of benzothiophene[5] with the spectra of naphthalene[5] and styrene,[7] Fig. 1),[8] its reaction with methyl iodide to form a high melting solid containing both nitrogen and sulfur, and its conversion to a crystalline picrate of elementary analyses appropriate for I monopicrate.

Hansch and Carpenter[9] were unable to isolate any thienopyridine upon treating 4-vinylpyridine with hydrogen sulfide in the manner of Moore and Greensfelder.[2] Instead, they obtained a yellow liquid which formed a crystalline dipicrate and was presumed to be β,β-di(4-pyridyl)ethyl sulfide.

EXPERIMENTAL

The apparatus used was modified from that previously reported.[1, 2] The ferrous sulfide–alumina catalyst was prepared by impregnating activated alumina (Fisher Scientific Co., 8–14 mesh) with 1.25*M* aqueous ferric nitrate solution, sulfiding, and calcining.[2] Commercial hydrogen sulfide was used directly from the cylinder. 2-Vinylpyridine (Reilly Tar and Chemical Corp., Indianapolis) was distilled from its inhibitor just prior to use. In a typical run which furnished maximum yields of total products condensable above 0°, the reaction temperature was 603 ± 3°; the flow rates of hydrogen sulfide and 2-vinylpyridine were 475 ml./min. and 29.5 g./hr., respectively (molar ratio 4.1:1); the calculated contact time (assuming the catalyst bed was a total void, *i.e.*, 700 ml.) was 24 sec.; and the total reaction time was 80 min.

The dark liquid (15 g.) which collected in air- and ice water–cooled receivers was distilled under reduced pressure in a nitrogen atmosphere. From earlier fractions of distillate were obtained ethyl mercaptan (positive colorimetric test with sodium nitroprusside, converted to ethyl 2,4-dinitrophenyl sulfide), diethyl sulfide (converted to sulfone), pyridine (converted to picrate), thiophene (converted to 2-mercurichloride derivative), and sulfur. Sulfur and each of the preceding crystalline derivatives were identified by melting point and mixture melting point with authentic samples of the same substances.

Thieno[3,2-b]pyridine (I) was collected from the higher boiling fraction as a yellow liquid, b.p. 82–84° (2 mm.), yield 0.8 g. (1.6%); $\lambda_{max}^{C_2H_5OH}$ 230 mμ (log ε 4.42), 278 (3.71), 285–290 (3.65)-shoulder, *ca.* 315 (2.4)-shoulder; soluble in ethanol, ether, benzene, and dilute hydrochloric acid; insoluble in water and aqueous sodium hydroxide. I darkened upon exposure to air at room temperature for a few hours, but it remained yellow for several weeks when stored under nitrogen at 0°.

Treatment of I with an equimolar quantity of picric acid in methanol gave green-yellow needles of *picrate*, recrystallized from ethyl acetate to constant m.p., 195.5–197.5°.

Anal. Calcd. for $C_{13}H_8N_4O_7S$: C, 42.86; H, 2.21; N, 15.38; S, 8.80. Found: C, 43.17; H, 2.18; N, 15.38; S, 8.26.

Treatment of I with excess methyl iodide gave pale yellow needles, presumably the methiodide, m.p. 217–219.5° with previous darkening, not obtained sufficiently pure for elementary analysis but giving positive qualitative sodium-fusion tests for the presence of nitrogen and sulfur.

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(7) G. Allard, *Helv. Chim. Acta*, **19**, 1270 (1936).

(8) W. Herz and L. Tsai, *J. Am. Chem. Soc.*, **75**, 5122 (1953) have noted a "marked resemblance" between the spectra of isoquinoline and thieno[2,3-*c*]pyridine.

(9) C. Hansch and W. Carpenter, *J. Org. Chem.*, **22**, 936 (1957).

3-Hydroxycoumarins

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3-Hydroxycoumarin has an inhibiting effect on the growth of *avena* roots[1] and 3-aminocoumarins, which are intermediates in the synthesis of 3-hydroxycoumarins, are found to have antibacterial properties.[2] The present work deals with the synthesis of some substituted 3-hydroxycoumarins and a study of the pattern of substitution in 3-hydroxycoumarin.

5-Bromo-, 3,5-dibromo-, 3-nitro-, 5-nitro-, and 3,5-dinitrosalicylaldehyde, methyl 2,4-dihydroxy-3-formylbenzoate and 2,4-dihydroxy-3-formylacetophenone were condensed according to Shaw, McMillen, and Armstrong[3] with acetylglycine in the presence of sodium acetate and acetic anhydride and the 3-acetamidocoumarins formed hydrolyzed with alcoholic 3*N*-hydrochloric acid to the 3-hydroxycoumarins. The intermediate 3-aminocoumarins could not be isolated even under controlled hydrolysis with acid or alkali.

The ketonic character of the 3-hydroxycoumarin has been shown by the formation of a phenylhydrazone and a quinoxaline derivative with *o*-phenylenediamine.[4] It is now found that 3-hydroxycoumarin gives the isonitroso derivative with nitrous acid. With bromine in acetic acid it gave the 4-bromoderivative and with iodine and iodic acid the 4-iodo derivative, both of which gave the original coumarin on reduction with zinc and acetic acid. Further bromination did not succeed, but the 6-bromo- and 6,8-dibromo-3-hydroxycoumarin were brominated in the 4-position. 3-Acetoxycoumarin underwent Fries migration to give the 4-acetyl derivative which was also obtained in the Friedel-Crafts acetylation of 3-hydroxycoumarin. On oxidation it gave salicylic acid. 3-Hydroxycoumarin when treated with formaldehyde gave 4-4′-methylenebis(3-hydroxycoumarin).

EXPERIMENTAL

Synthesis of 3-hydroxycoumarins. An equimolecular mixture of the salicylaldehyde derivative, acetylglycine, and anhydrous sodium acetate and acetic anhydride (2 moles) was heated on a steam bath for 1 hr. The 3-acetamidocoumarin derivative obtained on dilution with water was crystallized from acetic acid (Table I).

The acetamidocoumarin was dissolved in a minimum quantity of alcohol and refluxed with 3*N* hydrochloric acid for 3 to 4 hr. The 3-hydroxycoumarin obtained on cooling

(1) R. H. Goodwin and G. Taves, *Am. J. Botany*, **37**, 224 (1950).

(2) G. Rodighiero and C. Antonello, *Bull. Chim. Farm.*, **97**, 592 (1958).

(3) K. N. F. Shaw, A. McMillen, and M. D. Armstrong, *J. Org. Chem.*, **21**, 601 (1956).

(4) E. Erlenmeyer, Jr., and W. Stadlin, *Ann.*, **337**, 283 (1904).

TABLE I

3-ACETAMIDOCOUMARIN DERIVATIVES

No.	Aldehyde	3-Acetamido-coumarin	M.P.	Formula	Analyses	
					Found	Calcd.
1	5-Bromosalicylaldehyde	6-Bromo-,[a]	261–262°	$C_{11}H_8O_3NBr$	Br, 28.57	Br, 28.36
2	3,5-Dibromosalicylaldehyde	6,8-Dibromo-,	279°	$C_{11}H_7O_3NBr_2$	Br, 44.66	Br, 44.32
3	5-Nitrosalicylaldehyde	6-Nitro-,	278°	$C_{11}H_8O_5N_2$	N, 11.09	N, 11.3
4	3-Nitrosalicylaldehyde	8-Nitro-,	268°	$C_{11}H_8O_5N_2$	N, 11.14	N, 11.3
5	3,5-Dinitrosalicylaldehyde	6,8-Dinitro-,	225°	$C_{11}H_7O_7N_3$	N, 14.54	N, 14.33
6	Methyl-2,4-dihydroxy-3-formylbenzoate	5-Acetoxy-6-carbomethoxy-,	255°	$C_{15}H_{13}O_7N$	N, 4.57	N, 4.52
7	2,4-Dihydroxy-3-formylacetophenone	5-Acetoxy-6-acetyl-,	290°	$C_{15}H_{13}O_6N$	N, 4.95	N, 4.62

[a] F. W. Linch (*J. Chem. Soc.*, 1758 (1912)) prepared it by a different route and gave the m.p. 266°. The hydrolysis of this product with dilute sulfuric acid did not give the 3-aminocoumarin derivative as reported by Linch but gave the 3-hydroxycoumarin derivative.

TABLE II

3-HYDROXYCOUMARIN DERIVATIVES

No.	3-Hydroxycoumarin	M.P.	Formula	Analyses	
				Found	Calcd.
1	6-Bromo-,	252°	$C_9H_5O_3Br$	Br, 33.23	Br, 33.02
2	6,8-Dibromo-,	261°	$C_9H_4O_3Br_2$	Br, 49.82	Br, 50.0
3	6-Nitro-,	256°	$C_9H_5O_5N$	N, 6.9	N, 6.76
4	8-Nitro-,	220°	$C_9H_5O_5N$	N, 6.7	N, 6.76
5	6,8-Dinitro-,	185°	$C_9H_4O_7N_2$	N, 10.8	N, 11.11
6	5-Hydroxy-6-carbomethoxy-,	225°	$C_{11}H_8O_6$	C, 60.24	C, 60.0
				H, 3.62	H, 3.64
7	5-Hydroxy-6-acetyl-,	230°	$C_{11}H_8O_5$	C, 55.52	C, 55.9
				H, 3.02	H, 3.39
8	4-Bromo-,[a]	210°	$C_9H_5O_3Br$	Br, 33.15	Br, 33.02
9	4,6-Dibromo-,[b]	273°	$C_9H_4O_4Br_2$	Br, 50.15	Br, 50.0
10	4,6,8-Tribromo-,[c]	230°	$C_9H_9O_3Br_3$	Br, 59.6	Br, 60.1

[a] Obtained by the bromination of 3-hydroxycoumarin. [b] Obtained by the bromination of 6-bromo-3-hydroxycoumarin. [c] Obtained by the bromination of 6,8-dibromo-3-hydroxycoumarin.

was crystallized from alcohol (Table II). All the 3-hydroxycoumarins gave a characteristic green coloration with alcoholic ferric chloride, and were soluble in sodium hydroxide solution in the cold on standing.

4-Isonitroso-2,3-diketochroman. A mixture of 3-hydroxy coumarin (1 g.) in a minimum quantity of acetic acid and 5 ml. concd. hydrochloric acid was kept in an ice bath and sodium nitrite solution (0.5 g. in 5 ml. of water) was added dropwise. Sodium bicarbonate solution was added to neutralize the solution, which was then extracted with ether. The product obtained from ether crystallized from a benzene-ligroin mixture in stout yellow needles, m.p. 185° dec.

Anal. Calcd. for $C_9H_5O_4N$: N, 7.3. Found: N, 7.1.

Brominations. To 3-hydroxycoumarin or its derivative in acetic acid a molecular quantity of bromine in acetic acid was added and the reaction mixture stirred for 0.5 hr. The product which separated was crystallized from acetic acid (Table II).

4-Iodo-3-hydroxycoumarin. To 3-hydroxycoumarin (1.72 g.) and iodine (1.16 g.) dissolved in a minimum quantity of alcohol, iodic acid (0.4 g.) was added with stirring. The product which separated was filtered and crystallized from alcohol as pale yellow needles, m.p. 223° dec.

Anal. Calcd. for $C_9H_5O_3I$: I, 44.06. Found: I, 43.74.

Reductions. 4-Bromo- or 4-iodo-3-hydroxycoumarin (0.5 g.) was dissolved in acetic acid (25 ml.) and zinc dust (1 g.) was added. The reaction mixture was refluxed for 2 hr. It was filtered hot and diluted with water. The product which separated was crystallized from alcohol; melting point and mixed melting point with 3-hydroxycoumarin was 151°.

3-Acetoxycoumarin was obtained by heating 3-hydroxycoumarin with pyridine and acetic anhydride. It crystallized from benzene in colorless needles; m.p. 105–106°. It did not give any coloration with alcoholic ferric chloride.

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.71; H, 3.93. Found: C, 64.81; H, 4.3.

4-Acetyl-3-hydroxycoumarin. A mixture of 3-acetoxycoumarin (1 mole) and anhydrous aluminum chloride (2 moles) was heated in an oil bath at 140° for 2 hr. The reaction mixture was worked up as usual. The product obtained was dried and extracted with hot petroleum ether (b.p. 60–80°). The product obtained on repeated crystallization from the same solvent gave colorless needles, m.p. 85°. The same product was obtained in the Friedel-Crafts acetylation of 3-hydroxycoumarin (1.6 g.) by heating it with anhydrous aluminum chloride (2.5 g.) and acetic anhydride (4 ml.) on a steam bath for 3 hr. It gave a green coloration with alcoholic ferric chloride.

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.71; H, 3.93. Found: C, 64.84; H, 3.88.

The 2:4-dinitrophenylhydrazone, prepared as usual, melted at 236–238° dec.

Anal. Calcd. for $C_{17}H_{11}O_7N_4$: N, 11.59. Found: N, 11.7.

Oxidation. 4-Acetyl-3-hydroxycoumarin (1 g.) was dissolved in sodium hydroxide (10%; 10 cc.) and heated with potassium permanganate (0.5 g.) on a steam bath for 3 hr.

The product obtained on working up as usual melted at 156°. Mixed melting point with salicylic acid was not lowered.

4,4'-Methylenebis(3-hydroxycoumarin). A mixture of 3-hydroxycoumarin (1 g.), alcohol (20 ml.), and formalin (40% soln. 3 ml.) was refluxed for 3 hr. The separated product was filtered hot and crystallized from alcohol as colorless needles, m.p. 266°.

Anal. Calcd. for $C_{19}H_{12}O_6$: C, 67.85; H, 3.57. Found: C, 67.46; H, 3.35.

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The Mechanism of the Rearrangement of 2-Phenyl-4-hydroxymethylene-5-oxazolone[1,2]

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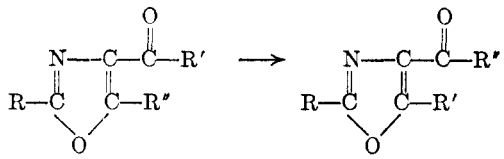
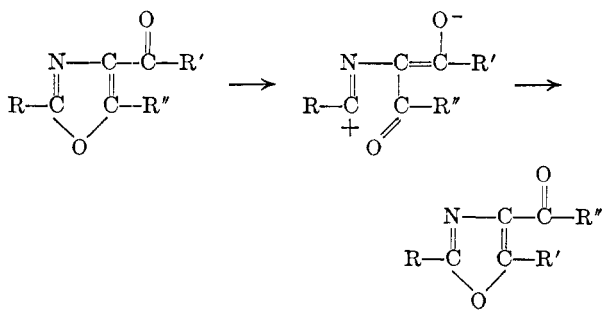
Synthetic work directed toward the synthesis of the erroneously postulated thiazolidine-oxazolone structure for penicillin led to a considerable advance in the chemistry of oxazolones. During the course of these studies a substance isomeric with 2-benzyl-4-hydroxymethylene-5-oxazolone was isolated from a reaction involving the latter compound. This isomeric compound was subsequently proved to be 2-benzyloxazole-4-carboxylic acid.[4a] Later several examples of the same general type of rearrangement came to light. The reaction can be formulated in general as an intramolecular rearrangement of 5-substituted oxazoles having a carbonyl carbon at C_4.[4b]



A direct interchange of R′ and R″ is rather unlikely. A more plausible mechanism, suggested by Cornforth,[4b] involves oxazole ring opening at C_2 followed by recyclization at the carbonyl oxygen.



We have substantiated this mechanism with C^{14} as a tracer.

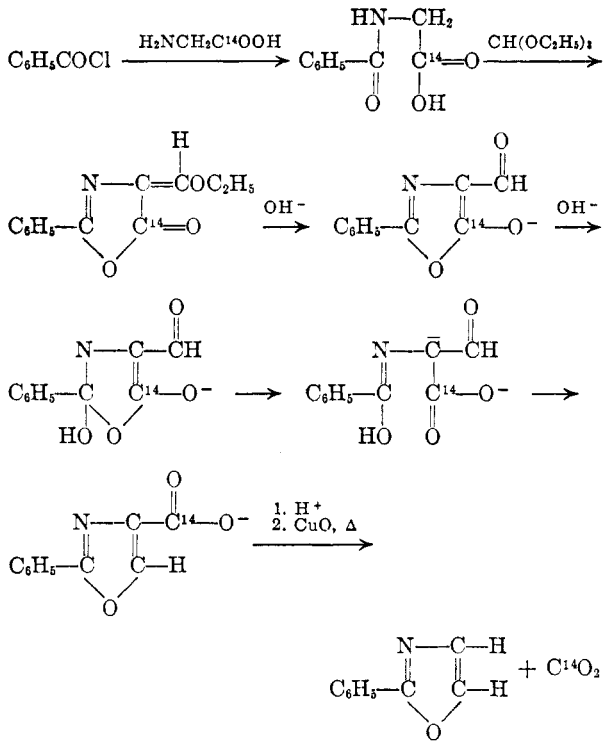


Table I shows that all of the radioactive carbon was in the carbon dioxide obtained by decarboxylation of the rearrangement product, 2-phenyloxazole-4-carboxylic acid.

TABLE I

COUNTING DATA FOR PERTINENT COMPOUNDS

Compound	Sample, Wt., Mg.	Count[a] per Min.	Background Count per Min.	Av. Count[b] per Min.
2-Phenyloxazole-4-carboxylic acid	106.2	2946	28	
	76.2	3024	28	2957
Barium carbonate	129.3	3166	30	
	122.1	3156	30	3131
2-Phenyloxazole	238.5	31	30	0

[a] After coincidence correction was applied. [b] All samples were of infinite thickness so that the total count is proportional to the specific activity.

Several attempts were made to prepare 2-phenyl-5-ethoxyoxazole-4-carboxylic acid from 2-phenyl-4-bromo-5-ethoxyoxazole *via* reaction with cuprous cyanide and with *n*-butyllithium. Neither reaction was successful under a wide variety of conditions.

(1) Abstracted from a Masters thesis by Dan Powers.

(2) Presented before the 134th meeting of the American Chemical Society, Chicago, Ill., Sept. 12, 1958.

(3) Present address: Department of Chemistry, Washington University, Seattle, Wash.

(4) H. T. Clarke, J. R. Johnson, and Sir Robert Robinson, *The Chemistry of Penicillin*, Princeton University Press, Princeton, N. J., 1949: (a) p. 694, (b) pp. 699–700, (c) p. 803.