Another recrystallization from 2:1 Skellysolve B–ether gave 0.251 g. of long needles, m.p. 136–137.5°.

Anal. Calcd. for $C_9H_{14}O_3N_2$: C, 54.6; H, 7.12; N, 14.14. Found: C, 54.6; H, 7.10; N, 13.93.

The melting points of mixtures of V with authentic samples of barbital and N-methylbarbital were greatly depressed.

Rearrangement of IV and V to N-Methylbarbital.—Samples of IV (0.116 g.) and V (0.110 g.) were heated at 250–260° for 6 hours in sealed tubes evacuated to 1 mm. The nearly colorless liquids obtained crystallized on cooling. These were sublimed at 155° and 6 mm., and recrystallized from water. The yield from rearrangement of IV was 0.044 g., m.p. 148–150°, and from the rearrangement of V was 0.046 g., m.p. 150–151°.

Anal. Calcd. for $C_9H_{14}O_3N_2$: C, 54.6; H, 7.12; N, 14.14. Found for N-methylbarbital from IV: C, 54.6; H, 7.12; N, 14.42. Found for N-methylbarbital from V: C, 54.6; H, 7.10; N, 13.86.

The melting points of mixtures of the products from IV and V, and of each with authentic N-methylbarbital showed no depression.

Conversion of IV and V to Barbital.—Samples of IV (0.071 g.) and V (0.067 g.) were dissolved in 2 ml. of water with gentle heating. Two ml. of 30% hydrochloric acid was added, the mixtures were cooled to room temperature and then placed at 5° overnight. The crystals were filtered, washed with two 1-ml. portions of water, dried 12 hours *in vacuo* over potassium hydroxide and sublimed at 150° and 7 mm. The yield from IV was 0.048 g., m.p. 185–186°. The yield from V was 0.047 g., m.p. 184–185°.

Anal. Calcd. for $C_8H_{12}O_3N_2$: C, 52.2; H, 6.57; N, 15.19. Found for barbital from IV: C, 52.4; H, 6.54; N, 14.94. Found for barbital from V: C, 52.4; H, 6.59; N, 15.19.

The melting points of mixtures of the products from IV and V, and of each with authentic barbital showed no depression.

Acknowledgment.—We wish to thank our colleague, Dr. C. E. Ballou, for his kindness in reviewing the manuscript prior to its submission. We are also indebted to Mr. Tien-Hui Lin for his preparation of III in the quantity necessary for this study, and to Mr. Collin H. Schroeder for all carbon, hydrogen and nitrogen microanalyses.

MADISON 6, WISCONSIN

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF WISCONSIN]

Studies on 4-Hydroxycoumarins. XII. 3-Substituted-aminomethyl-4-hydroxycoumarin Derivatives by the Mannich Reaction[1]

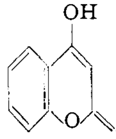
BY DALE N. ROBERTSON AND KARL PAUL LINK

RECEIVED NOVEMBER 22, 1952

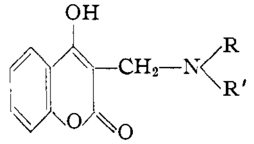
A series of 3-substituted-aminomethyl-4-hydroxycoumarins has been synthesized by an application of the Mannich reaction. A number of secondary amines gave the amine salts of 3,3′-methylenebis-4-hydroxycoumarin (III) (Dicumarol ®) instead of the expected Mannich products. Regeneration of 3,3′-methylenebis-4-hydroxycoumarin from the amine salts was effected by acidification with dilute hydrochloric acid at 25°. By heating an aqueous acid solution of 3-piperidinomethyl-4-hydroxycoumarin (IV) at 100° for 24 hours, III was obtained in essentially quantitative yield (97%). A mechanism for the conversion of IV to III is proposed.

Previous papers in this series have demonstrated the reactivity of the 3-position of 4-hydroxycoumarin (I) in the aldol[2] and Michael[3] addition reactions.

We have employed the Mannich reaction to obtain the 3-aminomethyl derivatives (II) of I.



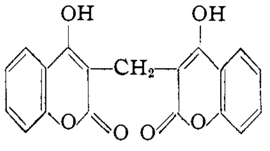
I



II

where R is hydrogen or alkyl and R′ is alkyl or aralkyl, or where –NRR′ makes up a heterocyclic ring

Attempts to prepare the desired compounds from paraformaldehyde and the amine hydrochlorides did not give the Mannich base, but exclusively the bis product, 3,3′-methylenebis-4-hydroxycoumarin (III) (Dicumarol®). Since the reaction between I and formaldehyde to form III is very rapid, the order in which the reactants are added is important. In this work, a solution of the amine (1.25 moles) and formaldehyde[4] (1.00 mole) in absolute ethanol was poured at room temperature into a solution of I (1.00 mole) in absolute ethanol. The procedure of Leffler and Hathaway[5] for the preparation of 2-hydroxy-3-substituted-aminomethyl derivatives of naphthoquinone in which the amine and lawsone (2-hydroxy-1,4-naphthoquinone) are mixed prior to addition of the formaldehyde also gave satisfactory results.



III

The reaction of 4-hydroxycoumarin (I) with primary amines and formaldehyde proceeded very rapidly. The 3-substituted-aminomethyl-4-hydroxycoumarins separated from the reaction mixture in an analytically pure crystalline state. An additional 10 to 15% of the products could be realized by diluting the mother liquors with absolute ether.

In contrast to the other products, 3-isobutylaminomethyl-4-hydroxycoumarin and 3-benzylaminomethyl-4-hydroxycoumarin underwent slight

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[1] Published with the approval of the Director of the Wisconsin Agricultural Experimental Station. Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

[2] W. R. Sullivan, C. F. Huebner, M. A. Stahmann and K. P. Link, THIS JOURNAL, **65**, 2288 (1943).

[3] M. Ikawa, M. A. Stahmann and K. P. Link, *ibid.*, **66**, 902 (1944).

[4] Formalin—37% formaldehyde.

[5] M. T. Leffler and R. J. Hathaway, THIS JOURNAL, **70**, 3222 (1948).

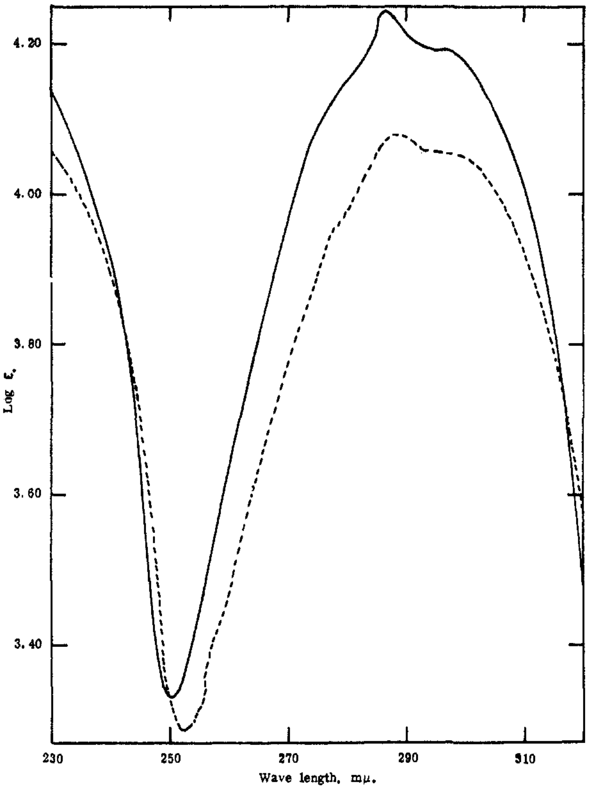


Fig. 1.—Absorption spectra: —, 4-hydroxycoumarin in 1% sodium hydroxide; - - - -, 3-piperidinomethyl-4-hydroxycoumarin in 95% ethanol.

decomposition when recrystallized from ethanol.

The reaction of 4-hydroxycoumarin (I) with the secondary amines dimethylamine and piperidine proceeded rather slowly. The reactants were mixed at the boiling point of the ethanolic solutions. After the solution reached room temperature, it was kept at 5° from one to four days to assure complete crystallization. A number of secondary amines did not undergo the Mannich reaction. Of the aliphatic secondary amines employed, only dimethylamine gave the desired product while diethyl-, diisopropyl- and dibenzylamines gave the amine salts of III. Leffler and Hathaway[5] had shown that diethylamine formed only a salt of the bis product in the Mannich reaction with lawsone.

All of the derived bases melt with decomposition. They are all insoluble in ether, soluble in alkali and the lower members of the series are moderately soluble in water. Their solubility in dilute acid decreases rapidly with increasing length of the alkyl group of the amine; thus, while the products from methylamine, dimethylamine, ethylamine and piperidine are soluble in 5% hydrochloric acid, the others are insoluble in this reagent. These facts, and the known acidity of I ($K_a = 2.3 \times 10^{-6}$)[6] indicate their probable existence as zwitterions.

The ultraviolet absorption spectra of I in ethanol and dilute sodium hydroxide and of IV in ethanol and dilute hydrochloric acid provide further evidence that the Mannich bases of 4-hydroxycoumarin exist as zwitterions. Blout, *et al.*,[7] have shown that alkali causes a typical shift in absorption of enolic β-diketones due to ionization of the compounds. The maxima are shifted to longer wave lengths and absorption is intensified. The spectra of I in dilute alkali and of IV in ethanol (Fig. 1) indicate that the 4-hydroxycoumarin moiety of both compounds is in the anionic form and thus that the Mannich base is ionized. When this ionization is suppressed by dissolving IV in dilute acid, its spectrum more closely resembles that of undissociated 4-hydroxycoumarin (Fig. 2).

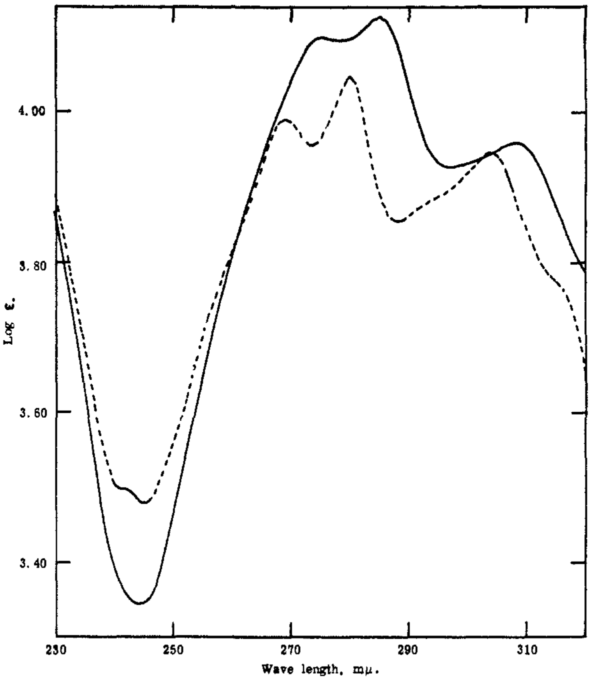
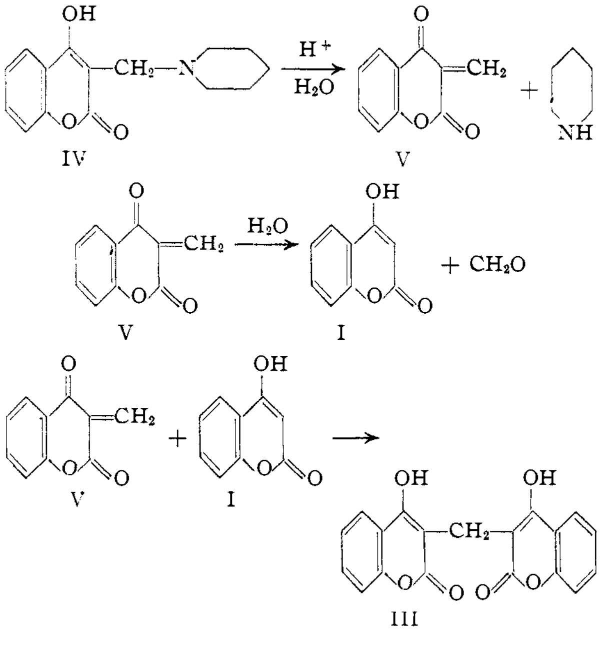


Fig. 2.—Absorption spectra: —, 3-piperidinomethyl-4-hydroxycoumarin in 1% hydrochloric acid; - - - -, 4-hydroxycoumarin in 95% ethanol.

By heating an aqueous acid solution of 3-piperidinomethyl-4-hydroxycoumarin (IV) at 100° for



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(6) C. F. Huebner and K. P. Link, THIS JOURNAL, **67**, 99 (1945).

(7) E. R. Blout, V. W. Eager and D. C. Silverman, *ibid.*, **68**, 566 (1946).

TABLE I

3-SUBSTITUTED-AMINOMETHYL-4-HYDROXYCOUMARINS

3-Substituent		Yield,	M.p.,		Carbon, %		Hydrogen, %	
R	R′	%	°C.[d]	Formula	Calcd.	Found	Calcd.	Found
H	CH_3	49.2	237–241	$C_{11}H_{11}NO_3$	64.38	64.37	5.40	5.66
H	C_2H_5	77.1	185	$C_{12}H_{13}NO_3$	65.74	65.73	5.93	6.18
H	C_2H_4OH	55.5	177	$C_{12}H_{13}NO_4$	61.29	61.31	5.57	5.71
H	$CH(CH_3)_2$	55.5	160	$C_{13}H_{15}NO_3$	66.92	66.77	6.48	6.49
H	C_4H_9[a]	58.0	155	$C_{14}H_{17}NO_3$	67.99	67.89	6.93	7.01
H	$CH_2(CH)(CH_3)_2$[b]	57.1	146	$C_{14}H_{17}NO_3$	67.99	67.86	6.93	7.02
H	$CH_2C_6H_5$[c]	69.0	159	$C_{17}H_{15}NO_3$	72.58	72.77	5.38	5.44
H	$(CH_2)_2C_6H_5$	77.7	180	$C_{18}H_{17}NO_3$	73.21	73.19	5.80	5.84
CH_3	CH_3	53.2	186	$C_{12}H_{13}NO_3$	65.74	65.86	5.98	5.75
$N(CH_2)_5$		79.6	182	$C_{15}H_{17}NO_3$	69.47	69.45	6.61	6.73

[a] Original m.p. of 133° was raised to 155° by drying over P_2O_5 at 65° and 3–4 mm. pressure for six hours. [b] Recrystallization gradually decomposes the compound, resulting in lower melting points. [c] Analyzed without recrystallization because of decomposition on heating. [d] All compounds melt with decomposition.

24 hours, III was obtained in essentially quantitative yield (97%).

A characteristic property of many of the products obtained in the Mannich reaction, especially those derived from secondary amines, is decomposition into the amine and an unsaturated compound.[8]

Accordingly, it can be postulated that III is formed by the following series of reactions, which depend on a similar initial decomposition of the Mannich base (IV) into the intermediate V. It is suggested that 4-hydroxycoumarin is formed from V by a reverse aldol reaction. A Michael addition of I to V would give 3,3′-methylenebis-4-hydroxycoumarin (III). This is supported by the isolation of a compound similar to V in the reaction between 4-hydroxycoumarin and salicylaldehyde reported by Sullivan, *et al.*[2]

Experimental

Preparation of 3-Substituted-aminomethyl-4-hydroxycoumarins.—The following procedure was found to be generally applicable for the preparation of the Mannich bases of 4-hydroxycoumarin.

A solution of 0.03 mole of the desired amine in 25 ml. of absolute ethanol was treated with 0.025 mole (as CH_2O) of aqueous formalin. To this solution was added 0.025 mole of 4-hydroxycoumarin in 50 ml. of absolute ethanol.

With the primary amines, the reactants were mixed at room temperature and the products usually began to separate at once. Crystallization was completed by allowing the reaction mixtures to stand in the refrigerator at 5° for one hour. The products were filtered and washed with absolute ether. By diluting the mother liquors with ether, additional quantities of the products were obtained. The yields are reported in Table I.

In the reactions with the two secondary amines, the reactants were mixed at the boiling point of the ethanolic solution, allowed to cool to room temperature and stored at 5° for one to four days. The products were separated as previously described.

Decomposition of 3-Piperidinomethyl-4-hydroxycoumarin.—A solution of 2.59 g. of 3-piperidinomethyl-4-hydroxycoumarin in 100 ml. of water containing 3 ml. of concentrated hydrochloric acid was heated on a steam-bath for 24 hours. The colorless solid was filtered, washed three times with water and air-dried; yield 1.63 g. (97%), m.p. 290–292°. An intimate mixture with authentic 3,3′-methylenebis-4-hydroxycoumarin melted at 292–295°.

Attempted Mannich Reaction with Diethylamine on 4-Hydroxycoumarin.—Using 2.2 g. (0.03 mole) of diethylamine, 2.02 g. (0.025 mole) of formalin and 8.1 g. (0.05 mole) of 4-hydroxycoumarin, the Mannich reaction was carried out as described above. When the reaction mixture was concentrated to about one-half volume crystals began to form. The reaction mixture was refrigerated for two hours, the product filtered, washed with absolute ethanol and ether and then dried. The product (4.82 g.) melted at 170–171.5°. Treatment with cold dilute hydrochloric acid gave 3,3′-methylenebis-4-hydroxycoumarin (III).

The diethylamine salt of 3,3′-methylenebis-4-hydroxycoumarin (III) was prepared from an authentic sample of III. A solution of 0.1 g. of III and 1 ml. of diethylamine in 10 ml. of absolute ethanol was diluted with 100 ml. of absolute ether and kept at 5° for two weeks. The product melted at 171–172° and showed no depression of melting point when mixed with the product isolated from the Mannich reaction with diethylamine.

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[8] Blicke in Adams, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 303.