[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

Furocoumarin Studies. Synthesis of Psoralene and Related Furocoumarins[1]

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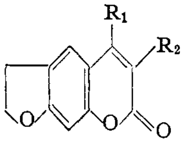
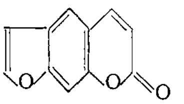
The preparation of 2,3-dihydropsoralene (I) and 6-carbethoxy-2,3-dihydrofuro(3,2-g)coumarin (II) was described in a previous paper.[3] This paper reports the synthesis of five compounds (III, IV, V, VI, VII) related to 2,3-dihydropsoralene (I) and the conversion of I and its relatives by catalytic dehydrogenation to furocoumarins including psoralene (VIII).



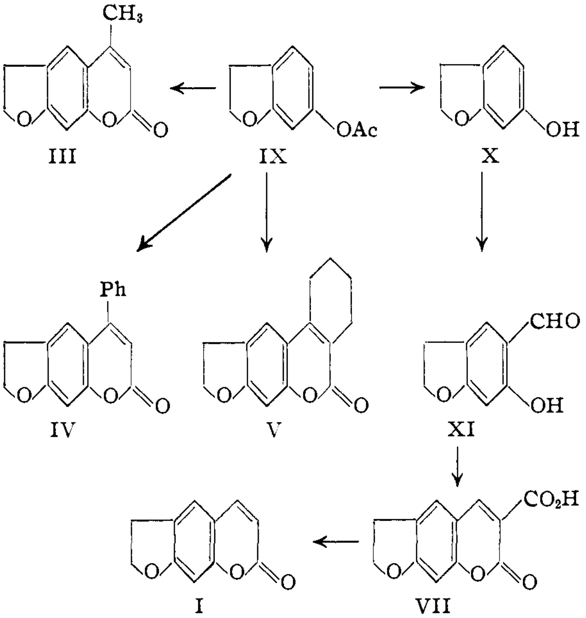
I–VII

I, R_1 = H, R_2 = H
II, R_1 = H, R_2 = CO_2Et
III, R_1 = CH_3, R_2 = H
IV, R_1 = Ph, R_2 = H
V, R_1 – R_2 = cyclohexeno
VI, R_1 = OH, R_2 = H
VII, R_1 = H, R_2 = CO_2H



VIII

The accompanying chart shows the routes by which these syntheses were effected.



Condensation of 6-acetoxycoumaran[3] (IX) with suitable β-ketoesters in the presence of 75% sulfuric acid gave the indicated dihydrofurocoumarins (III, IV, V) in 76–99% yield. The β-ketoesters employed were ethyl acetoacetate, ethyl benzoylacetate, and 2-carbethoxycyclohexanone.

In order to obtain 5-hydroxy-2,3-dihydrofuro-(3,2-g)coumarin (VI), 6-hydroxycoumaran[3] (X) was condensed with ethyl cyanoacetate in the presence of zinc chloride–hydrogen chloride. The iminoester formed in the reaction was hydrolyzed and cyclized to give the lactone (VI).

6-Carboxy-2,3-dihydrofuro(3,2-g)coumarin (VII) was prepared from XI in 94% yield by condensation of the aldehyde with malonic acid according to the method of Adams and Mathieu.[6] Preliminary attempts to prepare VII by the Doebner procedure were unsuccessful and XI was recovered unchanged. A review of reactions of this type appearing in the literature[4,5,6] indicated that the Knoevenagel and Doebner methods are often unsatisfactory when applied to *o*- or *p*-hydroxybenzaldehydes.

It was found that decarboxylation of VII to 2,3-dihydropsoralene could be effected by heating with copper bronze. After this work was completed, a similar reaction was described by Robertson, *et al.*,[7] although a different method was used for obtaining the acid (VII).

The catalytic dehydrogenation of heterocyclic compounds containing nitrogen as the heteroelement has been extensively studied, but very little information is available on the dehydrogenation of heterocycles containing oxygen as the heteroatom. The dehydrogenation of dihydrocoumarin and a few hydrogenated furocoumarins was investigated by Späth[8,9]; the method generally consisted in heating a mixture of the compound with palladium-black at 170° or higher, followed by distillation to remove the product from the catalyst. It was reported that 2,3-dihydropsoralene (I) was transformed into psoralene (VIII) in 20% yield by this method.

In this Laboratory dehydrogenations to furocoumarins were investigated in a high-boiling liquid medium using Hartung's[10] palladium–carbon catalyst. The best procedure consisted in heating a mixture of the dihydrofurocoumarin and catalyst in phenyl ether under reflux for four hours. By this procedure 2,3-dihydropsoralene was successfully dehydrogenated to psoralene in approximately 50% yield.

A difference in the melting point of our synthetic psoralene with that reported by Späth

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[1] Abstracted from the thesis of D. B. Reisner, presented to the Faculty of the Graduate School of the University of Pennsylvania in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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[3] Horning and Reisner, THIS JOURNAL, **70**, 3619 (1948).

[4] Kurien and Pandha, *J. Indian Chem. Soc.*, **11**, 823 (1934).

[5] Versatz, *J. prakt. Chem.*, **145**, 265 (1936).

[6] Adams and Mathieu, THIS JOURNAL, **70**, 2120 (1948).

[7] Foster, Robertson and (in part) Bushra, *J. Chem. Soc.*, 2254 (1948).

[8] Späth, *Ber.*, **70**, 83 (1937).

[9] Späth and Galinovsky, *ibid.*, **70**, 235 (1937).

[10] "Organic Syntheses," **26**, 77 (1946), method D.

made it necessary to review previous work on naturally occurring psoralene. This material was first isolated from the seeds of an Indian plant, *Psoralea corylifolia*, in 1933 by Jois, Manjunath and Rao,[11] who reported a melting point of 162°. In 1936, Okahara[12] extracted ficusin, m. p. 161–162°, (later shown to be psoralene) from the leaves of *Ficus carica*. A short time later, Späth[13] reported the synthesis of psoralene (VIII) and gave 171° as the melting point. He obtained a sample of ficusin from Okahara, and through purification of the natural material it was reported that the melting point was 166–167° (evacuated tube). Späth[14] also obtained natural psoralene (m. p. 162°) from Jois, *et al.*, and raised its melting point to 169–170°. A mixed melting point of natural psoralene (m. p. 169–170°) and synthetic psoralene (m. p. 171°) was 170–171°.

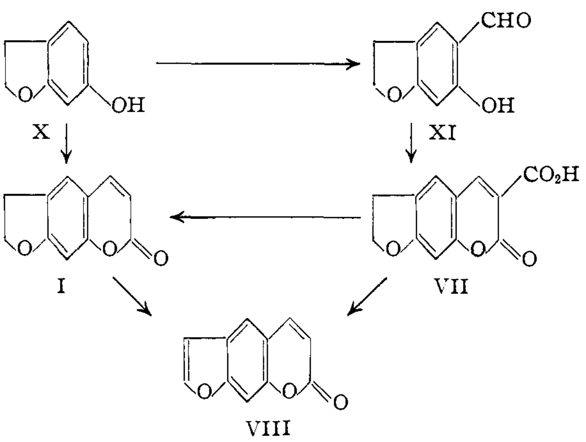
Later, Okahara[15] synthesized psoralene according to Späth's procedure and obtained a product melting at 161–162° instead of 171°. He also found that further purification of natural "ficusin" did not change its melting point.

In reply to Okahara, Späth[16] isolated psoralene from air-dried fig leaves from Italy and reported that a melting point of 160° was easily obtained. Raising the melting point was difficult, but it was reported that a recrystallized product melting at 166–167° (evacuated tube) was obtained. The melting point of synthetic psoralene was still accepted as 171°.

Synthetic psoralene obtained in this work melted at 162–162.5°, in good agreement with the independent reports of Okahara and Jois for natural psoralene. The melting point in an evacuated tube was unchanged. After completion of this synthesis, Robertson, *et al.*,[7] reported a dehydrogenation to psoralene, m. p. 167°. We have been unable to find evidence of a melting point above 162° in our samples.

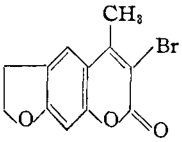
In the course of this work it was observed that psoralene could be obtained directly from 6-carboxy-2,3-dihydrofuro(3,2-g)coumarin (VII) by a one-step decarboxylation and dehydrogenation with a palladium–carbon catalyst. It is thus possible to obtain psoralene from 6-hydroxycoumaran (X) by three different routes, as shown in the chart.

Using the same general procedure for dehydrogenation, the dihydrofurocoumarins II, III, IV, and V were converted to the corresponding furocoumarins, XII, XIII, XIV and XV. 5-Hydroxy-2,3-dihydrofuro(3,2-g)coumarin (VI) was largely destroyed under dehydrogenation conditions found suitable for other compounds.

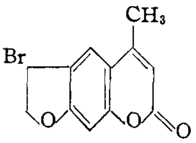


A possible alternative method for converting dihydrofurocoumarins into the corresponding furocoumarins was also investigated. 5-Methyl-2,3-dihydrofuro(3,2-g)coumarin was brominated according to the Ziegler procedure with N-bromosuccinimide. The yield of brominated product was high (95%), but all attempts to bring about dehydrobromination were unsuccessful. For example, a mixture of the bromo compound and collidine was heated under reflux for one hour, and after removal of the collidine the bromo compound was recovered unchanged. In view of this result, and with the fact that the brominated product did not give a positive test with alcoholic silver nitrate, it is presumed that the bromine atom is either on the benzene ring or on the lactone ring.

Lecocq and Buu-Hoï[17] and also Molko and Mentzer[18] reported that bromination of substituted coumarins using N-bromosuccinimide sometimes produced monobrominated products having a bromine atom in the 3 position of the lactone ring. By analogy with these results, the structure of the brominated product of 5-methyl-2,3-dihydrofuro(3,2-g)coumarin is most likely 6-bromo-5-methyl-2,3-dihydrofuro(3,2-g)-coumarin (XVI) rather than the desired 3-bromo-5-methyl-2,3-dihydrofuro(3,2-g)coumarin (XVII).



XVI



XVII

The fact that Ziegler bromination does not lead to substitution in the dihydrofuran ring makes it clear that this approach cannot be used as a general method for the preparation of furocoumarins.

In order to provide a series of compounds (III, XIII, XVIII) differing only in degree of saturation, for comparative studies of physical and physiological properties, 5-methyl-2,3-dihydrofuro(3,2-g)coumarin (III) was catalytically re-

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(11) Jois, Manjunath and Rao, *J. Indian Chem. Soc.*, **10**, 41 (1933).

(12) Okahara, *Bull. Chem. Soc., Japan*, **11**, 389 (1936).

(13) Späth, Okahara and Kuffner, *Ber.*, **70**, 73 (1937).

(14) Späth, Manjunath, Pailer and Jois, *ibid.*, **69**, 1087 (1936).

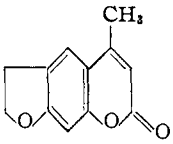
(15) Okahara, *Bull. Chem. Soc., Japan*, **13**, 653 (1938).

(16) Späth and Hillel, *Ber.*, **72**, 1577 (1939).

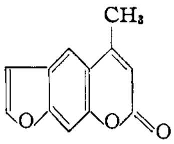
(17) Lecocq and Buu-Hoï, *Compt. rend.*, **224**, 937 (1947).

(18) Molko and Mentzer, *ibid.*, **223**, 1141 (1946).

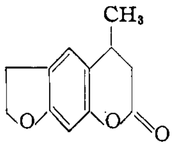
duced to 5-methyl-2,3,5,6-tetrahydrofuro(3,2-g)-coumarin (XVIII).



III



XIII



XVIII

Acknowledgment.—The authors are indebted to Mrs. Sarah Miles Woods for the analyses.

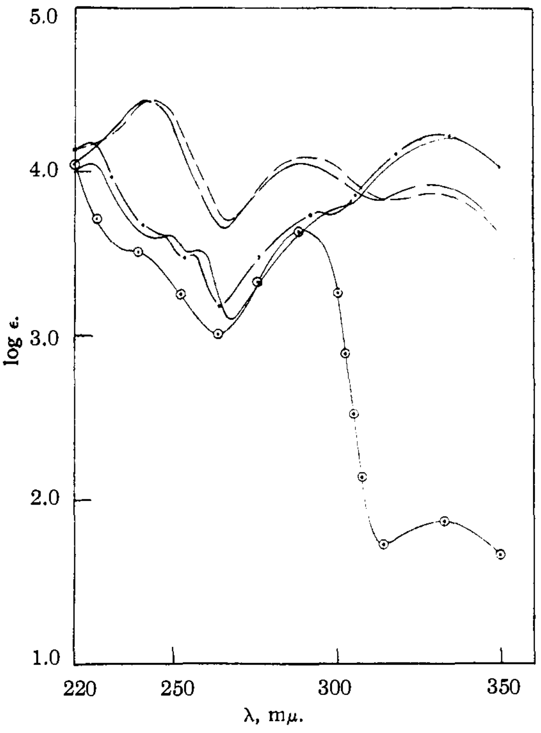


Fig. 1.—Ultraviolet absorption spectra in ethanol: ————, 2,3-dihydropsoralene (I): — — — —, psoralene (VIII); ⊙————⊙, 5-methyl-2,3,5,6-tetrahydrofuro(3,2-g)coumarin (XVIII); ●————●, 5-methyl-2,3-dihydrofuro(3,2-g) coumarin (III); ——— ———, 5-methylfuro(3,2-g)coumarin (XIII).

Experimental

All melting points are corrected.

5-Methyl-2,3-dihydrofuro(3,2-g)coumarin (III).—A solution of 17.8 g. (0.10 mole) of 6-acetoxycoumaran[3] in 13.0 g. (0.10 mole) of ethyl acetoacetate was heated on a steam cone and then, with stirring, 100 ml. of 75% (by vol.) sulfuric acid was added. The solution was heated on a steam cone for one hour with continued stirring, cooled to room temperature, and poured into 300 ml. of cold water. The resulting mixture was chilled overnight, filtered with suction, and the precipitate was washed with cold water. The yield of crude 5-methyl-2,3-dihydrofuro(3,2-g)coumarin melting at 157–163° was 17.7 g. (88%). This material was sublimed at reduced pressure (150–175° at 0.1 mm.), and recrystallized from ethyl acetate to yield an analytical sample melting at 170–171°.

Anal. Calcd. for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.29; H, 4.99.

5-Phenyl-2,3-dihydrofuro(3,2-g)coumarin (IV).—A solution of 6.0 g. (0.034 mole) of 6-acetoxycoumaran in 6.5 g. (0.036 mole) of ethyl benzoylacetate was heated on a steam cone and then, with stirring, 34 ml. of 75% (by vol.) sulfuric acid was added dropwise. The product was isolated in the usual way. The yield of crude material melting at 170–175° was 6.8 g. Recrystallization from acetic acid (charcoal) provided an analytical sample melting at 202–203°.

Anal. Calcd. for $C_{17}H_{12}O_3$: C, 77.26; H, 4.58. Found: C, 77.26; H, 4.64.

Cyclohexeno(c)-2,3-dihydrofuro(3,2-g)coumarin (V).—In a 200 ml. three-necked flask equipped with a stirrer, condenser, and addition tube were placed 8.9 g. (0.05 mole) of 6-acetoxycoumaran and 8.6 g. (0.05 mole) of 2-carbethoxycyclohexanone. The mixture was heated (steam) with stirring and 50 ml. of 75% (by vol.) sulfuric acid was added dropwise. Heating and stirring were continued for one hour, and the product was then treated with 300 ml. of ice-water. After chilling, the product was removed by filtration, washed well with cold water, and dried at 110°. The yield of crude cyclohexeno(c)-2,3-dihydrofuro(3,2-g.)coumarin melting at 161–165° was 12.0 g. Two recrystallizations from ethyl acetate gave an analytical sample melting at 190.5–191.5°.

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 74.36; H, 5.82. Found: C, 74.12; H, 5.62.

5-Hydroxy-2,3-dihydrofuro(3,2-g)coumarin (VI).—Dry hydrogen chloride was passed for two hours through a well stirred mixture of 5 g. (0.037 mole) of 6-hydroxycoumaran,[3] 5.7 g. (0.050 mole) of ethyl cyanoacetate, 3.0 g. of powdered anhydrous zinc chloride, and 30 ml. of dry ether. The precipitated ketimine hydrochloride was separated by decanting the ether, and was washed twice with 20 ml. portions of dry ether. The solid was transferred to a 500-ml. flask with 200 ml. of water, and the mixture was boiled for one hour. A yellow solid (3.76 g.) was removed by filtration from the chilled solution. This was added to 100 ml. of 50% (by vol.) sulfuric acid in a 250 ml. flask and the solution was heated (steam) for ninety minutes. The solution was added to 200 ml. of water, heated to boiling point, and cooled. From the cooled solution 3.25 g. of crude 5-hydroxy-2,3-dihydrofuro(3,2-g)coumarin, m. p. 252.5–254.5° (dec.) was obtained. Recrystallization from absolute ethanol, with the aid of charcoal, gave an analytical sample melting at 261.5–263.5° (dec.).

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.71; H, 3.95. Found: C, 65.10; H, 4.12.

6-Carboxy-2,3-dihydrofuro(3,2-g)coumarin (VII).—A mixture of 4.92 g. (0.03 mole) of 5-formyl-6-hydroxycoumaran,[3] 6.24 g. (0.06 mole) of malonic acid and 0.2 g. of aniline in 10 ml. of pyridine was heated at 55° for four hours. To the cooled mixture 100 ml. of 5% hydrochloric acid was added. The yellow 6-carboxy-2,3-dihydrofuro-(3,2-g)coumarin was removed by filtration and dried. The yield was 6.52 g. (94%); m. p. 241.5–243.5°. Recrystallization from ethylene chloride–ether did not change the melting point.

Anal. Calcd. for $C_{12}H_8O_5$: C, 62.07; H, 3.47. Found: C, 62.05; H, 3.47.

Decarboxylation of 6-Carboxy-2,3-dihydrofuro(3,2-g)-coumarin to 2,3-Dihydropsoralene.—6-Carboxy-2,3-dihydrofuro(3,2-g)coumarin (2.00 g.) (m. p. 239–241°) and 0.50 g. of copper metal (bronze) were mixed in a sublimation tube connected to a condenser. The mixture was heated with a free flame under reduced pressure (25 mm.). Crude 2,3-dihydropsoralene (1.25 g.) was removed from the walls of the vessels and recrystallized from 95% ethanol; the melting point was 193.5–195.5°. A mixed melting point of this material was taken with a sample of dihydropsoralene (m. p. 199.5–201°) prepared by the malic acid method[3]; the melting point of this mixture was 193.5–198.5°. Evidently decarboxylation occurred and it was later found that decarboxylation and dehydrogenation could be accomplished at the same time (in low yield) with a palladium–carbon catalyst.

Furo(3,2-g)coumarin (VIII).—A mixture of 2.19 g. of crude 2,3-dihydropsoralene[3] (m. p. 175–180°), 2 g. of 5%

palladium–carbon catalyst and 25 ml. of phenyl ether was heated under reflux for four hours. The catalyst was removed from the hot solution by filtration, and washed with 15 ml. of hot phenyl ether. Removal of phenyl ether by steam distillation, followed by filtration of the chilled aqueous solution yielded 1.08 g. of crystalline solid, m. p. 153–157°. Two recrystallizations from ether–pentane (Dry Ice) and sublimation at reduced pressure (163–170° at 15 mm.) provided an analytical sample; m. p. 162–162.5°.

Anal. Calcd. for $C_{11}H_6O_3$: C, 70.91; H, 3.25. Found: C, 71.16; H, 2.94.

In view of Spath's reported m. p. of 171° for synthetic psoralene, this procedure was repeated several times and the products purified by repeated crystallization and sublimation. Melting points of independent samples taken in a capillary tube were in the range 160–162.5°. The m. p. was not changed in a sealed, evacuated tube.

Psoralene from 6-Carboxy-2,3-dihydrofuro(3,2-g)coumarin.—A mixture of 2.32 g. of 6-carboxy-2,3-dihydrofuro(3,2-g)coumarin, 2.0 g. of 5% palladium–carbon catalyst and 30 ml. of phenyl ether was heated under reflux for four hours. The catalyst was removed by filtration and washed with 100 ml. of hot acetone and 40 ml. of hot absolute alcohol. The acetone and alcohol were evaporated and the phenyl ether removed by steam distillation. Crystalline psoralene was obtained from the chilled aqueous solution. The yield of dried product was 0.60 g., m. p. 137–145°. Recrystallization from ether gave a product melting at 160.5–161.5°. A mixed melting point with synthetic psoralene prepared through dehydrogenation of 2,3-dihydropsoralene did not show a depression.

6-Carbethoxyfuro(3,2-g)coumarin (XII).—A mixture of 3.80 g. (0.015 mole) of 6-carbethoxy-2,3-dihydrofuro(3,2-g)coumarin,[3] 3.0 g. of 5% palladium–carbon catalyst and 30 ml. of phenyl ether was heated under reflux for four hours. The yield of 6-carbethoxyfuro(3,2-g)coumarin after steam distillation of the solvent was 2.85 g., m. p. 122–130°. Recrystallization from ethyl acetate–pentane gave an analytical sample melting at 148–149°.

Anal. Calcd. for $C_{14}H_{10}O_5$: C, 65.12; H, 3.90. Found: C, 64.94; H, 4.08.

5-Methylfuro(3,2-g)coumarin (XIII).—Method A: A mixture of 5.00 (0.0248 mole) of 5-methyl-2,3-dihydrofuro(3,2-g)coumarin (m. p. 168–170°), 3.0 g. of 5% palladium–carbon catalyst and 40 ml. of phenyl ether was heated under reflux for four and one-half hours. The product was 3.93 g. (80%) of solid melting at 159–170°. Recrystallization from ethyl acetate gave glistening cream-colored needles of 5-methylfuro(3,2-g)coumarin, m. p. 187.5–188.5°.

Anal. Calcd. for $C_{12}H_8O_3$: C, 72.00; H, 4.02. Found: C, 71.87; H, 3.80.

Method B. The same general method was used, but the reflux period was extended to six and one-half hours. The crude product was removed from the chilled aqueous solution and triturated (after drying) with pentane to yield 4.20 g. (84%) of solid melting at 159–181°. Pure 5-methylfuro(3,2-g)coumarin was obtained by recrystallization from ethyl acetate. This increase in reaction time led to only a very slight increase in yield of product.

5-Phenylfuro(3,2-g)coumarin (XIV).—A mixture of 1.5 g. of 5-phenyl-2,3-dihydrofuro(3,2-g)coumarin, 2.0 g. of 5% palladium–carbon catalyst, and 20 ml. of phenyl ether was heated under reflux for four hours. The yield of product was 1.4 g. (93%); m. p. 155–167°. After recrystallization from ethyl acetate the material melted at 178–179°.

Anal. Calcd. for $C_{17}H_{10}O_3$: C, 77.85; H, 3.84. Found: C, 77.64; H, 3.97.

Benzo(c)furo(3,2-g)coumarin (XV).—A mixture of 5.0 g. of cyclohexeno(c)-2,3-dihydrofuro(3,2-g)coumarin, 3.0 g. of 5% palladium–carbon catalyst, and 40 ml. of phenyl ether was heated under reflux for four hours. After drying and triturating with pentane the yield of product was 4.10 g., m. p. 148–172°. A sample recrystallized twice from ethyl acetate and sublimed at 12 mm. (bath temperature, 195–210°) failed to yield a sample with a sharp melting point.

In view of the fact that the dehydrogenation was evidently incomplete, a mixture of 2.20 g. of the mixed products (m. p. 148–172°), 2.0 g. of 5% palladium–carbon catalyst and 30 ml. of phenyl ether was heated under reflux for four hours. The product was isolated as before. The yield of material melting at 148–161° was 1.83 g. Recrystallization from ethyl acetate gave 0.58 g. of solid melting at 193.5–195.5°. A second recrystallization gave an analytical sample melting at 197.5–198.5°. The analytical data for this material indicated complete dehydrogenation to form benzo(c)furo(3,2-g)coumarin.

Anal. Calcd. for $C_{15}H_8O_3$: C, 76.27; H, 3.41. Found: C, 76.10; H, 3.60.

From the filtrate remaining from the first crystallization, 0.05 g. of a solid melting at 234.5–243.5° crystallized out, and after removal of this substance, a third fraction weighing 0.60 g. and melting at 188–195° was obtained. Recrystallization of the latter fraction from 95% ethanol gave a product melting at 197–198°. This substance gave no depression when mix-melted with benzo(c)furo(3,2-g)-coumarin obtained in the first fraction.

A total yield of 1.18 g. of benzo(c)furo(3,2-g)coumarin was obtained by re-working the filtrates. The second small high-melting fraction (234.5–243.5°) was not investigated.

(X)-Bromo-5-methyl-2,3-dihydrofuro(3,2-g)coumarin.—A mixture of 1.37 g. (0.0068 mole) of 5-methyl-2,3-dihydrofuro(3,2-g)coumarin and 1.21 g. (0.0068 mole) of N-bromosuccinimide in 30 ml. of dry carbon tetrachloride was stirred and heated for one hour; a negative test with starch–potassium iodide was obtained at this time. The solvent was evaporated and 40 ml. of water was added. The aqueous mixture was boiled for ten minutes and filtered while hot. The remaining solid was washed with hot water and dried. The yield of discolored crystalline (X)-bromo-5-methyl-2,3-dihydrofuro(3,2-g)coumarin was 1.80 g.; m. p. 181.5–187.5°. Recrystallization from ethyl acetate–pentane (charcoal) gave an analytical sample melting at 206–207°.

Anal. Calcd. for $C_{12}H_8BrO_3$: C, 51.27; H, 3.23. Found: C, 51.50; H, 3.40.

The position of the bromine atom in this compound is not certain, except that it is almost certainly not in the expected 3-position. The compound was stable under conditions which ordinarily would lead to dehydrohalogenation.

Attempted Dehydrohalogenation of (X)-Bromo-5-methyl-2,3-dihydrofuro(3,2-g)coumarin.—Numerous attempts were made to dehydrobrominate the bromo derivative of 5-methyl-2,3-dihydrofuro (3,2-g)coumarin; in all cases the bromo compound was recovered unchanged.

A mixture of (X)-bromo-5-methyl-2,3-dihydrofuro-(3,2-g)coumarin and *sym*-collidine, allowed to stand overnight at room temperature and then warmed on a steam cone for three hours, failed to effect dehydrohalogenation. A mixture was also heated under reflux for one hour. Unchanged starting material was isolated.

In another approach, experiments were carried out to obtain a quaternary salt using trimethylamine in ether or acetone, prior to deamination, but no salt formed and starting material was recovered.

Attempted Dehydrogenation of 5-Hydroxy-2,3-dihydrofuro (2,3-g)coumarin.—Numerous attempts were made to carry out the dehydrogenation of this material to the corresponding furocoumarin in phenyl ether with a 5% palladium–carbon catalyst. The attempts were not successful; the usual result was decomposition of the starting material.

5-Methyl-2,3,5,6-tetrahydrofuro(3,2-g)coumarin (XVIII).—A mixture of 6.0 g. (0.03 mole) of 5-methyl-2,3-dihydrofuro(3,2-g)coumarin, 2.0 g. of 5% palladium–carbon catalyst, and 60 ml. of acetic acid was shaken with hydrogen (initial pressure, 40 lb.) in a Parr hydrogenation apparatus at approximately 65°. Reaction ceased after one equivalent of hydrogen was absorbed. The catalyst was removed by filtration and washed with acetone. The acetone was removed by evaporation and the acetic acid solution was added to about 200 ml. of water. The mixture was chilled and filtered to provide 5.0 g. (83%) of colorless 5-methyl-2,3,5,6-tetrahydrofuro(3,2-g)coumarin, m. p. 62–65°. Recrystallization from ether–cyclohexane gave an analytical sample melting at 68.5–69.5°.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.58; H, 5.93. Found: C, 70.42; H, 5.73.

Summary

A study of the dehydrogenation of a number of 2,3-dihydrofurocoumarins to the corresponding furocoumarins is described.

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A Cleavage Reaction of α-Allylbenzylamines

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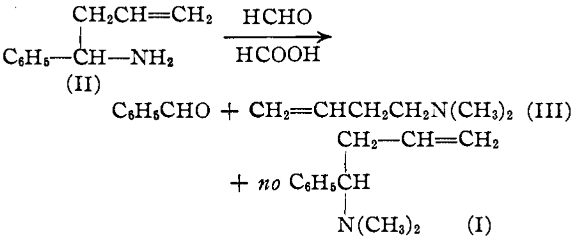
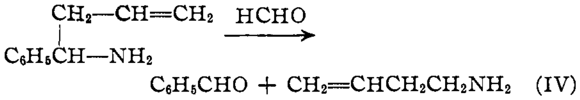
In an attempt to prepare α-allylbenzyldimethylamine (I), α-allylbenzylamine (II) was treated with formic acid and formaldehyde under the conditions described by Clarke, Gillespie and Weisshaus.[1] Instead of the methylation of II to I, the reaction took a different course, leading to cleavage of II with the formation of benzaldehyde and 1-dimethylaminobutene-3 (III)



$$\begin{array}{l} CH_2CH{=}CH_2 \\ \quad | \\ C_6H_5{-}CH{-}NH_2 \\ \quad \text{(II)} \end{array} \xrightarrow[\text{HCOOH}]{\text{HCHO}} C_6H_5CHO + CH_2{=}CHCH_2CH_2N(CH_3)_2 \text{ (III)} + \textit{no}\ \begin{array}{l} CH_2{-}CH{=}CH_2 \\ \quad | \\ C_6H_5CH \\ \quad | \\ N(CH_3)_2 \end{array} \text{ (I)}$$

Examination of this reaction disclosed that the cleavage was brought about by the action of formaldehyde on II, III being formed by the subsequent methylation of the 1-aminobutene-3 (IV) produced in the initial phase of the reaction. This was demonstrated by carrying out the reaction in the absence of formic acid. The products were benzaldehyde and IV

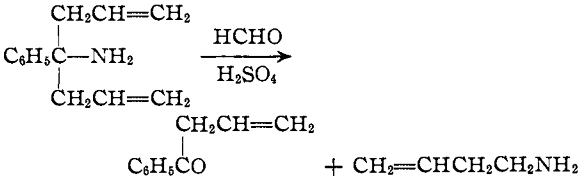


$$\begin{array}{l} CH_2{-}CH{=}CH_2 \\ \quad | \\ C_6H_5CH{-}NH_2 \end{array} \xrightarrow{\text{HCHO}} C_6H_5CHO + CH_2{=}CHCH_2CH_2NH_2 \text{ (IV)}$$

The structure of the butenylamine was demonstrated by its reduction to *n*-butylamine, identified by means of the picrate. 1-Dimethylaminobutene-3 was identified by comparing its picrate and methiodide with those of an authentic sample prepared by the method of Robinson and Robinson[2] who prepared the diethylamino analog by the reaction of allylmagnesium chloride with butoxymethyldiethylamine. The use of butoxymethyldimethylamine led to III.

In view of this unusual result, it was of importance to prove conclusively that the starting compound (II) was indeed α-allylbenzylamine, and that the cleavage of the carbon chain had not occurred at some earlier stage. α-Allylbenzylamine was prepared in excellent yield by the Hofmann degradation of α-allylphenylacetamide. That the product of this reaction was indeed II was shown by the preparation of an alkali-soluble benzenesulfonamide, a 3-nitrophthalimide, and a trimethylammonium iodide. The latter upon Hofmann degradation afforded 1-phenylbutadiene, identified by the preparation of its dibromide.

The reaction of formaldehyde with α,α-diallylbenzylamine was also examined, and it was found that cleavage occurred in the same manner as before, leading to 1-aminobutene-3 and a ketone, presumably allyl phenyl ketone. The characterization of the ketone by means of its 2,4-dinitrophenylhydrazone yielded a product which did not show a sharp melting point until it had been recrystallized repeatedly. The final product showed the correct analysis for allyl-(or propenyl) phenyl ketone. It seems likely that the melting point range of the derivative is explainable by a partial isomerization of the double bond either in the reaction in which the ketone was formed or in the preparation of the dinitrophenylhydrazone. The point was not of importance to the cleavage reaction, however, since hydrogenation of the unsaturated ketone yielded *n*-butyrophenone, thus establishing the fact that the cleavage reaction proceeded as shown



$$\begin{array}{l} CH_2CH{=}CH_2 \\ \quad | \\ C_6H_5C{-}NH_2 \\ \quad | \\ CH_2CH{=}CH_2 \end{array} \xrightarrow[H_2SO_4]{\text{HCHO}} \begin{array}{l} CH_2CH{=}CH_2 \\ \quad | \\ C_6H_5CO \end{array} + CH_2{=}CHCH_2CH_2NH_2$$

α,α-Diallylbenzylamine was prepared by the action of excess allylmagnesium bromide on benzonitrile, a reaction analogous to many investigated by Henze and his collaborators.[3] Its structure is established by the method used for its synthesis. It was characterized by the preparation of its benzenesulfonamide and the thiourea formed by the action of phenyl isothiocyanate. The course of the cleavage reaction can be formulated as

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(1) Clarke, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

(2) Robinson and Robinson, *J. Chem. Soc.*, **123**, 532 (1923).

(3) Henze, Allen and Leslie, THIS JOURNAL, **65**, 87 (1943).