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THE REACTION OF DICOUMAROL WITH ANILINE[1]

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ABSTRACT.—Dicoumarol [**1**] has been reported to yield 2 mol of 4-anilidocoumarin [**2**] (the anil of 4-hydroxycoumarin) when allowed to react with aniline. It is now shown that only 1 mol of 4-anilidocoumarin is formed, with the rest of the molecule being converted into a new compound, 1,4-dihydro-1-benzaz[3,2-*c*]-1,2-benzopyrone [**3**] (meancoumarin). The spectral properties of **3** are reported and compared to those of **2**, as well as to two other synthetic anils **4** and **5**.

Dicoumarol [**1**] is an anticoagulant often present in moldy clover, It is a cause of sickness and death in cattle (1,2), which has resulted in development of a variety of techniques for its quantitative measurement in clover (3,4). Its structure was determined by Stahman *et al.* in 1941 (5), partly by means of its reaction with aniline. It was reported that the reaction of dicoumarol with aniline at 180° yielded 2 mol of 4-anilidocoumarin [**2**] in almost quantitative amounts. However there was no indication of the fate of the methylene group during the reaction.

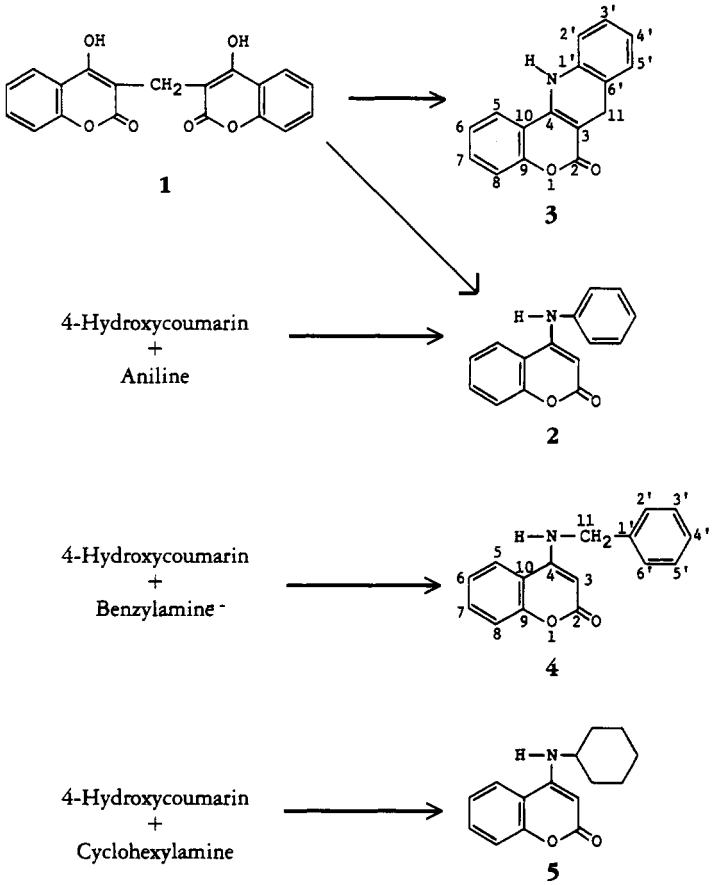
The reaction of dicoumarol with aniline has been repeated many times under a variety of conditions. Although a yield of material similar to that reported by Stahman *et al.* (5) has always been obtained, it was obvious that the product was not solely **2**. Rather it was an equimolar mixture of two compounds, one of which was **2**, the other being a new and different compound whose solubility characteristics were almost identical to those of **2**. The second compound has now been identified as 1,4-dihydro-1-benzaz[3,2-*c*]-1,2-benzopyrone [**3**], to which was assigned the trivial name meancoumarin (Scheme 1). The name was derived from the fact that it still contained the methylene group and yet was a derivative of the anil. Considering the difficulty of isolation and separation the name seemed appropriate.

Since dicoumarol contains a methylene group, simple formation of two molecules of **2** would result in the loss of a carbon atom. Attempts to identify or isolate such an atom (for example as CO_2, HCO_2H, or formaldehyde) gave negative results. A reaction using ^{14}C-methylene-labelled dicoumarol resulted in a product mixture containing essentially all of the ^{14}C in the isolated material. It was subsequently determined that the ^{14}C resided in the new compound **3**, and thus it was realized that **3** must retain the methylene group as part of its structure.

Extreme difficulty was encountered in any attempt to isolate **3** and separate it from **2**. The solubility characteristics of the two compounds are very similar, making fractional crystallization difficult. In addition **3** appears to decompose readily under many conditions. As a result, attempts to separate **2** and **3** by chromatographic means under a variety of mild conditions and solvents were not only unsuccessful but caused decomposition and resulted in mixtures that defied analysis.

Eventually fractional crystallization and flash chromatography provided pure samples of **3** (mp 290-292°). It analyzed for $C_{16}H_{11}O_2N$, and ms measurements confirmed a mol wt of 250. The ir spectrum showed the presence of an NH band at 3328 cm^{-1} but no OH absorption and showed the typical coumarin absorption at 1660–1680, 1610, and 1550–1570 cm^{-1}. The ^1H-nmr spectrum showed the presence of 8 aromatic protons at 7.0–

[1]This paper is dedicated to the memory of Professor Edward Leete.



SCHEME 1. Reaction of dicoumarol and 4-hydroxycoumarin with amines.

8.5, the two protons of the methylene group at 3.8, and a single proton on the nitrogen at 9.5 ppm. In addition the aromatic portion contained the typical resonances (integrating 1:1:2) of the four aromatic protons (8.25, 7.65, and 7.40 ppm) of an intact coumarin skeleton as well as the typical resonances for the benzene ring joined to the nitrogen atom (7.25 ppm). For comparison the 4-anilidocoumarin was synthesized, as were two other anils, by means of reaction with benzylamine and cyclohexylamine. The ^{13}C-nmr values are given in Table 1.

The values of meancoumarin correlate well with those of the three anils. However, the low solubility of the compound made the identification of the specific carbons in each aromatic ring uncertain.

These results lead to the structure of **3** as indicated. Analogues of the same ring system have recently been prepared by Martinez and co-workers (6,7), and a more aromatic system was earlier synthesized by Tabakovic *et al.* (8). Although the mechanism of the reaction has not been investigated, a reasonable mode of formation is suggested in Scheme 2.

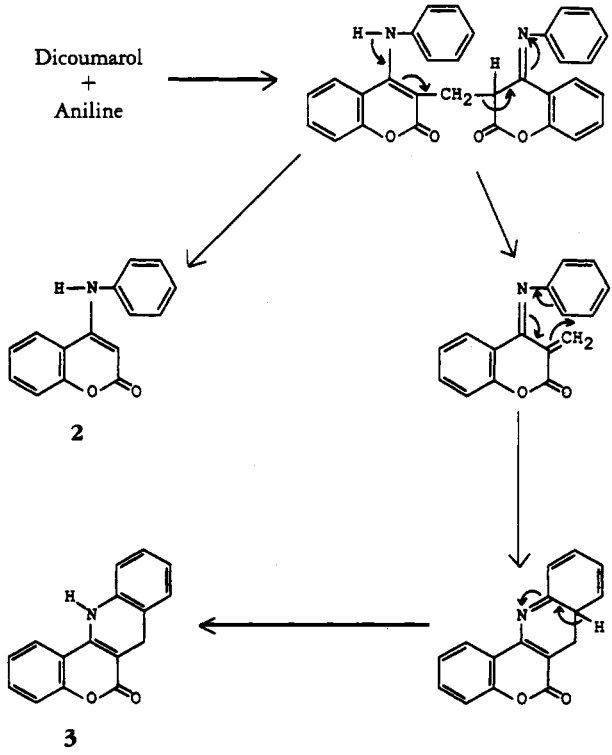
EXPERIMENTAL

REACTION OF DICOUMAROL WITH ANILINE.—Dicoumarol (1 g) was heated under reflux at 180° with aniline (15 ml) for 1 h. The reaction mixture was cooled, poured with stirring into 1 M HCl (200 ml), allowed to stand for 1 h, filtered, and dried. The solid material was added to boiling MeOH (1000 ml) and heated with stirring to complete solution. The solution was allowed to stand for 4 days at −5° and filtered. The solid material was recrystallized from MeOH or purified by flash chromatography (9) on Merck grade 60, 230–400 mesh, 60 Å, using MeOH-CH_2Cl_2 (15:85) as solvent, to yield meancoumarin [**3**]

TABLE 1. ^{13}C-nmr Assignments of Compounds **2–5**.

Carbon	Compound			
	2	**3**	**4**	**5**
C-2	161.4	162.0	161.5	161.6
C-3	84.3	92.1	82.5	81.3
C-4	153.3	145.0	153.1	153.2
C-5	122.7	116.8[a]	122.5	122.8
C-6	123.0	118.9[a]	123.5	123.1
C-7	132.3	131.5	132.0	131.8
C-8	117.0	116.0[a]	117.0	116.9
C-9	152.4	152.5	153.1	152.0
C-10	114.4	113.4	114.5	114.5
C-11	—	25.1	45.5	—
C-1′	138.2	137.0	137.8	51.1
C-2′	125.0	123.6[b]	127.1	31.6
C-3′	126.0	127.3[b]	128.6	31.6
C-4′	125.0	122.4	127.0	23.5
C-5′	126.0	128.7[b]	128.6	31.6
C-6′	125.0	123.4[b]	127.1	31.6

[a,b]Interchangeable.



SCHEME 2. Suggested mechanism of the reaction of dicoumarol with aniline.

(257 mg, 35%) mp 290–292°. Found C 76.85, H 4.42, N 5.09; calcd for $C_{16}H_{11}O_2N$, C 77.10, H 4.44, N 5.62. Ir ν max (KBr) 3328, 1660–1680, 1610, 1550–1570, 1490, 1450, 1380, 1230, 1210, 1180, 1160, 1060, 1040, 940, 760 cm^{-1}; ^1H nmr (DMSO, 250 MHz) δ 9.50 (s, -NH-), 7.00–8.25 (m, 8 aromatic H), 3.80 (s, 2H, $-CH_2-$); ^{13}C nmr see Table 1; eims $[M]^+$ 249.

The filtrate volume was reduced to 300 ml, allowed to stand for 3 days at −5°, and filtered. The solid material was recrystallized from MeOH to yield 4-anilidocoumarin [**2**] (230 mg, 35%), mp 260–262°, identical in all respects with a synthesized sample of **2**. Further reduction of the filtrate volume yielded a mixture of **2** and **3** (480 mg, 35%), which could be separated by a repetition of the above procedure. Reaction with aniline was also carried out on ^{14}C-methylenedicoumarol (specific activity 1.80×10^6 cpm·min^{-1}·$mmol^{-1}$). It yielded **3** (specific activity 1.46×10^6 cpm·min^{-1}·$mmole^{-1}$) and **2** (inactive).

Reaction of 4-hydroxycoumarin with amines.—4-Hydroxycoumarin (1 g) was heated under reflux with aniline (15 ml) for 1 h. The reaction mixture was cooled, poured with stirring into 1 M HCl (200 ml), allowed to stand for 1 h, filtered, and dried. The solid material was recrystallized from MeOH to yield 4-anilidocoumarin [**2**] (1.3 g, 90%): mp 260–262°; ir ν max (KBr) 3324, 1660–1680, 1610, 1550–1570, 1490, 1450, 1370, 1330, 1260, 1200, 1120, 1060, 1040, 950, 760 cm^{-1}; ^1H nmr (DMSO, 250 MHz) δ 9.35 (s, -NH-), 7.25–8.25 (m, 9 aromatic H), 5.32 (s, 1H, =C-); ^{13}C nmr see Table 1. The above procedure was repeated using benzylamine to yield 4-*N*-benzylaminocoumarin [**4**] (1.0 g, 65%), mp 243–244°. Found C 76.62, H 5.61, N 5.66; calcd for $C_{16}H_{13}O_2N$, C 76.46, H 5.22, N 5.58. Ir ν max (KBr) 3320, 1660–1680, 1610, 1550–1570, 1490, 1450, 1390, 1370, 1330, 1250, 1200, 1040, 990, 940, 760 cm^{-1}; ^1H nmr (DMSO, 250 MHz) δ 8.38 (t, 1H, -NH-), 7.25–8.20 (m, 9 aromatic H), 5.11 (s, 1H =CH-), 4.56 (d, 2H $-CH_2-$); ^{13}C nmr see Table 1. The above procedure was repeated using cyclohexylamine to yield 4-*N*-cyclohexylaminocoumarin [**5**] (450 mg, 30%), mp 194–196°. Found C 73.81, H 7.10, N 5.91; calcd for $C_{15}H_{17}O_2N$, C 74.03, H 7.05, N 5.76. Ir ν max (KBr) 3320, 1660–1680, 1610, 1550–1570, 1490, 1450, 1380, 1330, 1270, 1150, 1140, 1120, 1060, 1040, 940, 760. cm^{-1}; ^1H nmr (DMSO, 250 MHz) δ 7.30–8.30 (m, 4 aromatic H), 5.32 (s, 1H =CH-), 3.40 (s, 1H, -NH-), 1.00-2.10 (m, 11H-aliphatic); ^{13}C nmr see Table 1.

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