1,3,3-Trimethyl-2-(4-acetoxyphenyl)-5,7-diacetoxyindene (7c).—To a solution of 6 (1.0 g., 3.2 mmoles) in 15 ml. of chlorobenzene was added aluminum chloride (1.52 g., 11.5 mmoles). The solution immediately turned red. Upon heating, it slowly turned green, but after 20 min. at reflux it turned red again. Refluxing was continued for a total of 3 hr. and then the solution was worked up in the same way as for **7a**. White platelets, 180 mg. (15%), m.p. 177–178°, were obtained.

The infrared spectrum was identical with that of a by-product obtained in the reaction of a tetrahydropyranyl derivative of 3-(*p*-hydroxyphenyl)-4-methyl-7-hydroxycoumarin with methyl Grignard reagent.[2] A mixture melting point gave no depression. An O-acetyl analysis was carried out on this compound. (For C and H analyses, see preceding paper.[2])

Anal. Calcd. for $C_{24}H_{24}O_8$: acetyl, 31.78. Found: acetyl, 32.12.

Anomalous Reactions of 3-Substituted 4-(2-Hydroxyethylamino)coumarins with Strong Bases[1]

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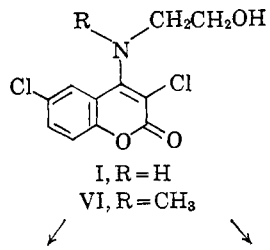
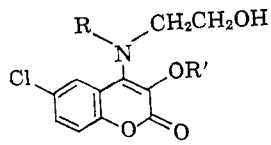
Treatment of 3,6-dichloro-4-(2-hydroxyethylamino)coumarin (I) in methanol, ethanol, and 2-propanol containing the corresponding alkoxide affords 3,6-dichloro-3-alkoxy-4-(2-hydroxyethylamino)coumarins when less than 1 equiv. of alkoxide ion is used. These alkoxycoumarins (III–V) are converted quantitatively into 9-chloro-2,3-dihydro[1]benzopyrano[3,4-*b*][1,4]oxazin-5(1H)-one (II) when treated with catalytic amounts of alkoxide ion in alcohol. Similar treatment of other related coumarins is also described. Possible paths for these reactions are discussed.

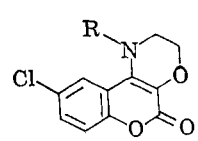
3,6-Dichloro-4-(2-hydroxyethylamino)coumarin (I) has been converted into 9-chloro-2,3-dihydro[1]benzopyrano[3,4-*b*][1,4]oxazin-5(1H)-one (II) on treatment with sodium hydride in tetrahydrofuran and into 6-chloro-4-(2-hydroxyethylamino)-3-isopropoxycoumarin (III) on treatment with sodium isopropoxide in isopropyl alcohol.[2] The formation of III was unexpected as apparently an intermolecular reaction was competing favorably with an intramolecular reaction of the same type since proton transfer between I and isopropoxide ion was assumed to be rapid. Moreover, the reaction ostensibly involved displacement of a vinylic chloride, yet proceeded under relatively mild conditions. Accordingly, further studies in this area were undertaken in order to better elucidate the conditions required for the formation of II and III and related compounds.



I, R = H
VI, R = CH_3



III, R = H; R′ = $CH(CH_3)_2$
IV, R = H; R′ = C_2H_5
V, R = H; R′ = CH_3
VII, R = CH_3; R′ = $CH(CH_3)_2$



II, R = H
VIII, R = CH_3

The original observation that I is converted mainly to III on treatment with sodium isopropoxide in isopropyl alcohol has been confirmed *if less than 1 equiv. of alkoxide* is added slowly to a hot solution of I in isopropyl alcohol. If more than 1 equiv. of isopropoxide is used, the product is entirely II. When III is treated with 0.1 equiv. of sodium isopropoxide, II is formed rapidly and in quantitative yield. Thus, the original[2] preparation of III was, in a sense, fortuitous as, if an excess of alkoxide had been used, the product would have been II.

Similarly, IV and V are obtained by treating I with slightly less than 1 equiv. of sodium ethoxide in ethanol or sodium methoxide in methanol, respectively. Both IV and V are converted to II upon treatment with sodium hydride in 1,2-dimethoxyethane. In one experiment in which I was treated with sodium *t*-butoxide in *t*-butyl alcohol, a 45% yield of II was obtained but no *t*-butyl ether corresponding to III. In this experiment, 28% of the starting material was recovered. In similar experiments with other alkoxides no starting material was present in sufficient quantity to be isolated at the conclusion of the reaction. Thus, II is being formed at a rate slower than III, IV, or V. The significance of this will become evident.

If a solution of III in isopropyl alcohol is treated with 0.1 equiv. of sodium isopropoxide, an almost quantitative yield of II is rapidly obtained. A similar result is obtained upon treatment of IV with a catalytic quantity of sodium ethoxide.

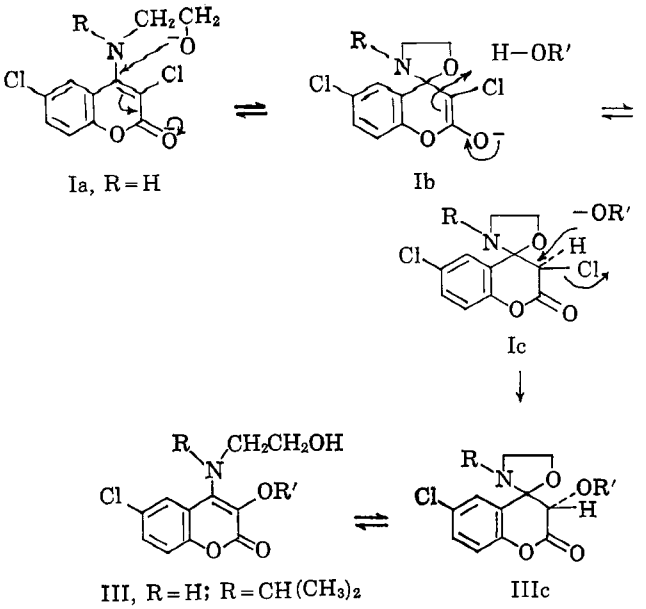
The facile formation of alkoxy compounds III, IV, and V might be rationalized by two reaction paths: (a) direct nucleophilic attack of the alkoxide at C-3 followed by elimination of chloride ion; or (b) a sequence of steps outlined at the top of col. 1, p. 4123.

Path a involves the direct displacement of the vinylic chlorine at the 3-position by external alkoxide ion and seems unlikely because of the ease with which reaction occurs.

In path b ion Ia, generated initially by proton exchange with alkoxide ion, undergoes an internal Michael addition to give an enolate, Ib, which accepts a proton from the solvent to yield Ic. The alkoxide ion remaining after donation of a proton to Ib is well located to displace the chlorine at C-3 to form IIIc which then undergoes a reverse Michael reaction to give III. The involvement of a spiran-type oxazolidine intermediate, such as Ic or IIIc, is supported by the fact that treat-

(1) This work was supported by U. S. Public Health Service Grant GM-7450 and in part by a special research grant from The Ohio State University.

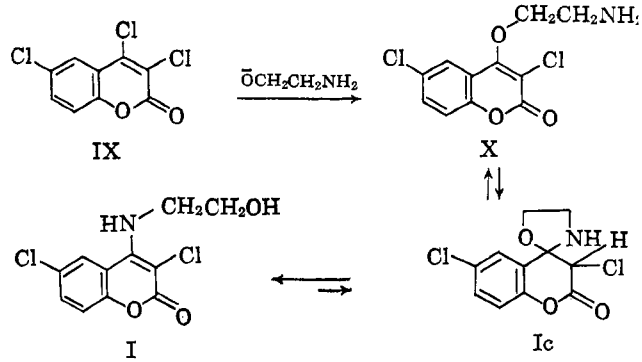
(2) M. S. Newman and C. Y. Peery, *J. Org. Chem.*, **28**, 116 (1963).



Ia, R = H Ib Ic

III, R = H; R = CH(CH$_3$)$_2$ IIIc

ment of 3,4,6-trichlorocoumarin (IX) with sodium 2-aminoethoxide in 1,2-dimethoxyethane yielded I in 59% yield. By analogy with reactions of other alkoxides with IX, 3,6-dichloro-4-(2-aminoethoxy)coumarin (X) was expected to be the reaction product. We believe that X was the first product of the reaction but was rapidly converted to I *via* Ic. Compounds X and I may be considered as a vinylogous ester and a vinylogous



IX X I Ic

amide. If we draw the analogy to the relative stability of amide *vs.* ester in the aminoethanol–benzoic acid case,[3] the equilibrium of X and I should lie far on the side of I. The quantitative recovery of 3,4-bis(2-hydroxyethylamino)-6-chlorocoumarin after refluxing in alcoholic sodium ethoxide for 4 hr.[2] may be cited as additional evidence of the difficulty of replacing an amino function in the 4-position of coumarin by an alkoxy group *via* a Michael-type addition–elimination sequence.

The cyclization of III to II, rapidly effected by catalytic (10%) amounts of alkoxide ion, may be explained by an extension of path b, as shown at right.

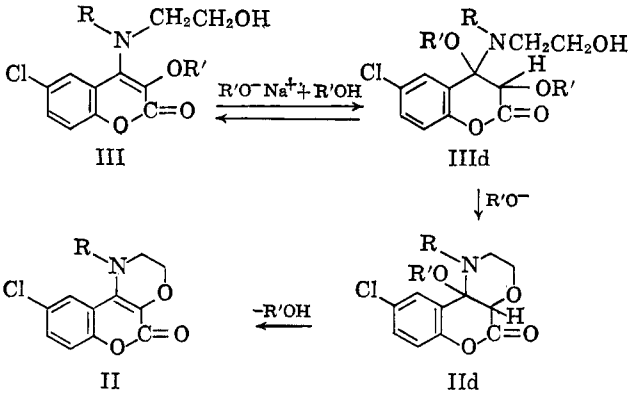
An intramolecular nucleophilic attack at C-3, similar to path a, is an unattractive alternate path. If one assumes that both the formations of III from I and of II from III proceed *via* path a, one is forced to the unreasonable conclusion that an intermolecular attack of alkoxide at C-3 of I proceeds faster than proton transfer between the alkoxide ion and the hydroxylic hydrogen of the hydroxyethylamino group at C-4 followed by cyclization of the resultant alkoxide ion.

In order to test whether hydrogen abstraction from the amino group of I plays a role in the reaction 3,6-dichloro-4-(N-methyl-2-hydroxyethylamino)coumarin (VI) was prepared by the reaction of 2-N-methylaminoethanol with IX. Treatment of VI with sodium isopropoxide in isopropyl alcohol led to the formation of VII or VIII depending on whether less or more than 1 equiv. of alkoxide was used. Since VII can be converted quantitatively to VIII by treatment with catalytic amounts (10%) of alkoxide in alcohol, we conclude that the N–H and N-methyl compounds react according to the same mechanism in alcohol and the N–H bond is not involved.

This similar behavior in alcohol–sodium alkoxide solution is to be contrasted with the fact that VI reacts much more slowly than I in 1,2-dimethoxyethane with sodium hydride as the base to yield VIII and II, respectively. Since the above-described mechanism cannot operate in aprotic solvents, we do not feel that these results detract from the mechanism proposed for reaction in alcohols. A direct intramolecular displacement of chloride ion by alkoxide (similar to path a described above) may be ruled out, since this fails to account for the different reactivities of the N–H (I) and N-methyl (VI) compounds unless a steric effect were involved.

In order to test the possible steric inhibition of the reaction in aprotic solvents, 3,6-dichloro-5,7-dimethyl-4-(2-hydroxyethylamino)coumarin (XII) was prepared. The first step in this synthesis afforded a test of the steric effects on the previously described[4] synthesis of 3,4-dichlorocoumarins. Condensation of 4-chloro-3,5-dimethylphenol with hexachloropropene afforded 3,4,6-trichloro-5,7-dimethylcoumarin (XI) in yields approximating those in which ring closure takes place at a position *ortho* to a hydrogen atom. Thus, this example indicates that there is no adverse steric effect in the coumarin synthesis. The conversion of XI to XII proceeded in poor yield in ethanol, but in good yield in 2-butanone. The relative ease of formation of the hydroxyethylaminocoumarins from the corresponding chlorocoumarins was I > VI > XII.

Treatment of XII with less than 1 equiv. of sodium ethoxide in ethanol led to the formation of 9-chloro-8,10-dimethyl-2,3-dihydro[1]benzopyrano[3,4-*b*][1,4]oxazin-5(1H)-one (XIII) (54%) and 6-chloro-3-ethoxy-5,7-dimethyl-4-(2-hydroxyethylamino)coumarin (XIV) (40%). Cyclization of XII to XIII with sodium

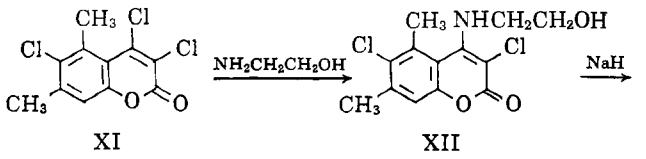


III IIId II IId

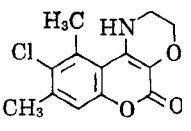
(3) See A. P. Phillips and R. Baltzly, *J. Am. Chem. Soc.*, **69**, 220 (1947); and references therein.

(4) M. S. Newman and S. Schiff, *ibid.*, **81**, 2266 (1959).

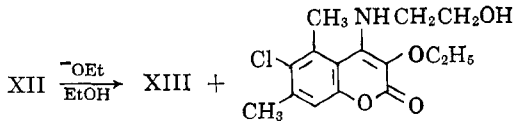
hydride in 1,2-dimethoxyethane was carried out in quantitative yield and proceeded rapidly. Therefore,



XI XII

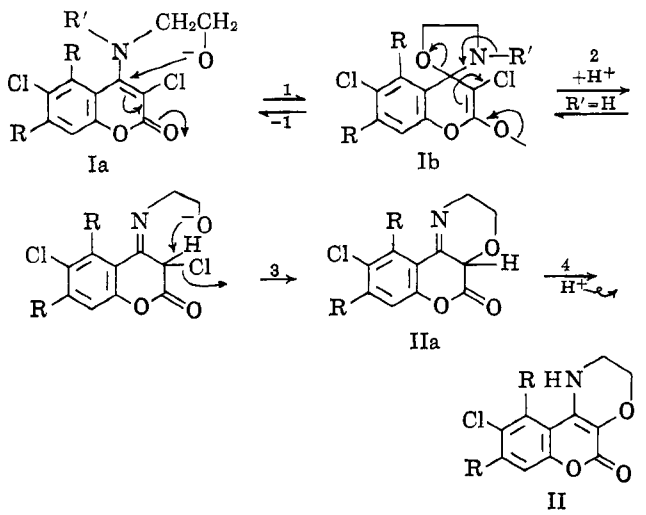


XIII



XIV

since a steric effect may be ruled out as the cause of the relatively slow conversion of VI to VIII in an aprotic solvent, the amino hydrogen apparently plays a role. A possible explanation is shown below. The abstrac-

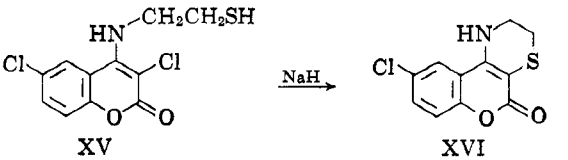


Ia Ib IIa

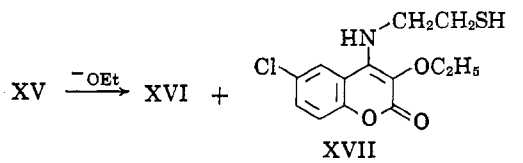
II

tion of the proton from the amino nitrogen in step 2 may be intra- or intermolecular; however, the driving force for this step seems minimal. If R′ = CH_3, step 2 cannot proceed and the proton source necessary to make C-3 sp^3 must be external (solvent or wet nitrogen). Steps 3 and 4, cyclization and prototropic change, seem reasonable. When R = CH_3, the reaction may proceed through direct attack of the nucleophile at the unsaturated C-3, a path which we have previously rejected when other alternatives were available.

In order to test further the competition between the intramolecular and intermolecular reactions in alcohol solution, 3,6-dichloro-4-(2-mercaptoethylamino)coumarin (XV) was prepared by the treatment of IX with 2-mercaptoethylamine. Owing to the extreme insolubility of XV in solvents previously employed in this study, the results cannot be rigorously compared. However, treatment of XV with sodium hydride in N,N-dimethylformamide led to a low yield of 9-chloro-2,3-dihydro[1]benzopyrano[3,4-*b*][1,4]thiazin-5(1H)-one (XVI). In addition, XV yielded a mixture of XVI and



XV XVI



XV XVI + XVII

6-chloro-3-ethoxy-4-(2-mercaptoethylamino)coumarin (XVII) upon reaction with less than 1 equiv. of sodium ethoxide in ethanol–N,N-dimethylacetamide. Thus, the so-called "intermolecular" reaction competes favorably with the intramolecular ring closure to give XVII. We believe that this reaction proceeds through a thiazolidine intermediate similar to oxazolidine intermediate Ic.

Experimental Section[5]

Reactions of 3,6-Dichloro-4-(2-hydroxyethylamino)coumarin (I) with Alkoxides. A. Less than 1 Equiv. of Sodium Isopropoxide.—In a typical experiment a solution containing 9.8 mmoles of sodium isopropoxide in 100 ml. of isopropyl alcohol was added during 30 min. to a refluxing solution of 2.74 g. (10.0 mmoles) of I[2] in 60 ml. of isopropyl alcohol. The resulting solution was held at reflux for an additional 30 min., and the isopropyl alcohol was then removed under reduced pressure. The residue 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 450 mg. (19%) of II,[2] m.p. 315–320° dec. The ethanol solution, upon concentration, yielded 1.97 g. (66%) of III,[2] m.p. 125–126°.

B. More than 1 Equiv. of Sodium Isopropoxide.—A solution containing 5.41 mmoles of sodium isopropoxide in 15 ml. of isopropyl alcohol was pipetted into a refluxing solution of 1.37 g. (5.00 mmoles) of I[2] in 35 ml. of isopropyl alcohol. After 15 min., a 10-ml. aliquot was added to 50 ml. of water. The precipitate was filtered and dried to yield 233 mg. (98%) of II.[2] After 2.75 hr., the remainder of the mixture was poured into water to yield 97% of II.

C. Less than 1 Equiv. of Sodium Ethoxide.—To a refluxing solution of 2.80 g. (10.2 mmoles) of I in 60 ml. of absolute ethanol was added a solution containing 9.42 mmoles of sodium ethoxide in 95 ml. of ethanol over a period of 80 min. After addition was complete, the reaction mixture was held at reflux for 30 min. After a work-up comparable with that described above, 177 mg. (8%) of II was obtained. The ethanol filtrate on concentration yielded 1.71 g. (64%) of 6-chloro-3-ethoxy-4-(2-hydroxyethylamino)coumarin (IV): m.p. 120–121°; infrared bands[6] 2.77 (w), 3.01 (w), 5.97 (s), 6.21 (s), 6.35 (m) μ; λ_{max}, mμ (log ϵ), 217 (4.16), 235 (4.11), 262 (4.04), 305 (3.97), 312 (4.00), 345 (4.00); λ_{min}, mμ (log ϵ), 223 (4.02), 281 (3.55), 320 (3.84).

Anal. Calcd. for $C_{13}H_{14}ClNO_4$: C, 55.0; H, 5.0; Cl, 12.5; N, 4.9. Found[b]: C, 55.0; H, 5.2; Cl, 12.6; N, 5.0.

D. Less than 1 Equiv. of Sodium Methoxide.—A refluxing solution of 2.74 g. (10.0 mmoles) of I in 60 ml. of methanol was treated with a solution of 9.52 mmoles of sodium methoxide in 100 ml. of methanol during 80 min. The resulting solution was held at reflux for 30 min. After filtration of the cooled reaction mixture, the precipitate was washed with several portions of methanol and then with water and dried to yield 486 mg. (21%) of

(5) All melting point determinations were made on a Fisher-Johns block and are uncorrected. Microanalyses marked b were by Bernhardt, Mülheim, Germany, and s by Schwartzkopf Laboratories, Woodside, N. Y. All infrared spectra were taken in chloroform solution unless otherwise indicated and were run on a Perkin-Elmer Model 137 Infracord spectrophotometer. All ultraviolet spectra were taken in 95% ethanol solution and were run on a Perkin-Elmer Model 202 spectrophotometer. All reaction solvents were dried over molecular sieves.

(6) Infrared spectra are in microns; bands are indicated by weak, w, medium, m, and strong, s.

II. The methanol filtrate was concentrated to yield 1.71 g. (67%) of 6-chloro-3-methoxy-4-(2-hydroxyethylamino)coumarin (V): m.p. 133–135°; infrared (KBr) bands 2.94 (m), 6.01 (s), 6.26 (s), 6.41 (m) μ; λ_{max}, mμ (log ϵ), 212 (4.42), 235 (4.36), 263 (4.12), 305 (3.99), 314 (4.04), 347 (4.03); λ_{min}, mμ (log ϵ), 223 (4.31), 284 (3.74), 320 (3.89).

Anal. Calcd. for $C_{12}H_{12}ClNO_4$: C, 53.4; H, 4.5; Cl, 13.2; N, 5.2. Found[b]: C, 53.3; H, 4.4; Cl, 13.3; N, 5.3.

E. Less than 1 Equiv. of Sodium *t*-Butoxide.—A solution of 2.74 g. (10.0 mmoles) of I in 60 ml. of *t*-butyl alcohol was treated with a solution of 9.80 mmoles of sodium *t*-butoxide in 100 ml. of *t*-butyl alcohol during 85 min. The reaction mixture was held at reflux an additional 30 min., cooled to room temperature, and filtered. The filter cake was washed thoroughly with water and dried to yield 1.05 g. (45%) of II. The filtrate was evaporated to dryness under reduced pressure. The residue was washed with water and recrystallized from hot ethanol to yield 770 mg. (28%) of starting material.

Reactions of III, IV, and V with Bases. A. Reaction of III with 0.1 Equiv. of Sodium Isopropoxide.—A solution of 295 mg. (0.990 mmole) of III[2] in 10 ml. of refluxing isopropyl alcohol was treated with 1 ml. of a 0.1 *M* solution of sodium isopropoxide in isopropyl alcohol. The solution was held at reflux for 20 min. although precipitation of II was significant within 1 min. after addition of the base solution. The reaction mixture was evaporated to dryness under reduced pressure. The residue was washed with water and dried to yield 222 mg. (94%) of II.

B. Reaction of IV with 0.1 Equiv. of Sodium Ethoxide.—A refluxing solution of 310 mg. (1.09 mmoles) of IV in 10 ml. of ethanol was treated with 1 ml. of a 0.1 *M* solution of sodium ethoxide in ethanol. The reaction mixture was held at reflux for 15 min. although a heavy white precipitate formed within 3 min. after addition of the base solution. The solvent was removed under reduced pressure. The residue was washed with water and dried to yield 246 mg. (95%) of II.

C. Reaction of IV with Sodium Hydride.—A refluxing solution of IV (308 mg., 1.08 mmoles) in 10 ml. of 1,2-dimethoxyethane was treated with 76.5 mg. of a 54.7% dispersion of sodium hydride (1.74 mmoles) in mineral oil. The reaction mixture was kept under nitrogen and was held at reflux for 15 min., cooled to room temperature, and poured into 100 ml. of water. The precipitated was collected and dried to yield 252 mg. (98%) of II.

D. Reaction of V with Sodium Hydride.—A refluxing solution of 265 mg. (0.981 mmole) of V in 10 ml. of 1,2-dimethoxyethane was treated with 72.2 mg. of a 53% dispersion of sodium hydride (1.6 mmoles) in mineral oil. The reaction mixture was kept under nitrogen and was held at reflux for 20 min. and worked up as above to yield 74 mg. (32%) of II.

Reaction of I with Sodium 2-Aminoethoxide.—A solution of 690 mg. (11.3 mmoles) of 2-aminoethanol in 10 ml. of 1,2-dimethoxyethane was added dropwise to a refluxing slurry of 274 mg. (11.4 mmoles) of sodium hydride in 10 ml. of 1,2-dimethoxyethane. When the hydrogen evolution had ceased, a solution of 2.75 g. (11.0 mmoles) of 3,4,6-trichlorocoumarin (IX) in 20 ml. of 1,2-dimethoxyethane was added over a period of 20 min. under nitrogen. The resulting orange suspension was held at reflux an additional 2 hr. Addition of 10 ml. of water to the cooled mixture afforded a homogeneous solution which was poured into 200 ml. of water and extracted with four 11-ml. portions of ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and evaporated to dryness, and the residue was recrystallized from hot ethanol to yield 1.76 g. (59%) of I.

3,6-Dichloro-4-(N-methyl-2-hydroxyethylamino)coumarin (VI).—To a refluxing solution of 5.00 g. (20.0 mmoles) of IX in 100 ml. of absolute ethanol was added a solution of 3.00 g. (40.0 mmoles) of 2-methylaminoethanol in 20 ml. of absolute ethanol over a period of 10 min. The resulting solution was held at reflux an additional 2.5 hr. and cooled to room temperature. The mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. A 200-ml. benzene solution of the resulting oil was washed with 100 ml. of 3 *N* hydrochloric acid and then with water until the wash water was neutral, dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness under reduced pressure. The resulting oil was crystallized from ethanol to yield 3.61 g. (63%) of VI: m.p. 95–96°; infrared bands 2.95 (w), 5.83 (s), 6.30 (m), 6.52 (m) μ; λ_{max}, mμ (log ϵ), 215 (sh) (4.08), 224 (4.39), 228 (sh) (3.46), 258 (sh) (3.96), 272 (4.00), 330 (4.00); λ_{min}, mμ (log ϵ), 241 (3.85), 298 (3.63).

Anal. Calcd. for $C_{12}H_{11}Cl_2NO_3$: C, 50.0; H, 3.9; Cl, 24.6; N, 4.9. Found[5]: C, 50.0; H, 3.8; Cl, 25.0; N, 4.8.

Reaction of VI with Less than 1 Equiv. of Sodium Isopropoxide.—A refluxing solution of 2.63 g. (9.13 mmoles) of VI in 60 ml. of isopropyl alcohol was treated with a solution of 8.23 mmoles of sodium isopropoxide in 100 ml. of isopropyl alcohol during 40 min. The resulting solution was held at reflux for 30 min., then evaporated to dryness under reduced pressure. The resulting oil was crystallized from ether to yield 2.17 g. (85%) of 6-chloro-3-isopropoxy-4-(N-methyl-2-hydroxyethylamino)coumarin (VII): m.p. 72–73°; infrared bands 2.94 (w), 5.94 (s), 6.37 (m) μ; λ_{max}, mμ (log ϵ), 213 (4.33), 249 (4.19), 304 (3.92), 311 (3.94), 353 (3.81); λ_{min}, mμ (log ϵ), 228 (3.95), 284 (3.70), 323 (3.62).

Anal. Calcd. for $C_{15}H_{18}ClNO_4$: C, 57.8; H, 5.8; Cl, 11.4; N, 4.5. Found: C, 57.6; H, 5.8; Cl, 11.7; N, 4.6.

Reaction of VI with More than 1 Equiv. of Sodium Isopropoxide.—A solution of 10.6 mmoles of sodium isopropoxide in 100 ml. of isopropyl alcohol was added to a refluxing solution of 2.89 g. (10.0 mmoles) of VI in 60 ml. of isopropyl alcohol during 45 min. The resulting mixture was held at reflux an additional 35 min. and evaporated to dryness under reduced pressure. The resulting oil was washed with 50 ml. of water and the residue was crystallized from ethanol to yield 1.25 g. (50%) of VIII: m.p. 193–195°; infrared bands 5.95 (s), 6.31 (m), 6.39 (m) μ; λ_{max}, mμ (log ϵ), 210 (4.29), 238 (4.25), 268 (sh) (3.81), 302 (3.92), 310 (4.00), 353 (3.90); λ_{min}, mμ (log ϵ), 223 (4.01), 280 (3.54), 321 (3.65).

Anal. Calcd. for $C_{12}H_{10}ClNO_3$: C, 57.3; H, 4.0; Cl, 14.1; N, 5.6. Found[5]: C, 57.5; H, 3.9; Cl, 14.0; N, 5.7.

The ethanolic mother liquors were evaporated to dryness and chromatographed over 50 g. of silica gel. Elution with 20% chloroform in benzene yielded 410 mg. (13%) of VII.

Reaction of VII with 0.1 Equiv. of Sodium Isopropoxide.—A refluxing solution of 321 mg. (1.03 mmoles) of VII in 10 ml. of isopropyl alcohol was treated with 1 ml. of a 0.1 *M* solution of sodium isopropoxide in isopropyl alcohol. The resulting solution was held at reflux for 45 min. and evaporated to dryness under reduced pressure. The residue was washed with several portions of water and dried to yield 221 mg. (85%) of VIII, m.p. 194.5–195.5°.

Reaction of VI with Sodium Hydride.—A refluxing solution of 1.44 g. (5.00 mmoles) of VI in 50 ml. of 1,2-dimethoxyethane was treated under nitrogen with 256 mg. of a 53% dispersion of sodium hydride (5.6 mmoles) in mineral oil. A 10-ml. aliquot was quenched in 50 ml. of water after 25 min. No VIII was obtained. (A control experiment run simultaneously with I gave a 66% yield of II after the same reaction time.) At the end of 1.5 hr., another aliquot was removed and a 44% yield of crude VIII, m.p. 180–189°, was obtained. At the end of 5 hr., the remainder of the reaction mixture was quenched with 150 ml. of water, and a 74% yield of crude VIII, m.p. 194–196°, was obtained. This experiment was repeated with different batches of VI and sodium hydride dispersion and similar results were obtained.

3,4,6-Trichloro-5,7-dimethylcoumarin (XI).—A solution of 15.7 g. (0.100 mole) of 4-chloro-3,5-dimethylphenol in 100 ml. of dichloromethane was added to a slurry of 31.0 g. (0.233 mole) of powdered anhydrous aluminum chloride in 50 ml. of dichloromethane. The resulting orange suspension was allowed to stir at room temperature for 10 min. and then cooled in an ice bath. Hexachloropropene (26.2 g., 0.105 mole) was added dropwise to the cold solution. After further stirring for 30 min. at 0°, the brown solution was poured onto a slurry of ice and concentrated hydrochloric acid and stirred until all of the solid dissolved. Combined dichloromethane extracts of the mixture were washed with water until neutral, dried over magnesium sulfate, filtered, and evaporated to dryness. After washing and trituration with ether, the residue was recrystallized from hot ethanol to yield 18.0 g. (65%) of XI: m.p. 172–173°; infrared bands 5.76 (s), 6.27 (m), 6.37 (m), 6.60 (m) μ; λ_{max}, mμ (log ϵ), 220 (4.36), 304 (4.11), 340 (3.86); λ_{min}, mμ (log ϵ), 263 (3.44). No attempt was made to raise the yield by purifying the mother liquors.

Anal. Calcd. for $C_{11}H_7Cl_3O_2$: C, 47.6; H, 2.5; Cl, 38.3. Found[7]: C, 47.8; H, 2.6; Cl, 38.2.

3,6-Dichloro-5,7-dimethyl-4-(2-hydroxyethylamino)coumarin (XII).—A solution of 1.40 g. (5.04 mmoles) of XI and 660 mg. (10.8 mmoles) of 2-aminoethanol in 100 ml. of 2-butanone was

(7) Analysis was by Galbraith Laboratories, Knoxville, Tenn.

held at reflux for 3 days and then evaporated to dryness under reduced pressure. The residue was washed with water and recrystallized from hot ethanol to yield 979 mg. (64%) of XII: m.p. 156–158°; infrared (KBr) bands 2.92 (w), 3.00 (w), 3.08 (w), 5.92 (s), 6.31 (s), 6.53 (m) μ; λ_{max} mμ (log ϵ), 217 (4.37), 249 (4.22), 325 (4.18); λ_{min}, mμ (log ϵ), 240 (4.18), 283 (3.62).

Anal. Calcd. for $C_{13}H_{13}Cl_2NO_3$: C, 51.7; H, 4.3; Cl, 23.5; N, 4.6. Found[b]: C, 51.6; H, 4.3; Cl, 23.6; N, 4.5.

Reaction of XII with Less than 1 Equiv. of Sodium Ethoxide.—To a refluxing solution of 3.10 g. (10.3 mmoles) of XII in 50 ml. of absolute ethanol was added 100 ml. of a 0.102 *M* solution of sodium ethoxide in ethanol during 34 min. The reaction mixture was held at reflux an additional 30 min., cooled to room temperature, and filtered. The precipitate was washed with several portions of distilled water and dried to yield 1.47 g. (54%) of XIII: m.p. 310–312°; infrared (KBr) bands 2.95 (m), 6.09 (s), 6.30 (s), 6.43 (s) μ; λ_{max} mμ (log ϵ), 212 (4.22), 238 (4.22), 298 (4.02), 308 (4.14), 338 (3.99); λ_{min}, mμ (log ϵ), 225 (4.03), 275 (3.38), 320 (3.89).

Anal. Calcd. for $C_{13}H_{12}ClNO_3$: C, 58.8; H, 4.6; Cl, 13.4; N, 5.3. Found[a]: C, 58.8; H, 4.5; Cl, 13.4; N, 5.3.

The ethanolic filtrate from the above was evaporated to dryness under reduced pressure and the residue was recrystallized from 95% ethanol to yield 1.26 g. (40%) of XIV: m.p. 107–109°; infrared (KBr) bands 3.07 (broad), 6.00 (s), 6.27 (s), 6.42 (s) μ; λ_{max}, mμ (log ϵ), 211 (4.23), 240 (4.22), 263 (sh) (3.98), 295 (sh) (4.17), 302 (4.23), 306 (4.23), 330 (sh) (3.91); λ_{min}, mμ (log ϵ), 224 (4.11), 274 (3.75), 304 (4.20).

Anal. Calcd. for $C_{15}H_{13}ClNO_4$: C, 57.8; H, 5.8; Cl, 11.4; N, 4.5. Found[a]: C, 57.9; H, 5.8; Cl, 11.3; N, 4.5.

Reaction of XII with Sodium Hydride.—A refluxing solution of 1.51 g. (5.00 mmoles) of XII in 50 ml. of 1,2-dimethoxyethane was treated with 255 mg. of a 53% dispersion of sodium hydride (5.67 mmoles) in mineral oil. The resulting mixture was held at reflux under nitrogen. After 25 min., a 10-ml. aliquot was removed and quenched with 50 ml. of water to yield 227 mg. (85%) of XIII. The remainder of the solution was quenched with 100 ml. of water after 4.5 hr. to yield 996 mg. (94%) of XIII.

3,6-Dichloro-4-(2-mercaptoethylamino)coumarin (XV).—A solution of 4.80 g. (42.0 mmoles) of 2-mercaptoethylamine hydrochloride in 50 ml. of methanol was added to a methanol solution (50 ml.) containing 40.5 mmoles of sodium methoxide. This solution of free 2-mercaptoethylamine was then added to a refluxing solution of 5.02 g. (20.1 mmoles) of 3,4,6-trichlorocoumarin in 100 ml. of methanol. The resulting mixture was held at reflux for 1 hr., cooled to room temperature, and filtered. The precipitate was washed with several portions of water, triturated with benzene, washed with acetone, and dried thoroughly to yield 5.54 g. (95%) of XV: m.p. 262–264° dec.; infrared (KBr) bands 2.99 (m), 5.99 (s), 6.26 (s), 6.54 (s) μ. No solvent could be found for recrystallization. The ultraviolet absorptions for a saturated solution were λ_{max} 210, 223, 240, 250, and 300–342 mμ; λ_{min} *ca.* 275 mμ.

Anal. Calcd. for $C_{11}H_5Cl_2NO_2S$: C, 45.5; H, 3.1; Cl, 24.4; N, 4.8; S, 11.1. Found[a]: C, 45.2; H, 2.8; Cl, 24.3; N, 4.6; S, 11.0.

Reaction of XV with Sodium Hydride.—A solution of 1.48 g. (5.10 mmoles) of XV in 50 ml. of N,N-dimethylformamide was held at a bath temperature of 145° and treated with 299 mg. of a 53% dispersion of sodium hydride (6.63 mmoles) in mineral oil. The reaction mixture was maintained under an atmosphere of nitrogen at 145° for 2 hr. and was then poured into 400 ml. of water. The mixture was filtered and the precipitate was dried and recrystallized from hot acetone to yield 375 mg. (29%) of 9-chloro-2,3-dihydro[1]benzopyrano[3,4-*b*][1,4]thiazin-5(1H)-one (XVI): m.p. 300–302° dec.; infrared (KBr) bands 3.02 (m), 6.02 (s), 6.24 (m), 6.49 (s) μ; λ_{max}, mμ (log ϵ), (222 (4.24), 243 (4.01), 264 (3.85), 320 (3.44), 365 (3.89); λ_{min}, mμ (log ϵ), 290 (3.24).

Anal. Calcd. for $C_{11}H_6ClNO_2S$: C, 52.1; H, 3.2; Cl, 14.0; N, 5.5; S, 12.6. Found[a]: C, 52.0; H, 3.4; Cl, 14.3; N, 5.8; S, 12.9.

Reaction of XV with Less than 1 Equiv. of Sodium Ethoxide.—To a solution of 2.91 g. (10.0 mmoles) of XV in 100 ml. of N,N-dimethylformamide held at a bath temperature of 95–100° was added 100 ml. of a solution containing 9.97 mmoles of sodium ethoxide during 60 min. The reaction mixture was allowed to stir at elevated temperature for an additional 30 min., cooled, and filtered. The precipitate was washed with water and dried to yield 59 mg. (2%) of starting material. The filtrate was poured into 200 ml. of water and allowed to stand overnight. The mixture was filtered, and the precipitate was triturated with 2-butanone. The residue was dried to yield 347 mg. (14%) of XV. The butanone solution, upon concentration, yielded 1.11 g. (37%) of 6-chloro-3-ethoxy-4-(2-mercaptoethylamino)coumarin (XVII): m.p. 170–172°; infrared (KBr) bands 3.03 (w), 6.08 (s), 6.26 (s), 6.42 (s) μ; λ_{max} (saturated solution) 210, 235, 260 (sh), 290 (sh), 305, 314, 347 mμ; λ_{min} 223, 280, 321 mμ.

Anal. Calcd. for $C_{13}H_{14}ClNO_3S$: C, 52.1; H, 4.7; Cl, 11.8; N, 4.7. Found[a]: C, 52.2; H, 4.7; Cl, 11.9; N, 4.7.

The Rearrangement of 3,4-Disubstituted Coumarins to Coumarilic Acid Derivatives in Basic Media[1]

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The reaction of 3-chlorocoumarin (I) with sodium methoxide to produce methyl coumarilate (II) has been shown to proceed only if methanol is present. A mechanism for this reaction is proposed. Several 4-substituted 3,6-dichlorocoumarins have been converted into alkyl 3-substituted 5-chlorocoumarilates. In earlier work, these dichlorocoumarins had supposedly been converted into other coumarin derivatives. The correct structures for the compounds in question are shown. All are derivatives of coumarilic acid.

Because of the unexpected reactivity of the 3-chloro substituent in certain 4-substituted aminocoumarins,[2] a study of the reactivity of the 3-chlorine in coumarins bearing different substituents in the 4-position was started. During this study certain errors in previously reported work[3,4] were discovered and are herein corrected. In addition, the general picture of the reaction of 4-substituted 3-chlorocoumarins with alkoxide ions is clarified.

On treatment of 3-chlorocoumarin (I)[5] with sodium methoxide in methanol a good yield of methyl coumarilate (II)[6] was obtained. Although analogous reactions of 3-chloro- and 3-bromocoumarin with alcoholic potassium hydroxide are known,[7] to our knowledge no attempt has been made to explain the results. At first

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