 hr and then at 20° for 24 hr. The ppt (**2**) was collected and dried (32 g): mp 189–190° dec; [α]D −502°. *Anal.* ($C_{22}H_{28}O_2N_2$) C, H.

16-Methyl-9β,10α-pregna-4,6,16-triene-3,20-dione (3). **2** (31 g) was added in small portions to a mixt of paraffin oil (60 ml) and pyridine (1 ml) kept at a temp of 190°. After the decompn of **2** (no further elimination of N_2), the mixt was cooled and *n*-hexane was added. The ppt was collected, dried, and crystd from CH_2Cl_2–*n*-hexane, yielding 16.8 g of **3**: mp 157–159°. *Anal.* ($C_{22}H_{28}O_2$) C, H.

16-Methyl-9β,10α-pregna-4,16-diene-3,20-dione (5). A soln of **3** (6.4 g) in $PhCH_3$ (130 ml) was hydrogenated (110% H_2) in the presence of 5% Pd–$CaCO_3$ (3 g). The product obtained was crystd after filtration and evapn of the solvent from Me_2CO–*n*-hexane, yielding 5.5 g of **5**: mp 99–101°; [α]D −138°. *Anal.* ($C_{22}H_{30}O_2$) C, H.

16,17α-Epoxy-16-methyl-9β,10α-pregn-4-ene-3,20-dione (6). To a stirred soln of **5** (75 g) in 1,2-$C_2H_4Cl_2$ (2.25 l.), 3-$ClC_6H_4CO_3H$ (90 g) was added at 24°. After stirring for 60 min at this temp, the excess of the peracid was decompd by the slow addn of a $NaHSO_3$ soln (10%). The solids were removed by filtration, and the filtrate was washed with $NaHCO_3$ (5%) and H_2O. After drying and evapn of the solvent, the residue was crystd from *i*-Pr_2O, yielding 45 g of **6**: mp 141–147°; analytical sample, mp 155–157° (*i*-Pr_2O). *Anal.* ($C_{22}H_{30}O_3$) C, H.

16,17α-Epoxy-16-methyl-9β,10α-pregna-4,6-diene-3,20-dione (4). A stirred soln of **3** (75 g) in 1,2-$C_2H_4Cl_2$ (2.25 l.) was epoxidized, as described for **6**, with 3-$ClC_6H_4CO_3H$ (92 g). The residue obtained after work-up was crystd from *i*-Pr_2O, yielding 8.25 g of **4**. The filtrate was concd to dryness and chromatographed over SiO_2. Elution with a mixt of Et_2O–petroleum ether (40–60°) gave 27 g of **4**: analytical sample, mp 156–159° (*i*-Pr_2O). *Anal.* ($C_{22}H_{28}O_3$) H; C: calcd, 77.61; found, 77.00.

17α-Hydroxy-16-methylene-9β,10α-pregna-4,6-diene-3,20-dione (8a). A soln of **4** (7.7 g) in dry $PhCH_3$ (200 ml) was refluxed with TsOH (310 mg) for 4 hr. The reaction mixt was cooled and added to ice H_2O. The organic layer was washed successively with H_2O, dild $NaHCO_3$ soln, and H_2O. The residue (7.8 g), obtained after drying and evapn of the solvent, was chromatographed over SiO_2. Elution with C_6H_6–Me_2CO (95:5) gave 6.13 g of nearly pure **8a**: analytical sample, mp 206–208° (Et_2O). *Anal.* ($C_{22}H_{28}O_3$) C, H.

17α-Hydroxy-16-methylene-9β,10α-pregn-4-ene-3,20-dione (9e). The same procedure as described for **8a** was used for the conversion of **6** into **9e**: yield, 72%, analytical sample, mp 171–173° (MeOH). *Anal.* ($C_{22}H_{30}O_3$) C, H.

17α-Hydroxy-16-methylene-9β,10α-pregn-4-ene-3,20-dione 17-Acetate (9f). **9e** was acetylated analogously to **8b** to yield **9f**:

‡Melting points were determined on a Büchi apparatus (W. Büchi, Glasapparatefabrik, Flawil, Switzerland) and are uncorrected, uv spectra are of MeOH solutions, rotations are in $CHCl_3$ at 25° at about 1% concentration, and ir spectra are in KBr. The nmr spectra are measured on a Varian HA-100 spectrometer in $CDCl_3$ (Me_4Si). In those cases in which incomplete uv, ir, and nmr spectral data are given, they were consistent with the assigned structures. All reactions were carried out in a N_2 atmosphere and solns were dried over anhyd Na_2SO_4. Elemental analyses were performed by Dr. F. Pascher, Mikroanalytisches Lab, 53 Bonn 1, West Germany. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Table I. Progestational Potency after Oral Administration in the Clauberg Test[a]

Compounds	Potency (95% confidence limits)	Relative potency (progesterone sc = 1)	
		9β,10α (retro)	9α,10β (natural)
Dydrogesterone[b]	1	0.07	
Progesterone sc	14 (11–17)[l]		1
16a, 3-oxo	60 (20–130)	4	1.5,[d] 3[c]
8b, 3-oxo,16-CH_2	710 (560–890)[l]	50	13[d]
12b, 3-oxo,1,2β;16-diCH_2	2100 (1400–3200)	150	
10d, 3-OAc,16-CH_2	~1000[o]	70	
11b, 3-oxo,Δ[1],16-CH_2	900 (600–1600)	65	
16b, 3-oxo,6-Cl	1250 (900–1750)[m]	90	30,[c] 33,[d,i] 37[e]
8c, 3-oxo,6-Cl,16-CH_2	3900 (2300–6800)[m]	280	55[f], 75[e]
12c, 3-oxo,6-Cl,1,2β;16-diCH_2	1700 (900–2800)	120	16[g]
10e, 3-OAc,6-Cl,16-CH_2	2800 (1500–5400)	200	47[f]
15, 3-oxo,4,6-diCl,16-CH_2	~3000[p]	210	20[k]
11c, 3-oxo,Δ[1],6-Cl,16-CH_2	~1000[n]	70	76[g]
16c, 3-oxo,6-F	1250 (950–1700)[m]	90	about 15[h]
8d, 3-oxo,6-F,16-CH_2	8600 (6800–11,000)[m]	610	50[q]
12d, 3-oxo,6-F,1,2β;16-diCH_2	~1500[o]	110	
10f, 3-OAc,6-F,16-CH_2	1700 (800–3100)	120	
11d, 3-oxo,Δ[1],6-F,16-CH_2	~1200[o]	85	
20, 3-oxo,6-CH_3,16-CH_2	190 (120–290)	13	about 30[j,d]

[a]For experimental details see Experimental Section. [b]9β,10α-Pregna-4,6-diene-3,20-dione. [c]See ref 15. [d]See ref 2a. [e]See ref 2b. [f]See ref 12b. [g]See ref 2c. [h]See ref 17 (calcd from data given there). [i]Value of 460 (360–610), from own laboratory against dydrogesterone, recalcd to progesterone sc. [j]Calcd from data given in ref 2a and 10. [k]See ref 18. [l]Average of 3 expts. [m]Average of 2 expts. [n]Only 2 doses against 1 dose of the ref. [o]Nonparallelism of dose–response curves. [p]Slope of ref not significant. [q]Value from own laboratory.

mp 195–197° (Me_2CO); [α]D −260°. *Anal.* ($C_{24}H_{32}O_4$) C, H.

17α-Hydroxy-16-methylene-9β,10α-pregna-4,6-diene-3,20-dione 17-Acetate (8b). A mixt of **8a** (2.16 g) and TsOH in AcOH (105 ml) and Ac_2O (21 ml) was stirred at 23° for 1.5 hr. The soln was then dild with cold H_2O (1 l.) and extd with CH_2Cl_2. The ext was washed with NaOH (0.5 *N*) and H_2O, dried, and concd. The crude **8b** was crystd from Me_2CO–*n*-C_6H_{14}, yielding **8b** (1.3 g): mp 147–148°; [α]D −706°. *Anal.* ($C_{24}H_{30}O_4$) C, H.

3,17α-Dihydroxy-16-methylene-9β,10α-pregna-3,5-dien-20-one 3,17-Diacetate (7a). A mixt of **6** (66 g) and TsOH (1 g) in $PhCH_3$ (1500 ml) and Ac_2O (225 ml) was heated, and solvent (~1000 ml) was distd off for 4 hr. The remaining soln was poured out into a mixt of H_2O (2000 ml) and pyridine (500 ml). The $PhCH_3$ layer was washed neutral, dried, and concd to dryness. The residue was crystd from MeOH (100 ml) yielding 54 g of **7a**: mp 155–158°; analytical sample, mp 161–163°. *Anal.* ($C_{26}H_{34}O_5$) C, H.

Fluorination of 7a. A mixt of gaseous $FClO_3$ § and N_2 (1:1) was introduced into a stirred soln of **7a** (54 g) in Me_2CO (1000 ml) and anhyd AcOK (25 g) in EtOH (700 ml) at 0° until the mixt was satd. Then the introduction of the gas mixt was kept at such a rate that only a small amt of $FClO_3$ passed through the soln and the temp was allowed to rise to room temp. The fluorination was complete after 7 hr (tlc) and the excess of $FClO_3$ was blown out with N_2. The soln was poured out into H_2O (6000 ml) and extn was performed with CH_2Cl_2. The residue (52 g) obtained after washing and concn of the ext was chromatographed on SiO_2 in mixts of $PhCH_3$–Me_2CO. The following compds were obtained in order of increasing polarity: **6α-fluoro-17α-hydroxy-16-methylene-9β,10α-pregn-4-ene-3,20-dione** 17-acetate (**9b**, 6g), analytical sample, mp 203–206° (Me_2CO), nmr δ 5.04, dm, $J_{6\beta,F}$ = 50.0 Hz (C_6-βH), 5.88, d, $J_{6\alpha,4}$ = 4.0 Hz (C_4-H) ppm [*Anal.* ($C_{24}H_{31}O_4F$) C, H]; a mixt of **9b** and **9c** (29.5 g); **6β-fluoro-17α-hydroxy-16-methylene-9β,10α-pregn-4-ene-3,20-dione** 17-acetate (**9c**, 4 g), analytical sample, mp resin, nmr δ 5.28, dm, $J_{6\alpha,F}$ = 48 Hz (C_6-αH), 6.10, s (C_4-H) ppm [*Anal.* ($C_{24}H_{31}O_4F$) H; C: calcd, 71.61; found, 70.07]; **6β,17α-dihydroxy-16-methylene-9β,10α-pregn-4-ene-3,20-dione** 17-acetate (**9d**, 4.8 g), mp 229–234° (Me_2CO), [α]D −219°, nmr 4.50, q (C_6-αH), 6.19, d (C_4-H) ppm, ν_{max} 3450 cm^{-1} [*Anal.* ($C_{24}H_{32}O_5$) H; C: calcd, 71.97; found, 71.09].

Chlorination of 7a. To a stirred mixt of **7a** (8.1 g) and AcOK (15 g) in Et_2O (130 ml), AcOH (330 ml), and H_2O (55 ml) was added at about −5° in 5 min, a soln of Cl_2 (1.5 g) in AcOH (37 ml). Stirring was continued for 30 min. Then the mixt was poured out into H_2O–ice, and, after extn with Et_2O, the ext was washed with $NaHCO_3$ soln (5%) and H_2O. The residue obtained after drying and evapn of the solvent was chromatographed on SiO_2 in mixts of CH_2Cl_2 and Me_2CO yielding **9a** (7.9 g) as a mixt of **6α-** and **6β-chloro-17α-hydroxy-16-methylene-9β,10α-pregn-4-ene-3,20-dione** which was used in the next step.

6-Chloro-17α-hydroxy-16-methylene-9β,10α-pregna-4,6-diene-3,20-dione 17-Acetate (8c). To a mixt of **9a** (7.9 g) in anhyd dioxane (150 ml), $(EtO)_3CH$ (7.5 ml) and TsOH (0.3 g) were added. The soln was kept in the dark for 18 hr at 20°. The **3-ethoxy-6-chloro-17α-hydroxy-9β,10α-pregna-3,5-dien-20-one** 17-acetate (**7b**) thus obtained was added without purification, in 2 min, to a vigorously stirred suspension of MnO_2 (35 g) in 90% AcOH (440 ml) and stirring was continued for 30 min. The filtrate, obtained after filtration of the mixt, was concd and, after diln with CH_2Cl_2, washed neutral. The residue resulting after evapn of the solvents was purified by chromatography on SiO_2 in CH_2Cl_2–Me_2CO mixts yielding **8c** (3.45 g): mp 194–196° dec (Et_2O–*n*-hexane); λ_{max} 285.5 nm (ε 21,800); nmr δ 0.79, s (C_{13}-CH_3), 1.43, s (C_{10}-CH_3), 2.00, s (C_{17}-$OCOCH_3$), 2.15, s (C_{20}-CH_3), 5.48 and 5.60 (C_{16}=CH_2), 6.34, s (C_4-H and C_7-H) ppm. *Anal.* ($C_{24}H_{29}O_4Cl$) C, H.

6-Fluoro-17α-hydroxy-16-methylene-9β,10α-pregna-4,6-diene-3,20-dione 17-Acetate (8d). A mixt of **9b** and **9c** (5 g) was enol etherified into **7c** (**3-ethoxy-6-fluoro-17α-hydroxy-16-methylene-9β,10α-pregna-3,5-dien-20-one** 17-acetate), mp 180–182° [*Anal.* ($C_{26}H_{35}O_4F$) C, H], as described for the conversion of **9a** into **8c**; **7c** was thereafter oxidized with MnO_2 (25 g) and 90% AcOH (290 ml). After chromatography on SiO_2 in CH_2Cl_2–Me_2CO and crystn (Me_2CO), pure **8d** (2.35 g) was obtained: mp 209–210°; [α]D −498°; λ_{max} 284 nm (ε 23,800); nmr δ 0.79, s (C_{13}-CH_3), 1.45, s (C_{10}-CH_3), 2.01, s (C_{17}-$OCOCH_3$), 2.15, s (C_{20}-CH_3), 5.47 and 5.60 (C_{16}=CH_2), 5.72, 2d, $J_{F,7}$ = 16 Hz, $J_{7,8}$ = 5 Hz (C_7-H), 6.08, s (C_4-H) ppm. *Anal.* ($C_{24}H_{29}O_4F$) C, H.

17α-Hydroxy-16-methylene-9β,10α-pregna-1,4,6-triene-3,20-dione (11a). A mixt of **8a** (0.5 g) and DDQ (0.46 g) in a dioxane–HCl soln (10 ml; 1 mg of HCl/ml) was stirred for 1.5 hr. $CaCO_3$ (0.5 g) was added and stirring was continued for 15 min, then the solids were removed by filtration, and the filtrate was refluxed for 1.5 hr. Evapn *in vacuo* afforded a residue, which was extd with CH_2Cl_2. The ext was washed with H_2O, 1 *N* NaOH, and H_2O, dried, and concd to give crude **11a** (0.38 g). Chromatography on SiO_2 and crystn yielded pure **11a** (0.31 g): mp 203–205° (*n*-hexane–Me_2CO). *Anal.* ($C_{22}H_{26}O_3$) mass spectrum *m/e* 338. Following the same procedure as described for **11a**, the compds **8b**, **8c**, and **8d** were dehydrogenated, resulting in **17α-hydroxy-16-methylene-9β,10α-pregna-1,4,6-triene-3,20-dione** 17-acetate (**11b**), mp 203–204°, **6-chloro-17α-hydroxy-16-methylene-9β,10α-pregna-1,4,6-triene-3,20-dione** 17-acetate (**11c**), mp 162–163.5° [*Anal.* ($C_{24}H_{27}O_4Cl$) mass spectrum *m/e* 414], and **6-fluoro-17α-hydroxy-16-methylene-9β,10α-pregna-1,4,6-triene-3,20-dione** 17-acetate (**11d**), mp 199–201° [*Anal.* ($C_{24}H_{27}O_4F$) C, H].

17α-Hydroxy-1,2β;16-bis(methylene)-9β,10α-pregna-4,6-diene-3,20-dione (12a). A mixt of trimethylsulfoxonium iodide (32.4 g) and NaH (7.64 g of a 50% oil suspension) in DMSO (380 ml) was

§Warning: As a violent explosion occurred once,[3b] all fluorination experiments were carried out in an explosion-guarded hood.

stirred for 1.5 hr, then filtered and added to a soln of 11a (18.9 g) in THF (190 ml). After 25 hr at 22°, the mixt was dild with H_2O, and the ppt was extd with C_6H_6. The ext was washed neutral and the residue obtained after evapn of the solvent was chromatographed on SiO_2. Elution with CH_2Cl_2–Me_2CO yielded **12a** (10.15 g): analytical sample, mp 237–239° (Me_2CO–*n*-hexane); ν_{max} 996 cm^{-1} (cyclopropyl). *Anal.* ($C_{23}H_{28}O_3$) C, H.

17α-Hydroxy-1,2β;16-bis(methylene)-9β,10α-pregna-4,6-diene-3,20-dione 17-Acetate (12b). Similarly to the procedure described for **8b**, 12a was acetylated to **12b**: yield, 79%; mp 228–230° (Me_2CO). *Anal.* ($C_{25}H_{30}O_4$) mass spectrum *m/e* 394.

17α-Hydroxy-1,2β;16-bis(methylene)-9β,10α-pregn-4-ene-3,20-dione (13a). According to the method described for **5**, 12a was hydrogenated yielding **13a** (67% after chromatog): mp 180–184° (Me_2CO–*n*-hexane). *Anal.* ($C_{23}H_{30}O_3$) C, H.

3,17α-Dihydroxy-1,2β;16-bis(methylene)-9β,10α-pregna-3,5-dien-20-one 3,17-Diacetate (14a). A soln of **13a** (1.8 g) and TsOH (0.69 g) in anhyd C_6H_6 and isopropenyl acetate (18 ml) was refluxed. Solvent (70 ml) was distd off gradually in 3.5 hr. Work-up was performed by diln with H_2O and extn with Et_2O. The crude product was crystd from MeOH in the presence of a few drops of pyridine, giving **14a** (0.5 g): mp 94–98°; λ_{max} 248.5 nm (ε 13,500). *Anal.* ($C_{27}H_{34}O_5$) C, H. Chromatography of the mother liq resulted in an addnl 0.65 g of **14a.**

6β-Chloro-17α-hydroxy-1,2β;16-bis(methylene)-9β,10α-pregn-4-ene-3,20-dione 17-Acetate (13b). As described for 9a, 14a was chlorinated to **13b** (0.96 g chromatographically pure): mp 116–118°; λ_{max} 233 nm (ε 10,800); nmr 4.8, m (C_6-αH), 6.17, s (C_4-H) ppm.

6-Chloro-17α-hydroxy-1,2β;16-bis(methylene)-9β,10α-pregna-4,6-diene-3,20-dione 17-Acetate (12c). As described for 8c, **13b** (0.9 g) was converted into the 3-enol ether (**14b**), which was oxidized with MnO_2 to 12c (0.6 g after chromatography): mp 216–219° dec (Me_2CO–*n*-hexane). *Anal.* ($C_{25}H_{29}O_4Cl$) H; C: calcd, 70.00; found, 68.95.

Fluorination of 14a. As described for **9b** and 9c, 14a (4.2 g) was fluorinated with $FClO_3$. After chromatography, the following products were obtained: **6α-fluoro-17α-hydroxy-1,2β;16-bis(methylene)-9β,10α-pregn-4-ene-3,20-dione 17-acetate (13c)** (0.12 g), mp 216–217° dec (Me_2CO–*n*-hexane), nmr, δ 5.04, dm, $J_{6\beta,F}$ = 50 Hz (C_6-βH), 5.67, d, $J_{6\alpha,4}$ = 5 Hz (C_4-H) ppm [*Anal.* ($C_{25}H_{31}O_4F$) C, H]; **6β-fluoro-17α-hydroxy-1,2β;16-bis(methylene)-9β,10α-pregn-4-ene-3,20-dione 17-acetate (13d)** (0.09 g), mp 223–225° (Me_2CO–*n*-hexane), nmr δ 5.27, dm, $J_{6\alpha,F}$ = 50 Hz (C_6-αH), 5.89, s (C_4-H) ppm [*Anal.* ($C_{25}H_{31}O_4F$) C, H]; and a mixt of **13c** and **13d** (2.9 g).

6-Fluoro-17α-hydroxy-1,2β;16-bis(methylene)-9β,10α-pregna-4,6-diene-3,20-dione 17-Acetate (12d). As described for 8c, a mixt of 13c and 13d (3 g) was converted into the 3-enol ether (**14c**) which was then oxidized with MnO_2, yielding 12d (1.81 g after chromatography): mp 207–210° (Me_2CO); nmr δ 5.62, 2d, $J_{F,7}$ = 16 Hz, $J_{7,8}$ = 4 Hz (C_7-H), 5.92, s (C_4-H) ppm. *Anal.* ($C_{25}H_{29}O_4F$) C, H.

3α,17α-Dihydroxy-16-methylene-9β,10α-pregna-4,6-dien-20-one 3,17-Diacetate (10d). To a soln of **8b** (0.6 g) in THF (15 ml) was added LiAlH(O-*tert*-Bu)$_3$ (2 g) after which the mixt was stirred at 20° for 20 hr. The ppt obtained after acidification with AcOH (pH 6) and diln with H_2O was extd with CH_2Cl_2. The ext was washed neutral and concd to dryness, and the residue was crystd from Et_2O, yielding **10a**: mp 182–183°. *Anal.* ($C_{24}H_{32}O_4$) C, H. **10a** (0.167 g) in pyridine (0.8 ml) was acetylated with Ac_2O (0.4 ml) in 20 hr. The mixt was added to H_2O and the ppt was extd with CH_2Cl_2. The ext was evapd to dryness, and the residue was crystd from Et_2O to give **10d**: mp 150–152°; nmr δ 2.06, s (C_3-αOCOCH$_3$), 5.35, m (C_3-βH), 5.60, s (C_4-H), 5.67, d (C_7-H), 6.02, d (C_6-H) ppm. *Anal.* ($C_{26}H_{34}O_5$) C, H.

Similarly to the method of conversion of **8b** to **10d** were prepared: **6-chloro-3α,17α-dihydroxy-16-methylene-9β,10α-pregna-4,6-dien-20-one 3,17-diacetate (10e)**, mp 211–212°, nmr δ 2.08, s (C_3-αOCOCH$_3$), 5.40, m (C_3-βH), 5.94, 2s (C_4-H and C_7-H) ppm [*Anal.* ($C_{26}H_{33}O_5Cl$) C, H]; and **6-fluoro-3α,17α-dihydroxy-16-methylene-9β,10α-pregna-4,6-dien-20-one 3,17-diacetate (10f)**, mp 183–185°, nmr δ 2.04, s (C_3-αOCOCH$_3$), 5.24, q (C_7-H), 5.72, d (C_4-H), 5.35, m (C_3-βH) ppm [*Anal.* ($C_{26}H_{33}O_5F$) C, H].

4,6-Dichloro-17α-hydroxy-16-methylene-9β,10α-pregna-4,6-diene-3,20-dione 17-Acetate (15). To a stirred soln of 8c (0.5 g) in DMF (4.8 ml) and Et_2O (2.4 ml) was added at 0°, Cl_2 (0.12 g) in $EtCO_2H$ (1.5 ml). The mixt was kept at 0° for 48 hr and then added to H_2O. The ppt was extd with CH_2Cl_2, and the ext was washed neutral and evapd to dryness. The residue was purified by chromatography on SiO_2 in C_6H_6–Me_2CO mixts. Crystn from Et_2O gave **15** (13 mg): mp 215–217° dec; λ_{max} 296 nm (ε 16,300). *Anal.* ($C_{24}H_{28}O_4Cl_2$) mass spectrum *m/e* 450.

17α-Hydroxy-6-methyl-16-methylene-9β,10α-pregna-4,6-diene-3,20-dione 17-Acetate (20). To a boiling solution of **9f** (1 g) in MeOH (10 ml) was added pyrrolidine (0.5 ml) and, after 5 min of addnl boiling, the mixt was allowed to cool to 0°. The cryst material (0.75 g of **17**, mp 164–165°) was collected and then dissolved in C_6H_6 (50 ml) and EtOH (50 ml). Formaline (1.2 ml, 35%) was added and, after stirring for 30 min at 20°, the mixt was dild with H_2O and extd with CH_2Cl_2, and the crude **18** obtained was purified by chromatography on SiO_2. This resulted in a mixt of the two 6-CH_2OH isomers (0.41 g); 0.4 g of this product (**18**) was treated with concd HCl (0.8 g) in dioxane (10 ml) for 2 hr. Work-up, performed as described for **18**, gave **19**: 0.25 g; nmr δ 4.99 and 5.16 (C_6=CH_2) ppm. To a refluxing mixt of **19** (0.23 g), $MeCO_2Na$ (0.23 g), and 5% Pd/C (0.3 g) in EtOH (10 ml) was added, in the course of 7 hr, a soln of 1% cyclohexene in EtOH (50 ml). Refluxing was continued for 15 hr, then the mixt was cooled and dild with H_2O. The solid material was isolated by extn and purified by chromatography on SiO_2. Combination of the appropriate fractions and crystn from Et_2O resulted in **20** (42 mg): mp 172–174°; nmr δ 1.92, s (C_6-CH_3) ppm. *Anal.* ($C_{25}H_{32}O_4$) C, H.

Clauberg Method. Immature female rabbits (C.P.B. strain#), 6 weeks old, body wt 800–1000 g, were pretreated with oestradiol monobenzoate for 8 days (sc, dose 0.4 μg/daily, except on day 2). The compounds were tested orally as a soln in arachis oil. During the administration of the test compound from day 10 until 14, a sustaining dose of 0.08 μg/day of oestradiol monobenzoate was given. As a rule the compounds were orally administered to groups of 4 animals at 4 dose levels (dose increment 3), against 3 dose levels of the standard, *i.e.*, progesterone sc (daily doses 50, 150, and 450 μg/animal) and dydrogesterone orally (daily dose 500, 1500, and 4500 μg/animal). The progestational effect was judged in 4–8 slices of different parts of each uterus on the basis of the histol development of the endometrium. The relative potency was calcd in comparison with the standard by rank numbering of the microphotographs of the uterine sections of each animal in the test.[19]

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References

(1) S. J. Halkes, J. Hartog, A. M. de Wachter, and L. Morsink, *J. Med. Chem.*, 15, 1288 (1972) (paper 38).
(2) (a) Z. Cekan, M. Seda, J. Mikulaskova, and K. Syhora, *Steroids*, 4, 415 (1964), and ref cited therein; (b) *ibid.*, 8, 205 (1966); (c) E. L. Shapiro, T. L. Popper, L. Weber, R. Neri, and H. L. Herzog, *J. Med. Chem.*, 12, 631 (1969), and ref cited therein.
(3) (a) P. Westerhof and J. Hartog, *Recl. Trav. Chim. Pays-Bas*, 84, 918 (1965); (b) P. Westerhof, J. Hartog, and S. J. Halkes, *ibid.*, 84, 863 (1965).
(4) W. F. van der Waard, D. van der Sijde, and J. de Flines, *ibid.*, 85, 712 (1966).
(5) A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944).
(6) K. Syhora and R. Mazac, *Collect. Czech. Chem. Commun.*, **31**, 2768 (1966).
(7) K. Syhora and R. Mazac, *ibid.*, **29**, 2351 (1964).
(8) Searle and Co., British Patent 871487; *Chem. Abstr.*, **54**, 22732*i* (1960).
(9) G. W. Krakower and H. A. Van Dine, *J. Org. Chem.*, 31, 3467 (1966).
(10) G. W. Duncan, S. C. Lyster, J. W. Hendrix, J. J. Clark, and H. D. Webster, *Fert. Steril.*, **15**, 430 (1964).
(11) (a) R. Wiechert, *Experientia*, 24, 767 (1968); (b) R. W. Kierstead, J. Blount, K. E. Fahrenholtz, A. Faraone, R. A. LeMahieu, and P. Rosen, *J. Org. Chem.*, **35**, 4141 (1970).
(12) (a) C. Revesz, U. K. Banik, and F. Herr, *Steroids*, **10**, 291 (1967); (b) T. L. Popper, F. E. Carlon, E. L. Shapiro, and R. Neri, *J. Med. Chem.*, 14, 33 (1971).

#C.P.B. = Centraal Proefdieren Bedrijf T.N.O.–Zeist, The Netherlands.

(13) Dr. A. Fürst of F. Hoffmann-La Roche and Co., A. G., personal communication.
(14) The British Drug House Ltd., Belgian Patent 622.955; *Chem. Abstr.*, **60**, 9336*a* (1964).
(15) R. Wiechert and F. Neumann, *Arzneim.-Forsch.*, **15**, 244 (1965).
(16) F. Hoffmann-La Roche and Co., A.G., South African Patent 6804457; *Chem. Abstr.*, **72**, 21840 (1970).
(17) H. J. Ringold, E. Batres, A. Bowers, J. Edwards, and J. Zderic, *J. Amer. Chem. Soc.*, 81, 3485 (1959).
(18) A. Boris, L. De Martino, and T. Trmal, *Acta Endocrinol.*, **63**, 476 (1970).
(19) R. van Strik, "Quantitative Methods in Pharmacology," H. de Jonge, Ed., North Holland Publishing Co., Amsterdam, 1961, p 88.
(20) Th. J. de Boer and H. J. Backer, *Recl. Trav. Chim. Pays-Bas*, **73**, 229 (1964).

Antiinflammatory Activity of Some Indan-1-carboxylic Acids and Related Compounds

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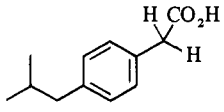
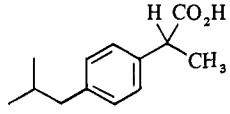
A series of indan-1-carboxylic acids and derivatives was prepared as potential antiinflammatory agents. Many of the indan compounds showed potent antiinflammatory activity when tested orally in the rat. Structure-activity relationships are discussed, and a resemblance is noted between structural requirements for these antiinflammatory agents and for certain plant growth regulators.

Of all the chemical classes that have been examined in recent years for potential nonsteroidal antiinflammatory agents, none has received wider attention than the aryl- and heteroarylalkanoic acids.[1] Features of a typical molecule which are important for activity include a carboxyl group separated by one or more carbon atoms from a flat, aromatic nucleus which is further substituted by a large lipophilic group.

Of particular interest have been the arylacetic acids. From lead compounds such as ibufenac[2] (**1**) have come ibuprofen[3] (**2**) and (*S*)-(+)-3-chloro-4-cyclohexyl-α-methylphenylacetic acid[4] (**3**). In this paper we now describe the synthesis of some indan-1-carboxylic acids (**4**) and related compounds, some of which have been found to exhibit potent antiinflammatory activity in the rat. Since our initial disclosure[5] of this work, papers have appeared [6] which confirm the antiinflammatory properties of 6-chloro-5-cyclohexylindan-1-carboxylic acid (**17**).

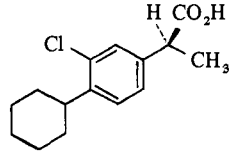


1

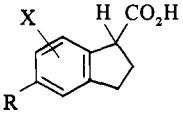


2, (±)

Chemistry. Our initial goal was to prepare 5-H-, 5-alkyl-, and 5-cycloalkylindan-1-carboxylic acids having the general structure **12.** This was accomplished as outlined in Scheme I, and the compounds prepared are listed in Tables I-VI.



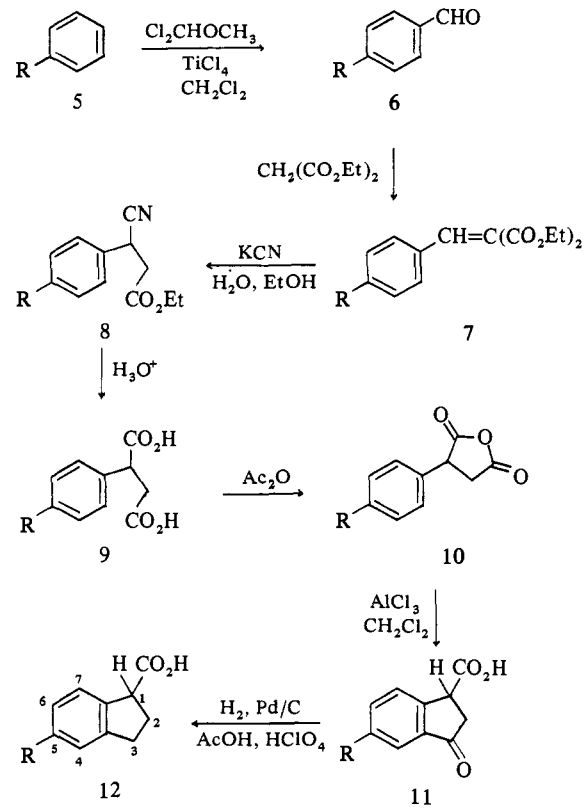
3, (*S*)-(+)



4, R = H, alkyl, cycloalkyl; X = monosubstituent

A more efficient, alternative synthesis (Scheme II) was developed for the 5-cyclohexyl compound **12e.** 5-Cyclohexyl-1-indanone (**15**) was prepared from cyclohexylbenzene (**13**) and β-chloropropionyl chloride (**14**) by a method similar to the one described by Hart and Tebbe[7] for the preparation of 1-indanone. The indanone **15** was converted to **12e** *via* the intermediate **16**, an approach based on a general

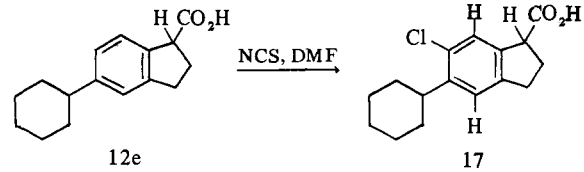
Scheme I



5 **6** **8** **7** **9** **10** **12** **11**

procedure for the conversion of ketones to acids using 1,3-dithiane.[8] The overall yield from **13** to **12e** was 37%.

Optimal antiinflammatory activity (see Structure-Activity Relationships) was found for the 5-cyclohexyl compound **12e** which was selected for further modification. The 6-chloro derivative **17** (Table VI) was obtained by treatment of **12e** with NCS in DMF.[9] The nmr spectrum of the monochloro product showed singlets at δ 7.20 (1 H) and 7.50



12e **17**