By dissolving a sample of the quinone in hydrochloric acid and titrating with sodium hydroxide it was determined that the pH of the color change was about 3.07.

A sample of 6a-azonianaphthacenequinone bromide was heated for 24 hr. on the steam bath with an equimolar amount of hydroxylamine hydrochloride in 48% hydrobromic acid (cyclizing conditions). No insoluble material was formed, and only starting material could be recovered from the solution.

The **perchlorate** of 6a-azonianaphthacenequinone (V) crystallized from water as yellow needles, m.p. 331.5–332°.

Anal. Calcd. for $C_{17}H_{10}ClNO_6$: C, 56.76; H, 2.80; N, 3.91. Found: C, 56.87; H, 2.91; N, 4.07.

1-(1,4-Dimethoxy-2-naphthylmethyl)-2-benzoylpyridinium Bromide (VII).—A solution of 4 g. of 2-(bromomethyl)-1,4-dimethoxynaphthalene and 3.1 g. of 2-benzoylpyridine in 10 ml. of dimethylformamide was allowed to stand at room temperature for 4 days. The addition of ether precipitated 3.9 g. (60%) of a yellow solid, m.p. 132–133°. The analytical sample crystallized from methanol–ethyl acetate as yellow needles, m.p. 132–133°.

Anal. Calcd. for $C_{25}H_{22}BrNO_3$: C, 64.66; H, 4.78; N, 3.02. Found: C, 64.44; H, 4.69; N, 3.39.

11-Phenyl-6a-azonianaphthacenequinone (VIII) Bromide.—A mixture containing 1.5 g. of the 2-benzoylpyridinium salt (VII) and 15 ml. of 48% hydrobromic acid was heated for 16 hr. on the steam bath. The acid was removed under reduced pressure, and the yellow residue recrystallized from methanol–ethyl acetate, yield 0.99 g. (74%), m.p. above 350°. The analytical sample formed yellow plates, m.p. >350°, and a strong absorption at 5.87 μ (carbonyl region).

Anal. Calcd. for $C_{23}H_{14}BrNO_2 \cdot {}^1/_2\ H_2O$: C, 64.95; H, 3.56; N, 3.29. Found: C, 64.84; H, 3.48; N, 3.54.

This compound formed green solutions in distilled water and in the common polar organic solvents. The green color was turned to yellow by the addition of mineral acid.

The **perchlorate** crystallized from methanol as yellow plates, m.p. 332–334°.

Anal. Calcd. for $C_{23}H_{14}ClNO_6$: C, 63.38; H, 3.23; N, 3.21. Found: C, 63.11; H, 3.24; N, 3.38.

The Reaction of 3-Acyl-4-hydroxycoumarins with Ammonium Salts[1]

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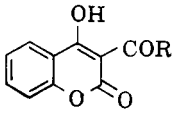
Ammonium acetate or amines in acetic acid react readily with 3-acetyl- or 3-benzoyl-4-hydroxycoumarin to form amino or imino substitution products. By using H_2O^{18} it was shown that the substitution took place in the 3α-position of the 3-acylcoumarin.

The reaction of 3-acyl-4-hydroxycoumarins with ammonium salts represents an interesting extension of the well established[3] reaction of β-diketone systems with amines.



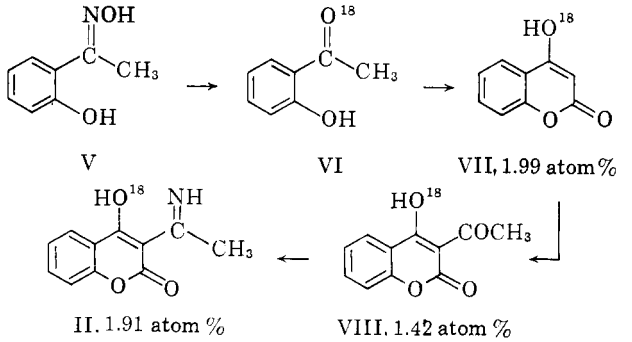
Ia. R = CH_3
Ib. R = C_6H_5

In our initial experiments ammonium acetate, the acylcoumarin, and ethyl cyanoacetate were refluxed in benzene in an attempted Knoevenagel condensation. 3-Acetyl- (Ia) and 3-benzoyl-4-hydroxycoumarin (Ib) yielded the corresponding amino or imino compounds II and III. It is of interest to note that Iguchi and Hisatune[4] assigned structure II to a product obtained by treatment of Ia with ammonia. No supporting evidence was given.

When 3-carbethoxy-4-hydroxycoumarin, 4-hydroxycoumarin, and dibenzoylmethane were treated with ammonium acetate in benzene, no imino compounds were formed. When ethylamine, isopropylamine, aniline, or ethanolamine reacted with equimolar quantities of acetic acid and Ib, good yields of the corresponding amino or imino compounds were obtained. Diethylamine and piperidine under the same conditions gave only the salts of Ib.

The nitrogen function could enter Ia and Ib either at the 2-, 4-, or 3α-position. Substitution at the 2-position was considered least likely since aniline[5] and morpholine[6] substitute in position 4 of 4-hydroxycoumarin (IV). If ammonium acetate reacted with Ia labeled with O^{18} in position 4, the position of the nitrogen substitution could be shown by the retention or loss of the O^{18}. Scheme A shows the approach used. Hydrolysis of *o*-hydroxyacetophenone oxime (V) in acidified H_2O^{18} formed *o*-hydroxyacetophenone-C=O^{18} (VI). This was condensed with diethyl carbonate to form 4-hydroxy-O^{18}-coumarin (VII). 3-Acetyl-4-hydroxy-O^{18}-coumarin (VIII) was obtained by the reaction of VII with acetyl chloride in pyridine. It was found that VIII (1.42 atom % excess) and ammonium acetate yielded II (1.91 atom % excess). The calculated value was 1.89 atom % excess for II if the nitrogen entered the 3α-position.

Both Davis and Hurd[7] and Dudek and Holm[8] have assigned specific structures to the β-diketone derivatives they investigated; we feel that the analogy between the



SCHEME A

(1) Published with the approval of the director of the Wisconsin Agricultural Experiment Station. Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation. This work is from the Ph.D. theses of Robert A. Kloss, 1956, and C. Wiener, 1960, done under the supervision of Professor Karl Paul Link.

(2) Department of Chemistry, Northern Illinois University, DeKalb, Ill.

(3) N. H. Cromwell, *Chem. Rev.*, **38**, 83 (1946).

(4) S. Iguchi and K. Hisatune, *J. Pharm. Soc. Japan*, **77**, 98 (1957).

(5) R. Anschütz, *Ann.*, **367**, 204 (1909).

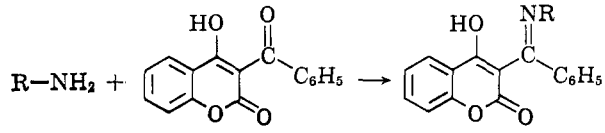
(6) O. P. Spaulding, H. S. Mosher, and F. C. Whitmore, *J. Am. Chem. Soc.*, **72**, 5338 (1950).

(7) R. B. Davis and P. Hurd, *ibid.*, **77**, 3284 (1955).

(8) G. O. Dudek and R. M. Holm, *ibid.*, **84**, 2691 (1962).

TABLE I

REACTION OF 3-BENZOYL-4-HYDROXYCOUMARIN WITH PRIMARY AMINES

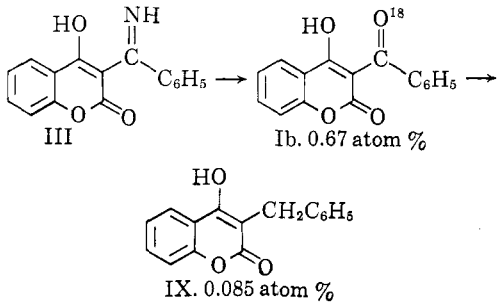


R—	M.p., °C.	Yield, %	Formula	Analysis: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_3CH_2—	129–130	78.5	$C_{18}H_{15}NO_3$	73.77	73.37	5.16	5.56
CH_2OH—CH_2—	119–121	91.0	$C_{18}H_{15}NO_4$	69.89	69.28	4.89	5.07
C_6H_5—	155–157	95.0	$C_{22}H_{15}NO_3$	77.40	77.77	4.43	4.43
$(CH_3)_2CH$—	136–138	97.2	$C_{19}H_{17}NO_3$	74.25	74.72	5.58	5.91

reported compounds and ours is not sufficiently close to permit assignment of a specific tautomer.

The reaction sequence shown in Scheme A could not be used to locate the nitrogen in the product from Ib, since Ib cannot be synthesized directly from VII.[9]

Compound III, when hydrolyzed in acetic acid–sulfuric acid–H_2O^{18}, gave Ib containing 0.66 atom % excess O^{18}. The Ib was in turn hydrogenolyzed[10] to 3-benzyl-4-hydroxycoumarin (IX), which was found to contain 0.085 atom % excess O^{18}. This approach is shown in Scheme B.



SCHEME B

A control experiment showed that Ib became labeled by exchange when subjected to the conditions used for the hydrolysis of III. Hydrogenolysis of this labeled Ib (0.57 atom % excess) gave IX with a residual O^{18} content of 0.089 atom % excess.

The control experiment shows that the 3α-position in Ib exchanges extensively, but if the nitrogen were not at the 3α-position of III, two positions would become labeled during hydrolysis. The structure 3-(α-iminobenzyl)-4-hydroxycoumarin (III) is, therefore, assigned.

The residual O^{18} in the samples of IX obtained by hydrogenolysis of Ib shows that there is some exchange of oxygen in the 4-hydroxycoumarin moiety. This would be expected from O^{18} studies which showed that the carbonyl oxygen of dimedone is replaced in the acid-catalyzed formation of dimedone enol ether.[11]

The definitive proof of structure of the products resulting from the reaction of the two 3-acyl-4-hydroxycoumarins with various amines has not been attempted.

(9) H. R. Eisenhauer, and K. P. Link, *J. Am. Chem. Soc.*, **75**, 2046 (1953).
(10) I. M. Hellbron and D. W. Hill, *J. Chem. Soc.*, **1927**, 1705,
(11) K. B. Wiberg and K. A. Saegebarth, *J. Org. Chem.*, **25**, 832 (1960).

Experimental

Preparation of Iminocoumarins.—The synthesis of II and III illustrates the method. The same methods were used with other ammonium salts and with the various amines and acetic acid. See Table I for compounds obtained from amines.

3-(α-Iminoethyl)-4-hydroxycoumarin (II)—3-Acetyl-4-hydroxycoumarin(Ia)[12,13] (10.2 g.) and 4.0 g. of ammonium acetate refluxed in 50 ml. of ethanol for 12 hr. gave 10.5 g. (quantitative yield) of II, m.p. 221–225°. Recrystallization from dioxane gave II, m.p. 230–231°; λ_{max}^{KBr} 3.05 (w), 3.43, 5.85 (w), 6.20 μ.

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46. Found: C, 64.83; H, 4.50.

3-(α-Iminobenzyl)-4-hydroxycoumarin (III).—3-Benzoyl-4-hydroxycoumarin (Ib)[9] (6.65 g.) in 50 ml. of absolute ethanol gave, when treated with 2 g. of ammonium acetate, 6.3 g. (94%) of colorless crystals, m.p. 223–226°; λ_{max}^{KBr} 3.00, 3.15, 3.44, 5.96, 6.15, 6.21 μ.

Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.43; H, 4.18. Found: C, 72.30; H, 4.53.

Materials and Methods Used in the Oxygen-18 Analyses.—The methods used for O^{18} analyses were similar to those reported by Rittenberg and Ponticorvo.[14]

Each of the samples (8–10 mg.) was mixed with 100 mg. of mercuric chloride and heated in a Pyrex tube at 510–550° for 1.5 hr.

When the ratio of masses 46:44 of tank carbon dioxide deviated from the normal (0.00409), the measured ratios for the enriched samples were corrected accordingly.[15] The O^{18} contents were determined in duplicate or triplicate. The deviations from the mean were less than 1.5% of the average value.

***o*-Hydroxyacetophenone-C=O^{18} (VI).**—To O^{18} enriched water (1.8 ml., 6.48 atom % excess) saturated with hydrogen chloride was added 15.1 g. of *o*-hydroxyacetophenone oxime. The solution was refluxed for 1.5 hr., cooled, and extracted twice with 50-ml. portions of ether. The ether was dried (magnesium sulfate) and evaporated. The remaining oil was distilled at 95–98° (0.05 mm.).

4-Hydroxy-O^{18}-coumarin (VII).—A method similar to that reported by Dickenson[16] was used. Diethyl carbonate (50 g.), 3.4 g. of sodium ethoxide, and 10 g. of the labeled *o*-hydroxyacetophenone (VI) were heated on a steam bath 4 hr. Water (150 ml.) was added and the aqueous layer was separated and acidified with hydrochloric acid. Crystallization from ethanol–water yielded 5.2 g., m.p. 209–212°, O^{18} content, 1.99 atom % excess.

3-Acetyl-4-hydroxy-O^{18}-coumarin (VIII).—A procedure similar to that reported by Eisenhauer and Link[13] was used for this preparation. The product from 3.0 g. of 4-hydroxy-O^{18}-coumarin was crystallized from ethanol–water to yield 2.1 g., m.p. 130–131°, O^{18} content, 1.42 atom % excess.

(12) T. Ukita, N. Shosichi, and H. Matsumoto, *J. Am. Chem. Soc.*, **72**, 5143 (1950).
(13) H. R. Eisenhauer and K. P. Link, *ibid.*, **75**, 2044 (1953).
(14) D. Rittenberg and L. Ponticorvo, *J. Appl. Radiation Isotopes*, **1**, 208 (1956).
(15) W. G. Miller and L. Anderson, *Anal. Chem.*, **31**, 1668 (1959).
(16) H. G. Dickenson, U. S. Patent 2,449,162 (1949).

3-(α-Iminoethyl)-4-hydroxy-O^{18}-coumarin (Labeled II). 3-Acetyl-4-hydroxy-O^{18}-coumarin (1.0 g.) and 0.3 g. of ammonium acetate were refluxed in 10 ml. of absolute ethanol for 9 hr. The solid which separated on cooling was recrystallized from absolute ethanol; yield 0.9 g., m.p. 233–235°, O^{18} content, 1.91 atom % excess.

3-Benzoyl-4-hydroxy-O^{18}-coumarin (Labeled IB). A. By the Hydrolysis of III in an O^{18} Enriched Medium.—Acetic acid (3.10 ml.), 1.68 ml. of O^{18} enriched water (6.48 atom % excess), 0.21 ml. of concentrated sulfuric acid, and 0.3 g. of III were refluxed 1.5 hr. The product which separated was crystallized twice from absolute ethanol; yield 0.2 g., m.p. 145°, O^{18} content, 0.667 atom % excess.

This seemingly low O^{18} value results from isotopic exchange with the acetic and sulfuric acids.[17] The theoretical O^{18} content is 0.70 atom % excess.

B. By Equilibration of 3-Benzoyl-4-hydroxycoumarin with an O^{18} Enriched Solution (Control Experiment).—When 0.3 g. of Ib was treated in the same manner as reported for the hydrolysis of III, the product had an O^{18} content of 0.561 atom % excess.

3-Benzyl-4-hydroxycoumarin (IX). A. By Hydrogenolysis of O^{18} Labeled Ib Obtained from III.—Labeled Ib obtained from the hydrolysis of III (80 mg.) was shaken for 3 hr. in 10 ml. of anhydrous methanol with 80 mg. of 10% palladium on charcoal and hydrogen at 38–40 p.s.i. The catalyst was removed and the solvent was evaporated to 1 ml. by a stream of nitrogen. Cooling to −10° yielded 40 mg. of product, m.p. 205°, O^{18} content, 0.085 atom % excess.

B. By Hydrogenolysis of O^{18} Labeled Ib Obtained from Equilibration with O^{18} Water (Control Experiment).—3-Benzoyl-4-hydroxy-O^{18}-coumarin obtained in the exchange experiment with 3-benzoyl-4-hydroxycoumarin and O^{18} water was reduced as in part A. The starting material had an O^{18} content of 0.561 atom % excess; the product was found to have an O^{18} content of 0.089 atom % excess.

(17) T. C. Hoering and J. W. Kennedy, *J. Am. Chem. Soc.*, **79**, 56 (1957).

Acknowledgment.—The writers are indebted to Professor Karl Paul Link and his associates, Dr. Bruce D. West and Dr. C. H. Schroeder, for valuable suggestions in the development of this work. Professor Laurens Anderson kindly loaned us his apparatus for isotope analysis and also helped with the interpretation of the analytical data and the preparation of the manuscript.

1,2-Dicarbonyl Derivatives Resulting from the Action of Nitrosyl Chloride on Alcohols

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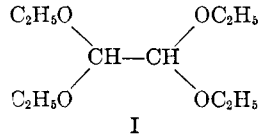
From the synthesis of phenylglyoxal diethyl acetal by the reaction of nitrosyl chloride with acetophenone in ethanol solution, considerable yields of an unknown by-product were isolated. This proved to be 1,1,2,2-tetraethoxyethane and resulted from the action of nitrosyl chloride upon ethanol, presumably by way of oxidation of the intermediate ethyl nitrite. Treatment of a large excess of ethanol with nitrosyl chloride afforded about 50% yields of 1,1,2,2-tetraethoxyethane, assuming four moles of nitrosyl chloride are required for the oxidation, at 30–50° and with a reaction time of three to four hours. The reaction was not accelerated upon illumination with an intense source of visible light. Application of the reaction to 1-propanol led to an inseparable mixture which, however, yielded derivatives of pyruvaldehyde upon treatment with carbonyl reagents. Isopropyl alcohol with nitrosyl chloride afforded a low yield of pyruvohydroxamyl chloride as the only isolable product. Both ethylene glycol and propylene glycol yielded complex mixtures upon treatment with nitrosyl chloride. Although none of the reaction products were positively identified in either case, it was possible to demonstrate the presence of glyoxal-yielding compounds in the ethylene glycol product and pyruvaldehyde-yielding compounds in the propylene glycol product by treatment of the distilled products with 2,4-dinitrophenylhydrazine and identification of the corresponding 2,4-dinitrophenylosazone derivatives.

During a recent study[1] of the preparation of phenylglyoxal diethyl acetal by the reaction of nitrosyl chloride with acetophenone in ethanol solution, a by-product [b.p. 80–84° 10 (mm.)] was observed in yields amounting to as much as one-third of the weight of the desired phenylglyoxal acetal. Elemental and infrared analyses and molecular weight determination suggested the identity of the by-product to be 1,1,2,2-tetraethoxyethane (I). Confirmation of the structure then was obtained



I

by acid hydrolysis of the by-product to ethanol and glyoxal followed by conversion of the latter to glyoxime by reaction with hydroxylamine. The possibility that the glyoxal acetal (I) arose solely from reaction of nitrosyl chloride with the solvent then was considered. Nitrosyl chloride was fed to a large excess of ethanol while maintaining the solution at slightly above room temperature. Upon warming to 38° a vigorous reflux of ethyl nitrite occurred and an exothermic reaction began, accompanied by rapid evolution of a mixture of nitric oxide, nitrous oxide, and nitrogen. The reaction mixture was allowed to stand for several hours and, after treatment with hot aqueous sodium hydroxide to remove any acidic or ester by-products, was distilled to give 1,1,2,2-tetraethoxyethane in an amount equivalent to 38.5% of the weight of nitrosyl chloride employed. In subsequent trials the time required for completion of the nitrosyl chloride reaction was found to be as short as three to four hours. Despite the uncertainty surrounding the mechanism, it is likely that at least three and possibly four moles of nitrosyl chloride are required for oxidation of the methyl and methylol groups of ethanol, the latter situation being represented by the following over-all equation.

$$4NOCl + 5C_2H_5OH \longrightarrow (C_2H_5O)_2CHCH(OC_2H_5)_2 + 2H_2O + 2NO + N_2O + 4HCl \quad (1)$$

A requirement of three moles of nitrosyl chloride corresponds to a yield of 37% while a four-mole requirement would indicate a 49% yield.

Study of this surprising oxidation occurring under the mild condition of a ketone nitrosation was then

(1) David T. Manning and Harry A. Stansbury, Jr., *J. Org. Chem.*, **26**, 3755 (1961).