We have also prepared some 3-enol ethers of 17α,21-acetals,[8] either by enoletherification of the preformed 17α,21-acetal or by acetalization of a 3-enol ether.

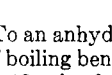
The usefulness of all these compounds as intermediates for several reactions is quite evident; a further advantage is the possibility of obtaining, in 11β,17α,21-trihydroxy steroids, an adequate protection either of the three hydroxy groups or of those of the side chain only, by employing the benzaldehyde and the cyclopentanone acetals, respectively.

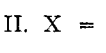
Moreover, some of these acetals are of peculiar biological interest. For instance, prednisolone acetonide (administered orally in oily solution) and prednisolone cyclopentylidenedioxy derivative (applied locally) exhibit an enhanced anti-inflammatory activity in comparison with that of the parent alcohol.[9]

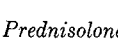
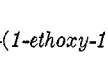
EXPERIMENTAL[10]

The following examples are given to illustrate the methods used to prepare the compounds listed in Table I.

17α,21-Cyclopentylidenedioxy-Δ^4-pregnene-3,11,20-trione. A suspension of 2 g. of cortisone in 800 ml. of benzene containing 5 mg. of *p*-toluenesulfonic acid was rendered anhydrous by brief distillation, at which point 5 ml. of cyclopentanone diethyl acetal was added, the distillation being vigorously continued for 20 min. Neutralization with pyridine, solvent evaporation, and addition of methanol, gave 2.2 g. of the cyclopentylidenedioxy compound, m.p. 232–235°. One crystallization from methanol raised the melting point to 239–240°. Rotation and analytical data are recorded in Table I. Hydrolysis of this acetal (250 mg.) by heating in methanol with a few drops of *N* hydrochloric acid for 15 min. yielded 205 mg. of cortisone, m.p. 217–220°.

17α,21-Cyclopentylidenedioxy-$\Delta^{1,4}$-pregnadiene-11β-ol-3,20-dione (I. X =  , Δ^1). To an anhydrous suspension of 5 g. of prednisolone in 900 ml. of boiling benzene containing 10 mg. of *p*-toluenesulfonic acid, 10 ml. of cyclopentanone diethyl acetal was added, and the mixture was heated with rapid distillation of the solvent. In 15 min. prednisolone was completely dissolved. After 30 min. of distillation a few drops of pyridine was added; the solvent was partially evaporated and the residue chromatographed on 100 g. of Florisil. Elution with petroleum ether–benzene mixtures gave 3.85 g. of the product, m.p. 225–228°, which was recrystallized from methanol.

17α,21-Benzylidenedioxy-$\Delta^{1,4}$-pregnadiene-11β-ol-3,20-dione 11-(α-ethoxy)benzyl ether. (II. X =  , Y = C_2H_5, Δ^1). The reaction of prednisolone (3 g.) with 5 ml. of benzaldehyde diethyl acetal in the presence of 5 mg. of *p*-toluenesulfonic acid, performed according to the general procedure, yielded directly, after solvent evaporation and digestion with methanol, 2.3 g. of product, m.p. 195–210°. The melting point rose to 213–215° after one crystallization from methanol. Hydrolysis of the acetal (300 mg.) with methanolic hydrochloric acid as above described gave 175 mg. of prednisolone, m.p. 234–236°.

Prednisolone 17α,21-acetonide (I. X =  , Δ^1) *and its 11-(1-ethoxy-1-methyl)ethyl ether* (II. X =  , Y = C_2H_5, Δ^1). A. The oily product obtained from the reaction of 3 g. of prednisolone with 15 ml. of acetone diethyl ketal and 9 mg. of *p*-toluenesulfonic acid, carried out in benzene as described above, was chromatographed on 60 g. of Florisil. Elution with petroleum ether–benzene mixtures afforded 1.1 g. of a glass with infrared spectrum and analytical data (recorded in Table I) corresponding to the bisacetal II. Further elution with benzene–ether mixtures yielded 750 mg. of prednisolone acetonide, m.p. 238–241°.

B. The reaction of 5 g. of prednisolone with 8 ml. acetone diethyl ketal performed with the same procedure gave, after solvent evaporation, digestion with petroleum ether and crystallization from methanol, 2.7 g. of acetonide I, m.p. 238–240°. The bisacetal II was detected on papergram only. Hydrolysis of both compounds furnished prednisolone in 95% yield.

17α,21-Cyclopentylidenedioxy-Δ^4-pregnene-3,11,20-trione 3-ethyl enol ether. A suspension of 2 g. of cortisone cyclopentylidenedioxy derivative in 1.9 ml. of ethyl orthoformate, 1.5 ml. of tetrahydrofuran, and 1 ml. of ethanol was treated with 30 mg. of *p*-toluenesulfonic acid and stirred at room temperature for 15 min., at the end of which time the product was completely dissolved. After an additional 30 min., pyridine was added and most of the solvent was removed *in vacuo;* the residue was crystallized by addition of methanol, yielding 1.35 g. of enol ether, m.p. 123–126°. The same compound was also prepared by treating cortisone 3-ethyl enol ether[12] with cyclopentanone diethyl acetal as described above.

Prednisolone 11-(α-ethoxy)benzyl ether 21-acetate. The reaction of prednisolone 21-acetate (2 g.) with benzaldehyde diethyl acetal (5 ml.), carried out according to the general procedure, gave an oily product which was chromatographed on 40 g. of Florisil. Elution with benzene-ether mixtures afforded 300 mg. of the mixed acetal, m.p. 198–200°; $[\alpha]_D^{20}$ + 161°.

Anal. Calcd. for $C_{32}H_{40}O_7$: C, 71.62; H, 7.51. Found: C, 71.46; H, 7.70.

VISTER RESEARCH LABORATORIES
CASATENOVO (COMO), ITALY

(8) A. L. Nussbaum, E. Yuan, D. Dincer, and E. P. Oliveto (*in press*, personal communication) have obtained simultaneous formation of 3-methyl enol ether and 17α,21-acetonide by the use of dimethoxypropane. Such enoletherification does not occur when our milder procedure is used.

(9) Biological tests performed by Dr. Giovanni Falconi.

(10) Melting points are uncorrected. Rotations are in dioxane. The authors are indebted to Dr. Sergio Cairoli for the microanalyses and to Dr. Cesare Pedrali for the infrared spectra.

(12) A. Ercoli and R. Gardi, *J. Am. Chem. Soc.* **82**, 746 (1960).

Synthetic Furocoumarins. IV.[1] 2-Methyl-8*H*-furo[3,2-*h*][1]benzopyran-8-one, a Furocoumarin Derived from Catechol

KURT D. KAUFMAN AND WILLIAM E. RUSSEY

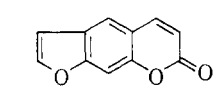
Received August 14, 1961

Several compounds containing the psoralene (I) system of a furan ring fused to the benzene portion of a coumarin have recently attracted much atten-

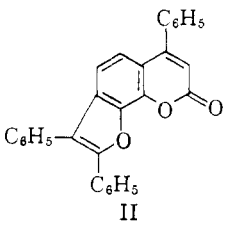
(1) Part III. K. D. Kaufman and L. R. Worden, *J. Org. Chem., in press.*

tion[2] because of their photosensitizing activity and their enhancement of human skin pigmentation. It was natural to look for similar activity in other furocoumarin systems, and this paper describes the synthesis of a methyl substituted furocoumarin, theoretically derived from catechol.

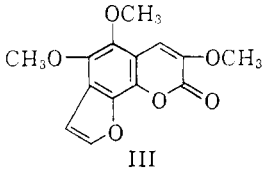
Very little has been published concerning furocoumarins of this type. The synthesis of only one such compound, 2,3,6-triphenyl-8*H*-furo[3,2-*h*][1]benzopyran-8-one (II),[3] has been reported and the method employed does not appear to be applicable to the synthesis of derivatives without the aryl substituents.[4] The naturally occurring compound Halfordin has been found to have either structure III or IV[5] and so may be another example of a furocoumarin containing the catechol system.



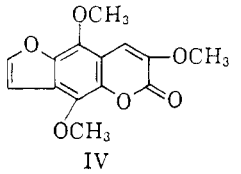
I



II



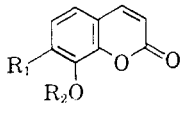
III



IV

In the present study the general method described in part I[6] of this series has been successfully utilized for the synthesis of 2-methyl-8*H*-furo[3,2-*h*][1]benzopyran-8-one (VII). It was found to be without any observable photosensitizing activity as determined by the erythemal response of guinea pig skin to ultraviolet radiation.[7] Details of the biological evaluation will soon be published elsewhere.

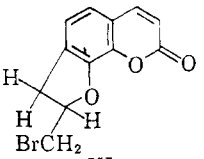
The starting material for the synthesis was 8-hydroxycoumarin (Va) obtained in 65% yield from



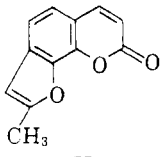
Va. $R_1 = R_2 = H$
b. $R_1 = H$; R_2 = allyl
c. R_1 = allyl; $R_2 = H$
d. R_1 = allyl; R_2 = acetyl
e. $R_1 = CH_2BrCHBrCH_2$—; R_2 = acetyl

o-vanillin[8] by the method of Cingolani.[9] Treatment with allyl bromide and potassium carbonate in acetone gave 8-allyloxycoumarin (Vb) as an oil, which was not purified (99% crude yield). The crude allyl ether was refluxed in diethylaniline for two hours and pure 7-allyl-8-hydroxycoumarin (Vc) was isolated (71% yield over two steps). Acetylation with acetic anhydride in pyridine gave an 87% yield of 8-acetoxy-7-allylcoumarin (Vd), which reacted with one molar equivalent of bromine to produce 8-acetoxy-7-(2′,3′-dibromopropyl)coumarin (Ve) in 84% yield.

Cyclization of Ve to a furocoumarin did not proceed as readily as in earlier examples.[6] Refluxing for two hours with sodium ethoxide in absolute ethanol gave a very small yield of an alkali insoluble compound $C_{12}H_9O_3Br$, m.p. 164–174°. Although elemental and spectral analyses were satisfactory, a sharply melting sample of this compound was never obtained and the possibility remains that it is a mixture of isomers. The structure of 2-bromomethyl-2,3-dihydro-8*H*-furo[3,2-*h*][1] benzopyran-8-one (VI) appears most probable for this com-



VI



VII

pound in view of the elemental analysis and the infrared spectrum, which showed no hydroxyl absorption. Analogous compounds have been isolated by Adams and Rindfusz,[10] who obtained a good yield of 2-bromomethylcoumaran by refluxing 2-(2′,3′-dibromopropyl)phenyl acetate in ethanol containing one molar equivalent of sodium ethoxide. As expected, additional refluxing of $C_{12}H_9O_3Br$ with sodium ethoxide in ethanol gave 2-methyl-8*H*-furo[3,2-*h*][1]benzopyran-8-one (VII), m.p. 158–159.5°, in 45% yield.

EXPERIMENTAL[11]

7-Allyl-8-hydroxycoumarin (Vc). 8-Hydroxycoumarin (Va, 59.0 g., 0.364 mole), prepared by the method of Cingolani[9] in 65.3% yield from *o*-vanillin, was refluxed in acetone (*ca.* 1 l.) with anhydrous potassium carbonate (202 g., 1.46 moles) and allyl bromide (221 g. 1.83 moles) for 20 hr. Suspended solid was removed by filtration and the filtrate was concentrated on a steam bath to a brown oil. An ether solution of the oil was shaken with 5% aqueous sodium hydroxide, 3% hydrochloric acid, and finally with water. After drying ($MgSO_4$), and evaporation of ether on a steam bath, 72.95 g. of crude 8-allyloxycoumarin (Vb) remained, as a brown oil.

(2) Psoralens and Radiant Energy, proceedings of a symposium, *J. Invest. Dermatol.*, **32**, 131–391 (1959); *cf.* earlier papers in this series.

(3) O. Dischendorfer and W. Limontschew, *Monatsh.*, **80**, 741–748 (1949).

(4) L. Musajo, G. Rodighiero, G. Caporale, and C. Antonello; *Farmaco (Pavia) Ed. Sci.*, **13**, 355–362 (1958), report that the introduction of a phenyl substituent on the furan ring of psoralene eliminates photosensitizing activity.

(5) M. P. Hegarty and F. N. Lahey, *Australian J. Chem.*, **9**, 120 (1956).

(6) K. D. Kaufman, *J. Org. Chem.*, **26**, 117 (1961).

(7) M. A. Pathak, private communication.

(8) Available from K and K Laboratories, Inc., 177-10 93rd Ave., Jamaica 33, N. Y.

(9) E. Cingolani, *Gazz. chim. ital.*, **84**, 843 (1954).

(10) R. Adams and R. E. Rindfusz, *J. Am. Chem. Soc.*, **41**, 648 (1919).

(11) All melting points were determined on a Fisher-Johns melting point apparatus and are corrected.

Without further purification, this material (72.89 g.) was refluxed in diethylaniline (*ca.* 250 ml.) for 2 hr. and, on cooling, a solid separated. Refrigeration caused the separation of more solid, all of which was collected by filtration. A solution of the solid in ether was washed with two small portions of 5% hydrochloric acid followed by two portions of saturated aqueous sodium chloride. Evaporation of the ether left a colorless solid which crystallized from ethanol as colorless needles (52.30 g., 71% yield from 8-hydroxycoumarin), m.p. 158.5–159.5°.

Anal. Calcd. for $C_{12}H_{10}O_3$: C, 71.27; H, 4.99. Found: C, 71.35; H, 5.31.

8-Acetoxy-7-allylcoumarin (Vd). Acetic anhydride (10 ml., 0.0935 mole) was added rapidly to a stirred solution of 7-allyl-8-hydroxycoumarin (10.0 g., 0.0495 mole) in pyridine (60 ml.). After 2 hr. of continued stirring, the solution was poured into a mixture of ice and water (*ca.* 600 ml.) and a colorless solid (10.55 g., 87%), m.p. 82–84°, was collected by filtration. Recrystallization from ethanol gave colorless needles, m.p. 84–85°.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.88; H, 5.11.

8-Acetoxy-7-(2',3'-dibromopropyl)coumarin (Ve). A solution of bromine (6.84 g., 0.0430 mole) in chloroform was added to a stirred solution of 8-acetoxy-7-allylcoumarin (m.p. 82–84°, 10.50 g., 0.0430 mole) in chloroform at such a rate as to allow decolorization after each drop. Evaporation of the chloroform on a steam bath left a nearly colorless oil, which solidified on contact with 95% ethanol, and crystallized from the same solvent as colorless prisms (14.54 g., 84%), m.p. 141.5–143°.

Anal. Calcd. for $C_{14}H_{12}O_4Br_2$: C, 41.61; H, 3.00; Br, 39.55. Found: C, 41.48; H, 2.90; Br, 39.62.

2-Bromomethyl-2,3-dihydro-8H-furo[3,2-h][1]benzopyran-8-one (VI). 8-Acetoxy-7-(2',3'-dibromopropyl)coumarin (11.90 g., 0.0295 mole) was added to a refluxing solution of sodium (3.38 g., 0.147 mole) in absolute ethanol (*ca.* 250 ml.) under an atmosphere of nitrogen. After 2 hr. the hot solution was poured into 2.5 l. of a mixture of ice, water, and concentrated hydrochloric acid (15 ml.). A chloroform extract of the aqueous suspension was washed thoroughly with 5% aqueous sodium hydroxide, 5% aqueous hydrochloric acid, and then water, and dried over anhydrous magnesium sulfate. Filtration through a pad of Celite, followed by evaporation of the chloroform left a residue, which was triturated with petroleum ether (b.p. 30–60°) and sublimed under vacuum. Washing the sublimate with 5% aqueous sodium hydroxide left a colorless solid, which crystallized from ethanol as ivory colored plates (1.80 g.), m.p. 169–171°. Three recrystallizations from ethanol gave colorless needles (0.65 g., 7.8%), m.p. 164–174°. The third recrystallization did not alter the m.p. Infrared and ultraviolet spectra were consistent with the proposed structure.

Anal. Calcd. for $C_{12}H_8O_3Br$: C, 51.29; H, 3.23; O, 17.01; Br, 28.43. Found: C, 50.91; H, 3.64; O, 17.45; Br, 28.09.

2-Methyl-8H-furo[3,2-h][1]benzopyran-8-one (VII). 2-Bromomethyl-2,3-dihydro-8*H*-furo[3,2-*h*][1]benzopyran-8-one (0.500 g., 0.00177 mole) was added to a refluxing solution of sodium (0.125 g., 0.00543 mole) in absolute ethanol (10 ml.) under an atmosphere of nitrogen. After 2 hr., the hot solution was poured into 150 ml. of a mixture of ice, water, and concentrated hydrochloric acid (3 ml.). The resultant precipitate (0.258 g.), m.p. 149–156°, was collected and recrystallized from 95% ethanol to give colorless needles (0.158 g., 44%), m.p. 158–159.5°. Both infrared and ultraviolet spectra were consistent with the proposed structure.

Anal. Calcd. for $C_{12}H_8O_3$: C, 72.00; H, 4.03; O, 23.97. Found: C, 72.22; H, 3.99; O, 24.00.

Acknowledgment. This investigation was carried out under a grant from the National Science Foundation (NSF-G5795), whose support is gratefully acknowledged. Microcombustion analyses and spectral determinations were performed in the Physical and Analytical Chemistry Dept., The Upjohn Co., Kalamazoo, Mich.

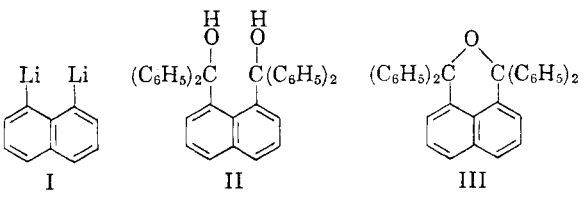
DEPARTMENT OF CHEMISTRY
KALAMAZOO COLLEGE
KALAMAZOO, MICH.

Peri-Substituted Naphthalene Compounds. V.[1,2] 1,8-Dilithionaphthalene

R. L. LETSINGER, J. A. GILPIN, AND W. J. VULLO

Received August 14, 1961

In connection with the synthesis of peri-substituted naphthalene compounds it was desirable to have available 1,8-dilithionaphthalene (I). We



I II III

have found that this reagent may be obtained conveniently by the exchange reaction between 1,8-dibromonaphthalene and butyllithium. The dilithium product was characterized by conversion (a) to 1,8-naphthalic anhydride (85% yield based on dibromonaphthalene) by treatment with carbon dioxide and (b) to the diol, 1,8-bisdiphenylhydroxymethylnaphthalene (II) (58% yield) by reaction with benzophenone. The structure of the diol was deduced from the analysis, spectral data, mode of formation, and the facile dehydration to an ether (III). Analogous dehydration reactions have been reported with *o*-bisdiphenylhydroxymethylbenzene[3] and 1,8-bisphenylhydroxymethylnaphthalene.[4]

A practical route to 1,8-dibromonaphthalene was needed for this synthesis. Fieser and Seligman,[5] modifying an earlier procedure of Meldola and Streatfeild,[6] obtained 1,8-dibromonaphthalene in three steps from 1,8-diaminonaphthalene. When we prepared dibromonaphthalene in this way, however, the procedure was tedious and time consuming. Two shorter preparative methods have been reported. One involves direct tetrazotization of 1,8-

(1) This work was supported by the National Science Foundation.

(2) For the previous paper in this series see R. L. Letsinger and W. J. Vullo, *J. Org. Chem.*, **25**, 1844 (1960).

(3) G. Wittig and F. Bickelhaupt, *Ber.*, **91**, 883 (1958).

(4) R. L. Letsinger and P. T. Lansbury, *J. Am. Chem. Soc.*, **81**, 935 (1959).

(5) L. F. Fieser and A. M. Seligman, *J. Am. Chem. Soc.*, **61**, 136 (1939).

(6) R. Meldola and F. W. Streatfeild, *J. Chem. Soc.*, **63**, 1054 (1893).