Oxidation of 1,1-dichloro-2,2-bis(5-nitro-2-thienyl)ethylene (III). A mixture of 3.51 g. (0.01 mole) of III and 50 ml. of acetic acid was heated to reflux, and a solution of 3 g. of chromic oxide in 10 ml. of water was added over a period of 10 min. The solution was refluxed for 6 hr. The hot solution was diluted with 20 ml. of water and allowed to cool slowly. The pale yellow crystals of bis(5-nitro-2-thienyl) ketone (IV) were removed, washed with water, and recrystallized from acetic acid to give 1.2 g. of pale yellow needles, m.p. 152–154°.

Anal. Calcd. for $C_9H_4N_2O_5S_2$: N, 9.85; S, 22.56. Found: N, 9.91; S, 22.99.

The 2, 4-dinitrophenylhydrazone of the ketone(IV) was prepared in the usual manner, m.p. 222–223°.

Anal. Calcd. for $C_{15}H_8N_6O_8S_2$: N, 18.10. Found: N, 18.32.

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Mannich Reaction with Hydroxycoumarins[1]

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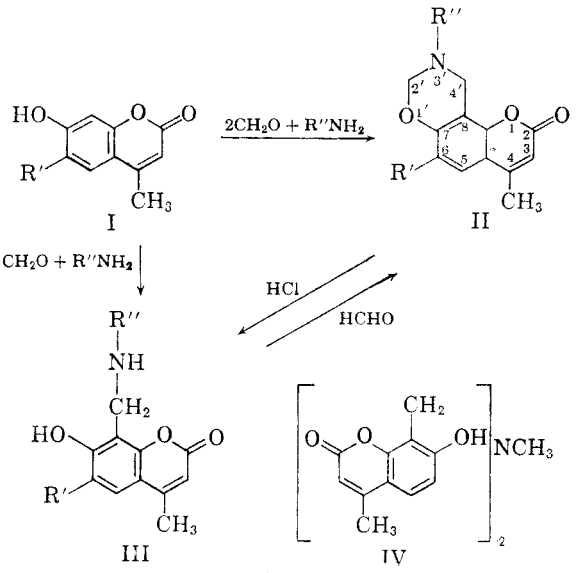
Although a considerable effort has gone into the condensation of phenols and naphthols with formaldehyde and amines,[3] there appears to have been only a single publication[4] dealing with the use of a hydroxycoumarin as the reactive nucleus in this reaction. Since Robertson and Link confined their study to 4-hydroxycoumarins which have the hydroxyl group in the heterocyclic ring, it seemed of interest to investigate the behavior of hydroxycoumarins having the hydroxyl group attached to the benzenoid ring. The present communication describes the reaction of formaldehyde and primary amines with 7-hydroxy-, 6-hydroxy-, and 5-hydroxy-coumarin derivatives. From 7-hydroxy-4-methylcoumarin derivatives (I), by reaction with benzylamine or aniline, it was possible to obtain either 7,8-(3′-substituted-4′-dihydro)-*m*-oxazino-4-methylcoumarins (II) or 7-hydroxy-8-substituted aminomethyl-4-methylcoumarins (III), depending upon whether two equivalents or only one equivalent of formaldehyde was used. The oxazino derivatives (II) could be formed by addition of formaldehyde to the simple Mannich reaction products (III), and hydrolysis of the oxazino derivatives yielded the Mannich-type products.



(R′, R″, see Table I)

Under all experimental conditions tried the major product obtained from 7-hydroxy-4-methylcoumarin with methylamine was the secondary amine IV.

In all cases it was assumed that, as in formylation,[5] the Claisen rearrangement,[6] and the Fries shift[7] with 7-hydroxy-4-methylcoumarin, the new substituent would appear at position 8. In one case (III, R″ = $C_6H_5CH_2$) it was shown that position 6 was not occupied, for it was proved that the bromination product was the 3,6-dibromo derivative. Under the usual Mannich conditions 7-methoxy- and 6-hydroxy-4-methylcoumarins do not react, while 5-hydroxy-4,7-dimethylcoumarins appeared to give only complex products with formaldehyde and aniline or methylamine. Under the proper conditions benzylamine afforded what is believed to be 5,6-(3′-benzyl-4-dihydro)-*m*-oxazino-4 7-dimethylcoumarin.[8,9] On the basis of the present study 7-hydroxycoumarins seem more suited for the Mannich reaction than do the 5- or 6-hydroxy analogs.

EXPERIMENTAL[10]

General methods for the synthesis of benzo-α-pyroneoxazines. Procedure A. A solution of 1.2 g. (0.4 mole) of paraformaldehyde in 5 ml. of absolute ethanol containing 0.015 g. of potassium hydroxide was prepared by gentle warming.

(1) Abstracted from the thesis presented by the author in fulfillment of the requirements for the Ph.D. degree at the University of Bombay.

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(10) Melting points were taken in open capillary tubes and are uncorrected.

TABLE I

CONVERSION OF 7-HYDROXYCOUMARINS (I) TO OXAZINOCOUMARINS (II)

R′	R″	Yield, II, %	M.P.	Formula	N, % Calcd.	N, % Found
H	$C_6H_5CH_2$	85	132–134	$C_{19}H_{17}NO_3$	4.56	4.49
H	C_6H_5	80–85	144–146	$C_{18}H_{15}NO_3$[a]	4.78	4.31
C_2H_5	$C_6H_5CH_2$	60[b]	103–105	$C_{21}H_{21}NO_3$	4.18	4.23
C_2H_5	C_6H_5	90	146–148	$C_{20}H_{19}NO_3$	4.36	4.03
C_2H_5	CH_3	70	151–153	$C_{15}H_{17}NO_3$	5.40	5.72

[a] Calcd.: C, 73.72; H, 5.12. Found: C, 73.51; H, 4.96. [b] Yield was, however, 30% by Method B.

TABLE II

8-AMINOMETHYL DERIVATIVES (III) OF 7-HYDROXYCOUMARINS (I)

R′	Amine R″	Yield (Method A), III, %	M.P.	Formula	N, % Calcd.	N, % Found
H	$C_6H_5CH_2$	45[a]	143–145	$C_{18}H_{17}NO_3$	4.7[b]	5.1
H	C_6H_5	60	165–166	$C_{17}H_{15}NO_3$	4.98	4.74
H	CH_3	20[c,d]	204–206	$C_{12}H_{13}NO_3$	6.4	6.6
C_2H_5	$C_6H_5CH_2$	50	123–124	$C_{20}H_{21}NO_3$	4.33	4.58
C_2H_5	C_6H_5	45	170–172	$C_{19}H_{19}NO_3$	4.53	4.34
C_2H_5	CH_3	70	188–190	$C_{14}H_{17}NO_3$	5.7	5.3

[a] Hydrolysis of the related oxazino derivative (Method B) afforded a 70% yield of this product. [b] Calcd.: C, 73.22; H, 5.76. Found: C, 73.35; H, 5.53. [c] The acetyl derivative was prepared as usual and recrystallized from ethanol, m.p. 201–203. *Anal.* Calcd. for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.61; N, 4.62. Found: C, 63.70; H, 5.29; N, 4.62. [d] The product was accompanied by an ethanol-insoluble solid which did not melt or decompose. It had an analysis corresponding to IV. *Anal.* Calcd. for $C_{23}H_{21}NO_6$: C, 67.81; H, 5.16; N, 3.44. Found: C, 67.23; H, 5.11; N, 3.46. Also on refluxing with acetic anhydride and pyridine it gave the same acetyl derivative as described in *c*.

To this solution 0.02 mole of the appropriate amine was added portionwise with cooling (tap water). To this were added 0.02 mole of the hydroxycoumarin and 5 ml. of absolute ethanol, and the mixture was refluxed on the steam bath for 2 hr. The resulting product crystallized when the mixture was cooled.

Procedure B. To an alcoholic solution containing 0.3 g. (0.01 mole) of paraformaldehyde (prepared as in A) 0.05 mole of the aminomethyl derivative (III) was added, and the mixture heated at reflux temperature for 2 hr. The solid which separated on cooling was recrystallized from ethanol. The results are summarized in Table I.

7,6(3′-Benzyl-4′-dihydro)-m-oxazino-8-ethyl-4-methylcoumarin. To a solution of 0.6 g. (0.02 mole) of paraformaldehyde in 5 ml. of alcohol (containing 0.015 g. of potassium hydroxide), 1.1 ml. (0.01 mole) of benzylamine was added with cooling. After addition of 2.04 g. (0.01 mole) of 7-hydroxy-8-ethyl-4-methylcoumarin, the mixture was refluxed gently for 2 hr., with enough ethanol being added to dissolve the sparingly soluble coumarin completely. A large quantity (1.1 g.) of unchanged coumarin was recovered on concentrating the reaction mixture. From the pasty residue left on complete removal of the solvent a small amount of product, soluble in benzene and petroleum ether (b.p. 40–60°), was obtained. Recrystallization from aqueous dioxane afforded 20–40 mg. (0.5–1%) of product, m.p. 146–148°.

Anal. Calcd. for $C_{21}H_{21}NO_3$: C, 75.22; H, 6.27; N, 4.2. Found: C, 75.34; H, 6.13; N, 4.7.

5,6-(3′-Benzyl-4′-dihydro)-m-oxazino-4,7-dimethylcoumarin. This substance was obtained from 5-hydroxy-4,7-dimethylcoumarin in 70% yield by following essentially Procedure A. Recrystallized from ethanol, it melted at 177–179°.

Anal. Calcd. for $C_{20}H_{19}NO_3$: N, 4 4. Found: N, 4.7.

Mannich bases (III) *from 4-methyl-7-hydroxycoumarins* (I). *Method A.* To an alcoholic solution prepared as before from 0.6 g. (0.02 mole) of paraformaldehyde, 0.02 mole of the amine was added in portions with cooling (tap water). To this was added 0.02 mole of the hydroxycoumarin (I) followed by 5 ml. of absolute ethanol. The reaction mixture was gently heated to reflux temperature on a water bath for 2 hr. The product, which crystallized on cooling the solution, was recrystallized from ethanol.

Method B. To 0.01 mole of the oxazinomethylcoumarin (II) in 10 ml. of ethanol, 5 ml. (0.11 mole) of concd. hydrochloric acid was added and the reaction mixture distilled slowly. During the course of the distillation 20 ml. of 1:1 aqueous ethanol was added and the distillation continued until a solid started to separate. The solid was dissolved in hot ethanol and the solution neutralized by addition of solid sodium bicarbonate. The product which separated was recrystallized from ethanol. The results are summarized in Table II.

7-Hydroxy-3,6-dibromo-8-benzylaminomethyl-4-methylcoumarin. I. *By bromination of the Mannich base.* A solution containing 1.6 g. of bromine (0.01 mole) in 16 ml. of acetic acid was added slowly to a solution of 1.5 g. (0.005 mole) of 7-hydroxy-8-benzylaminomethyl-4-methylcoumarin (III; R′ = H, R″ = $C_6H_5CH_2$) with constant shaking. The solid which separated was recrystallized from acetic acid m.p. 203–205°.

II. *From 7-hydroxy-3,6-dibromo-8-benzylaminomethyl-4-methylcoumarin by the Mannich reaction.* Following general procedure A the same product was obtained in 70% yield, m.p. 203–205°. Mixed melting point determinations with the product obtained by procedure I gave no depression.

Anal. Calcd. for $C_{18}H_{15}Br_2NO_3$: Br, 35.32. Found: Br, 35.55.

5-Hydroxy-6-benzylaminoethyl-4,7-dimethylcoumarin. This substance was obtained in 85% yield by hydrolysis of 5,6-(3′ - benzyl - 4′ - dihydro) - *m* - oxazino - 4,7 - dimethylcoumarin. Since it was sparingly soluble in most solvents, it was purified by repeated washings with ethanol, m.p. 152°.

Anal. Calcd. for $C_{19}H_{20}NO_3Cl$: N, 4.0. Found: N, 3.7.

The free base was recrystallized from aqueous methanol, m.p. 138–140°.

Anal. Calcd. for $C_{19}H_{19}NO_3$: N, 4.5. Found: N, 4.3.

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A Synthesis of (±)-Isocorydine

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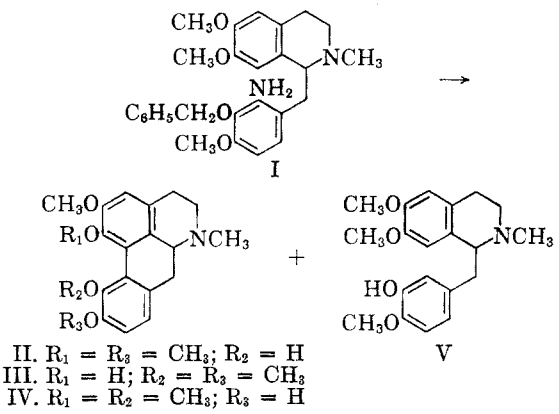
By keeping the diazonium salts of certain substituted 2′-aminobenzyl-*N*-methyltetrahydroisoquinolines in solution for a certain time and then adding catalytic copper and heating, Hey and co-workers[1] used successfully the Pschorr reaction for the synthesis of phenolic aporphine alkaloids. Difficulties were encountered by Hey and Palluel[1b] in a tentative synthesis of (±)-isocorydine (II); they could only isolate the hydrochloride of a base different from the desired alkaloid.

The successful synthesis by the same method of the closely related alkaloid (±)-corydine (III)[1b] and of 3-hydroxy-4,5,6-trimethoxyaporphine (pseudocorydine) (IV),[2] a base that has not been found in nature, induced us to reinvestigate the synthesis of (±)-isocorydine (II) by this method.

While this work was in progress, Kikkawa[3] published a synthesis of (±)-isocorydine in which the acid solution of the diazonium salt, after standing, was boiled without addition of copper, for a short time.

We found that (±)-isocorydine (II) is formed and can be isolated under the same conditions employed for the synthesis of (±)-corydine (III)[1b] and (±)-pseudocorydine (IV).[2] The yield is very poor (0.82% as hydrochloride) for the picrolonate of the benzyloxy-*N*-methylisoquinoline base (I). The benzylisoquinoline alkaloid, (±)-laudanidine (V), is produced in larger amounts (2.3% yield), and two other contaminating bases were also present. Separation



II. $R_1 = R_3 = CH_3$; $R_2 = H$
III. $R_1 = H$; $R_2 = R_3 = CH_3$
IV. $R_1 = R_2 = CH_3$; $R_3 = H$

of the four bases could only be effected by column chromatography.

The method employed by Kikkawa[3] gave a larger yield of the (±)-isocorydine (II) than of (±)-laudanidine (V) and also a third basic substance.

A similar increase in yield of the aporphine base (±)-corydine when changing from copper decomposition to simple heating has been described by Amurugan, Govindachari, Nagarajan, and Rao.[4]

EXPERIMENTAL

Melting points are not corrected. Descending paper chromatography on Whatman No. 1 was employed. Mobile phase was the upper layer of a mixture of methyl isobutyl ketone with a sodium acetate–acetic acid buffer of *p*H 5.6 (1:1). Dragendorff reagent was used for developing the alkaloidal spots.

3-Benzyloxy-4-methoxy-2-nitrophenylacetic acid. To 10 g. of 3-hydroxy-4-methoxy-2-nitrophenylacetic acid, dissolved in 10 ml. of ethanol-water (1:1), 50 ml. of benzyl chloride was added and refluxed for 3.5 hr. with good agitation. After boiling, 150 ml. of water was added and the mixture distilled with steam until all the unchanged benzyl chloride was eliminated. The crude benzyl ester of the acid remained in the flask as a heavy oil, and was hydrolyzed by boiling for 30 min. with 200 ml. of water and 160 ml. of 5*N* sodium hydroxide. By acidification the free acid precipitated in crystalline condition. After good cooling, 11.5 g. (82%) of pale yellow needles were collected, m.p. 140–145°. Recrystallized several times from ethanol, it melted 145–146°.

Anal. Calcd. for $C_{16}H_{15}NO_6$: C, 60.56; H, 4.77; N, 4.42. Found: C, 60.42; H, 4.55; N, 4.60.

3′-Benzyloxy-4′-methoxy-2′-nitrophenyl-N-2-(3,4-dimethoxyphenyl)ethyl-acetamide. This compound was prepared by condensing in the usual way[2]—the chloride of the former acid with 3,4-dimethoxyphenylethylamine. The chloride was prepared by reaction with thionyl chloride and employed without further purification. Long, almost white needles, m.p. 108–109°, were obtained.

Anal.: Calcd. for $C_{26}H_{28}N_2O_7$: C, 64.99; H, 5.87; N, 5.83. Found: C, 64.55; H, 5.65; N, 5.41.

Hey and Palluel[1b] gave a m.p. 45–46° for this compound, containing one mole of water. Recrystallization of the high-melting amide from 80% methanol gave a product, m.p. 48–50°.

Pschorr reaction with 1-(2′-amino-3′-benzyloxy-4′-methoxybenzyl)-N-methyl-6,7-dimethoxytetrahydroisoquinoline (I). The picrolonate of this isoquinoline was prepared from the former amide according to Hey and Palluel.[1b] One gram of the picrolonate was suspended in 5 ml. of methanol, and 5 ml.

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