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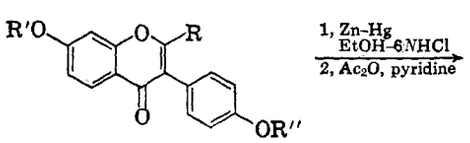
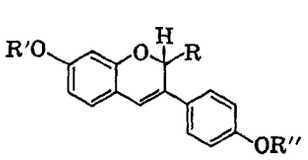
During a study of methods applicable to the exhaustive reduction of 2-alkylisoflavone systems, the Clemmensen reduction was tested and found to result in a direct conversion of 2-alkylisoflavones to 2-alkyl-Δ³-isoflavenes. Reduction of a 2-unsubstituted isoflavone gave an isoflavene characterized as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

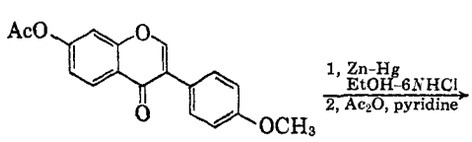


1a, R = R″ = CH_3; R′ = CH_3CO
b, R = CH_3; R′ = R″ = CH_3CO
c, R = C_2H_5; R′ = R″ = CH_3CO



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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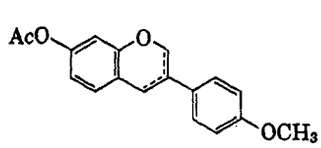


4a, Δ³ isomer
b, Δ² isomer

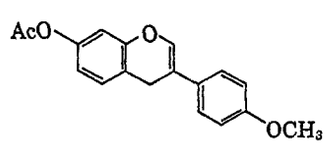
In order to further substantiate this point, an unambiguous synthesis of the Δ³-isoflavene **4a** was carried out. This synthesis utilized 7-tetrahydropyranyloxy-4′-methoxyisoflavone (**5**),[2] and entailed an exhaustive borohydride reduction,[2] a mild acid-catalyzed dehydra-

(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.

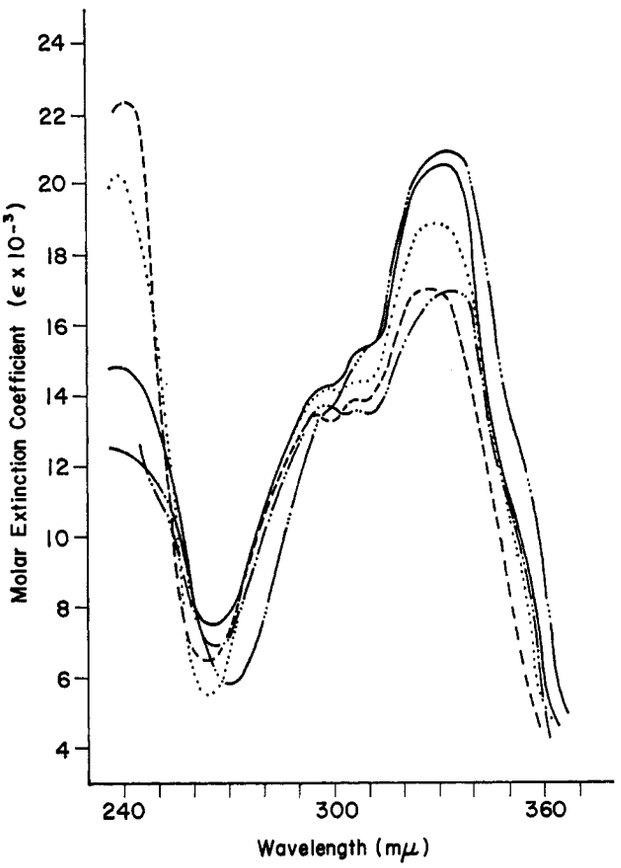
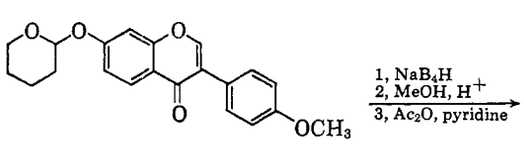


Figure 1.—The ultraviolet spectra measured from methanolic solutions of —···—, 7-acetoxy-4′-methoxy-Δ^3-isoflavone (**4a**); ———, 2-methyl-7-acetoxy-4′-methoxy-Δ^3-isoflavene (**2a**); ····, 2-methyl-7,4-diacetoxy-Δ^3-isoflavene (**2b**); – – – –, 2-ethyl-7,4′-diacetoxy-Δ^3-isoflavene (**2c**); —··—, 7-acetoxy-4′-methoxy-$\Delta^{3,2}$-isoflavene (**4**).

tion,[5] and, finally, an acetylation step.[6] The infrared spectrum of authentic **4a** was nearly identical with that of the mixture **4**, but lacked two peaks at 1660 and 1170 cm^{-1}.



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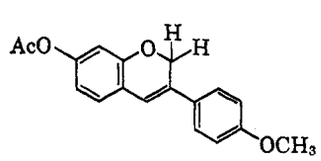


4a

Some Light-Absorption Properties of Δ^3-Isoflavenes. —As can be seen in Figure 1, the ultraviolet spectrum of the Clemmensen product **4** is strikingly similar to those recorded for the other Clemmensen products **2a–c**. A clue for Δ^2 unsaturation lay in comparing the spectra of the Clemmensen products by graphical means (ϵ *vs.* wavelength), or by examining the spectra of the free phenols, which were generated by a simple operation carried out in the cuvette. This latter procedure consisted of acidifying with concentrated sulfuric acid a standard base solution of compound.

(5) The facile dehydration of 4-alkylisoflavanols (derived from Grignard addition to an isoflavanone) has been described in the preceding publication. In a similar manner, the step here utilizing a catalytic amount of hydrochloric acid in methanol serves two purposes, cleavage of the tetrahydropyranylether group and dehydration of the secondary, benzylic hydroxyl group.

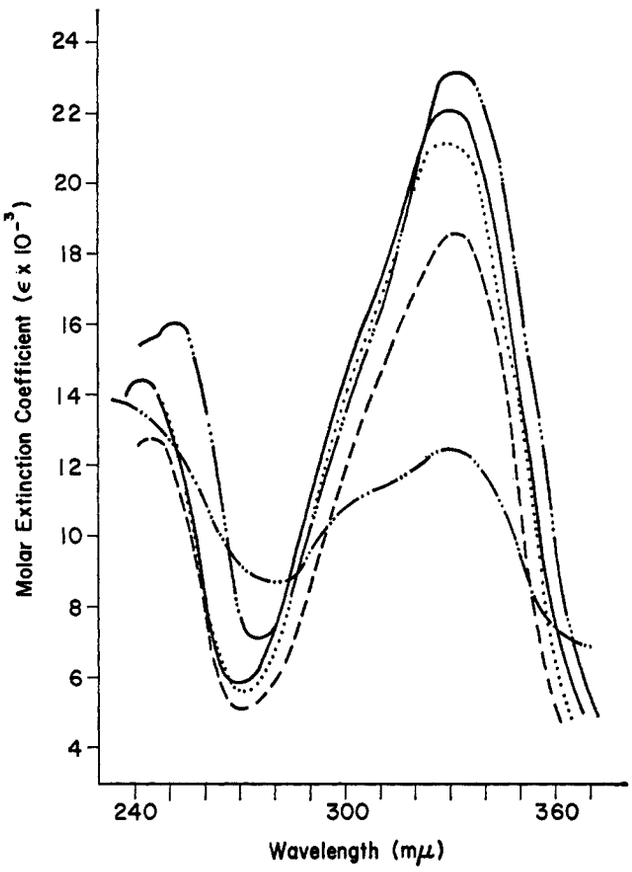
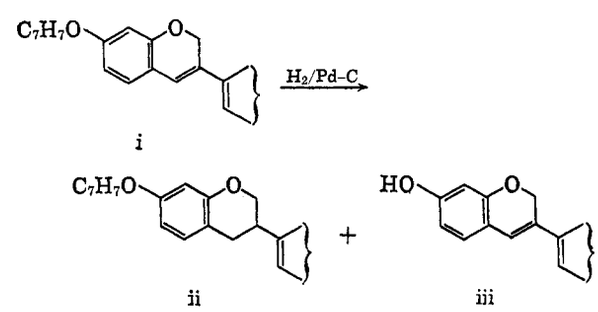


Figure 2.—The ultraviolet spectra of the phenolic forms produced, as described in the text, from the isoflavenes mentioned in Figure 1. The legend in Figure 1, when applied here, pertains to each corresponding phenolic form.

The results of applying this operation to solutions of the Clemmensen products are depicted in Figure 2. The spectra of the Clemmensen products **2a–c**, as the free phenols, were significantly altered in that the long-wavelength band in the 335-mμ region was devoid of blue-side band structure. In these cases, the curves were identical with absorption spectra reported for some of the corresponding 7-O-alkyl derivatives.[7] On the other hand, after removal of acetyl groups, a comparison of the spectrum of the Clemmensen product **4** with

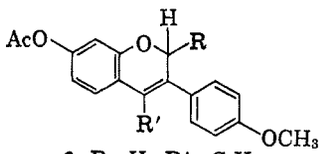
(6) In conjunction with this approach, the deblocking of 7-benzyloxy-4′-methoxy-Δ^3-isoflavene (i) by hydrogenolysis was investigated. The products, isolated by fractional recrystallization, were the corresponding and deblocked isoflavans (ii and iii, respectively).



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

that of the authentic Δ^3-isoflavene **4a** indicated that the Δ^2 component of **4** had suffered decomposition during the hydrolytic cleavage.

We have examined the spectra of several other Δ^3-isoflavenes, in order to determine the effect of 7-O-acetyl groups on the spectral patterns. The effect observed in the case of a 4-alkyl-Δ^3-isoflavene was even more pronounced than those observed with the 2-alkyl series **2a–c**. As illustrated in Figure 3, the spectrum of 4-ethyl-7-acetoxy-4′-methoxy-Δ^3-isoflavene (**6**) contained double maxima at 316 and 285 mμ. The spectrum of the corresponding phenol (produced by the hydrolytic procedure) resembled that measured for 4-ethyl-7,4′-dimethoxy-Δ^3-isoflavene, λ_{max}^{EtOH} 315 mμ with a broad shoulder at 290 mμ. In contrast to these spectral changes, cleavage of the 7-O-acetyl group from 2,4-dialkyl-7-acetoxy-4′-methoxy-Δ^3-isoflavenes (**7a** and **b**) resulted in essentially no change in the absorption curves, other than the usual slight increase (10%) in the molar extinction coefficient (Figure 3).



6, R = H; R′ = C_2H_5
7a, R = R′ = CH_3
b, R = CH_3; R′ = C_2H_5

Experimental Section[8]

2-Ethyl-7-propionoxy-4′-methoxyisoflavone.[9]—A solution of α-(4-methoxyphenyl)-2,4-dihydroxyacetophenone (20 g) in a mixture of propionic anhydride (200 ml) and tributylamine (100 ml) was stirred and heated at 180° (oil bath temperature) for 6.5 hr, then kept at deep freeze temperature (0 to −10°) for several days (unless seeded), and the crop of white prisms (22.7 g, 83%, mp 119–121°) was collected, washed with methanol, and vacuum dried (lit.[7] mp 122°). A sample recrystallized from methanol gave mp 121–123°.

2-Methyl-7-acetoxy-4′-methoxy-Δ^3-isoflavene (2a).—A suspension of 2-methyl-7-acetoxy-4′-methoxyisoflavone (2.0 g) and zinc amalgam[10] (15 g) in absolute ethanol (80 ml) was stirred magnetically (Teflon egg-shaped stirring bar, 1.6 in. long, 0.75 in. in diameter) under a reflux condenser, and the solution was brought to boiling with the aid of an external oil bath maintained at 110°. To the refluxing solution was added 6 *N* hydrochloric acid solution (80 ml) in one portion, and exactly 20 min thereafter, the reaction was quenched by decanting into 500 ml of ice-cold water. A little ethanol was used to rinse the unused amalgamated zinc.

The yellow, turbid solution was extracted with several portions of methylene chloride. The combined methylene chloride extract (~300 ml) was then washed four times with water (to which, when necessary, was added saturated sodium chloride solution to break the emulsion). The organic layer was dried over anhydrous sodium sulfate and then evaporated under reduced pressure to yield an orange foam. This residue was dissolved in a minimum volume of benzene and filtered through a column of Woelm neutral alumina (activity III, column packing 2 × 10 cm) using benzene as eluent. The first fraction contained a small amount of orange matter but was heavily concentrated with the desired Δ^3-isoflavene. The integrity of each fraction was ascertained by tlc (10% ethyl acetate–benzene) and/or measurement of the ultraviolet spectrum and, after combining, the benzene was removed under reduced pressure. The foamy residue was transferred to a smaller flask with the aid of ether, reevaporated, and dissolved in acetic anhydride (5 ml), and 5 drops of pyridine was added. Upon addition of pyridine, the orange solution became very pale yellow. After the solution had been stirred for 1 hr at room temperature, tlc (10% ethyl acetate–benzene) indicated that acetylation was complete. Excess acetic anhydride was decomposed with methanol, and the product precipitated by adding cold water. The collected white solid was recrystallized from the minimum volume of methanol to yield **2a** as heavy prisms (0.61 g), mp 89–90°. The infrared spectrum contained major bands at 1765 (s), 1610 (s), 1590 (w), and 1518 (s). The ultraviolet spectrum contained λ_{max}^{MeOH} 333 mμ (log ε 4.31) and inflections at 310 (4.18) and 300 (4.15); $\lambda_{max}^{0.0\ N\ NaOH}$ 350 mμ (log ε 4.42). A second crop (0.11 g, mp 86–90°) was isolated by concentrating the mother liquor.

Anal. Calcd for $C_{19}H_{18}O_4$ (310.3): C, 73.53; H, 5.85. Found: C, 73.28; H, 6.10.

In a separate experiment under identical conditions, the progress of the reaction was monitored at 5-min intervals by recording the ultraviolet spectrum in the region 290–360 mμ. For the measurements, 0.1-ml aliquots were withdrawn from the reaction and diluted with methanol to 100 ml. Assuming an extinction value of 22,000, it was estimated that the reaction mixture contained ~1.3 g of isoflavene after a 20-min duration.

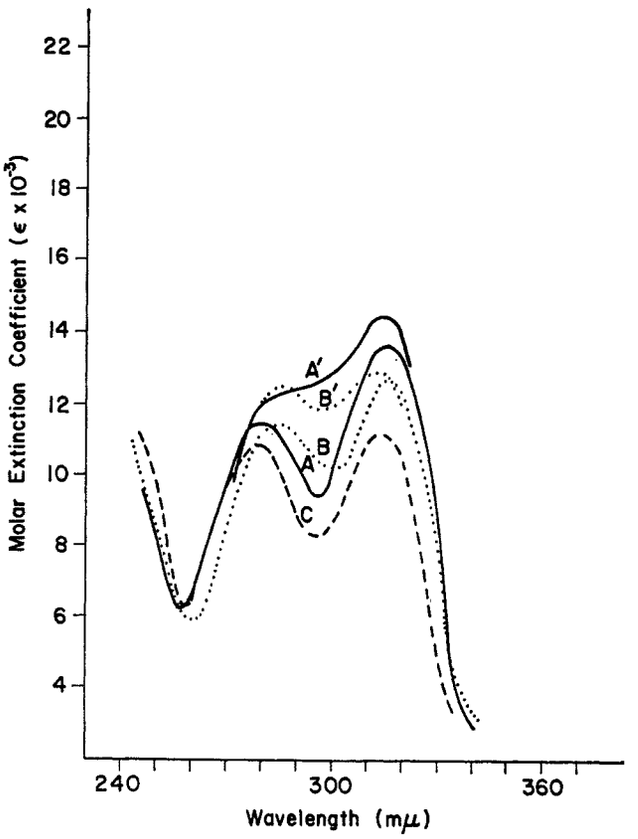


Figure 3. — The ultraviolet spectra measured from A, a methanolic solution of 4-ethyl-7-acetoxy-4′-methoxy-Δ^3-isoflavene (**6**); A′, an aqueous solution of the phenolic form produced from compound **6**; B, a methanolic solution of 2,4-dimethyl-7-acetoxy-4′-methoxy-Δ^3-isoflavene (**7a**); B′, an aqueous solution of the phenolic form produced from **7a**; C, a methanolic solution of 2-methyl-4-ethyl-7-acetoxy-4′-methoxy-Δ^3-isoflavene (**7b**).

(8) 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. For producing the phenols of the Δ^3-isoflavenes described in the text, 2–3 drops of concentrated sulfuric acid was added directly to the *cuvette* containing a basic solution of the phenolate ion. Nmr spectra were recorded in deuteriochloroform on a Varian Model A-60, using tetramethylsilane as an internal standard. Infrared spectra were measured with a Perkin-Elmer 221 spectrophotometer; 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. 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).

(9) This isoflavone is required for the preparation of **1c**. This reaction modification has been employed previously for the preparation of 2-methyl-7-acetoxy-4′-methoxyisoflavone (**1a**) in 90% yield (*cf.* ref 2).

(10) The zinc amalgam was prepared using zinc powder as described in "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 786.

TABLE I

Time, min	Absorbance, at 333 mμ
10	0.488
15	0.650
20	0.743
25	0.652
30	0.640
35	0.530

Table I contains the absorbance values read at 333 mμ as a function of time.

2-Methyl-7,4'-diacetoxy-Δ³-isoflavene (2b).—The Clemmensen reduction was carried out on 2-methyl-7,4'-diacetoxyisoflavone (2.0 g) as described in the procedure for **2a**. On decantation of the hot solution into water, a resinous material separated which, for the most part, was insoluble in methylene chloride. The combined methylene chloride extract was handled in the usual manner, but a clean-up chromatography step was not necessary for obtaining the final product **2b** in crystalline form. The Δ³-isoflavene derivative **2b** was obtained as needle (0.28 g), mp 111–114°, by recrystallization from methanol (lit.[11] 112–115°). The infrared spectrum contained major bands at 1770 and 1760 (strong doublet), 1635 (w), 1615 (m), and 1589 (m), cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 330 mμ (log ε 4.28), 297 (4.13), and an inflection at 310 (4.14); $\lambda_{max}^{0.1\ N\ NaOH}$ 358 mμ (log ε 4.48).

Anal. Calcd for $C_{20}H_{18}O_5$ (338.3): C, 70.99; H, 5.36. Found: C, 71.24; H, 5.65.

2-Ethyl-7,4'-diacetoxy-Δ³-isoflavene (2c).—The Clemmensen reduction of 2-ethyl-7,4'-diacetoxyisoflavone was carried out under several sets of conditions. Employing 1.0 g of isoflavone, prorated quantities of reagents, and the procedure for **2a** (20-min reaction duration, and clean-up chromatography omitted), the Δ³-isoflavene **2c** was isolated as needles (0.19 g), mp 155–157.5°, after recrystallization from methanol. When the ratio of amalgam was doubled (14.0 g of amalgam to 1.0 g of isoflavone), the yield of **2c** was 0.17 g. When 8 *N* hydrochloric acid (40 ml) was used, the yield of **2c** was 0.13 g.

When the Clemmensen reduction was carried out on a 2.0-g sample of isoflavone, the yield of pure Δ³-isoflavene was 0.28 g, mp 154–156°. In another experiment a 4.0-g sample of isoflavone and prorated quantities were employed, and in this case a mechanical stirrer was utilized for good dispersion of the amalgam. The yield of **2c** was 0.98 g, mp 153–156°. The infrared spectrum contained major bands at 1770 (s), 1638 (w), 1615 (w), and 1592 (m) cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 327 mμ (log ε 4.23), 295 (4.13), and an inflection at 307 (4.14); $\lambda_{max}^{0.1\ N\ NaOH}$ 354 mμ (log ε 4.45).

Anal. Calcd for $C_{21}H_{20}O_5$ (352.4): C, 71.58; H, 5.72. Found: C, 71.68; H, 6.01.

7-Acetoxy-4'-methoxy-Δ³,²-isoflavene (4).—Upon decantation into water of the Clemmensen reduction solution of 7-acetoxy-4'-methoxyisoflavone (2.0 g), a white solid immediately separated. The solid was isolated with methylene chloride and handled, without clean-up chromatography, in the usual manner. The crude yellow acetyl derivative **4** crystallized from ethyl acetate as colorless, thin platelets (0.47–0.67 g). The melting points of several samples ranged from 145–150 to 148–153°. The melting range (5°) was not improved by repeated recrystallization from ethyl acetate. When a thin layer chromatogram was eluted with benzene, two zones of similar R_f value were developed by PMA.

When the reduction was carried out on 4.0-g samples of isoflavone (prorated quantities of reagents), the yields varied from 0.6 to 0.9 g, and the melting points ranged from 145–150 to 146–151°. The infrared spectrum conained major bands at 1755 (s), 1660 (w), 1610 (m), and 1585 (w), cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 335 mμ (log ε 4.23), 297 (4.14), and an inflection at 310 (4.13); $\lambda_{max}^{0.1\ N\ NaOH}$ 353 mμ (log ε 4.32).

Anal. Calcd for $C_{18}H_{16}O_4$ (296.3): C, 72.96; H, 5.44. Found: C, 73.21; H, 5.51.

Nmr Spectra of the Clemmensen Products.—The nmr spectra of the Clemmensen reduction products contained signals for the C-2 protons in the region 306–328 cps; thus, the C-2 protons of **4** (306 cps, doublet, J = 1.5 cps), the C-2 proton of **2a** (326 cps, quartet, J = 6.5 cps), the C-2 proton of **2b** (328 cps, quartet, J = 6.5 cps), the C-2 proton of **2c** (316 cps, four lines of equal intensity, X portion of an ABX system, signal width = 12 cps).

7-Acetoxy-4'-methoxy-Δ³-isoflavene (4a).—7-Tetrahydropyranyloxy-4'-methoxyisoflavone (2.0 g) was reduced with sodium borohydride (0.5 g) in absolute ethanol (100 ml), and the syrupy isoflavanol was isolated as previously described.[2,12] The colorless syrup was dissolved in absolute methanol (80 ml) containing concentrated hydrochloric acid (3 ml). A thin layer chromatogram of the stirred solution after 15 min, developed with PMA, contained five zones; after 1.5 hr, four zones; after 18 hr, one principal zone. After 18 hr, the red solution was evaporated under reduced pressure without the aid of heat. The residue was obtained as a yellow-brown solid, insoluble in benzene, but almost completely soluble in methylene chloride. The solid was extracted with several small portions of methylene chloride, and the combined extract concentrated and applied to a short column of Woelm neutral alumina (activity III, column packing 2 × 8.5 cm). Methylene chloride was used as the eluent, and, after ~100 ml of eluate had been collected, tlc indicated that the desired Δ³-isoflavene was being eluted from the column. The fractions were randomly collected (15–30 ml), and the integrity of each established by tlc (10% ethyl acetate–benzene, PMA). Evaporation of the combined fractions provided an off-white solid: λ_{max}^{MeOH} ~334 mμ, $\lambda_{max}^{0.1\ N\ NaOH}$ ~350 mμ.

A portion (0.10 g) was recrystallized by adding water to its warm, filtered ethanolic solution. 7-Hydroxy-4'-methoxy-Δ³-isoflavene was obtained as small white plates (0.07 g), mp 158–162°. The infrared spectrum contained major bands at 3425 (s), 1618 (s), 1591 (m), and 1518 (s) cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 333 mμ (log ε 4.35), 254 mμ (log ε 4.12); $\lambda_{max}^{0.1\ N\ NaOH}$ 350 mμ (log ε 4.44), 254 mμ (log ε 4.12).

Anal. Calcd for $C_{16}H_{14}O_3$ (254.3): C, 75.57; H, 5.55. Found: C, 75.46; H, 5.52.

The remainder of the crude Δ³-isoflavene (0.25 g) was dissolved in acetic anhydride (6 ml) containing 4 drops of pyridine. This solution was stirred overnight at room temperature, excess acetic anhydride was decomposed with methanol, and the crude acetyl derivative **4a** was precipitated with water. Recrystallization of the solid from ethyl acetate provided colorless plates (0.15 g), mp 154–156.5°. The infrared spectrum contained major bands at 1754 (s), 1608 (s), 1585 (w), and 1518 (m) cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 335 mμ (log ε 4.32) and inflections at 310 (4.19) and 300 (4.14), $\lambda_{max}^{0.1\ N\ NaOH}$ 334 mμ (log ε 4.44), 256 mμ (log ε 4.12).

Anal. Calcd for $C_{18}H_{16}O_4$ (296.3): C, 72.96; H, 5.44. Found: C, 73.14; H, 5.43.

7-Benzyloxy-4'-methoxy-Δ³-isoflavene. A. 7-Benzyloxy-4'-methoxyisoflavone.—A suspension of 7-hydroxy-4'-methoxyisoflavone (8.0 g), potassium iodide (8.0 g), and anhydrous potassium carbonate (225 g) in acetone (2 l.) containing benzyl chloride (8.0 g) was stirred under reflux for 9 hr, the acetone was distilled to dryness, and the solid residue was suspended in water (500 ml) and filtered. The solid was washed well with water, then with methanol, and recrystallized from ethyl acetate to give needles (8.2 g), mp 178–180°, lit. mp 180–182°.[13]

B. 7-Benzyloxy-4'-methoxyisoflavanol.—A mixture of 7-benzyloxy-4'-methoxyisoflavone (5.0 g) and sodium borohydride (0.75 g) in ethanol (300 ml) was stirred at 60–65° for 1.25 hr, heating discontinued, but stirring continued until all starting material was consumed (tlc, 10% ethyl acetate–benzene). The ethanol was removed under reduced pressure, and the solid was collected from its suspension in water and washed with water and a little methanol. The product crystallized from its concentrated solution in methanol as a mixture of rods and plates (3.2 g), mp 130–139°. Tlc (10 or 20% ethyl acetate–benzene) showed the product to be a mixture of two components of similar R_f values. Attempts to improve the melting point by repeated recrystallization were unsuccessful. The infrared spectrum contained major bands at 3420 (s), 1618 (s), and 1583 (s) cm^{-1}.

Anal. Calcd for $C_{23}H_{22}O_4$ (362.4): C, 76.22; H, 6.12. Found: C, 76.09; H, 6.06.

(11) R. A. Micheli, A. N. Booth, A. L. Livingston, and E. M. Bickoff, *J. Med. Chem.*, **5**, 321 (1962).

(12) The ultraviolet spectrum of the syrupy isoflavanol in methanol contain λ_{max} ~278 mμ. When 2 drops of concentrated hydrochloric acid was added to the cuvette, and the ultraviolet spectrum was recorded several times over a 15-min period, an absorption band at 335 mμ appeared and increased in intensity with time, but the rate of increase in the absorbance value was definitely not so fast as that observed with the 4-alkylisoflavanols (derived from Grignard addition to isoflavanones; *cf.* ref 2).

(13) S. C. Bhrara, A. C. Jain, and T. R. Seshadri, *Tetrahedron*, **20**, 1141 (1964).

The faster moving component was isolated by thick layer chromatography (silica gel H or alumina plates, 10% ethyl acetate–benzene) and had mp 140–142°. Attempts to isolate the slower moving component were unsuccessful, the band containing significant amounts of the faster moving substance.

When the isoflavanol (1.0 g), mp 130–139°, was oxidized by the Jones procedure, 7-benzyloxy-4′-methoxyisoflavanone (0.57 g), mp 130.5–132.5°, was obtained as needles after recrystallization from methanol. The infrared spectrum contained major bands at 1689 (s), 1620 (s), 1587 (s), and 1521 (s), cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 315 mμ (log ε 3.95) and 274 mμ (log ε 4.27).

Anal. Calcd for $C_{23}H_{20}O_4$ (360.4): C, 76.65; H, 5.59. Found: C, 76.61; H, 5.55.

C. 7-Benzyloxy-4′-methoxy-Δ³-isoflavene.—A solution of the isoflavanol (4.0 g), mp 131–139°, in chloroform (200 ml) was stirred at 0–5° and a stream of dry hydrogen chloride passed through with the aid of a gas dispersion tube. The reaction was allowed to proceed for 4 hr, after which tlc (10% ethyl acetate–benzene) indicated complete dehydration. The deep orange organic solution was washed repeatedly with water until the aqueous layer afforded a pH reading of 5 and the organic layer was nearly colorless. After drying over a mixture of anhydrous sodium sulfate and sodium carbonate, the solvent was removed under reduced pressure to give a white, crystalline residue that, when dissolved in a minimum amount of boiling benzene and precipitated with methanol, provided a chromatographically uniform, white, microcrystalline solid (3.8 g), mp 142–150°. When recrystallized from benzene, the product was isolated as colorless plates (2.0 g), mp 154–155°. The infrared spectrum contained major bands at 1605 (s), 1570 (m), and 1500 (s) cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 335 mμ (log ε 4.43) and 251 mμ (log ε 4.22).

Anal. Calcd for $C_{23}H_{20}O_3$ (344.4): C, 80.21; H, 5.85. Found: C, 80.48; H, 6.02.

Hydrogenation of 7-Benzyloxy 4′-methoxy-Δ³-isoflavene.—A suspension of the Δ³-isoflavene (0.3 g, 0.874 mmole) in glacial acetic acid (20 ml) was hydrogenated at atmospheric pressure over 10% palladium–charcoal (50 mg). Complete dissolution of starting material was observed after approximately 43 ml of hydrogen had been consumed (theoretical value for 1 mole = 20.8 ml). The solution was filtered free of the catalyst by gravity and the filtrate was diluted with water to precipitate a crystalline solid. This solid consisted of two components (tlc, benzene–PMA), which were facilely separated by fractional crystallization. When dissolved in methanol (10 ml), 7-benzyloxy-4′-methoxyisoflavan (53 mg), mp 126–127.5°, crystallized as chromatographically pure platelets. The infrared spectrum contained bands at 1620 (s), 1585 (m), and 1510 (s) cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 284 mμ (log ε 3.76) and inflections at 289 (3.63) and 280 (3.73). Another crop (10 mg) was obtained by careful concentration of the mother liquor.

Anal. Calcd for $C_{23}H_{22}O_3$ (346.4): C, 79.74; H, 6.40. Found: C, 79.51; H, 6.74.

The mother liquor from the above recrystallization was allowed to evaporate to dryness at room temperature, and the white, crystalline residue was recrystallized from benzene–petroleum (bp 30–60°) ether to give 7-hydroxy-4′-methoxyisoflavan (66 mg), mp 157–158.5°, with slight softening at 153°. This crop was chromatographically uniform in two solvent systems, benzene and 10% ethyl acetate–benzene. The infrared spectrum contained major bands at 3424 (s), 1605 (s), 1590 (s), and 1500 (s) cm^{-1}. The ultraviolet spectrum contained λ_{max}^{MeOH} 284 mμ (log ε 3.73) and inflections at 289 (3.67) and 279 (3.69); $\lambda_{max}^{0.1\ N\ NaOH}$ 296 mμ (log ε 3.72) and inflections at 286 (3.70) and 278 (3.60). A second crop (17 mg) was isolated as a result of further dilution with petroleum ether. Tlc showed this fraction to be contaminated to a very slight extent by the benzyloxy derivative.

Anal. Calcd for $C_{16}H_{16}O_3$ (256.3): C, 74.98; H, 6.29. Found: C, 75.14; H, 6.31.

Registry No.—**2a**, 10499-07-7; **2b**, 10499-08-8; **2c**, 10499-09-9; **4a**, 10499-10-2; **4b**, 10499-11-3; **6**, 10499-12-4; **7a**, 10499-13-5; **7b**, 10499-14-6; 7-hydroxy-4′-methoxy-Δ³-isoflavene, 10535-63-4; 7-benzyloxy-4′-methoxyisoflavanol, 10535-64-5; 7-benzyloxy-4′-methoxyisoflavone, 10499-15-7; 7-benzyloxy-4′-methoxy-Δ³-isoflavene, 10499-16-8; 7-benzyloxy-4′-methoxyisoflavan, 10535-65-6; 7-hydroxy-4′-methoxyisoflavan, 10499-17-9.

The Synthesis of 17-Bromo-16α-methylprogesterones

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In situ bromination of 16α-methylpregnane-20-magnesium enolates gives a mixture of the 17α-bromo- and 17β-bromo-20-keto derivatives. Utilizing this reaction, 17α-bromo-16α-methylprogesterone and 17β-bromo-16α-methyl-17-isoprogesterone were prepared from 16-dehydropregnenolone acetate.

In recent years there has been considerable interest in the synthesis of 17α-bromoprogesterone[1] and some of its 6-substituted derivatives[2–5] in view of the enhanced progestational activity exhibited by this class of compounds. An earlier communication from these laboratories[6] described the preparation of a number of 16-alkylated progesterones. We now report the synthesis of 17α-bromo-16α-methylprogesterone (VI) and 17β-bromo-16α-methyl-17-isoprogesterone (VII).

The reaction of 16-dehydropregnenolone acetate (I) with methylmagnesium bromide in the presence of cuprous chloride, followed by *in situ* bromination of the resulting Grignard complex, afforded, after treatment with sodium iodide to debrominate any 5,6-dibromide, a mixture of 17α-bromo-16α-methylpregnenolone acetate (II)[7] and 17β-bromo-16α-methyl-17-isopregnenolone acetate (III). The 17α-bromo compound II, the major component of the mixture (90–95%), was obtained pure after column chromatography on silica gel. Fermentation of II with a culture of *Flavobacterium dehydrogenans*[6,8,9] gave 17α-bromo-16α-methylprogesterone (VI).

Direct dehydrohalogenation of the bromination mixture (II and III) with lithium bromide and lithium

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