Antiinflammatory Δ^4-Pregnenolone Derivatives

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The synthesis of a number of steroidal allylic alcohols, ethers, and esters of interest as topical antiinflammatory substances is reported. Pertinent physicochemical and pharmacologic data are also presented.

The value of the local application of antiinflammatory steroids in dermatology has long been established. When applied topically, however, cortisol,[1,2] its 9α-fluoro analog,[3,4] and their polysubstituted derivatives[5] are partly absorbed through the skin and unwanted systemic action may be encountered, particularly if large areas are being treated or if the steroid is applied under occlusive dressing.

We describe here a new series of steroid derivatives obtained in the course of a systematic effort to achieve separation between antiinflammatory and unwanted "corticoid" activity. 6α-Fluoro-16α,17α-dihydroxypregn-4-ene-3,20-dione (Ia)[6] was microbiologically hydroxylated with *Aspergillus ochraceus* to give the corresponding triol Ib. The structure of this compound was established by elemental analysis, by nmr evidence for the presence of the pregnane side chain, indicating that the D-homo rearrangement peculiar to this type of structure[7] had not taken place, and by its subsequent transformation to other products. The corresponding 16α,17α-acetonide II was then converted through the conventional steps (see Experimental Section) to the fluorohydrin IV or oxidized to the triketone III by the Kiliani–Jones mixture[8] (see Scheme I). The carbonyl functions present in III or IV exhibit different reactivity toward hydride reagents for obvious steric reasons in the order 3 > 11 > 20 allowing the preparation of the corresponding allylic alcohols V–VII (R = H). Various ester and ether derivatives were then prepared, as listed in Table I.

In Table II the antiinflammatory and glucocorticoid activities of the compounds prepared are presented and compared to hydrocortisone taken as 1. Compound VI (R = CH_3CO) appears to have the most pronounced dissociation of activities, being almost inactive as a glucocorticoid and yet retaining antiinflammatory properties.

Recently, a correlation has been established between the percutaneous absorption of topical steroids, their aqueous solubility and their water–ether partition coefficient.[9] In Table III we report the solubilites in water saturated with ether, W_E initial, and after extraction with ether, W_E extracted. The concentration in the organic phase is given by their difference. The partition coefficient (PC) and the square root of molar solubility ($\sqrt{C_s}$) in water are also reported. The product ($C_s^{1/2}PC$) has been correlated[9] with topical efficacy as measured by the McKenzie–Stoughton vasoconstriction test.[10] From the table it appears that the solubilities in water of some of our compounds are immeasurably low in comparison with polyhydroxylated steroids and the partition coefficients are therefore meaningless. Compound VI (R = H), however, is soluble in water to the extent of 102 mg/l. (W_E initial) and has a PC of 27. The reported[9] values for fluocinolone acetonide are 108 and 17, respectively. One might, therefore, predict that the percutaneous absorption of VI (R = H) would be optimal for topical activity among the compounds prepared in this study.

TABLE I

Compd	R	Mp, °C dec	$[\alpha]^{23}D$, deg
Allylic alcohols, esters, and ethers			
V	CH_3CO	212	+67
V	$(CH_3)_3CCH_2CO$	246	+74
VI	H	148	+77
	CH_3CO	182	+89
	C_6H_5CO	168	+49
	$(CH_3)_3CCH_2CO$	209	+58
	CH_3	163	+88
	2-Tetrahydropyranyl	152.5	+65
VII	CH_3CO	204	+82
Corresponding Δ^4-3-ketone			
IV		264	+127
VIII		245	+133
III		225	+188

Experimental Section

Optical rotations were determined as 1% solutions in $CHCl_3$ at 23° if not otherwise indicated; ultraviolet spectra were determined in ethanolic solution. Melting points are corrected. Nmr spectra were determined in $CDCl_3$ and values are quoted in ppm downfield from $(CH_3)_4Si$ as internal reference.

6α-Fluoro-11α,16α,17-trihydroxypregn-4-ene-3,20-dione (Ib).—6α-Fluoro-16α,17-dihydroxypregn-4-ene-3,20-dione[6] was incubated with spores of *Aspergillus ochraceus* according to a previously described procedure.[11] The spore count in suspension was 8×10^8/ml and the incubation time was 72 hr. Selective hydroxylation in 11α was obtained. The product was obtained in close to quantitative yield and was recrystallized from acetone–hexane for analysis; mp 221–222°, $[\alpha]^{23}D$ +53° (CH_3OH), $\epsilon_{237.5}$ 14,400, nmr, 21-methyl ketone protons at 2.20 ppm.

Anal. Calcd for $C_{21}H_{29}FO_5$: C, 66.29; H, 7.68; F, 5.00. Found: C, 66.31; H, 7.67; F, 5.21.

6α-Fluoro-11α-hydroxy-16α,17-isopropylidenedioxypregn-4-ene-3,20-dione (II).—Triol Ib (7.8 g) was dissolved in acetone (120 ml), $HClO_4$ (0.2 ml) was added, and the mixture was left

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SCHEME I

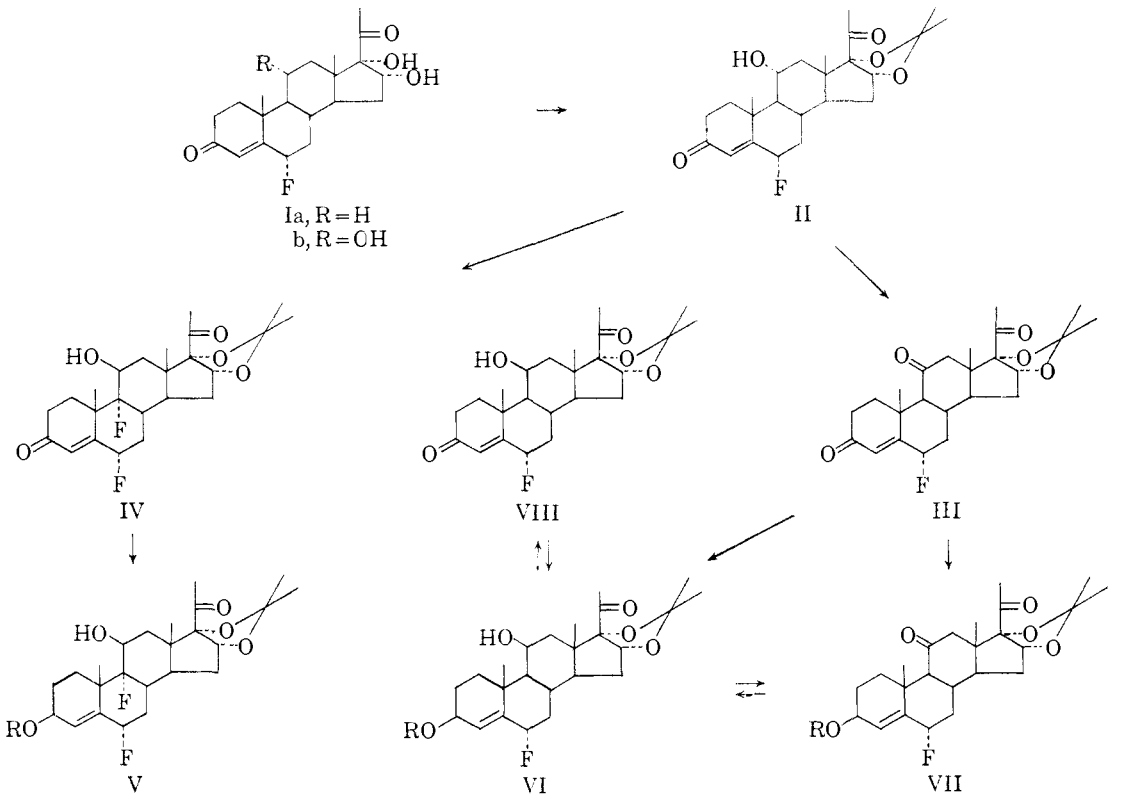

TABLE II

Compd	R	Antiinflammatory activity[a] Pouch[b] Local	Pouch[b] Systemic	Arthritis[c] Topical	Arthritis[c] Systemic	Glucocorticoid (systemic) activity[a,d] Thymus involution	Hyperglycemia	Glycogen deposition
Hydrocortisone		1[d]	1	1	1	1	1	1
Triamcinolone acetonide		200	60	200	200	30	60	18
VI	2-Tetrahydropyranyl	10	<1	...	...	<1	≃3	
VI	CH_3	10	1	...	...	1	≃3	5
IV		200	40	30	50	30	20	15
V	CH_3CO	50	15	12	...	2	20	2
VII	CH_3CO	<1	...	...	...	...	...	...
V	$(CH_3)_3CCH_2CO$	13	...	...	...	<1	≃20	...
III		...	...	...	...	<1	<1	<1
VI	CH_3CO	40	<1	3	20	<1	<1	<1
VI	H	20	...	8	15	2	3	5
VI	C_6H_5CO	8	...	...	10	<1	<1	<1
VI	$(CH_3)_3CCH_2CO$	...	...	...	4	<1	<1	<1
VIII		200	15	20	50	9	20	5

[a] Relative potencies are approximate as estimated from ED_{50} (log dose relationships). [b] Croton oil granuloma pouch assay: A. Robert and J. E. Nezamis, *Acta Endocrinol.*, **25**, 105 (1957). [c] Adjuvant arthritis assay, adapted from B. B. Newbould, *Brit. J. Pharmacol. Chemotherapy*, **21**, 127 (1963). [d] Combination assay for corticoid activity: J. G. Rochefort and A. Sproule, in preparation.

at room temperature for 2.5 hr. A few drops of pyridine was added, the solution was concentrated *in vacuo*, and the residue was extracted with CH_2Cl_2. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to give 8.6 g of crude product. Recrystallization from acetone gave the pure product, mp 283–285°, $[\alpha]^{23}D$ +101°, ϵ_{237} 14,400, nmr, 21-methyl ketone protons at 2.20 ppm.

Anal. Calcd for $C_{24}H_{33}FO_5$: C, 68.54; H, 7.91; F, 4.52. Found: C, 68.61; H, 7.68; F, 4.65.

6α-Fluoro-16α,17-isopropylidenedioxypregn-4-ene-3,11,20-trione (III).—The alcohol II (1.40 g) was dissolved in 40 ml of acetone and oxidized at 0° with 2.8 ml of 8 *N* chromic acid during 4 min. The mixture was poured into water, extracted with ether, and washed ($NaHCO_3$, H_2O). Evaporation of the solvent gave 1.28 g of III, which was crystallized from acetone–ether to mp 225–226°, $\epsilon_{233.5}$ 14,800, $[\alpha]^{23}D$ +188°.

Anal. Calcd for $C_{24}H_{31}FO_5$: C, 68.88; H, 7.46; F, 4.54. Found: C, 68.64; H, 7.31; F, 4.72.

6α-Fluoro-16α,17-isopropylidenedioxypregn-4-ene-11,20-dion-3β-ol Acetate (VII, R = Ac).—The trione III (100 mg, 0.24 mmole) in 2 ml of tetrahydrofuran (THF) was stirred at room temperature for 4 hr with 182 mg (0.716 mmole) of lithium aluminum tri-*t*-butoxyhydride. Acetone (1 ml) was added and the mixture was treated with a saturated solution of $(NH_4)_2SO_4$, then extracted with CH_2Cl_2. The residue crystallized from ether–hexane to give needles (35 mg), mp 143° dec. This crude product was acetylated at room temperature overnight with acetic anhydride in pyridine. The usual work-up gave a semicrystalline residue which was chromatographed on a silica gel column to give crystalline VII (R = Ac), mp 204° dec (from ether), $[\alpha]^{23}D$ +82°.

Anal. Calcd for $C_{26}H_{35}FO_6$: C, 67.51; H, 7.63; F, 4.11. Found: C, 67.57; H, 7.73; F, 4.24.

3β-Acetoxy-6α-fluoro-11β-hydroxy-16α,17-isopropylidenedioxypregn-4-en-20-one (VI, R = Ac).—The trione III (897 mg) was dissolved in 20 ml of THF and reduced with 2.69 g of lith-

TABLE III

Compd	R	Aqueous phase —solubility, mg/l.— W_E initial	W_E extracted	$\sqrt{C_s}$	PC	$C_s^{1/2}PC$
Hydrocortisone[a]		585	258	40.1	1.3	52
Hydrocortisone		604	244	41	1.48	60
Triamcinolone acetonide[a]		41	3	9.7	12.7	123
Triamcinolone acetonide		45.6	3.8	10.2	11.4	117
Fluocinolone acetonide[a]		108	6	15.4	17	262
VI	H	102	3.2	15.5	27	418
VI	2-Tetrahydropyranyl	4	0	2.78	...	...
VI	CH_3	18	0.1	6.41	(166)	(1060)
VI	CH_3CO	24.5	6	7	3.1	22
VI	C_6H_5CO	0	...	...	...	...
VI	$(CH_3)_3CCH_2CO$	44.5	5.5	9.36	7.8	73
VII	CH_3CO	0	...	...	...	...
V	CH_3CO	0.8	0	0.13	...	...
IV		6.8	0	3.92	...	...
VIII		44.5	0	10.3	...	...

[a] Values taken from Katz and Shaikh.[9]

ium aluminum tri-*t*-butoxyhydride with stirring at room temperature for 6 hr. The mixture was worked up and acetylated as described in the previous example yielding 1.1 g of a crude material which crystallized from acetone–hexane to give 442 mg of product, mp 182–183° dec (observed also mp 209–210° dec), $[\alpha]^{23}D$ +89°.

Anal. Calcd for $C_{26}H_{37}FO_6$: C, 67.22; H, 8.03; F, 4.09. Found: C, 67.02; H, 7.82; F, 4.65.

Oxidation of VI (R = Ac) with pyridine–chromic acid complex gave the dione VII (R = Ac) previously described.

3β,11β-Dihydroxy-6α-fluoro-16α,17-isopropylidenedioxypregn-4-en-20-one (VI, R = H).—The acetate VI (R = Ac) (100 mg) was suspended in 10 ml of methanol and refluxed for 30 min with 100 mg of anhydrous K_2CO_3 and 1 ml of water. Part of the solvent was evaporated at low temperature, the residue was extracted with ether, and the organic layer was washed with water, dried, and evaporated to give 95 mg of a crude product which crystallized from acetone–hexane to mp 148–150° dec, $[\alpha]^{23}D$ +77° (dioxane).

Anal. Calcd for $C_{24}H_{35}FO_5$: C, 68.22; H, 8.35; F, 4.50. Found: C, 68.01; H, 8.21; F, 4.36.

Reacetylation of this product with acetic anhydride in pyridine gave the acetate VI (R = Ac) previously described.

6α-Fluoro-11β-hydroxy-16α,17-isopropylidenedioxypregn-4-ene-3,20-dione (VIII).—To the allylic alcohol VI (R = H) (32.8 g), dissolved in 400 ml of dioxane, was added 40.5 g of 2,3-dichlorodicyanoquinone (DDQ), and the mixture was stirred overnight at room temperature. The precipitated hydroquinone was filtered, and the organic layer was concentrated *in vacuo* at low temperature, then diluted with ether, and washed six times with $NaHCO_3$ and twice with water. Evaporation of the dried solvent gave 33 g of a brown foam from which the product crystallized in several crops from methanol or ether–methanol; mp 245° dec, $[\alpha]^{23}D$ +133°, $\epsilon_{237.5}$ 15,150.

Anal. Calcd for $C_{24}H_{33}FO_5$: C, 68.54; H, 7.91; F, 4.52. Found: C, 68.22; H, 7.64; F, 4.53.

6α,9α-Difluoro-11β-hydroxy-16α,17-isopropylidenedioxypregn-4-ene-3,20-dione (IV).—The alcohol II (840 mg) in 10 ml of CH_2Cl_2 was treated with 1 ml of pyridine and 0.23 ml of methanesulfonyl chloride at room temperature for 22 hr. The mixture was diluted with ether, washed with dilute HCl and $NaHCO_3$ solution, then water, dried, and evaporated to give 1.0 g of colorless crystals, mp 160–162° (from CH_2Cl_2–methanol) representing crude 11α-mesylate. The crude mesylate (17.5 g) was dissolved with warming in 180 ml of acetic acid. Sodium acetate (35 g) was added and the mixture refluxed under N_2 for 2 hr. The usual work-up gave 14.1 g of a yellow solid which crystallized from CH_2Cl_2–methanol to give 6.77 g of a homogeneous product, mp 226° dec. Chromatography of the mother liquors afforded more (2 g) of the same product, mp 235° dec. The two fractions, representing crude 6α-fluoro-16α,17-isopropylidenedioxypregna-4,9(11)-diene-3,20-dione, were combined. This olefin (115 mg), dissolved in 2 ml of CH_2Cl_2 and 5.8 ml of *t*-butyl alcohol, was treated with 0.375 ml of 70% $HClO_4$ in 2.5 ml of water followed by a solution of 50 mg of N-bromoacetamide in 2.2 ml of *t*-butyl alcohol. After stirring at room temperature for 15 min there was added 88 mg of Na_2SO_3 in 4 ml of H_2O. The solvent was partly removed *in vacuo*, water was added to the residue, and the precipitate was filtered and washed with water to give 130 mg of a crude bromohydrin, mp 175° dec. This bromohydrin (10 g) in acetone (350 ml) was refluxed overnight with 24 g of potassium acetate. The acetone was removed *in vacuo*, the residue was diluted with CH_2Cl_2, washed with water, and dried to give 8.52 g of a crystalline residue which was chromatographed on activated magnesium silicate (Florisil). A 9β,11β-oxido compound was obtained (5.3 g), mp 205–209°. This compound (4.965 g) in 50 ml of CH_2Cl_2, was added dropwise with stirring at −80° within 15 min to a mixture of 20 g of anhydrous THF and 10 g of anhydrous HF. The mixture was kept at 0° for 17 hr then poured cautiously into ice-cold $NaHCO_3$ solution. The steroid was extracted with CH_2Cl_2 and chromatographed on magnesium silicate. There was obtained 4.2 g of IV, mp 264–265° dec (from acetone–ether), ϵ_{234} 16,200, $[\alpha]^{23}D$ +127°.

Anal. Calcd for $C_{24}H_{32}FO_5$: C, 65.73; H, 7.36; F, 8.66. Found: C, 65.81; H, 7.39; F, 8.58.

3β-Acetoxy-6α,9α-difluoro-11β-hydroxy-16α,17-isopropylidenedioxypregn-4-en-20-one (V, R = Ac).—The diketone IV (422 mg) in 8 ml of THF was reduced with 725 mg of lithium aluminum tri-*t*-butoxyhydride at room temperature for 4 hr. The residue, after the usual work-up, represented a mixture, probably of the two epimeric 3-alcohols (375 mg, mp 165° dec). This mixture was acetylated overnight with 1 ml of acetic anhydride in 5 ml of pyridine and the amorphous product (410 mg) was chromatographed through 20 g of silica gel. The major fraction (400 mg) crystallized from ether to mp 212–213° dec, $[\alpha]^{23}D$ +67°.

Anal. Calcd for $C_{26}H_{36}F_2O_6$: C, 64.71; H, 7.52; F, 7.87. Found: C, 64.76; H, 7.45; F, 7.89.

6α-Fluoro-11β-hydroxy-16α,17-isopropylidenedioxy-3β-methoxypregn-4-en-20-one (VI, R = CH_3).—A mixture of 5.0 g of the alcohol VI (R = H), 100 ml of methanol, and 1.5 ml of 70% $HClO_4$ was stirred overnight at room temperature. Water (150 ml) was added with cooling and the colorless solid was filtered and crystallized first from benzene and then from acetone–hexane, yielding 2.60 g of VI (R = CH_3), mp 153° dec. The analytical sample melted at 162–163° dec, $[\alpha]^{23}D$ +87.5°.

Anal. Calcd for $C_{25}H_{37}FO_5$: C, 68.77; H, 8.54; F, 4.35. Found: C, 68.68; H, 8.32; F, 4.21.

6α-Fluoro-11β-hydroxy-16α,17-isopropylidenedioxy-3β-(2-tetrahydropyranyl)oxypregn-4-en-20-one (VI, R = C_5H_9O).—A suspension of 5.0 g of VI (R = H) in 200 ml of benzene was distilled at reduced pressure until about 15 ml of solvent had been removed to ensure dryness. Dihydropyran (3 ml) and 25 mg of *p*-toluenesulfonic acid were added and the mixture was stirred at room temperature for 1.5 hr. Solution was complete after 30 min. Pyridine (0.1 ml) was added, the solution was washed twice with water, dried, and chromatographed on 50 g of alumina (activity III). Elution with benzene and benzene-

ether mixtures, followed by crystallization from acetone–hexane gave 3.17 g of the tetrahydropyranyl ether, mp 148.5° dec. The analytical sample had mp 152.5° dec, $[\alpha]^{23}D$ +65°.

Anal. Calcd for $C_{29}H_{42}FO_6$: C, 68.74; H, 8.55; F, 3.75. Found: C, 68.53; H, 8.45; F, 3.94.

6α,9α-Difluoro-3β,11β-dihydroxy-16α,17-isopropylidenedioxypregn-4-en-20-one 3β-*t*-butylacetate (V, R = $(CH_3)_3CCH_2CO$) was prepared from the corresponding 3β-alcohol V (R = H) and *t*-butylacetyl chloride in pyridine; mp 246–248° dec, $[\alpha]^{23}D$ +74.4°.

Anal. Calcd for $C_{30}H_{44}F_2O_6$: C, 66.89; H, 8.23; F, 7.05. Found: C, 66.64; H, 8.19; F, 7.03.

6α-Fluoro-3β,11β-dihydroxy-16α,17-isopropylidenedioxypregn-4-en-20-one 3β-*t*-butylacetate (VI, R = $(CH_3)_3CCH_2CO$) was prepared from the corresponding 3β-alcohol VI (R = H); mp 209–210° dec, $[\alpha]^{23}D$ +58°.

Anal. Calcd for $C_{30}H_{45}FO_6$: C, 69.20; H, 8.71; F, 3.65. Found: C, 69.08; H, 8.62; F, 3.76.

6α-Fluoro-3β,11β-dihydroxy-16α,17-isopropylidenedioxypregn-4-en-20-one 3β-benzoate (VI, R = C_6H_5CO) was prepared from the corresponding 3β-alcohol VI (R = H) and benzoyl chloride in pyridine; mp 168–170° dec, $[\alpha]^{23}D$ +49°.

Anal. Calcd for $C_{31}H_{39}FO_6$: C, 70.70; H, 7.46; F, 3.61. Found: C, 70.42; H, 7.21; F, 3.77.

Derivatives of 3,4-Diphenylchromanes as Estrogens and Implantation Inhibitors

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A number of substituted 3,4-diphenylchromanes have been prepared from isoflavanones. Their chemical, spectral, and biological properties, *i.e.*, estrogenic and antifertility activity, are discussed.

Several years ago Gaunt and co-workers[1] emphasized the necessity of the extension of classical endocrinology into broad endocrine pharmacology. While classical endocrinology is primarily concerned with the isolation, synthesis, and improvement of natural hormones, endocrine pharmacology would imply the study of nonhormonal compounds to elucidate hormonal and enzymic mechanisms and by this route to detect substances which would be able to restore deranged endocrine homeostasis.

Diverse nonsteroidal compounds such as amphenones, pyridyl ketones, aminoindenes,[2] 2,3-diphenylindenes,[3] 1,2-diaryldihydro- and 1,2-diaryltetrahydronaphthalenes,[4] isoflavones,[5] 2,2-dialkyl-3-isoflavens,[6] diarylpropionitriles,[7] 3,4-diphenylcoumarins,[8] and 2,3-diphenylbenzofurans[9] have shown specific interactions with endocrines. Moreover, a recent communication from our laboratories outlines the synthesis and biological properties of some new *cis* and *trans* isomers of 1,2,3,4-tetrahydro-1,2-diarylnaphthalene derivatives.[4c] It was shown that some of these compounds exhibited marked estrogenic activity as well as potent antifertility activity in the female rat. It has been noted also that 3-pyridyl-4-chromone derivatives have specific effects on the adrenal glands and in the gonads.[10] Hence it was our aim to investigate compounds structurally related to both the 1,2-diarylnaphthalenes and chromones which would possess little or no estrogenic potency while still retaining or possibly eliciting an increased antifertility activity. Therefore, the 3,4-diphenylchromanes, a group of compounds which had not been explored heretofore, were selected for study in this regard.

Over a decade ago Bradbury and White showed that isoflavones and their derivatives possessed estrogenic activity.[11] Some of these were isolated from subterranean clover which had been found to be responsible for infertility in sheep in Western Australia. Bradbury prepared 3,4-diaryl-substituted chromenes by treating a substituted phenyl Grignard reagent with the corresponding isoflavanones.[12] The isoflavanones were derived from the isoflavones by catalytic hydrogenation.[13] Inove recently described a method for the synthesis of 7-methoxyisoflavanone from 7-methoxy-3-hydroxyisoflavanone or 7-methoxy-3-acetoxyisoflavanone by zinc dust–acetic acid reduction.[14] However, since both of these methods do not lend themselves to a convenient preparation of 3-phenylchromanones, the method of DaRe and Verlicchi was used in the course of our study.[15] These investigators found that the condensation of formaldehyde with an *o*-hydroxyphenyl benzyl ketone derivative in basic medium yields the desired isoflavanone directly.

Thus, *o*-hydroxyphenyl *p*-chlorobenzyl ketone and paraformaldehyde were allowed to react in aqueous sodium hydroxide solution at 55° to afford 3-*p*-chlorophenyl-4-chromanone (I) in 64% yield (see Scheme I). This substance was then treated with the *p*-methoxy-

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