13012-23-2; XIV, 13012-24-3; XVI, 13012-25-4; XVII, 13012-26-5; XIX, 13012-27-6; XX, 13012-28-7; XXI, 13012-29-8; XXII, 13012-30-1; XXIII, 13012-31-2; XXIV, 13012-32-3; XXV, 13012-33-4; XXVI, 13012-34-5; XXVII, 13012-35-6; 4-dimethylamino-2,6-dimethylisophthalodialdoxime, 13012-36-7.

Acknowledgment.—The research of which this publication forms a part was supported by Public Health Service Research Grants CA-07272-93 and -04 of the National Cancer Institute, Bethesda, Md. The authors are indebted to Mrs. J. M. Dean for the preparation of several intermediates.

Flavonoids. III. Studies on the Synthesis of 2,4-Dialkyl-7-acetoxy-4′-methoxy-Δ^3-isoflavenes[1,2]

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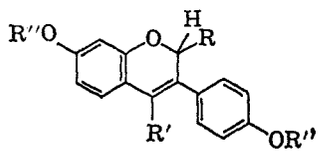
A method is described for the conversion of 2-methyl-7-tetrahydropyranyloxy-4′-methoxyisoflavone to 2,4-dialkyl-7-acetoxy-4′-methoxy-Δ^3-isoflavenes. The incorporation of the tetrahydropyranyloxy group, as contrasted with alkyl ether groups, permits a facile cleavage of the protecting group (required for the borohydride reduction step) at a later stage in the synthesis. The synthesis entails the steps: 7-tetrahydropyranyloxyisoflavone → 7-tetrahydropyranyloxyisoflavanol → 7-tetrahydropyranyloxyisoflavanone → 4-alkyl-7-tetrahydropyranyloxyisoflavanol → 4-alkyl-7-hydroxy-Δ^3-isoflavene → 4-alkyl-7-acetoxy-Δ^3-isoflavene.

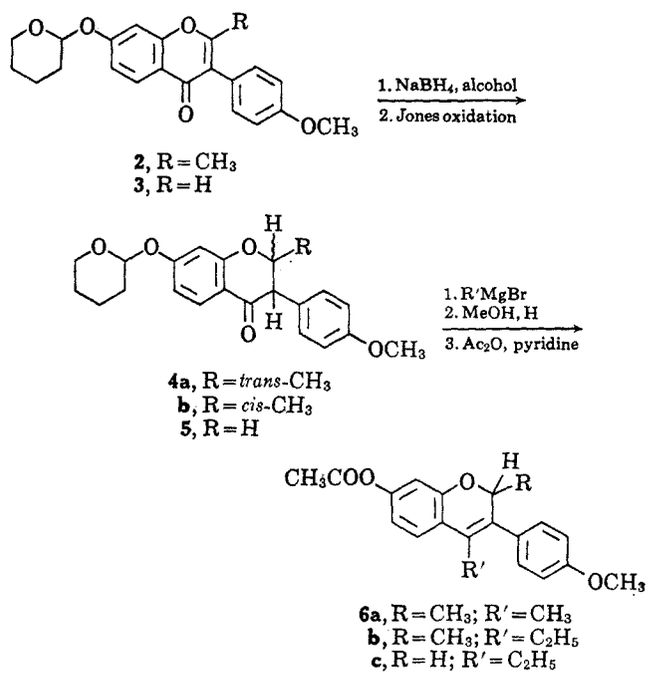
The present study was commenced for the purpose of demonstrating a method of synthetic utility for obtaining 2,4-dialkyl-Δ^3-isoflavenes **1** in the form of free phenols or corresponding acetate derivatives.[3] Previous synthetic endeavors along these lines suffered from low yields[3] or undesirable reactions at the final state of the synthesis.[4]



1

Synthesis of 2,4-Dialkyl-Δ^3-isoflavenes.—The method described here is fundamentally identical with those on record[3,5,6] and involved the steps shown in Scheme I. Because of the difficulties observed with catalytic hydrogenations of isoflavones,[3,7,8] a two-step procedure consisting of exhaustive borohydride reduction[7,9,10] and Jones oxidation was employed for the conversion of isoflavone to isoflavanone. However, a suitable blocking agent was required during the borohydride reduction step, for inhibiting *in situ* conjugate base formation of isoflavone.[11] The tetrahydropyranyl ether group was selected in this synthesis, in view of the

SCHEME I



(1) This research was carried out under Contract SA-43-pH-4351 of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health.

(2) C. E. Cook, R. C. Corley, and M. E. Wall, *J. Org. Chem.*, **30**, 4114 (1965).

(3) In reviewing the estrogenic activities of flavonoids and the Δ^3-isoflavene problem in general, Micheli, *et al.*, have discussed the biological significance of having Δ^3-isoflavenes in the form of free phenols or the corresponding acetate derivatives: R. A. Micheli, A. N. Booth, A. L. Livingston, and E. M. Bickoff, *J. Med. Chem.*, **5**, 321 (1962).

(4) (a) W. Lawson, *J. Chem. Soc.*, 4448 (1954); (b) C. E. Cook, R. C. Corley, and M. E. Wall, *J. Org. Chem.*, **30**, 4120 (1965).

(5) R. B. Bradbury and D. E. White, *J. Chem. Soc.*, 871 (1953).

(6) C. A. Anirudhan, W. B. Whalley, and (in part) M. M. E. Badran, *ibid.*, 629 (1966).

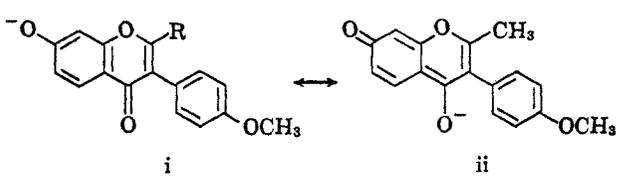
(7) W. D. Ollis in "The Chemistry of the Flavonoid Compounds," T. A. Geissman, Ed., The Macmillan Co., New York, N. Y., 1962, pp 353–405.

(8) During the course of this study, we were unable to confirm the isolation of a 2-methyl-7-acetoxy-4′-methoxyisoflavanone, mp 176–179° (*cf.* ref 5), by the catalytic hydrogenation of 2-methyl-7-acetoxy-4′-methoxyisoflavone. The compound of Bradbury and White, mp 176–179°, would undoubtedly be the *cis* derivative, for which we obtained mp 71–81° and mp 80–83° (best sample).

(9) M. Miyano and M. Matsui, *Chem. Ber.*, **91**, 2044 (1958).

(10) (a) L. R. Row, A. S. R. Anjaneyulu, and C. S. Krishna, *Current Sci.* (India), **32**, 67 (1963); (b) A. S. R. Anjaneyulu, C. S. Krishna, and L. R. Row, *Tetrahedron*, **21**, 2677 (1965).

(11) The failure of 2-methyl-7-hydroxy-4′-methoxyisoflavone and 7-hydroxy-4′-methoxyisoflavone (or the corresponding 7-acetoxy and 7-trimethylsilyloxy derivatives) to undergo reduction by alcoholic borohydride solution is undoubtedly due to salt formation *in situ*. Anion formation (i ↔ ii) would be expected to lessen the susceptibility of the α,β-unsaturated ketone system to hydride attack. In these cases, under normal and strenuous conditions, the 7-hydroxyisoflavone derivatives were observed (tlc), and reisolated, as sole reaction components (authors' unpublished experiments).



i ii

(12) J. F. W. McOmie in "Advances in Organic Chemistry: Methods and Results," Vol. 3, Interscience Publishers, Inc., New York, N. Y., 1963, p 191.

difficulties encountered with cleavages of methoxy groups at the latter stages of Δ^3-isoflavene synthesis.[4]

The borohydride reduction of the 2-methylisoflavone **2** was conducted in isopropyl alcohol at 75–80° and proceeded more sluggishly[13] than a similar reduction carried out in this laboratory on the corresponding 2-unsubstituted isoflavone **3**. Jones oxidation of the crude, resinous 2-methylisoflavanol gave, after short column clean-up chromatography, a partially crystalline ketonic product **4** which could be separated by fractional crystallization into two isomeric, crystalline compounds.

From the practical standpoint of the synthesis, isomeric isoflavanones of type **4** need not be separated. The addition of ethyl- or methylmagnesium bromide to the 2-methylisoflavanone **4** (as a mixture of *cis* and *trans* isomers) yielded a resin comprised of several components (multiple zones on tlc). However, a single reaction product (a 7-hydroxy-Δ^3-isoflavene) was formed in the next step, when a methanolic solution of the Grignard addition products was treated with a catalytic amount of hydrochloric acid and stirred briefly at room temperature. That dehydration of a tertiary hydroxyl group occurs in this latter step, in conjunction with the cleavage of the tetrahydropyranyl-ether group, was confirmed spectrophotometrically (Figure 1).

From Figure 1 it can be seen that the addition of a catalytic amount of hydrochloric acid to a methanolic solution of the Grignard addition products caused the (rapid) appearance of intense absorption above 300 mμ.[14] The maximum observed at 314 mμ in this particular case underwent a bathochromic shift (in the order of 10 mμ) when the pH of the solution was brought to the range 9–11, thus substantiating the cleavage of the protecting group. The crystalline 7-acetoxy-Δ^3-isoflavene derivatives **6** afforded light absorption spectra essentially identical with those observed during the monitoring processes.

The formulation of the final products in Scheme I as Δ^3-isoflavenes **6** was unequivocally established for each case by the ultraviolet and nmr spectral data. As an illustrative example, the ultraviolet spectrum of 2,4-dimethyl-7-acetoxy-4′-methoxy-Δ^3-isoflavene (**6a**) contained an intense light absorption band above 300 mμ.[5] The nmr spectrum (60 Mc, internal tetramethylsilane standard) contained signals at 75 (doublet, J = 6.5 cps), 116 (singlet), 137 (singlet), 230 (singlet), 306 (quartet, J = 6.5 cps), and 399–442 cps (aromatic multiplet) in the ratio 3:3:3:3:1:7, respectively. The peaks were assigned, respectively, to the 2-methyl, 4-methyl, acetyl, methoxyl, and C-2 protons.[15]

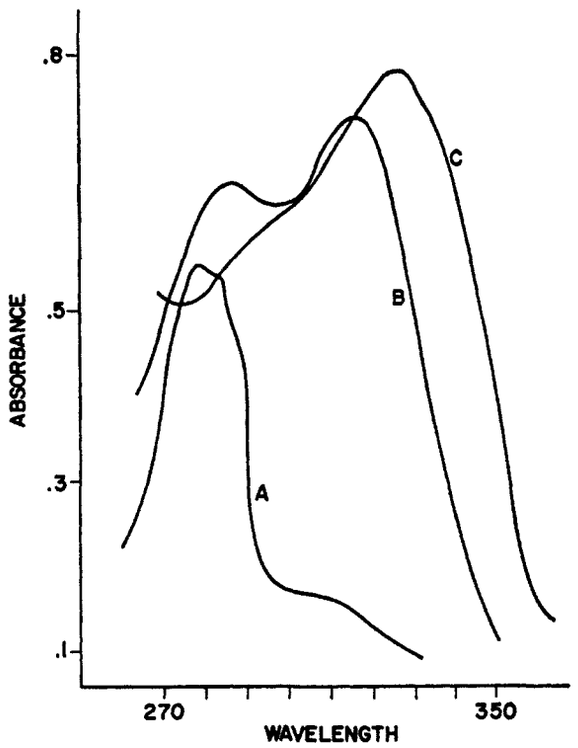


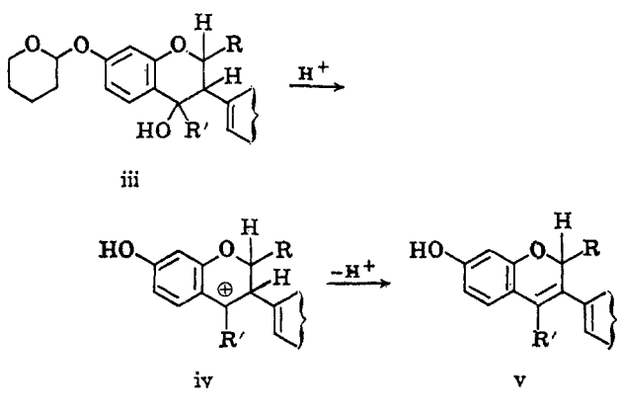
Figure 1.—Curve A, methanolic solution of crude Grignard addition product. Curve B, 1 drop of concentrated HCl added to cuvette containing the solution used for curve A. Curve C, the pH of solution used for curve B was adjusted to ~11 with 10% KOH.

The Stereochemical Aspects of the 2-Methylisoflavanones.—The isoflavanone **4a** ($J_{H_bH_c}$ = 11.5 cps) was obtained in relatively pure form by recrystallization of mixture **4a** and **4b** from ethyl acetate or ethyl acetate–petroleum ether. After collection of this product and evaporation of mother liquor, the residual syrup when covered with methanol yielded another crop of crystals which proved rich in the lower melting isoflavanone **4b** ($J_{H_aH_b}$ = 3.5 cps).

Each of the isoflavanones, **4a** and **4b**, was converted to the acetate derivative, **8a** and **8b**, respectively, by means illustrated in Scheme II. The H_a, H_b, and H_c protons of the isoflavanones gave rise to AMX spin systems. The H_b and H_c protons of **4a** and **8a** have been assigned a *trans* relationship on the basis of the larger magnitude of the coupling constant (11.5 cps) taken from the M portion (H_b) of the spectrum. The corresponding protons of **4b** and **8b** exhibited coupling constants in the order of 3.5 cps and, consequently, have been assigned a *cis* relationship. (See Table I.)

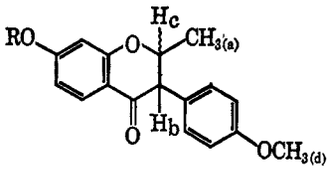
(13) Compare statements within ref 6 and 10.

(14) This facile dehydration appears to be general in nature for 4-alkyl-isoflavanols (partial structure iii) derived from both 2-substituted and 2-unsubstituted isoflavanones (**5** and **6**, respectively). The *ortho*- and *para*-oxygenated functions in the annelated benzonoid ring probably enhance both the rate of formation and the stability of the carbonium ion (partial structure iv) formed by the loss of the tertiary, benzylic hydroxyl group.



(15) This analysis is in good agreement with the interpretation of the simple nmr spectrum of 2,2,4-trimethyl-7-acetoxy-4′-methoxy-Δ^3-isoflavene (*cf.* ref 2). In connection with the chemical shift of the C-2 proton, the very recent work of Anirudhan, Whalley, and (in part) Badran (*cf.* ref 6), in which a pair of comparable Δ^2- and Δ^3-isoflavenes was studied, shows that there exists a significant difference in the chemical-shift parameters for the benzylic methylene ($CH_2C{=}CO$, 221 cps) and O-methylene ($C{=}CCH_2O$, 306 cps) protons. In light of these observations, the nmr data are conclusive evidence for the Δ^3-isoflavene structure for **6a**.

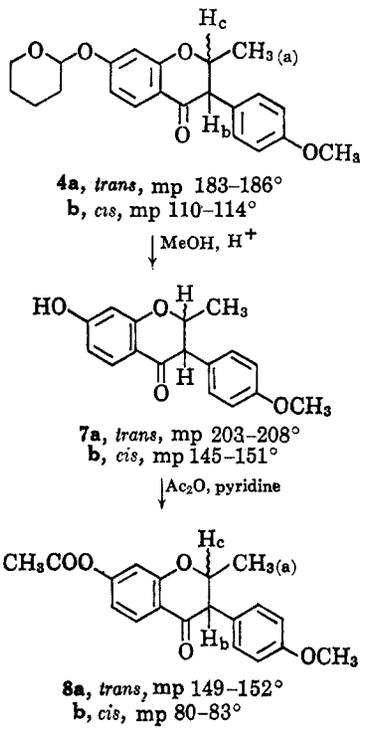
TABLE I
NMR SPECTRAL DATA OF *trans*- AND *cis*-2-METHYL-7-R-4'-METHOXYISOFLAVANONES[a]



Proton	*trans* **4a**	*cis* **4b**	*trans* **8a**	*cis* **8b**
H_a	79 (doublet), J_{HaHc} = 6.5 cps)	77 (doublet), J_{HaHc} = 6.5 cps)	79 (doublet), J_{HaHc} = 6.5 cps)	78 (doublet), J_{HaHc} = 6.5 cps)
H_b	215 (doublet, J_{HbHc} = 11.5 cps)	212.5 (doublet, J_{HbHc} = 3.5 cps)	219 (doublet, J_{HbHc} = 11.5 cps)	217.5 (doublet, J_{HbHc} = 3.5 cps)
H_c[b]	283 (multiplet, $J_{HaHc} + J_{HbHc}$ = 30 cps)	289 (multiplet, $J_{HaHc} + J_{HbHc}$ = 22 cps)	286 (multiplet, $J_{HaHc} + J_{HbHc}$ = 30 cps)	288 (multiplet, $J_{HaHc} + J_{HbHc}$ = 22 cps)
H_d	228 (singlet)	225 (singlet)	228 (singlet)	225 (singlet)

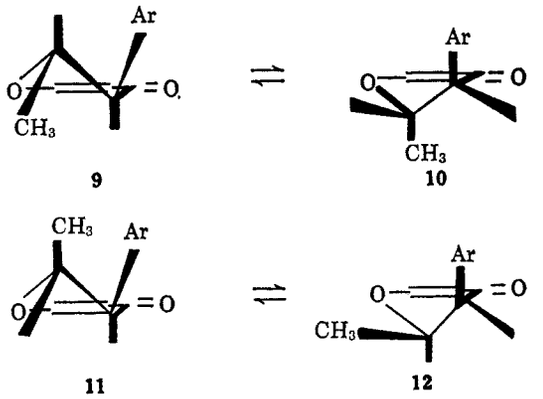
[a] Chemical shifts and coupling constants are expressed in cycles per second (cps). Proton signals attributed to the tetrahydropyranyloxy group in **4a** and **4b** were observed in the region 88–120 (methylene envelop, six protons), 210–240 (CH_2O, two protons), and at 330–331 cps (OCHO, one proton). Signals attributed to the acetate groups, in **8a** and **8b**, were observed at 138 cps (singlets, three protons). The ratio of intensities of the methoxyl peaks (H_d), in samples of **8a** and **8b**, may be used to approximate the degree of contamination by the other isomer. [b] The multiplets observed for H_c correspond to two overlapping quarters; the signal width is denoted by $J_{HaHc} + J_{HbHc}$.

SCHEME II



The two possible conformers for the *trans* compounds are represented by partial structures **9** and **10**. Conformer **9** exhibits a dihedral angle of approximately 170°, and conformer **10** exhibits a dihedral angle of approximately 55°, this latter value being inferred also for each of the two possible *cis* conformers (*e.g.*, **11** and **12**). The larger coupling constant (11.5 cps) is attributed to the 2H(axial) : 3H(axial) *trans* conformer **9** in which the dihedral angle approximates 170°.

It is more difficult to differentiate between conformers **11** and **12** for the *cis* compounds **4b** and **8b**. As a consequence of the annelated aromatic feature in the molecule, there are no apparent nonbonded interactions to suggest even to a degree which of the substituents (2-methyl or 3-*p*-methoxyphenyl) might prefer an axial orientation. The similarity in the chemical-shift values for the C-2 and C-3 protons of each of the *trans*- and *cis*-isoflavanones favors the assignment of conformer **11** to the *cis* compounds.[16] This similarity of values may, however, be a result of an "unusual combination of ring and substituent anisotropies."[17]



Experimental Section[18]

Isoflavones.—7-Hydroxy-4'-methoxyisoflavone was prepared by the ethyl orthoformate method.[7,19] 2-Methyl 7-hydroxy-4'-

(16) This assignment may be considered probable since chemical shifts of axial and equatorial hydrogens, adjacent to carbonyl groups, are influenced to a substantial degree by the anisotropy of the carbonyl function (*cf.* ref 17). The similar chemical-shift values for the C-3 protons could thus be attributed to *trans* and *cis* conformers which have equatorial *p*-methoxyphenyl groups, if the assumption is valid that the chemical shifts of the C-2 protons, adjacent to etheral-like oxygen atoms, are stereochemically independent.

(17) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 63–75.

(18) Melting points were determined on a Kofler hot-stage microscope using a calibrated thermometer. Ultraviolet spectra were measured with a Bausch and Lomb Spectronic 505; alkaline solutions were prepared by diluting 1–5 ml of stock solutions in methanol to 10 ml with 0.1 *N* sodium hydroxide solution. Nmr spectra were recorded in deuteriochloroform on a Varian Model A-60 spectrophotometer using tetramethylsilane as an internal standard. Infrared spectra were measured with a Perkin-Elmer 221 spectrophotomer; samples were prepared in the form of pressed KBr disks. Microanalyses were carried out by Triangle Chemical Laboratories, Carrboro, N. C., and Micro-Tech Laboratories, Skokie, Ill. Thin layer plates were prepared by coating microscope slides with silica gel H. Elution solvents were 20% (v/v) ethyl acetate–benzene (solvent system A) and 10% (v/v) ethyl acetate–benzene (solvent system B). Nonfluorescing compounds were developed by spraying with a 5% solution of phosphomolybdic acid in ethanol (PMA), and allowing the sprayed chromatogram to lay on the face of a hot plate controlled by a Variac (60 v or lower). A regulated source of heat (development time, 15–60 sec) was preferential in that different rates of appearance and characteristic colors were often observed for several of the compounds.

(19) L. Farkas and J. Varaday, *Chem. Ber.*, **92**, 819 (1959).

methoxyisoflavone was prepared in the usual manner[20] from 2-methyl-7-acetoxy-4'-methoxyisoflavone, the following modification being recommended for this latter compound.[21]

2-Methyl-7-acetoxy-4'-methoxyisoflavone.—A solution of α-(4-methoxyphenyl)-2,4-dihydroxyacetophenone (50 g) in a mixture of acetic anhydride (500 ml) and tributylamine (200 ml) was stirred and heated at ~170° (oil bath temperature) for a period of 7 hr, then kept at deep-freeze temperature (0 to −10°) overnight, and the crop of dense, white needles (57.5 g, 92%), mp 195–196° (lit.[5] mp 197°), was collected and vacuum dried. A sample recrystallized from toluene had mp 195–196°.

2-Methyl-7-tetrahydropyranyloxy-4'-methoxyisoflavone (2).—To a suspension of 2-methyl-7-hydroxy-4'-methoxyisoflavone (13.0 g) in a mixture of tetrahydrofuran (150 ml) and dihydropyran (250 ml) was added concentrated sulfuric acid (1 ml, sp g 1.84). The flask was fitted with a drying tube and the contents were stirred at room temperature for a total of 5 hr.

A clear, dark solution formed within 1 hr and crystalline product commenced thereafter to separate. The reaction progress was conveniently monitored by tlc (solvent system A): the isoflavones fluoresce blue light under an ultraviolet light source, and regardless of the quantity of dihydropyran added, the starting isoflavone was always observed in the eluted chromatogram.

The reaction mixture was poured into water (1 l.) containing sodium bicarbonate (50 g), and the product was isolated by extraction with generous portions of methylene chloride. (When a scale-up employing more than 10 g of isoflavone was carried out, the methylene chloride extraction, more than often, caused extensive emulsion formation). The emulsion usually separated upon standing overnight, thenceforth the organic layer was isolated, washed well with saturated sodium bicarbonate, dried over anhydrous potassium carbonate, and evaporated under reduced pressure. The solid residue was recrystallized from ethyl acetate as white needles (8.5 g), mp 180–184°, which proved chromatographically uniform in solvent system A. The infrared spectrum contained a major band at 1635 cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 245 mμ (log ε 4.41), 294 mμ (log ε 4.10).

Anal. Calcd for $C_{22}H_{22}O_5$ (366.4): C, 72.11; H, 6.05. Found: C, 72.14; H, 6.10

7-Tetrahydropyranyloxy-4'-methoxyisoflavone (4).—The preparation was carried out according to the procedure for **3**, using 7-hydroxy-4'-methoxyisoflavone (18.5 g), tetrahydrofuran (300 ml), dihydropyran (300 ml), and concentrated sulfuric acid (1 ml, sp g 1.84). After 4.5 hr, the mixture was poured into water (1.5 l.) containing sodium bicarbonate (50 g). The extensive emulsion was handled as in the former case, and the product was isolated and recrystallized from ethyl acetate as white needles (18.3 g), mp 172–176°. The infrared spectrum contained a major band at 1635 cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 265 mμ (log ε 4.43), λ_{sh}^{MeOH} 300 mμ (log ε 4.05).

Anal. Calcd for $C_{21}H_{20}O_5$ (352.4): C, 71.58; H, 5.72. Found: C, 71.61; H, 5.72.

The Preparation and Fractional Crystallization of *cis*- and *trans*-2-methyl-7-tetrahydropyranyloxy-4'-methoxyisoflavanone (4a and 4b). A. The Borohydride Reduction of 2.—A suspension of **2** (10.0 g) and sodium borohydride (2.1 g) in isopropyl alcohol (700 ml) was stirred, and the temperature of an external oil bath was maintained at 75–80° during the course of the reaction. Complete reduction required a reaction period of 70–118 hr.

The reaction progress was monitored by tlc in solvent system B. The isoflavone fluoresces blue light; the products were developed by PMA, and consisted of four zones which the reagent colored dark green (one component) and red (one more polar and two less polar components).

The crude isoflavanol was isolated by evaporating the isopropyl alcohol under reduced pressure, dissolving the residual pale yellow syrup in benzene, and washing the organic solution well with bicarbonate solution and water to ensure the complete removal of excess borohydride. After standing over anhydrous sodium sulfate, the benzene solution was filtered and evaporated under reduced pressure to yield a colorless syrup (9.0–10.3 g). A chromatogram (solvent system A, PMA) contained four zones as described above.

B. The Jones Oxidation of Crude Isoflavanol.—To a stirred solution of crude isoflavanol (~10 g) in purified acetone (1 l.) at 0–5° was added 8 *N* Jones reagent[17] (6.75 ml, 54.0 mequiv) from a buret over a period of 5 min. A thin layer chromatogram (solvent system A, PMA) indicated that the oxidation was complete within 10 min. The chromatogram contained one zone, which was colored blue by development with PMA.

The cold oxidation reaction was dumped into water (2.5 l.), and extracted with generous portions of methylene chloride. The combined methylene chloride extract was washed successively with bicarbonate solution and water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to yield an orange-red oil (6–8 g).

The oily ketone in a minimum volume of benzene was filtered through a short column of Woelm neutral alumina (activity III, packing 4 × 18 cm) using benzene as the eluent. The desired compound filtered through almost immediately (tlc), and the randomly collected fractions were combined after establishing the integrity of each by tlc [two faint zones (blue), in addition to the principal zone (blue) were developed by PMA]. Evaporation of the combined eluate under reduced pressure gave a partially crystalline, colorless residue (5–8 g).

C. The Fractional Crystallization of *trans*- and *cis*-Isoflavanones (4a and 4b).—The whole of the partially crystalline ketone from step B was dissolved in a minimum volume of boiling ethyl acetate, to which (while still hot) was added 30–60° petroleum ether (175–300 ml) with swirling. The crystallization of the *trans* compound **4a** commenced within 1 hr and, after the flask was kept overnight at room temperature, a crop of white needles (1.1–1.4 g), mp ~168–174°, was collected by filtration and washed with petroleum ether (mother liquor and washings were saved). A thin layer chromatogram, eluted with solvent system B and developed with PMA, showed one zone (blue). The infrared spectrum contained a major band at 1675 cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 272 mμ (log ε 4.22), 314 mμ (log ε 3.83).

Anal. Calcd for $C_{22}H_{24}O_5$ (368.4): C, 71.72; H, 6.57. Found: C, 71.75; H, 6.60.

The ethyl acetate–petroleum ether mother liquor afforded *cis* compound **4b** after removing the solvent under reduced pressure and covering the residual syrup with methanol (2–3 ml). The crystallization process was allowed to proceed first at room temperature and then in the cold. The supernatant liquor was decanted and the crystalline mass was washed with a little cold methanol by decantation. The product (1.3–1.6 g), mp ~99–110°, appeared under the microscope as prisms contaminated with needles (of the *trans* compound **4a**). A thin layer chromatogram (solvent system B, PMA) showed one zone (blue). When this product was applied at the same point as **4a** there was no apparent separation. The infrared spectrum contained a major band at 1682 cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 276 mμ (log ε 4.23), 315 mμ (log ε 3.85). The analytical sample, mp 110–104°, was prepared by recrystallization from methanol. [From 4.31 g of crude *cis* compound **4b** in methanol was obtained, as first crop, white needles (0.37 g, mp 147–177°, essentially *trans* compound **4a**. The filtrate was evaporated under reduced pressure, and the residue was recrystallized repeatedly from small volumes of warm methanol, each of which was insufficient to dissolve all of the sample, and from each of which a sacrificed, insoluble portion was removed by suction filtration.]

Anal. Calcd for $C_{22}H_{24}O_5$ (368.4): C, 71.72; H, 6.57. Found: C, 71.70; H, 6.48.

7-Tetrahydropyranyloxy-4'-methoxyisoflavanone (5).—A suspension of **3** (10.0 g) in absolute ethanol (500 ml) was warmed to 70° to partially dissolve the isoflavone. Sodium borohydride (2.5 g) was added and the suspension was stirred at room temperature.

When isoflavone still persisted in the reaction mixture after 24 hr (tlc, blue fluorescence), the temperature of the mixture was brought to 60–70°, and once again stirred at room temperature whereupon a clear, colorless solution formed shortly thereafter (which still contained isoflavone). After an additional 12-hr period (36-hr total), tlc indicated complete reduction. By evaporation of solvent, dissolution of the syrupy residue in methylene chloride, good washing of the organic solution with bicarbonate solution and water, drying of the organic layer over anhydrous sodium sulfate, and evaporation of solvent, the product was isolated as a colorless syrup (~10 g). Oxidation of this residue (~10 g) with 8 *N* Jones reagent (7.75 ml, 62.0

(20) W. Baker, R. Robinson, and N. M. Simpson, *J. Chem. Soc.*, 274 (1933).

(21) We are indebted to Dr. C. E. Cook, of this laboratory, who suggested and provided the initial data on this reaction modification.

mequiv), followed by usual work-up, gave a brown syrup which crystallized (without clean-up chromatography) when covered with methanol. Decantation of the supernatant liquid, and recrystallization of the solid mass from the minimum amount of methanol gave white needles (3.5 g), mp 109–121°. The product was chromatographically uniform (solvent system B, PMA), and was recrystallized from methanol for analysis. The infrared spectrum contained a major band at 1680 cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 273 mμ (log ε 4.16), 315 mμ (log ε 3.78).

Anal. Calcd for $C_{21}H_{22}O_5$ (354.4): C, 71.17; H, 6.26. Found: C, 70.87; H, 6.35.

7-Hydroxy-4′-methoxyisoflavanone.—A suspension of **5** (200 mg) in absolute methanol (20 ml) containing hydrochloric acid solution (5 drops, sp g 1.18) was warmed gently until all dissolved. The clear, colorless solution was stirred at room temperature for 3 hr (tlc solvent system B, PMA), water (60 ml) was added, and the turbid solution was allowed to stand at room temperature to yield slender needles (135 mg), mp 195–198.5°. The infrared spectrum contained major bands at 3300 and 1675 cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 278 mμ (log ε 4.19), 314 mμ (log ε 3.93), and $\lambda_{max}^{0.1\ N\ NaOH}$ 340 mμ (log ε 4.18).

Anal. Calcd for $C_{16}H_{14}O_4$ (270.3): C, 71.10; H, 5.22. Found: C, 71.08; H, 5.45.

***trans*-2-Methyl-7-hydroxy-4′-methoxyisoflavanone (7a).**—A solution of **4a** (500 mg, mp 167–176°) in absolute methanol (35 ml) containing hydrochloric acid solution (6 drops, sp g 1.18) was effected by gentle warming, and stirred at room temperature for 18 hr (tlc solvent system B, PMA). Water (150 ml) was added in portions, the mixture was stirred for 1 hr and chilled, and the product (350 mg) was collected. The product was recrystallized by adding water to its hot, methanolic solution, yielding 275 mg, mp 203–208°. The infrared spectrum contained major bands at 3350 and 1665 cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 276 mμ (log ε 4.22), 309 mμ (log ε 3.88), and $\lambda_{max}^{0.1\ N\ NaOH}$ 339 mμ (log ε 4.43), 255 mμ (log ε 3.86).

Anal. Calcd for $C_{17}H_{16}O_4$ (284.3): C, 71.82; H, 5.67. Found: C, 72.06; H, 5.61.

***cis*-2-Methyl-7-hydroxy-4′-methoxyisoflavanone (7b).**—From *cis* compound **4b** (200 mg, mp 99–110°) in absolute methanol (15 ml) and hydrochloric acid (6 drops, sp g 1.18), and using water (60 ml) to precipitate product, there were obtained white prisms (120 mg), mp 144–149°. The product was recrystallized by dissolution in methanol at room temperature and adding water until a permanent turbidity formed, giving white plates, mp 147–152°. The infrared spectrum contained major bands at 3350 and 1660 cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 279 mμ (log ε 4.16), 315 mμ (log ε 3.87), and $\lambda_{max}^{0.1\ N\ NaOH}$ 339 mμ (log ε 4.46), 255 mμ (log ε 3.93).

Anal. Calcd for $C_{17}H_{16}O_4$ (284.3): C, 71.82; H, 5.67. Found: C, 71.80; H, 5.50.

***trans*-2-Methyl-7-acetoxy-4′-methoxyisoflavanone (8a).**—A suspension of **7a** (275 mg, mp 203–208°) in acetic anhydride (1.0 ml) containing pyridine (3 drops) was stirred at room temperature for 18 hr. The dissolution of starting material was followed by separation of crystalline product, which was isolated by evaporation of solvent under reduced pressure and recrystallization of the white residue from methanol, yielding 220 mg, mp 149–152°. The infrared spectrum contained major bands at 1760 and 1690 cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 257 mμ (log ε 4.11), 317 mμ (log ε 3.68), and $\lambda_{max}^{0.1\ N\ NaOH}$ 339 mμ (log ε 4.45), 257 mμ (log ε 3.89).

Anal. Calcd for $C_{10}H_{18}O_5$ (326.3): C, 69.92; H, 5.56. Found: C, 69.77; H, 5.40.

***cis*-2-Methyl-7-acetoxy-4′-methoxyisoflavanone (8b).**—A solution of *cis* compound **7b** (320 mg, mp 143–152°) in acetic anhydride (2 ml) containing pyridine (5 drops) was stirred at room temperature for 1 hr (tlc solvent system B, PMA), evaporated under reduced pressure (vacuum pump, warm water bath), whereupon the product was isolated as a colorless oil. The oil crystallized as white prisms from its concentrated solution in methanol at deep-freeze temperature (−10 to −20°), yielding 50 mg, mp 71–81°, which contains approximately 16% of *trans* **8a**, as estimated from the nmr spectrum (ratio of intensities of CH_3O protons). An analytical sample, mp 80–83°, was prepared by recrystallizing product, mp 79–83°, obtained from another run. The infrared spectrum contained major bands at 1758 and 1683 cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 266 mμ (log ε 4.10), 319 mμ (log ε 3.64), and $\lambda_{max}^{0.1\ N\ NaOH}$ 340 mμ (log ε 4.47), 254 mμ (log ε 3.92).

Anal. Calcd for $C_{10}H_{18}O_5$ (326.3): C, 69.92; H, 5.56. Found: C, 69.77; H, 5.51.

2-Methyl-4-ethyl-7-acetoxy-4′-methoxy-Δ³-osoflavene (6b).—A solution of *trans* compound **4a** (1.0 g, mp 178–184°) in dry benzene (60 ml) was added dropwise over a 5-min period to a stirred mixture of 3 *M* ethylmagnesium bromide in ether (4 ml) and dry benzene (20 ml).

The Grignard addition reaction required approximately 15 min for completion, and was conveniently monitored by removing an aliquot, shaking with saturated ammonium chloride solution, and spotting the benzene layer on a thin layer chromatogram (solvent system B, PMA). The Grignard addition products were colored dull green by PMA, and the isoflavanone was colored blue.

Saturated ammonium chloride solution (100 ml) was added to the reaction mixture, the two-phased solution was transferred to a separatory funnel and shaken, and the aqueous layer was removed. The organic solution was washed successively with saturated ammonium chloride solution (three 100-ml portions) and water (100 ml), dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to yield a syrup which had a weak light absorption band at ~308 mμ. The syrup was dissolved in methanol (80 ml) containing hydrochloric acid solution (5 drops, sp g 1.18), and stirred at room temperature for 15 min. A thin layer chromatogram (solvent system B, PMA) indicated a single reaction product, the ultraviolet spectrum of which contained λ_{max}^{MeOH} 314 and 285 mμ. After the solvent was removed under reduced pressure, the dark, oily residue was taken up in a minimum amount of benzene and filtered through a short column of Woelm neutral alumina (activity III, packing 2.3 × 4 cm). The desired compound (λ_{max} 314 and 285 mμ), was rapidly eluted by benzene, the integrity of the randomly collected fractions being conveniently established by tlc and ultraviolet light absorption properties. The product was obtained as a colorless oil by evaporation of the combined benzene fractions. When dissolved in acetic anhydride (4 ml) containing pyridine (10 drops), a copious crop of white crystals separated from the solution within 30 min. The crystalline acetate **6b** was isolated by evaporation of solvent under reduced pressure, and recrystallization of the residual solid from ethanol as needles (510 mg), mp 140–142°. The infrared spectrum contained a major band at 1758 cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 314 mμ (log ε 4.05), 279 mμ (log ε 4.03), and $\lambda_{max}^{0.1\ N\ NaOH}$ 323 mμ (log ε 4.27.

Anal. Calcd for $C_{21}H_{22}O_4$ (354.4): C, 74.53; H, 6.55. Found: 74.48; H, 6.63.

When *cis* compound **4b** (1.0 g, mp 110–114°) was carried through the above procedure, employing same quantities of solvents and reagents, the Δ³-isoflavene **6b** (755 mg), mp 138–141°, was obtained and proved to be identical with product from *trans* compound **5a** by mixture melting point (137–141°) and comparison of infrared, ultraviolet, and nmr spectral data. The Grignard addition product of **4b** has nearly the same R_f value (tlc solvent system B, PMA), but is easily distinguished from **4b** by the colors produced with PMA. The Grignard addition reaction appeared complete (tlc) after 5 min.

When a mixture of *trans* and *cis* compounds, **4a** and **4b** (1.0 g, mp 90–155°), was employed under similar, but not identical conditions (with respect to reaction time and volumes of solvents), and methanol used as recrystallizing solvent, the Δ³-isoflavene **6b** was obtained as white needles (390 mg), mp 139.5–142.5°. A thin layer chromatogram of a solution of the isolated, syrupy Grignard addition products in methanol contained multiple zones (solvent system B, PMA), all of which were colored dull green. On addition of a catalytic amount of hydrochloric acid to the methanolic solution, a single reaction product, λ_{max}^{MeOH} 314 and 285 mμ, was formed (tlc).

2,4-Dimethyl-7-acetoxy-4′-methoxy-Δ³-isoflavene (6a).—Compound **6a** was prepared from *trans* compound **4a** (1.5 g, mp 157–163°), employing prorated quantities of reagents and solvents utilized in the procedure for **6b**. The crude product (1.2 g, air dried) was recrystallized from ethanol as white prisms, and isolated in three crops having mp 100–102° (390 mg), 98–102° (280 mg), and 96–101° (192 mg). The analytical sample had mp 101–103°. The infrared spectrum contained a major band at 1757 cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 316 mμ (log ε 4.14), 280 mμ (log 4.07), and $\lambda_{max}^{0.1\ N\ NaOH}$ 324 mμ (log ε 4.32).

Anal. Calcd for $C_{20}H_{20}O_4$ (324.4): C, 74.05; H, 6.22. Found: C, 74.21; H, 6.11.

A sample of **6a** crystallized from its concentrated solution in methanol as elongated, white needles, mp 91–93°. The nmr spectrum of a solution of this crystalline modification was identical with that of a solution prepared from prisms, mp 101–103°.

4-Ethyl-7-acetoxy-4′-methoxy-Δ³-isoflavene (6c).—Compound **6c** was prepared from isoflavanone **5** (1.0 g, mp 109–121°) empolying the quantities of solvents and reagents utilized in the procedure for **6b**. The crude, residual, white solid (obtained by evaporation of the acetic anhydride–pyridine) crystallized nicely from methanol as clusters of white needles (310 mg), mp 124–128°. The infrared spectrum contained a major band at 1765 cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 315 mμ (log ε 4.10) and 284 mμ (log ε 4.07), and $\lambda_{max}^{0.1\ N\ NaOH}$ 325 mμ (log ε 4.31).

Anal. Calcd for $C_{20}H_{20}O_4$ (324.4): C, 74.05; H, 6.22. Found: C, 73.99; H, 6.39.

Flavonoids. IV. A Novel Clemmensen Reduction. The Direct Conversion of 2-Alkylisoflavones to 2-Alkyl-Δ³-isoflavenes[1,2]

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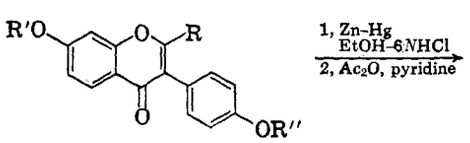
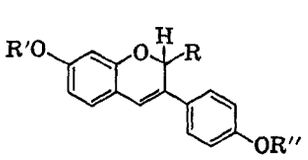
During a study of methods applicable to the exhaustive reduction of 2-alkylisoflavone systems, the Clemmensen reduction was tested and found to result in a direct conversion of 2-alkylisoflavones to 2-alkyl-Δ³-isoflavenes. Reduction of a 2-unsubstituted isoflavone gave an isoflavene characterized as a mixture of Δ² and Δ³ isomers. The light absorption properties of Δ³-isoflavenes are discussed.

The Clemmensen reductions here described utilized 2-alkylisoflavones having at least one acetoxy group, and ethanol–6 *N* hydrochloric acid (1:1) as medium for the reduction. In contrast with most Clemmensen reactions, which proceed slowly,[3] the isoflavones were rapidly converted to Δ³-isoflavenes characterized by light absorption bands at ~300–335 mμ. This absorption band proved most useful for determining the optimum time requirement for the reduction. Maximum product accumulation was observed to occur during a 20-min reaction period, and when the reaction was extended beyond this duration, product was consumed by overreduction or by generalized degradation under the severe reaction conditions. The hot reaction solutions were quenched by decanting into water and the Δ³-isoflavenes were isolated as the crystalline acetate derivatives **2a–c** in 15–35% over-all yields.

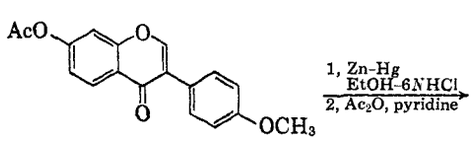


1a, R = R″ = CH_3; R′ = CH_3CO
b, R = CH_3; R′ = R″ = CH_3CO
c, R = C_2H_5; R′ = R″ = CH_3CO



2a, R = R″ = CH_3; R′ = CH_3CO
b, R = CH_3; R′ = R″ = CH_3CO
c, R = C_2H_5; R′ = R″ = CH_3CO

Unlike these examples, Clemmensen reduction of the 2-unsubstituted isoflavone (**3**) gave the mixture of isoflavenes **4**. The nonhomogeneity of the product was indicated by its infrared and nuclear magnetic resonance (nmr) spectra, which exhibited absorptions attributable to Δ² unsaturation.[4] From the nmr spectrum it was seen that the reaction product contained 20–30% of the Δ² isomer **4b**.



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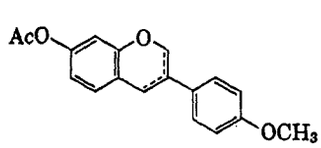


4a, Δ³ isomer
b, Δ² isomer

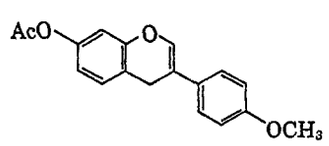
In order to further substantiate this point, an unambiguous synthesis of the Δ³-isoflavene **4a** was carried out. This synthesis utilized 7-tetrahydropyranyloxy-4′-methoxyisoflavone (**5**),[2] and entailed an exhaustive borohydride reduction,[2] a mild acid-catalyzed dehydra-

(1) This research was carried out under contract SA-43-ph-4351 of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health.

(2) Part III: K. H. Dudley, R. C. Corley, H. W. Miller, and M. E. Wall, *J. Org. Chem.*, **32**, 2312 (1967).

(3) (a) E. L. Martin, *Org. Reactions*, **1**, 155 (1942); (b) C. A. Anirudhan, W. B. Whalley, and (in part) M. M. E. Badran, *J. Chem. Soc.*, 629 (1966). The authors used the Clemmensen reduction for the conversion of isoflavanones to isoflavans.

(4) Absorption bands in the spectra of **4** have been assigned to the following structural features of 7-acetoxy-4′-methoxy-Δ²-isoflavene (**4b**). The



4b

1660-cm^{-1} band is attributed to the vinyl ether group [OCH=C(Ar)CH_2]. The nmr spectrum contained signals at 306 (1.45 proton, J = 1.5 cps) and 221 cps (0.54 protons, J = 1.0 cps). In the light of the very recent work of Anirudhan, *et al.* (*cf.* ref 3b), the signal at 221 cps is unequivocal evidence for the benzylic methylene group [OCH=C(Ar)CH_2] of the Δ²-isoflavene component.