mμ (ε 16,800). It was identified by analysis, ultraviolet spectrum, and comparison with a sample prepared in a different manner.[17]

Anal. Calcd. for $C_{24}H_{24}O_6$: C, 70.52; H, 5.96. Found: C, 70.57; H, 5.92.

2,2-Dimethyl-4-ethyl-4'7-diacetoxy-Δ³-isoflavene (11i).—Twenty grams (71 mmoles) of 4-ethyl-3-(4-hydroxyphenyl)-7-hydroxycoumarin (**6k**), 100 ml. of pyridine, and 30 ml. of hexamethyldisilazane were heated for 1 hr. under nitrogen in an oil bath at 80°. Evaporation (rotary evaporator connected to vacuum pump) and drying *in vacuo* until the pyridine odor was gone gave the bis(trimethylsilyl) ether of **6k** as an off-white solid, $\nu_{max}^{CCl_4}$ 1720 cm.$^{-1}$. This was dissolved in ether and treated with 3 *M* methylmagnesium bromide in ether at such a rate as to maintain a gentle reflux. The solution was then refluxed for 0.5 hr. and poured into a mixture of 90 g. of ammonium chloride, 100 g. of ice, and 150 ml. of water. Ether extraction was followed by washing the ether solution (total volume 700 ml.) with 30 ml. and two 15-ml. portions of concentrated hydrochloric acid, sodium bicarbonate, and ammonium chloride solutions. The dried (Drierite) solution was evaporated and the residue was refluxed for 2 hr. with 125 ml. of acetic anhydride. The cooled solution was treated with 125 ml. of methanol and allowed to stand overnight. Filtration then separated 16 g. ol white crystals. After two recrystallizations from 2-propanof (35 ml./g.) and two from acetone (10 ml./g.), white crystals weighing 10.85 g. were obtained, m.p. 174–176°. From the mother liquors two more crops were obtained: 2.69 g., m.p. 174–176°; and 1.30 g., m.p. 173–175°. The total yield was 14.84 g. (54%). For characterization see Table IV.

Flavonoids. II. Rearrangement of 2,2-Dimethyl-Δ³-isoflavenes to Indenes[1,2]

C. E. COOK, ROBERT C. CORLEY, AND MONROE E. WALL

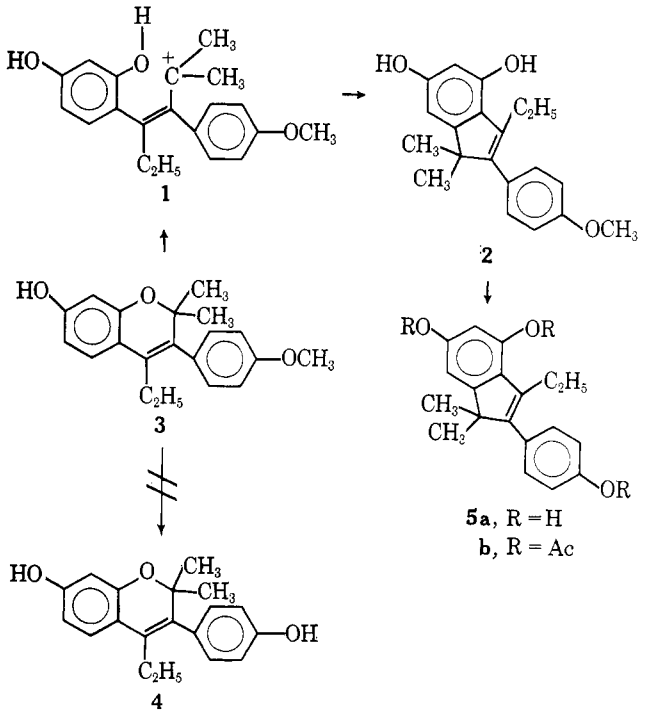
Natural Products Laboratory, Research Triangle Institute, Durham, North Carolina 27702

Received June 16, 1965

Attempts to demethylate methoxy derivatives of 2,2-dimethyl-Δ³-isoflavenes under acidic conditions (pyridine hydrochloride, aluminum chloride) led to facile rearrangement to the corresponding 7-hydroxyindenes.

In connection with the synthesis of Δ³-isoflavenes,[2] we wished to prepare 4',7-dihydroxy- (or diacetoxy-) 4-ethyl-2,2-dimethyl-Δ³-isoflavene (**4**). An obvious route was by demethylation of the readily obtainable 4'-methoxy-7-hydroxy-4-ethyl-2,2-dimethyl-Δ³-isoflavene (**3**) (see Chart I).[2] Attempts to carry out this reaction under acidic conditions led to an interesting rearrangement which forms the subject of this paper.

CHART I



An attempt by Lawson to demethylate a 2-monoalkyl-Δ³-isoflavene was reported to result in disruption of the molecule, but no details were given.[3] It is apparent that any method which involves attack of a Lewis acid on an ether oxygen should result first in the cleavage of the heterocyclic ring, since the carbonium ion **1** resulting from such cleavage would be highly stabilized by resonance with the aromatic ring. We therefore sought media in which the ring-opened product might be demethylated without further degradation, so that acid-catalyzed ring closure would yield the desired dihydroxy-Δ³-isoflavene.

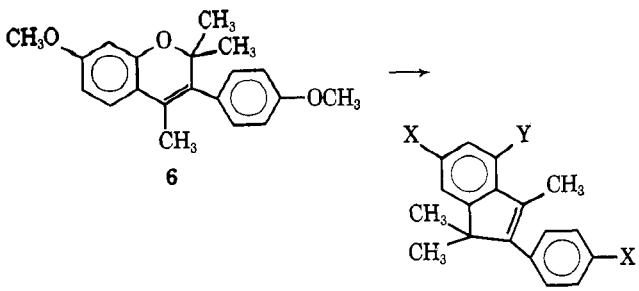
When isoflavene **3** was fused with pyridine hydrochloride, thin layer chromatography indicated the formation of a more polar compound (probably **2**, compare **6** → **7b**, Chart II) as an intermediate which was gradually converted to the yet more polar final product **5a**. After acetylation, the product was shown by elemental analyses to have the formula $C_{25}H_{26}O_6$. Acetyl analysis showed three hydrolyzable acetyl groups. The n.m.r. spectrum (60 Mc., internal tetramethylsilane standard) suggested the presence of six aromatic protons (area from 405 to 430 c.p.s.), two equivalent methyl groups (singlet at 73 c.p.s.), an ethyl group (triplet centered at 63 c.p.s., J = 7.5 c.p.s.—the methylene quartet was buried under the acetyl resonance), and three acetyl methyl groups (two peaks at 136 and 137 c.p.s.). The presence of three hydrolyzable acetyl groups requires that none of the oxygen functions be involved in a ring, the number of aromatic protons requires a total of six substituents, and the analytical results require the presence of 13 sites of unsaturation. These requirements are met by 1-ethyl-2-(4-acetoxyphenyl)-3,3-dimethyl-5,7-diacetoxyindene (**5b**), obtained by intramolecular rearrangement. The C-4 and C-6 protons appear as a pair of doublets centered at 407 and 416 c.p.s. (J = 2 c.p.s., indicative of *meta* coupling), while the protons of the acetoxyphenyl group appear as a single peak at 424 c.p.s.

(1) (a) Abstracted in part from work done by R. C. Corley in partial fulfillment of the requirements for the Ph.D. degree at North Carolina State University at Raleigh. (b) This work was carried out under Contract SA-43-ph-4351 of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health.

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

(3) W. Lawson, *J. Chem. Soc.*, 4448 (1954).

CHART II



6

7a, X = OCH_3; Y = OAc
b, X = OCH_3; Y = OH
c, X = Y = OAc

The ultraviolet spectrum of the indene **5b** was of some interest. Although this compound possesses the same chromophoric group as the Δ^3-isoflavenes and might thus be expected to have an absorption maximum above 300 mμ,[2] it in fact showed only a maximum at 269 mμ (ε 17,400). Apparently the steric crowding is so great on the five-membered ring that the aryl group must be twisted to the point where essentially no conjugation is possible between the aryl group and the indene ring.[4] [For comparison, 1-ethyl-2-(4-acetoxyphenyl)-7-acetoxyindene has a maximum at 295 mμ, with an ε of 24,000.[5]]

Results analogous to the above were also obtained in attempted aluminum chloride demethylations of dimethoxyisoflavene **6** (Chart II). When the reaction was carried out at room temperature in chlorobenzene and the initial product was acetylated, white plates, m.p. 133–134.5°, were isolated. The compound **7a**, $C_{22}H_{24}O_4$, had one acetyl group. N.m.r. clearly showed the two methoxyls (226 c.p.s.), the acetyl methyl (135 c.p.s.), the *gem*-dimethyl group (72 c.p.s.), and the indenyl methyl (114 c.p.s.), as well as the aromatic protons. Again the ultraviolet spectrum indicated clearly the lack of coplanarity of the aryl group with the indene ring [λ_{max} 278 mμ (ε 20,400)].

In order to establish with certainty that ring closure occurred prior to acetylation, the initial product from the aluminum chloride demethylation of **6** was isolated and shown to have the indene structure **7b** by analysis, ultraviolet, n.m.r., and infrared spectra. By heating the aluminum chloride reaction mixture it was possible to cleave the methoxy groups. After acetylation, the resulting product (**7c**) was found to be identical with a by-product from reaction of methyl Grignard reagent with a tetrahydropyranyl derivative of 3-(*p*-hydroxyphenyl)-4-methyl-7-hydroxycoumarin.[2] Acetyl analysis showed three hydrolyzable CH_3CO groups, and other physical data were in accord with an indene structure.

It is apparent that the initially formed carbonium ion is undergoing an intramolecular Friedel–Crafts reaction. While the only intramolecular position available for attack might be expected to be little, if any, more active than unsubstituted benzene,[6] the stereochemical relationships are exceedingly favorable, and the reaction proceeds rapidly. Thin layer chromatography indicated that the aluminum chloride catalyzed rearrangement was complete in 1 min. or less at room temperature.[7]

Experimental Section[8]

1-Ethyl-2-(4-acetoxyphenyl)-3,3-dimethyl-5,7-diacetoxyindene (5b).—In an atmosphere of carbon dioxide five small vials were each loaded with *ca.* 10 mg. of 2,2-dimethyl-4-ethyl-4′-methoxy-7-hydroxy-Δ^3-isoflavene (**3**)[2] and 100 mg. of pyridine hydrochloride. The vials were sealed with foil-lined screw caps and heated at 200–205° for 30 sec., 5, 10, 15, and 30 min., respectively. The contents were dissolved in methanol and examined by thin layer chromatography (3% isopropyl alcohol in benzene, silica gel G). Only starting material was present in vial 1. Vial 2 contained two products, one of which (the less polar) decreased in concentration to almost complete disappearance in vial 5, and one of which (the more polar) increased in concentration to become almost the sole substance in vial 5. Therefore, a mixture of 1.50 g. of **3** (4.84 mmoles) and 9.0 g. of pyridine hydrochloride was heated under carbon dioxide in a heavy-walled, capped vial in an oil bath at 200–210° for 40 min. The cooled melt was stirred with 40 ml. of water and extracted with 150- and 75-ml. portions of ether. Combined ether layers were extracted with two 5-ml. portions of concentrated hydrochloric acid (thin layer chromatography indicated this caused no change) and three 20-ml. portions of 30% ammonium sulfate. Drying and evaporation left 1.57 g. of a gum, which was refluxed for 2 hr. with acetic anhydride (10 ml.). Most of the acetic anhydride was removed under reduced pressure. The residue was stirred with methanol (20 ml.) for 2 hr., taken up in cyclohexane (150 ml.), and washed with water, sodium bicarbonate solution, and 30% ammonium sulfate. Evaporation of the dried (magnesium sulfate) solution left a gum. When a 325-mg. sample of this was purified by preparative thin layer chromatography (5% ethyl acetate in chloroform on silica gel H) and crystallization from methanol, 181 mg. of the white analytical sample, m.p. 103–105°, λ_{max} 269 mμ (ε 17,400), was obtained. The remainder of the crude product was crystallized from methanol to yield an additional 660 mg., m.p. 100–103°, for a total yield of 0.841 g. (41%).

Anal. Calcd. for $C_{25}H_{26}O_6$: C, 71.07; H, 6.20; acetyl, 30.80. Found: C, 70.80; H, 6.18; acetyl, 30.7.

1,3,3-Trimethyl-2-(4-methoxyphenyl)-7-acetoxy-5-methoxyindene (7a).—To a solution of 2,4,4-trimethyl-4′,7-dimethoxy-Δ^3-isoflavene (**6**, 0.5 g., 1.6 mmoles) in 10 ml. of chlorobenzene was added aluminum chloride (0.42 g., 3.2 mmoles). An intense red color formed immediately. The solution was stirred for 15 min. at room temperature and then poured into 40 ml. of 10% hydrochloric acid solution. The separated organic layer was dried over sodium sulfate and evaporated at reduced pressure to yield a white solid. This was dissolved in acetic anhydride and refluxed for 3 hr. The solution was cooled and an equal volume of methanol was added. Removal of solvents *in vacuo* and recrystallization from methanol gave 340 mg. (60%) of white plates, m.p. 133–134.5°, λ_{max} 278 mμ (ε 20,400).

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 74.97; H, 6.86; acetyl, 12.20. Found: C, 74.83; H, 6.89; acetyl, 11.00.

1,3,3-Trimethyl-2-(4-methoxyphenyl)-5-methoxy-7-hydroxyindene (7b).—Under the same conditions as above except that the reaction mixture was stirred for 3 hr., a white solid was obtained. This was not acetylated but was recrystallized from methanol, giving white needles: 310 mg. (77%); m.p. 202–205°; ν_{max} 3590, 1250 cm.$^{-1}$; λ_{max} 276 (ε 17,800).

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.53; H, 7.43.

(4) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, p. 389 ff.

(5) M. Silverman and M. T. Bogert, *J. Org. Chem.*, **11**, 34 (1946).

(6) For discussions of the influence of oxygen functions on the *meta* position see, *inter alia*, L. M. Stock and H. C. Brown, *J. Am. Chem. Soc.*, **82**, 1942 (1960); D. P. N. Satchell, *J. Chem. Soc.*, 463 (1959).

(7) N. O. Calloway [*J. Am. Chem. Soc.*, **59**, 1474 (1937)] reported reaction times of less than 1 min. at 30° for the reaction of butyl halides with benzene in carbon disulfide in the presence of aluminum chloride.

(8) Melting points were taken in capillary tubes (oil bath) and are uncorrected. Ultraviolet spectra were run in methanol on a Bausch and Lomb Spectronic 505. N.m.r. spectra were recorded in deuteriochloroform on a Varian Model A-60, using tetramethylsilane as an internal standard, by Miss D. Linker of the University of North Carolina at Chapel Hill, Charles Driscoll of Duke University, and Sam Justice of this laboratory. Microanalyses are by Micro Tech Laboratories, Skokie, Ill.

1,3,3-Trimethyl-2-(4-acetoxyphenyl)-5,7-diacetoxyindene (7c).—To a solution of 6 (1.0 g., 3.2 mmoles) in 15 ml. of chlorobenzene was added aluminum chloride (1.52 g., 11.5 mmoles). The solution immediately turned red. Upon heating, it slowly turned green, but after 20 min. at reflux it turned red again. Refluxing was continued for a total of 3 hr. and then the solution was worked up in the same way as for **7a**. White platelets, 180 mg. (15%), m.p. 177–178°, were obtained.

The infrared spectrum was identical with that of a by-product obtained in the reaction of a tetrahydropyranyl derivative of 3-(*p*-hydroxyphenyl)-4-methyl-7-hydroxycoumarin with methyl Grignard reagent.[2] A mixture melting point gave no depression. An O-acetyl analysis was carried out on this compound. (For C and H analyses, see preceding paper.[2])

Anal. Calcd. for $C_{24}H_{24}O_8$: acetyl, 31.78. Found: acetyl, 32.12.

Anomalous Reactions of 3-Substituted 4-(2-Hydroxyethylamino)coumarins with Strong Bases[1]

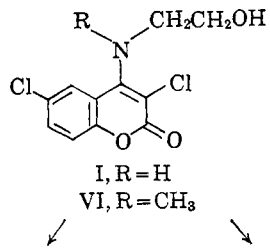
MELVIN S. NEWMAN AND CECILE K. DALTON

Evans Chemistry Laboratory, The Ohio State University, Columbus, Ohio 43210

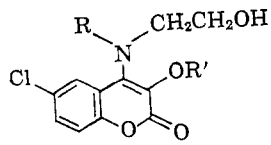
Received July 26, 1965

Treatment of 3,6-dichloro-4-(2-hydroxyethylamino)coumarin (I) in methanol, ethanol, and 2-propanol containing the corresponding alkoxide affords 3,6-dichloro-3-alkoxy-4-(2-hydroxyethylamino)coumarins when less than 1 equiv. of alkoxide ion is used. These alkoxycoumarins (III–V) are converted quantitatively into 9-chloro-2,3-dihydro[1]benzopyrano[3,4-*b*][1,4]oxazin-5(1H)-one (II) when treated with catalytic amounts of alkoxide ion in alcohol. Similar treatment of other related coumarins is also described. Possible paths for these reactions are discussed.

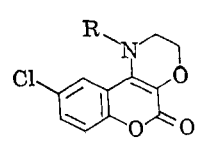
3,6-Dichloro-4-(2-hydroxyethylamino)coumarin (I) has been converted into 9-chloro-2,3-dihydro[1]benzopyrano[3,4-*b*][1,4]oxazin-5(1H)-one (II) on treatment with sodium hydride in tetrahydrofuran and into 6-chloro-4-(2-hydroxyethylamino)-3-isopropoxycoumarin (III) on treatment with sodium isopropoxide in isopropyl alcohol.[2] The formation of III was unexpected as apparently an intermolecular reaction was competing favorably with an intramolecular reaction of the same type since proton transfer between I and isopropoxide ion was assumed to be rapid. Moreover, the reaction ostensibly involved displacement of a vinylic chloride, yet proceeded under relatively mild conditions. Accordingly, further studies in this area were undertaken in order to better elucidate the conditions required for the formation of II and III and related compounds.



I, R = H
VI, R = CH_3



III, R = H; R′ = $CH(CH_3)_2$
IV, R = H; R′ = C_2H_5
V, R = H; R′ = CH_3
VII, R = CH_3; R′ = $CH(CH_3)_2$



II, R = H
VIII, R = CH_3

The original observation that I is converted mainly to III on treatment with sodium isopropoxide in isopropyl alcohol has been confirmed *if less than 1 equiv. of alkoxide* is added slowly to a hot solution of I in isopropyl alcohol. If more than 1 equiv. of isopropoxide is used, the product is entirely II. When III is treated with 0.1 equiv. of sodium isopropoxide, II is formed rapidly and in quantitative yield. Thus, the original[2] preparation of III was, in a sense, fortuitous as, if an excess of alkoxide had been used, the product would have been II.

Similarly, IV and V are obtained by treating I with slightly less than 1 equiv. of sodium ethoxide in ethanol or sodium methoxide in methanol, respectively. Both IV and V are converted to II upon treatment with sodium hydride in 1,2-dimethoxyethane. In one experiment in which I was treated with sodium *t*-butoxide in *t*-butyl alcohol, a 45% yield of II was obtained but no *t*-butyl ether corresponding to III. In this experiment, 28% of the starting material was recovered. In similar experiments with other alkoxides no starting material was present in sufficient quantity to be isolated at the conclusion of the reaction. Thus, II is being formed at a rate slower than III, IV, or V. The significance of this will become evident.

If a solution of III in isopropyl alcohol is treated with 0.1 equiv. of sodium isopropoxide, an almost quantitative yield of II is rapidly obtained. A similar result is obtained upon treatment of IV with a catalytic quantity of sodium ethoxide.

The facile formation of alkoxy compounds III, IV, and V might be rationalized by two reaction paths: (a) direct nucleophilic attack of the alkoxide at C-3 followed by elimination of chloride ion; or (b) a sequence of steps outlined at the top of col. 1, p. 4123.

Path a involves the direct displacement of the vinylic chlorine at the 3-position by external alkoxide ion and seems unlikely because of the ease with which reaction occurs.

In path b ion Ia, generated initially by proton exchange with alkoxide ion, undergoes an internal Michael addition to give an enolate, Ib, which accepts a proton from the solvent to yield Ic. The alkoxide ion remaining after donation of a proton to Ib is well located to displace the chlorine at C-3 to form IIIc which then undergoes a reverse Michael reaction to give III. The involvement of a spiran-type oxazolidine intermediate, such as Ic or IIIc, is supported by the fact that treat-

(1) This work was supported by U. S. Public Health Service Grant GM-7450 and in part by a special research grant from The Ohio State University.

(2) M. S. Newman and C. Y. Peery, *J. Org. Chem.*, **28**, 116 (1963).