# The Synthesis of New Heterocyclic Compounds from 3,4-Dichlorocoumarins

MELVIN S. NEWMAN AND CLIFFORD Y. PERRY[1,2]

*The Evans Chemistry Laboratory, Ohio State University, Columbus 10, Ohio*

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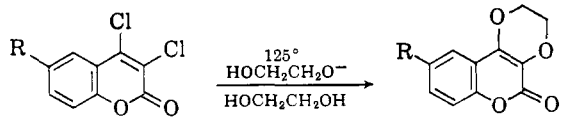
By reaction of 3,4-dichlorocoumarin and 3,4,6-trichlorocoumarin with difunctional reagents, several new heterocyclic types of compounds, having a heterocyclic ring fused at the 3,4-position of the coumarin nucleus, have been prepared for the first time.

On treatment with nucleophilic reagents, each of the chlorine atoms in 3,4-dichlorocoumarins is replaced, that in the 4-position considerably more easily than that in the 3-position.[3] Because of this behavior, the synthesis of compounds containing an additional heterocyclic ring fused to the 3,4-positions of the coumarin nucleus seemed possible. This objective was of interest because compounds having physiological activity might be produced since the coumarin ring system is present in several active compounds; *e.g.*, warfarin,[4] novobiocin,[5] and Dicumarol.[6]

In general, the construction of a new heterocyclic ring onto the 3,4-position of a coumarin was envisioned by causing a difunctional reagent to displace the 4-chlorine atom. The resulting 3-chloro-4-substituted coumarins could then be cyclized by an intramolecular displacement reaction to yield 3,4-heterocyclic coumarins. This objective has been attained by treating 3,4-dichlorocoumarin and 3,4,6-trichlorocoumarin[7] with ethylene glycol, catechol, 2-ethanolamine, and *o*-aminophenol. However, with ethylenediamine, *o*-phenylenediamine, butyramidine, guanidine, triphenylguanidine, thiourea, sodium $\alpha$-sodioacetate,[8] and sodium $\alpha$-sodiophenylacetate[9] none of the expected cyclic products was obtained. In general, the cyclization reactions, even in the successful cases, did not take place as easily as expected.

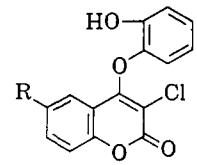
The reaction of 3,4-dichlorocoumarin (Ia) and 3,4,6-trichlorocoumarin (Ib) with ethylene glycol containing sodium 2-hydroxyethoxide yielded directly 2,3-dihydro-5H-*p*-dioxino[2,3-*c*][1]benzopyran-5-one (IIa) and the 9-chloro analog IIb. Because of the good yields obtained, no attempts were made to prepare the intermediate 3-chloro-4-$\beta$-hydroxyethyl ethers.



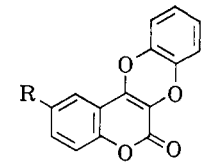

Ia. R = H
b. R = Cl

IIa, IIb

In similar experiments using the monoanion of catechol in excess molten (110°) catechol or in N-methyl-2-pyrrolidone (NMP) the monoethers, IIIa and IIIb, were obtained in excellent yields. However, cyclization of IIIb to 2-chloro-6H-benzopyrano[3,4-*b*][1,4]benzodioxin-6-one, IVb preceeded with difficulty and we were unable to obtain IVa from IIIa.

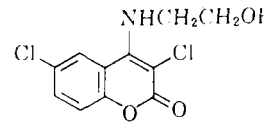



IIIa, b

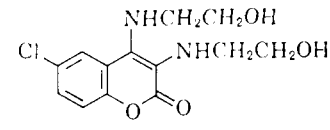



IVb

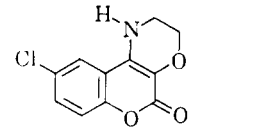
When Ib was treated with two equivalents of ethanolamine in refluxing methanol, 3,6-dichloro-4-(2-hydroxyethylamino)coumarin (V) was obtained in 80% yield. When Ib was treated with excess ethanolamine at 80°, 6 - chloro - 3,4 - bis(2 - hydroxyethylamino)-coumarin (VI) was obtained in 72% yield. The cyclization of V to 9-chloro-2,3-dihydro[1]benzopyrano-[3,4-*b*][1,4]oxazin-5(1H)-one (VII) by heating the sodium salt of V in tetrahydrofuran went in 87% yield. However, when sodium isopropoxide in isopropyl alcohol was used, V was converted into 6-chloro-4-(2-hydroxyethylamino)-3-isopropoxycoumarin (VIII) in 90% yield.[10]



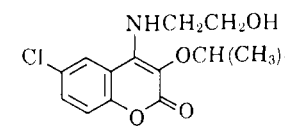

V




VI

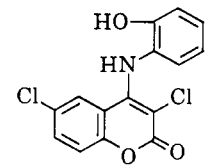



VII

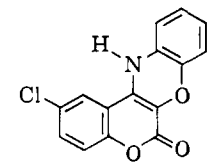



VIII

Similarly, Ib could be treated with *o*-aminophenol to yield 3,6-dichloro-4-(*o*-hydroxyanilino)coumarin (IX), and the latter could be cyclized to 2-chloro-(1)benzopyrano[3,4-*b*][1,4]benzoxazin-6(12H)-one (X).




IX




X

(1) This work was supported by a grant, RG-7450, from the U. S. Public Health Service, and formed part of the Ph.D. thesis of C. Y. Perry, Ohio State University, 1962.

(2) Sinclair Oil Company Fellow 1961–1962.

(3) M. S. Newman and S. Schiff, *J. Am. Chem. Soc.*, **81**, 2266 (1959).

(4) M. W. Schein, *Public Health Rept.* (U. S.), **65**, 368 (1950).

(5) E. A. Keazka, F. J. Wolf, F. P. Rathe, and K. Folkers, *J. Am. Chem. Soc.*, **77**, 6404 (1955).

(6) L. J. Audus and J. H. Quastel, *Nature*, **159**, 320 (1947).

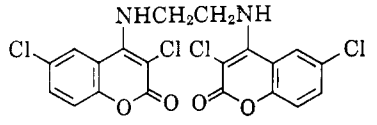
(7) The trichlorocoumarin was often used in preference to 3,4-dichlorocoumarin because (a) it was prepared more easily in higher yield and (b) the yields of reaction products were somewhat higher in general.

(8) Obtained through the courtesy of Dr. Rex Closson, The Ethyl Corp., Detroit, Mich.

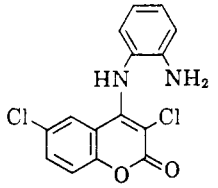
(9) Prepared as described by C. R. Hauser and R. B. Meyer, *J. Org. Chem.*, **26**, 3183 (1961).

(10) The reason for this unexpected result is under study now.

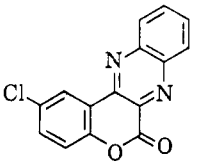
When Ib was treated with two equivalents of ethylendiamine in methanol a 35% yield of N,N'-bis(3,6-dichloro-4-coumarinyl)ethylenediamine (XI), was obtained. All attempts to prepare a monoethylenediamine product failed as did attempts to prepare a piperazine derivative. With *o*-phenylenediamine, Ib reacted to give 81% of 4-(*o*-aminoanilino)-3,6-dichlorocoumarin (XII), which could be cyclized in small yield to 2-chloro - 6H - (1)benzopyrano[3,4, - *b*]quinoxaline - 6-one (XIII) by heating in pyridine at 110–115°. If manganese dioxide[11] were present, the yield was increased to 70%.




XI

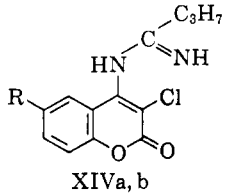



XII

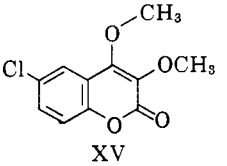



XIII

In an attempt to obtain a five-membered heterocyclic ring fused to the 3,4-positions of the coumarin nucleus, Ia and Ib reacted with *n*-butyramidine. The only products obtained, however, were N-(3-chloro-4-coumarinyl)butyramidine[12] (XIVa) and the corresponding 3,6-dichloro derivative (XIVb). Attempts at cyclization of XIVa,b failed. Ib was recovered unchanged after heating with *o*-aminopyridine in NMP at 100°.

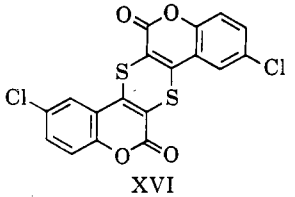



XIVa, b




XV

When Ib was treated with thiourea in methanol, a high melting (>450°) extremely insoluble compound was obtained in almost quantitative yield. Because of its great insolubility in all common reagents no further work was done with this compound which is most likely 2,9-dichloro-6H,13H-*p*-dithiino[2,3-*c*:5,6-*c'*]bis[1]benzopyrane-6,13-dione (XVI).[13]




XVI

When Ib was treated with guanidine in refluxing methanol, 6-chloro-3,4-dimethoxycoumarin (XV) was obtained. This was compared with an authentic sample prepared from Ib and sodium methoxide in methanol. On heating Ib with guanidine in diglyme (diethylene glycol dimethyl ether) at 98° a compound was obtained which has not been identified, but it is not any obvious reaction product. When Ib was heated with triphenylguanidine in diglyme at 100°, Ib was recovered unchanged.

Attempts to react Ib with ammonia, sodium amide, sodium $\alpha$-sodioacetate,[14] sodium $\alpha$-sodiophenylacetate,[15] sodiomalonic ester, ethoxymagnesium malonic ester,[16] urea, and sodium or potassium fluoride (NMP—100°) were unsuccessful. Either Ib was recovered unchanged or tars were obtained.

The amino alcohols V and VI were unique in that the former formed only the O-acetyl and the latter the bis-O-acetyl derivative on treatment with acetic anhydride or acetyl chloride in the presence of a tertiary amine. Normally, if amino alcohols form monoacetates, it is an N-acyl derivative.[17] We were unable to prepare a diacetate of V or a tetraacetate of VI. In further experiments 4-$\beta$-hydroxyethylaminocoumarin (XVII), $\beta$-O-toluidinoethanol, (XVIII), and 3,6-dichloro-4-propylaminocoumarin (XIX) were submitted to acetylation procedures. The fact that XVII formed only an O-monoacetyl derivative shows that the presence of a chlorine in position 3 of the coumarin nucleus is not the deciding factor in the formation of mono-O-acetyl derivatives in this class of compound. The fact that XVIII formed a diacetyl derivative shows that the steric hindrance provided by an *ortho* methyl group is not sufficient to prevent formation of the expected diacetyl derivative. The fact that XIX did not form an acetyl derivative in refluxing acetic anhydride shows that the hydroxy group on the 2-hydroxyethyl group is not responsible for the failure to N-acylate.

Both n.m.r.[18] and infrared analyses are consistent with the formulas of the monoacetate of V and diacetate of VI in which the NH group is present. This evidence rules out tautomeric structures which would remove the hydrogen on the nitrogen.

The fact that the unusual O-acetyl derivatives abovementioned really had free NH groups was determined in two ways: (a) they were basic and (b) they had a carbonyl absorption in the 6.00–6.14-$\mu$ (1667–1630-cm.$^{-1}$) region. Whenever there is no hydrogen on the nitrogen in the 4-position of the coumarin nucleus, the coumarin carbonyl groups absorption is in the 5.7–5.9-$\mu$ (1775–1695-cm.$^{-1}$) region. The reason for the inability to form N-acetyl derivatives of V, VI, and XIX

(11) Prepared as described by J. Attenburrow, *J. Chem. Soc.*, 1094 (1952). If the manganese dioxide were omitted, the yield of XIII dropped to 25–30% as oxidation–reduction processes occurred.

(12) The alternate structure with N=C—NH$_2$ cannot be ruled out. The n.m.r. analysis was not conclusive. We are indebted to Dr. G. Fraenkel for this determination.

(13) An isomeric structure in which the right-hand coumarin system is reversed can also be written.

(14) Obtained through the courtesy of Dr. Rex Closson, The Ethyl Corp., Detroit. Mich., whom we thank.

(15) Prepared as described by C. R. Hauser and R. B. Meyer, *J. Org. Chem.*, **26**, 3183 (1961).

(16) Prepared as described by K. Meyer and H. Bloch, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 637.

(17) For example, see G. Fodor and J. Kiss, *J. Am. Chem. Soc.*, **72**, 3495 (1950), and references therein.

(18) We thank Dr. G. Fraenkel for this analysis.

under normal conditions may be tied up with the fact that these compounds are vinylogous amides.[19]

## Experimental[20]

**9-Chloro-2,3-dihydro-5H-*p*-dioxino[2,3-*c*][1]benzopyran-5-one (IIb).**—To the solution made by treating 1.33 g. of sodium with 50 ml. of ethylene glycol was added 7.25 g. of 3,4,6-trichlorocoumarin.[3] The solution was rapidly heated to 125°, held at 115–125° for 1 hr. and poured onto 150 g. of ice. The resulting white solid was recrystallized from benzene (*ca.* 75 ml.) to yield 5.63 g. (81%) of IIb, m.p. 201–203° (5.80 μ, 1725 cm.$^{-1}$). Several recrystallizations from benzene gave the analytical sample, m.p. 202–203°.

*Anal.* Calcd. for $C_{11}H_7ClO_4$: C, 55.4; H, 3.0; Cl, 14.9. Found: C, 55.6; H, 3.1; Cl, 14.7.

**2,3-Dihydro-5H-*p*-dioxino[2,3-*c*][1]benzopyran-5-one (IIa).**—As above, 3,4-dichlorocoumarin[3] reacted with the sodium salt of ethylene glycol to give IIa, m.p. 162–163° (5.88 μ, 1701 cm.$^{-1}$), in 63% yield. The analytical sample melted at 163–164°.

*Anal.* Calcd. for $C_{11}H_8O_4$: C, 64.7; H, 3.9. Found: C, 64.4; H, 3.8.

**3,6-Dichloro-4-(*o*-hydroxyphenoxy)coumarin (IIIb).**—To a solution made by treating 0.12 g. of sodium in 5 g. of molten (110°) catechol was added 1.25 g. of 3,4,6-trichlorocoumarin. The solution was held at 110–115° for 15 min., cooled, and poured into 50 ml. of ice–water. The resulting white solid was recrystallized from 15 ml. of ethanol to yield 1.46 g. (95%) of IIIb, m.p. 174–176° (5.87 μ, 1706 cm.$^{-1}$). Several recrystallizations from ethanol gave the analytical sample, m.p. 176–177°.

*Anal.* Calcd. for $C_{15}H_8Cl_2O_4$: C, 55.7; H, 2.5; Cl, 21.9. Found: C, 56.0; H, 2.8; Cl, 21.9.

**3-Chloro-4-(*o*-hydroxyphenoxy)coumarin (IIIa).**—To a solution of 8 g. of catechol in 30 ml. of NMP was added 0.23 g. of sodium. The resulting solution was stirred for 15 min. and 2.15 g. of 3,4-dichlorocoumarin was added. The solution was heated to 110°, held at 110–115° for 15 min., cooled, and poured into 100 ml. of cold water. The resulting white solid was recrystallized by dissolving in 20 ml. of hot methanol and adding water to turbidity. The yield of IIIa, m.p. 159–162° (5.89 μ, 1699 cm.$^{-1}$), was 2.30 g. (80%). Several recrystallizations of IIIa from methanol–water gave the analytical sample, m.p. 160–162°.

*Anal.* Calcd. for $C_{15}H_9ClO_4$: C, 62.4; H, 3.1; Cl, 12.3. Found: C, 62.1; H, 3.0; Cl, 12.3.

**2-Chloro-6H-benzopyrano[3,4-*b*][1,4]benzodioxin-6-one (IVb).**—To a solution of 6 g. of catechol in 20 ml. of NMP was added 0.46 g. of sodium. The solution was stirred for 15 min. and 2.50 g. of 3,4,6-trichlorocoumarin was added. The resulting solution was heated to 150°, held at 145–150° for 80 min., cooled, and poured into 100 ml. of cold water. The resulting orange-white solid was recrystallized from acetone (*ca.* 25 ml.) to yield 1.23 g. (43%) of VI, m.p. 220–222° (5.80 μ, 1725 cm.$^{-1}$). Several recrystallizations from acetone gave the analytical sample, m.p. 222–223°.

*Anal.* Calcd. for $C_{15}H_7ClO_4$: C, 62.9; H, 2.5; Cl, 12.4. Found: C, 63.2; H, 2.5; Cl, 12.1.

Any large deviation from the specified reaction temperature and time leads to a lowering of the yield of IVb as does the use of molten catechol or dimethylformamide as solvent. If IIIb is used in the above experiment, the yield of IVb is no better.

Several attempts to prepare 6-H-benzopyrano[3,4-*b*][1,4]benzodioxin-6-one (IVa) from 3,4-dichlorocoumarin by similar procedures gave only tars.

**3,6-Dichloro-4-(2-hydroxyethylamino)coumarin (V).**—A solution of 1.22 g. of ethanolamine in 10 ml. of absolute methanol was added to a refluxing solution of 2.50 g. of Ib in 25 ml. of absolute methanol. The solution was refluxed an additional 45 min. and concentrated to dryness under reduced pressure. The resulting white solid was washed with 50 ml. of water and recrystallized from methanol (*ca.* 20 ml.) to yield 2.18 g. (80%) of V, m.p. 197–199° (6.08 μ, 1643 cm.$^{-1}$). Several recrystallizations from methanol gave the analytical sample, m.p. 198.0–199.5°.

*Anal.* Calcd. for $C_{11}H_9Cl_2NO_3$: C, 48.2; H, 3.3; Cl, 25.8; N, 5.1. Found: C, 48.3; H, 3.5; Cl, 25.9; N, 4.9.

**4-(2-Acetoxyethylamino)-3,6-dichlorocoumarin.**—A solution of 5.48 g. of V and 0.1 g. of fused sodium acetate in 10 ml. of acetic anhydride was refluxed for 3 hr. and cooled to 2°. The white needles which formed were collected by filtration, washed with 50 ml. of dry ether, and dried to yield 5.66 g. (92%) of the acetate, m.p. 159–162° (5.84 μ, 1715 cm.$^{-1}$) (6.01 μ, 1664 cm.$^{-1}$). Several recrystallizations from 95% ethanol (*ca.* 25 ml.) gave the analytical sample, m.p. 160–162°.

*Anal.* Calcd. for $C_{13}H_{11}Cl_2NO_4$: C, 49.5; H, 3.5; Cl, 22.4; N, 4.4. Found: C, 49.8; H, 3.8; Cl, 22.4; N, 4.6.

This acetate would not react with a mixture of acetyl chloride and 2,6-lutidine. It formed a hydrochloride (not analyzed).

**3,4-Bis(2-hydroxyethylamino)-6-chlorocoumarin (VI).**—To 40 ml. of ethanolamine maintained at a temperature of 75–80° was added, over a period of 30 min., 25 g. of 3,4,5-trichlorocoumarin. The solution was maintained at a temperature of 75–80° for an additional 45 min., cooled, and poured into 300 ml. of cold water. The resulting white solid was filtered, washed with 100 ml. of water, and recrystallized from acetone (*ca.* 50 ml.) to yield 21.5 g. (72%) of VI, m.p. 150–152° (6.14 μ, 1629 cm.$^{-1}$). Several recrystallizations from acetone gave the analytical sample, m.p. 151–152°.

*Anal.* Calcd. for $C_{13}H_{15}ClN_2O_4$: C, 52.3; H, 5.1; Cl, 11.9; N, 9.4. Found: C, 52.5; H, 5.0; Cl, 11.6; N, 9.6.

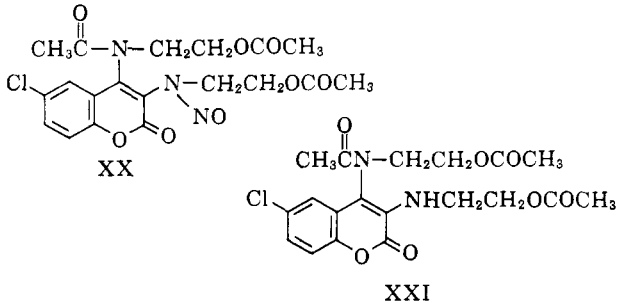
**3,4-Bis(2-acetoxyethylamino)-6-chlorocoumarin.**—A solution of 2.99 g. of VI and 0.1 g. of fused sodium acetate in 20 ml. of acetic anhydride was refluxed for 2 hr., cooled, and poured into 100 ml. of cold water. The pH was adjusted to about 7.5 by the addition of potassium carbonate and the resulting white solid was filtered, washed with 50 ml. of water, and recrystallized from acetone (*ca.* 15 ml.) to yield 3.65 g. (95%) of the diacetate, m.p. 92–94° (5.80 μ, 1725 cm.$^{-1}$), (6.10 μ, 1638 cm.$^{-1}$). Several recrystallizations from acetone gave the analytical sample, m.p. 93.0–94.5°.

*Anal.* Calcd. for $C_{17}H_{19}ClN_2O_6$: C, 53.3; H, 5.0; Cl, 9.2; N, 7.3. Found: C, 53.0; H, 5.1; Cl, 8.9; N, 7.0.

This amine did not react with a mixture of acetyl chloride and 2,6-lutidine or with phosgene in 2,6-lutidine. This amine (1.0 g.) was dissolved in a minimum of benzene (*ca.* 10 ml.) and treated with excess anhydrous hydrogen chloride. The resulting white precipitate was filtered and dried to give 1.0 g. (85%) of the hydrochloride (not analyzed). The infrared band assigned to the $NH_2^+$ absorption occurred at 3.60 μ, 2785 cm.$^{-1}$.

**3-(2-Acetoxyethylnitrosoamino)-4-(2-acetoxyethylacetamido)-6-chlorocoumarin (XX).**—A stirred mixture of 5.74 g. (0.015 mole) of the diacetate of VI and 4.0 g. of fused sodium acetate in 20 ml. of acetic anhydride and 10 ml. of glacial acetic acid was cooled to 2°. To the mixture was added over a period of 30 min. a solution of 1.12 g. of nitrosyl chloride in 4 ml. of acetic anhydride. During the addition the temperature was maintained at 5–8°. The resulting solution was held at 12–15° for 30 min. and poured into 150 ml. of cold water. The resulting yellow solid was filtered, washed with 100 ml. of water and recrystallized from methanol (*ca.* 20 ml.) to yield 6.35 g. (93%) of XX, m.p. 83–85° (5.79 μ, 1729 cm.$^{-1}$) (5.89 μ, 1700 cm.$^{-1}$) (6.00 μ,

(19) This suggestion was made by a referee. We had considered this possibility but because of the basicity of the compounds wondered how much the principle of vinylogy is responsible for the facts. In one case, an N-acetyl derivative was formed. The stability of this N-acetyl group shows that lack of stability is not the reason for failure to form N-acetyl compounds. When the di-O-acetate of VI was treated with nitrosyl chloride in acetic anhydride, XX was obtained. Denitrosation of XX yielded XXI. The structure XXI was assigned to this compound because of the infrared band at 5-83 μ (2727 cm.$^{-1}$) characteristic of coumarins not having an NH group in the 4-position.




XX




XXI

(20) All melting points are uncorrected. Melting points above 200° were taken in a heated aluminum block. All microanalyses by Schwarzkopf Laboratory, Woodside, N. Y. Infrared spectra were taken on a Baird Associates spectrophotometer, Model B. Only strong carbonyl bands are listed. Assistance in naming several compounds was provided by Mr. Don Walker of *Chemical Abstracts*, whom we thank.

1667 cm.$^{-1}$). The product gave a positive Liebermann nitroso test.[21] Several recrystallizations from methanol gave the analytical sample, m.p. 84.8–85.8°.

*Anal.* Calcd. for $C_{19}H_{20}ClN_3O_8$: C, 50.3; H, 4.4; Cl, 7.8; N, 9.3. Found: C, 50.5; H, 4.5; Cl, 7.6; N, 9.6.

**3-(2-Acetoxyethylamino)-4-(acetoxyethylacetamido)-6-chlorocoumarin (XXI).**—A solution of 4.54 g. of XX in 25 ml. of xylene was heated on a steam bath until gas evolution ceased (*ca.* 45 min.). The xylene was removed under reduced pressure and the resulting solid was recrystallized from absolute methanol (*ca.* 5 ml.) to yield 3.89 g. (91%) of XXI, m.p. 90–92° (5.79 μ, 1728 cm.$^{-1}$) (5.83 μ, 1718 cm.$^{-1}$) (6.00 μ, 1667 cm.$^{-1}$). The product gave a negative Liebermann nitroso test. Several recrystallizations from methanol gave the analytical sample, m.p. 91.5–93.0°.

*Anal.* Calcd. for $C_{19}H_{21}ClN_2O_7$: C, 53.8; H, 5.0; Cl, 8.3; N, 6.6. Found: C, 53.7; H, 5.0; Cl, 8.2; N, 6.3.

This amine would not react with refluxing acetic anhydride.

**9-Chloro-2,3-dihydro[1]benzopyrano[3,4-*b*][1,4]oxazin-5(1H)-one (VII).**—To a refluxing solution of 5.48 g. of V in 250 ml. of dry tetrahydrofuran was added, over a period of 30 min., 0.87 g. of a 53% suspension of sodium hydride in mineral oil.[22] A white precipitate formed during the addition. The mixture was refluxed an additional 45 min. and cooled. Methanol (2 ml.) was added to destroy any unchanged sodium hydride. The solvent was removed under reduced pressure and the resulting white solid was washed with 50 ml. of water and recrystallized from N,N-dimethylacetamide (*ca.* 40 ml.) to yield 4.10 g. (87%) of VII, m.p. 311–315° (6.08 μ, 1643 cm.$^{-1}$). Several recrystallizations from dimethylacetamide gave the analytical sample, m.p. 313–316°.

*Anal.* Calcd. for $C_{11}H_8ClNO_3$: C, 55.8; H, 3.4; Cl, 14.9; N, 5.9. Found: C, 55.8; H, 3.3; Cl, 15.2; N, 6.2.

This amine would not react with refluxing acetic anhydride (sodium acetate or pyridine catalyst) or with a mixture of acetyl chloride and 2,6-lutidine.

**6-Chloro-4-(2-hydroxyethylamino)-3-isopropoxycoumarin (VIII).**—To a refluxing solution of 2.74 g. of V in 60 ml. of isopropyl alcohol was added over a period of 30 min. a solution of 0.23 g. of sodium in 100 ml. of isopropyl alcohol. The solution was refluxed an additional 30 min. and the isopropyl alcohol was removed under reduced pressure. The resulting white solid was washed with 50 ml. of water and extracted with 150 ml. of refluxing 95% ethanol. The insoluble material was filtered and dried to yield 0.4 g. (2%) of VII, m.p. 310–314°. The filtrate was concentrated to about 30 ml., cooled, and filtered to yield 2.69 g. (90%) of VIII, m.p. 122–123° (6.14 μ, 1631 cm.$^{-1}$). Several recrystallizations from 95% ethanol gave the analytical sample, m.p. 122–123°.

*Anal.* Calcd. for $C_{14}H_{16}ClNO_4$: C, 56.5; H, 5.4; Cl, 11.9; N, 4.7. Found: C, 56.3; H, 5.7; Cl, 11.8; N, 4.8.

**3,6-Dichloro-4-(*o*-hydroxyanilino)coumarin (IX).**—A solution of 5.00 g. of Ib and 6.00 g. of *o*-aminophenol in 20 ml. of NMP was heated at 95–99° for 30 min., cooled, and poured into 600 ml. of cold water. The resulting solid was filtered and dissolved in 350 ml. of hot methanol. Water was added to turbidity. The solid which crystallized on cooling was filtered and dried to yield 5.79 g. (90%) of IX, m.p. 241–243° (6.03 μ, 1660 cm.$^{-1}$). Several recrystallizations from methanol gave the analytical sample, m.p. 241–243°. IX is soluble in 5% aqueous sodium hydroxide and gives a positive ferric chloride test.

*Anal.* Calcd. for $C_{15}H_9Cl_2NO_3$: Cl, 22.0. Found: Cl, 21.8.

**2-Chloro-[1]benzopyrano[3,4-*b*]benzoxazin-6(12H)-one, (X).**—To a solution of 6.44 g. of IX in 20 ml. of NMP was added 0.87 g. of a 53% dispersion of sodium hydride in mineral oil.[22] The resulting solution was heated at 135–140° for 30 min., cooled, and poured into 200 ml. of cold water. The resulting rust color solid was recrystallized from tetrahydrofuran (*ca.* 70 ml.) to yield 3.20 g. (56%) of X, m.p. 347–350° (6.01 μ, 1664 cm.$^{-1}$). Several recrystallizations from tetrahydrofuran gave the analytical sample, m.p. 349–352°.

*Anal.* Calcd. for $C_{15}H_8ClNO_3$: C, 63.1; H, 2.8; Cl, 12.4; N, 4.9. Found: C, 62.9; H, 3.1; Cl, 12.1; N, 4.6.

**N,N′-Bis(3,6-dichloro-4-coumarinyl)ethylenediamine (XI).**—To a stirred slurry of 7.50 g. of Ib in 150 ml. of absolute methanol maintained at a temperature of 2–3° was added, over a period of 10 min., 3.60 g. of ethylenediamine. The temperature was maintained at 2–3° for an additional 45 min. at which time solution was complete. The solution was allowed to warm up and was stirred at 24–28° for 12 hr. A white precipitate appeared after about 1 hr. and was quite heavy after 12 hr. The precipitate was filtered, washed with 25 ml. of cold methanol, and dried to yield 2.54 g. (35%) of XI, m.p. 340–344° (6.01 μ, 1664 cm.$^{-1}$). Only tar could be recovered from the methanol mother liquor. Several recrystallizations from dimethylacetamide (*ca.* 40 ml.) gave the analytical sample, m.p. 345–346°.

*Anal.* Calcd. for $C_{20}H_{12}Cl_6N_2O_4$: C, 49.5; H, 2.5; Cl, 29.1; N, 5.8. Found: C, 49.8; H, 2.8; Cl, 29.0; N, 5.5.

**4-(*o*-Aminoanilino)-3,6-dichlorocoumarin (XII).**—A solution of 3.00 g. of Ib and 3.00 g. of *o*-phenylenediamine in 15 ml. of NMP was heated on a steam bath for 10 min. The solution was diluted with 500 ml. of cold water and the resulting yellow solid was washed with 200 ml. of hot water and recrystallized from benzene (*ca.* 300 ml., dissolves slowly) to yield 3.13 g. (81%) of XII, m.p. 199–201° (6.02 μ, 1662 cm.$^{-1}$). Several recrystallizations from benzene gave the analytical sample, m.p. 200–202°.

*Anal.* Calcd. for $C_{15}H_{10}Cl_2N_2O_2$: C, 56.2; H, 3.1; Cl, 22.1; N, 8.8. Found: C, 56.3; H, 3.4; Cl, 21.8; N, 8.8.

**2-Chloro-6H-[1]benzopyrano[3,4-*b*]quinoxalin-6-one (XIII).**—A mixture of 2.1 g. of XII, 4.0 g. of manganese dioxide,[23] 10 ml. of NMP, and 25 ml. of pyridine was heated with stirring at 110–115° for 90 min. The manganese dioxide was removed by filtration and washed ten times with 30 ml. portions of pyridine. The combined organic fraction was concentrated to about 60 ml. under reduced pressure and diluted with 300 ml. of cold water. The resulting yellow solid was washed with water and recrystallized from glacial acetic acid (*ca.* 75 ml.) to yield 1.40 g. (70%) of XIII, m.p. 320–323° (5.77 μ, 1733 cm.$^{-1}$). Several recrystallizations from acetic acid gave the analytical sample, m.p. 323–324°.

*Anal.* Calcd. for $C_{15}H_7ClN_2O$: C, 63.8; H, 2.5; Cl, 12.6; N, 9.9. Found: C, 63.6; H, 2.5; Cl, 12.6; N, 9.7.

**N-(3,6-Dichloro-4-coumarinyl)butyramidine (XIVb).**—To a stirred solution of 3.69 g. of butyramidine hydrochloride[24] in 125 ml. of absolute methanol was added 7.5 ml. of methanol which contained 0.03 mole of sodium methoxide. A fine precipitate of sodium chloride was formed. The mixture was cooled to 2° and 2.50 g. of Ib was added. The mixture was stirred at 2–3° 45 min. at 28–31° for 90 min., and at reflux for 90 min. Methanol was distilled until the reaction mixture volume was about 25 ml. Water (*ca.* 75 ml.) was added over a 15-min. period with stirring. The resulting white solid was filtered, washed with 25 ml. of water, and recrystallized from methanol (*ca.* 5 ml.) to yield 2.40 g. (80%) of XIVb, m.p. 154–156° (6.00 μ, 1667 cm.$^{-1}$). Several recrystallizations from methanol gave the analytical sample, m.p. 155–156°.

*Anal.* Calcd. for $C_{13}H_{12}Cl_2N_2O_2$: C, 52.3; H, 4.1; Cl, 23.6; N, 9.4. Found: C, 52.2; H, 4.2; Cl, 23.8; N, 9.2.

Note that the molar ratio of butyramidine to coumarin was 3. This was intended as cyclization of XIVb was expected. However, the cyclization did not occur.

**N-(3-Chloro-4 coumarinyl)butyramidine (XIVa).**—As above, reacted with butyramidine to give XIVa, m.p. 115–118° (6.04 μ, 1658 cm.$^{-1}$), in 67% yield. The analytical sample melted at 119–121°.

*Anal.* Calcd. for $C_{13}H_{13}ClN_2O_2$: C, 59.0; H, 5.0; Cl, 13.4; N, 10.6. Found: C, 59.1; H, 5.0; Cl, 13.2; N, 10.5.

**5-Chloro-3,4-dimethoxycoumarin (XV).**—To a solution made by treating 0.46 g. of sodium with 40 ml. of absolute methanol was added 2.50 g. of Ib. The solution was refluxed for 1 hr. and the methanol was then removed under reduced pressure. The resulting white solid was washed with 30 ml. of water and recrystallized from absolute methanol (*ca.* 25 ml.) to yield 1.78 g. (74%) of XV, m.p. 100–102° (5.82 μ, 1720 cm.$^{-1}$). Several recrystallizations of I from methanol gave the analytical sample m.p. 101–102°.

*Anal.* Calcd. for $C_{11}H_9ClO_4$: C, 55.0; H, 3.8; Cl, 14.8. Found: C, 55.1; H, 4.0; Cl, 14.8.

To a solution of 3.66 g. of guanidine nitrate in 50 ml. of methanol was added an equivalent of sodium methoxide in methanol (10 ml.). After stirring at room temperature for 5 min., 2.50 g. of Ib was added and the reaction mixture was held at reflux for 3

(21) A. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., London, 1956, p. 649.

(22) Obtained from Metal Hydrides, Inc., Beverly, Mass.

(23) Prepared from potassium permanganate and manganese sulfate by the procedure of J. Attenburrow, *J. Chem. Soc.*, 1094 (1952). The manganese dioxide used was about 2 months old.

(24) Purchased from Winthrop Laboratories, New York 18, N. Y.

hr. The methanol was removed under reduced pressure and the solid remaining was washed with water. Recrystallization from methanol afforded 1.2 g. (50%) of XV, m.p. and mixed m.p. with authentic sample, 101–102°.

**2,9-Dichloro-6H,13H-*p*-dithiino[2,3-*c*:5,6-*c'*]bis[1]benzopyrane-6,13-dione (XVI).**—A solution of 2.50 g. of Ib and 2.28 g. of thiourea in 125 ml. of absolute methanol was refluxed for 5 hr. A yellow precipitate formed after about 20 min. and became progressively heavier. The yellow solid was filtered from the hot methanol, washed with hot methanol (*ca.* 100 ml.), washed with water (*ca.* 100 ml.), and dried to yield 1.98 g. (94%) of XVI, m.p. > 450° (5.88 μ, 1770 cm.$^{-1}$). The material could not be satisfactorily recrystallized from any of the solvents tried nor could it be sublimed under vacuum. The analytical sample was obtained by extracting 0.5 g. with 200 ml. of boiling methanol and sending the residue for analysis.

*Anal.* Calcd. for $C_{18}H_6Cl_2O_4S_2$: C, 51.3; H, 1.4; Cl, 16.8; S, 15.2. Found: C, 51.0, 51.1; H, 2.0, 1.8; Cl, 16.7; S, 15.3.

**4-(β-Hydroxyethylamino)coumarin (XVII).**—A solution of 1.80 g. of 4-chlorocoumarin[25] and 1.22 g. of ethanolamine in 40 ml. of absolute methanol was refluxed for 45 min. The methanol was removed under reduced pressure and the resulting solid was washed with 30 ml. of water and recrystallized from methanol (*ca.* 15 ml.) to yield 1.50 g. (74%) of XVII, m.p. 171–173° (6.00 μ, 1643 cm.$^{-1}$). Several recrystallizations from methanol gave the analytical sample, m.p. 172.5–174.0°.

*Anal.* Calcd. for $C_{11}H_{11}NO_3$: C, 64.5; H, 5.4; N, 6.8. Found: C, 64.8; H, 5.7; N, 7.0.

A solution of 1.02 g. of XVII and 0.05 g. of fused sodium acetate in 5 ml. of acetic anhydride was refluxed for 2 hr., cooled, and poured into 40 ml. of cold water. The pH was adjusted to about 7.3 by the addition of potassium carbonate and the resulting white solid was filtered, washed with 75 ml. of water, and recrystallized from methanol (*ca.* 10 ml.) to yield 1.12 g. (90%) of 4-(β-acetoxyethylamino)coumarin, m.p. 161–163° (5.84 μ, 1716 cm.$^{-1}$). Several recrystallizations from methanol gave the analytical sample, m.p. 162–163°.

*Anal.* Calcd. for $C_{13}H_{13}NO_4$: C, 63.3; H, 5.3; N, 5.7. Found: C, 63.5; H, 5.5; N, 6.0.

**N-(2-Acetoxyethyl)-N-acetyl-*o*-toluidine (XXII).**—A solution of 100 g. of β-*o*-toluidinoethanol[26] (XVIII) and 0.1 g. of fused sodium acetate in 100 ml. of acetic anhydride was refluxed for 1 hr., cooled, and poured into 500 ml. of cold water. The pH was adjusted to about 7.5 by the addition of potassium carbonate. The mixture was extracted twice with 100 ml. of benzene. The combined benzene extract was washed twice with 50 ml. of water and once with 50 ml. of a saturated aqueous sodium chloride solution. The benzene was removed under reduced pressure. Two distillations of the residual oil gave 10.5 g. (68%) of XXII, b.p. 150–153° (4 mm.), $n^{24}D$ 1.5138 (5.78 μ, 1730 cm.$^{-}$) (6.02 μ, 1661 cm.$^{-1}$).

*Anal.* Calcd. for $C_{13}H_{17}NO_3$: C, 66.4; H, 7.3; N, 6.0. Found: C, 66.4; H, 7.4; N, 6.0.

**3,6-Dichloro-4-(*n*-propylamino)coumarin (XIX).**—A stirred slurry of 2.50 g. of Ib in 25 ml. of absolute methanol was cooled to 2° and to it was added 1.18 g. of *n*-propylamine. The stirring was continued and the temperature was maintained at 2–3° for 1 hr. at which point solution was complete, at 24–26° for 2 hr., and at 40–50° for 3 hr. The methanol was removed under reduced pressure and the resulting white solid was washed with 25 ml. of water and recrystallized from absolute methanol (*ca.* 25 ml.) to yield 2.63 g. (97%) of XIX, m.p. 189–190° (6.01 μ, 1664 cm.$^{-1}$). Several recrystallizations from methanol gave the analytical sample, m.p. 189.6–190.2°.

*Anal.* Calcd. for $C_{12}H_{11}Cl_2NO_2$: C, 53.0; H, 4.1; Cl, 26.0; N, 5.1. Found: C, 53.3; H, 4.3; Cl, 25.8; N, 5.1.

All attempts to prepare the bis-*n*-propylamino compound failed. When XIX was treated with two equivalents of *n*-propylamine in methanol or NMP it was recovered unchanged. Then XIX was added to excess *n*-propylamine at 2° only tars were isolated. When XIX was treated with refluxing acetic anhydride (sodium acetate catalyst), it was recovered unchanged.

(25) Prepared from 4-hydroxycoumarin (Aldrich Chemical Co., Milwaukee, Wis.) by the procedure of D. P. Spalding, H. S. Mosher, and F. C. Whitmore, *J. Am. Chem. Soc.*, **72**, 5338 (1950).

(26) Purchased from Distillation Products Industries, Rochester 3, N. Y.

# Isolation, Identification, and Synthesis of Components of a "Styrene Dimer Fraction"

R. M. PARKHURST, J. O. RODIN, AND R. M. SILVERSTEIN

*Organic Research Department, Stanford Research Institute, Menlo Park, California*

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The following components were isolated and identified in a "styrene dimer fraction" obtained by refluxing styrene with a small amount of sulfur: 1,3-diphenylpropane (I), *cis*-1,3-diphenyl-2-butene (IV), 2,4-diphenyl-1-butene (III), and *trans*-1,3-diphenyl-2-butene (V). This paper illustrates the utility of the combination of mass, infrared, n.m.r., and ultraviolet spectrometry in the identification of small amounts of organic compounds isolated by gas chromatography.

A "styrene dimer fraction" was obtained by refluxing 104 g. (1.00 mole) of freshly distilled styrene and 0.32 g. (0.010 mole) of sulfur for three hours at 143–150° (pot temperature) under nitrogen. Distillation at 0.2 mm. through a Vigreux column (8 in. × 1 in.) at 0.2 mm. gave 3.9 g. of a "dimer fraction" (head temperature 80–135°). We are concerned here with the isolation, identification, and synthesis of the components of this mixture. Results of a continuing study[1] of styrene dimerization will be presented elsewhere.

Four pure components were isolated by gas chromatography. The initial separation was made on a DC-710 silicone substrate; each of the three initial cuts was subjected to further separation on a QF1–0065 fluorosilicone substrate. Heart cuts on the latter substrate were taken until each of the four components isolated appeared to be chromatographically homogeneous on both substrates. Tentative identification was made by mass, infrared, nuclear magnetic resonance, and ultraviolet spectrometry, and by derivatization when indicated. Comparison of spectral characteristics and gas chromatographic behavior with those of authentic samples afforded conclusive identification. The components are numbered in order of elution from the DC-710 silicone column.

(1) F. R. Mayo, Presented in part at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961.

## Identification

**Component No. 1.**—Components no. 1 and no. 2 were eluted together from the DC710 silicone column and were separated by repeated passes on the QF1–0065 fluorosilicone column. On the latter column, component no. 2 preceded component no. 1.