Studies on the 4-Hydroxycoumarins. XVIII.[1a] 3-[α-(Acetamidomethyl)benzyl]-4-hydroxycoumarin and Related Products[1b]

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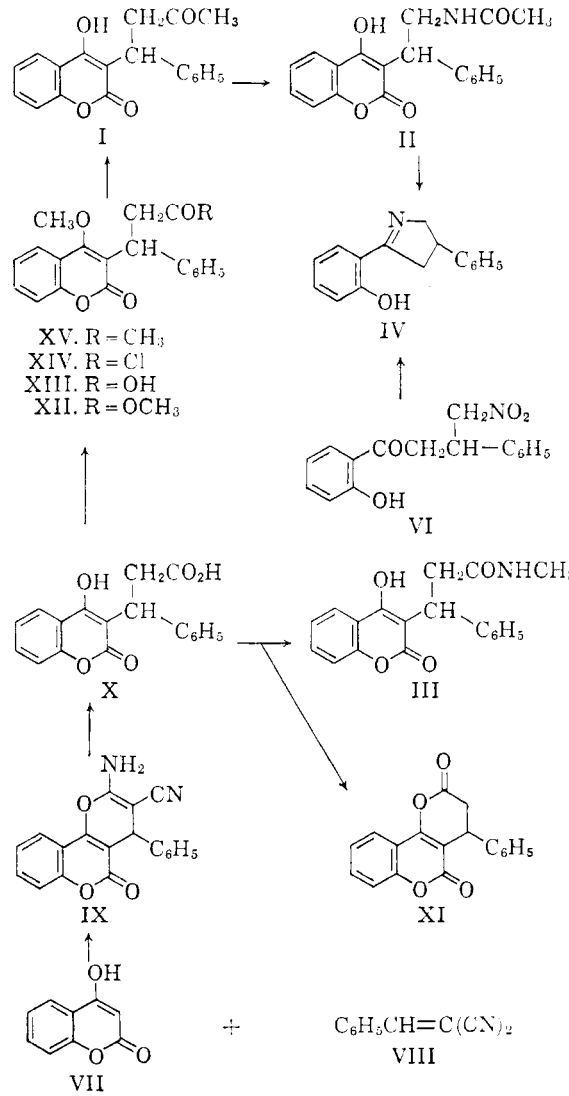
The Beckmann rearrangement of warfarin oxime and the action of hydrazoic acid on warfarin (Schmidt reaction) both yield 3-[α-(acetamidomethyl)benzyl]-4-hydroxycoumarin (II). Acid hydrolysis of II yields 2-(*o*-hydroxyphenyl)-4-phenyl-1-pyrroline (IV) which was also synthesized by an independent route. The other possible product of the above reactions, 3-[α-(methylcarbamoylmethyl)benzyl]-4-hydroxycoumarin (III), was made from 3-[α-(carboxymethyl)benzyl]-4-hydroxycoumarin (X), a new compound. The structure of X was proved by conversion to warfarin (I) *via* 3-(α-acetonylbenzyl)-4-methoxycoumarin (XV).

The oxime of warfarin, 3-(α-acetonylbenzyl)-4-hydroxycoumarin (I), was first prepared here by Seidman.[2] By heating this oxime in polyphosphoric acid (Beckmann rearrangement), Robertson[3] obtained a product assumed to be an amide of structure II or III. Attempts to hydrolyse this amide failed. In this paper we report that this product is also obtained by the action of hydrazoic acid on I.

Acid hydrolysis of this rearrangement product was finally achieved and the hydrolysis product was shown to be 2-(*o*-hydroxyphenyl)-4-phenyl-1-pyrroline (IV). It is clear that IV can arise from II but not from III, which allows assignment of the formula 3-[α-(acetamidomethyl)benzyl]-4-hydroxycoumarin to the Beckmann and Schmidt products.

The pyrroline backbone of IV was proved by synthesis after a method used by Kloetzel[4]; Nitromethane was added to 2′-hydroxychalcone (V) to give 1-(*o*-hydroxyphenyl)-3-phenyl-4-nitro-1-butanone (VI), which on reduction cyclized to IV. The position of the double bond in IV was deduced from two lines of evidence: (a) conversion by hydrazoic acid of optically active I to optically active II, which yielded optically active IV on hydrolysis. This eliminates Δ^3 and Δ^4 structures. (b) Proton magnetic resonance, which showed three peaks with areas in the ratio 10:2:3. This agrees with structure IV (Δ^1) which has ten aromatic (one phenolic) hydrogens, two hydrogens next to nitrogen, and three aliphatic hydrogens.[5]

While the above work was in progress, the other possible rearrangement product of warfarin oxime, 3-[α-(methylcarbamoylmethyl)benzyl]-4-hydroxycoumarin (III) was synthesized. Addition of 4-hydroxycoumarin (VII) to benzylidene malononitrile (VIII) gave 2-amino-3-cyano-4-phenyl-5-oxo-γ-pyrano[3,2-*c*][1]benzopyran (IX), which was readily hydrolyzed by acid to 3-[α-(carboxymethyl)benzyl]-4-hydroxycoumarin (X). The acid chloride of X could not be prepared because cyclization occurred, yielding the enol lactone, 2-oxo-3*H*-4-phenyl-5-oxo-γ-pyrano[3,2-*c*][1]benzoypyran (XI).



(1) (a) Previous paper in this series: B. D. West, S. Preis, C. H. Schroeder, and K. P. Link, *J. Am. Chem. Soc.*, **83**, 2676 (1961). (b) Published with the approval of the Director of the Agricultural Experiment Station. Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

(2) M. Seidman, Ph.D. thesis, University of Wisconsin (1950).

(3) D. N. Robertson, Ph.D. thesis, University of Wisconsin (1953).

(4) M. C. Kloetzel, *J. Am. Chem. Soc.*, **69**, 2271 (1947).

(5) We wish to thank Drs. Bernhard Witkop and Louis Cohen of the National Institutes of Health, Bethesda, Md., for measuring and evaluating the NMR spectra.

Thermal dehydration of the methylamine salt of X, however, gave the desired amide, 3-[α-(methylcarbamoylmethyl)benzyl] - 4 - hydroxycoumarin (III), in good yield.

The structure of X was substantiated by a series of reactions leading to warfarin (I). Treatment of X with diazomethane in excess gave 3-[α-carbomethoxymethyl)benzyl]-4-methoxycoumarin (XII). This ester ether was saponified to yield 3-[α-(carboxymethyl)benzyl]-4-methoxycoumarin (XIII), which was converted to the acid chloride (XIV). Warfarin methyl ether (XV) was obtained by the action of dimethylcadmium on XIV. Demethylation of XV with hydrobromic acid gave warfarin (I).

Experimental[6]

3-[α-(Acetamidomethyl)benzyl]-4-hydroxycoumarin (II).—To a solution of 30.8 g. (0.1 mole) of warfarin in 800 ml. of chloroform was added 8.0 g. of sodium azide. Concentrated sulfuric acid (100 ml.) was added over a period of 15 min. with mechanical stirring. After 2 hr., 1 l. of water was added and the stirring was continued an additional 30 min. The solid product was collected and washed with 50 ml. of ethanol followed by 50 ml. of ether. More product was obtained from the chloroform filtrate by concentration. Total yield 27 g. (90%) after crystallization from isopropyl alcohol, m.p. 285°.

Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.6; H, 5.30. Found: C, 70.5; H, 5.73.

The infrared spectra of II and of the rearranged warfarin oxime of Robertson[3] were identical and a mixture of the two products showed no melting point depression. λ_{max}^{KBr} 3.05, 3.38, 5.93, 6.15, and 6.43 μ.

Optically active I[1a] ($[\alpha]^{25}D$ −147°, *c* 1.2, 0.5 *N* NaOH) was converted in the same way to optically active II ($[\alpha]^{23}D$ −78.0°, *c* 2.0, 0.5 *N* NaOH).

2-*o*-Hydroxyphenyl-4-phenyl-1-pyrroline (IV). A. From II.—A mixture of 350 ml. of acetic acid, 15 ml. of concentrated hydrochloric acid, and 30 g. of II was refluxed 24 hr. and poured into cold water. After 2 hr. a small amount of starting material was filtered out, and the solution was made slightly basic with sodium hydroxide. The resulting oil was extracted into ether. The ether was dried with magnesium sulfate and distilled. The yield of IV, a viscous yellow oil, was 13.8 g. (61%), b.p. 136–138° (0.05 mm.).

Anal. Calcd. for $C_{16}H_{14}NO$: C, 80.1; H, 6.37. Found: C, 80.1; H, 6.24. $\lambda_{max}^{CS_2}$ 3.30, 3.41, 6.20, and 7.05 μ.

The hydrochloride of IV was prepared from IV and hydrogen chloride in ether and crystallized from isopropyl alcohol–ether, m.p. 184–186° (sealed tube).

Anal. Calcd. for $C_{16}H_{16}ClNO$: C, 70.2; H, 5.89. Found: C, 70.2; H, 6.22.

Optically active II ($[\alpha]^{23}D$ −78.0°, *c* 2.0, 0.5 *N* NaOH) was converted in the same way to optically active IV ($[\alpha]^{23}D$ −98.7°, *c* 0.4, absolute ethanol).

B. From VI.—A mixture of 183 g. (3 moles) of nitromethane, 33.6 g. (0.15 mole) of 2′-hydroxychalcone and 11 g. of diethylamine in 100 ml. of methanol was kept for five days at 37°. The volatile components were removed by vacuum distillation and the 1-*o*-hydroxyphenyl-3-phenyl-4-nitro-1-butanone (VI) was crystallized from absolute ethanol after charcoal treatment. Two recrystallizations yielded 30.8 g. (72%) of product, m.p. 87–88°.

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.8; H, 5.34. Found: C, 67.5; H, 5.73.

Compound VI (20 g., 0.07 mole) was added to 200 ml. of methanol and 4 g. of Raney nickel[7] in a 1-l. pressure bottle. The mixture was shaken with hydrogen at 40 p.s.i. for 16 hr. The catalyst was filtered off and the filtrate was distilled. The fraction boiling at 136–137° (0.05 mm.) weighed 10.0 g. The products from methods A and B and their hydrochlorides had identical infrared spectra.

2-Amino-3-cyano-4-phenyl-5-oxo-γ-pyrano[3,2-c][1]benzopyran (IX).—To 50 ml. of pyridine were added 16.2 g. (0.1 mole) of 4-hydroxycoumarin and 15.4 g. (0.1 mole) of benzylidenemalononitrile. After 30 min. 200 ml. of water was added and the product was collected by filtration. It was washed with water, ethanol, and ether and crystallized from a large volume of acetone, m.p. 273–275°. $\lambda_{max}^{fluorolube}$ 2.92, 3.01, 3.10, 3.40, 4.50, 5.81, 5.95, and 6.10 μ.

Anal. Calcd. for $C_{19}H_{12}N_2O_3$: C, 72.2; H, 3.80; N, 8.8. Found: C, 72.4; H, 3.79; N, 8.7.

3-[α-(Carboxymethyl)benzyl]-4-hydroxycoumarin (X).—To 150 ml. of glacial acetic acid and 25 ml. of concentrated hydrochloric acid was added 31.6 g. (0.1 mole) of IX. The mixture was refluxed 3 hr. and poured into ice and water. After several hours the oily product solidified and was collected by filtration. Recrystallization from 75% ethanol gave 26.0 g. (84%), m.p. 189–190° (dec.).

Anal. Calcd. for $C_{18}H_{14}O_5$: C, 69.7; H, 4.44. Found: C, 69.6; H, 4.92.

2-Oxo-3H-4-phenyl-5-oxo-γ-pyrano[3,2-c][1]benzopyran (XI).—A solution of 5 g. of X in 5 ml. of acetic anhydride was refluxed for 5 min. and poured into ice water. The alkali-insoluble product was recrystallized from 50% aqueous ethanol, m.p. 183–184°.

Anal. Calcd. for $C_{18}H_{12}O_4$: C, 74.0; H, 4.14. Found: C, 73.8; H, 4.52.

The same product was obtained by treating X with thionyl chloride or phosphorus oxychloride. Hydrolysis of XI to the starting acid (X) was achieved by refluxing with 10% sodium hydroxide followed by acidification.

3-[α-(Methylcarbamoylmethyl)benzyl]-4-hydroxycoumarin (III).—A mixture of 3.1 g. (0.01 mole) of X and 5 ml. of 25% aqueous methylamine in 250 ml. of benzene was dried by refluxing it under a water separator. The insoluble salt was collected by filtration, powdered and heated at 160° and 12 mm. for 1.5 hr. The crude amide was powdered, washed with water, and crystallized from absolute ethanol; yield 1.8 g., m.p. 247–250°. Hydrolysis of this product in 20% sodium hydroxide followed by acidification yielded the starting acid (X).

Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.6; H, 5.30. Found: C, 70.5; H, 5.69.

3-[α-(Carbomethoxymethyl)benzyl]-4-methoxycoumarin (XII).—A solution of 25.0 g. of X in 100 ml. of methanol was slowly added to a cold ether solution of excess diazomethane. Acetic acid was added to destroy the diazomethane and the solution was evaporated to dryness. The residue was dissolved in ether, washed with 5% sodium hydroxide and with water, dried (magnesium sulfate), and evaporated under vacuum. The residue was crystallized from ethanol-water; yield 15.1 g., m.p. 121–123°.

Anal. Calcd. for $C_{20}H_{18}O_5$: C, 71.0 ; H, 5.36. Found: C, 71.2; H, 5.03.

3-[α-(Carboxymethyl)benzyl]-4-methoxycoumarin (XIII).—To a solution of 15 g. of sodium hydroxide in 100 ml. of 50% aqueous ethanol was added 10.0 g. of XII. The solution was refluxed 1 hr. and poured into dilute hydrochloric acid and ice. The oily precipitate solidified on standing and was crystallized from ethanol to yield 8.0 g. of XIII, m.p. 189–191°.

Anal. Calcd. for $C_{19}H_{16}O_5$: C, 70.4; H, 4.97. Found: C, 70.2; H, 5.22.

3-[α-(Chloroformylmethyl)benzyl]-4-methoxycoumarin (XIV).—A solution of 5.0 g. (0.015 mole) of XIII and 3.5 g. (0.017 mole) of phosphorus pentachloride in 100 ml. of benzene was warmed, then kept at 25° for 30 min. The benzene was evaporated under vacuum to about 25 ml. and three 25-ml. portions of benzene were added and evaporated in the

(6) Melting points are uncorrected.

(7) E. C. Horning, *Org. Syntheses*, Coll. Vol. 3, 181 (1955).

same way. Hexane was added and the solution was held at 4°. The yield of crystalline XIV was 4.3 g., m.p. 95–96°.

Anal. Calcd. for $C_{19}H_{15}ClO_4$: C, 66.6; H, 4.41. Found: C, 66.7; H, 4.71.

3-(α-Acetonylbenzyl)-4-methoxycoumarin (XV).—To a stirred benzene solution of 0.015 mole of dimethylcadmium[8] was added 2.7 g. (0.015 mole) of XIV. The mixture was refluxed 15 min. and poured into 100 ml. of 5% hydrochloric acid and 50 ml. of ethyl acetate. The organic phase was separated and washed with 100-ml. portions of water, 5% sodium hydroxide and water. After drying with magnesium sulfate the solution was concentrated under vacuum to a dark oil which was dissolved in the minimum amount of methanol, treated with Darco KB charcoal and held at 4° for several days. The product was collected and recrystallized from methanol, m.p. 125–127°. The m.p. of a mixture with authentic XV[9] was not depressed. The product and authentic XV had essentially identical infrared spectra: $\lambda_{max}^{CHCl_3}$ 3.29, 5.85, and 6.19 μ.

Warfarin (I).—A solution of 0.5 g. of XV in 5 ml. of acetic acid and 5 ml. of 48% aqueous hydrobromic acid was refluxed 1 hr. and poured into 50 ml. of ice and water. The dark solid was collected, washed with water, and dissolved in 25 ml. of 1% sodium hydroxide. This solution was treated with Darco KB charcoal and acidified with concentrated hydrochloric acid. The gummy product was collected by centrifuging. It crystallized after standing several days at 4° in acetone-water. After recrystallization from acetone-water the product had m.p. 160–161° and an infrared spectrum identical to that of authentic I.

(8) J. Cason, *J. Am. Chem. Soc.*, **68**, 2080 (1946).

(9) M. Ikawa, Ph.D. thesis, University of Wisconsin (1948).

Pyrolysis of Esters. XXIII. 2,3-Divinyl-1,3-butadiene[1-3]

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2,3-Divinyl-1,3-butadiene was prepared in a three-step synthesis from commercially available 1,2,3,4-butanetetracarboxylic acid in an over-all yield of 20%. In the key step, pyrolysis of a tetraacetate at 50 mm. pressure and 590° gave a 25% yield of the tetraene. The structure of the tetraene was proved by analysis, hydrogenation to the known 3,4-dimethylhexane, conversion to solid Diels-Alder adducts, infrared and ultraviolet absorption spectra, and NMR spectrum.

In a research program on Diels-Alder polymerization it was necessary to prepare a series of polyfunctional dienes. Initially, 2-vinyl-1,3-butadiene was prepared by the pyrolysis of a triacetate[4] and this triene was used to prepare polymeric Diels-Alder adducts[5] with such bifunctional dienophiles as benzoquinone and the bismaleimides. More recently, we reported the synthesis of the very interesting 2-hydroxymethyl-1,3-butadiene[6] and showed how this polyfunctional compound could be converted to bifunctional dienes[7] for use in the Diels-Alder polymerization.[5] In order to make the Diels-Alder polymerization more general, a trifunctional diene which would produce a three-dimensional polymer was required. The simplest compound containing three diene systems is the tetraene, 2,3-divinyl-1,3-butadiene (I). This tetraene I was also of interest because it contained two overlapping cross-conjugated diene systems and would be of use in the preparation of polynuclear aromatic hydrocarbons through Diels-Alder reactions.[8]

The starting material for the synthesis of 2,3-divinyl-1,3-butadiene (I) was the commercially available 1,2,3,4-butanetetracarboxylic acid, which was esterified in a 72% yield to give tetraethyl 1,2,3,4-butanetetracarboxylate (II). By the method of reductive acetylation[4] with lithium aluminum hydride and acetic anhydride that was developed in this laboratory, the tetraester II was converted to 1,6-diacetoxy-3,4-di(acetoxymethyl)hexane (III) in an 84% yield. This method essentially involves the reduction of the tetraester II, but in place of the usual hydrolysis to the tetraol, which would be very difficult to isolate from the aqueous solution of the lithium and aluminum salts, the reduction product was acetylated to give the ether-soluble tetraacetate III. The structure of the tetraacetate III was indicated by hydrolysis to 3,4-di(hydroxymethyl)-1,6-hexanediol in a 93% yield.

When the tetraacetate III was dropped through the pyrolysis tube at 540°, a complex mixture of at least twenty products resulted. Gas phase chromatography indicated that only two of these components had a boiling point in the range of 105–123° by comparison of their retention times on a silicone column with those of octene-1, 4,4-dimethyl-1-hexene, toluene, and tetrachloroethylene. The materials corresponding to both of these peaks were collected from the chromatograph and one was tentatively assigned the structure of 2,3-divinyl-1,3-butadiene (I) on the basis of its absorption maximum in the ultraviolet at 217 mμ. Since this

(1) Previous paper in this series, *J. Org. Chem.*, **27**, 2732 (1962).

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(4) W. J. Bailey and J. Economy, *J. Am. Chem. Soc.*, **77**, 1133 (1955).

(5) W. J. Bailey, J. Economy, and M. E. Hermes, *J. Org. Chem.*, **27**, 3295 (1961).

(6) W. J. Bailey, W. G. Carpenter, and M. E. Hermes, *ibid.*, *Chem.*, **27**, 1975 (1962).

(7) W. J. Bailey and M. E. Hermes, *ibid.*, **27**, 2732 (1962).

(8) W. J. Bailey and C.-W. Liao, *J. Am. Chem. Soc.*, **77**, 992 (1955),