Reaction of 7-Substituted 2-Halotropones with Ethyl Sodiocyanoacetate

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In a previous paper, the formation of α-benzopyran, as well as of azulene derivatives, by the condensation of 2-chlorotropone and ethyl sodiocyanoacetate was reported[1]. In the present paper, the reaction of 2-halotropone derivatives and ethyl sodiocyanoacetate is examined and the results obtained are reported on.

The reaction of 2, 7-dibromotropone (I) and ethyl sodiocyanoacetate (II) in a mixed solvent of dioxane and ethanol affords colorless crystals of m. p. 117°C (III), $C_{17}H_{17}O_5N_2Br$, and of m. p. 150°C (IV), $C_{12}H_9O_4Br$. Under the same conditions, 2, 7-dichlorotropone (V) affords colorless crystals of m. p. 123°C (VI), $C_{17}H_{17}\cdot O_5N_2Cl$, and of m. p. 146°C (VII), $C_{12}H_9O_4Cl$, and orange-red crystals of m. p. 152°C (VIII), $C_{22}H_{22}O_8N_2$. The same reaction of 2-chloro-7-bromotropone (IX) gives colorless crystals of m. p. 223°C (X), $C_{10}H_5O_4Br$, besides VI and VII.

The reaction of 2-methoxy-7-bromotropone (XI) in ethanol affords colorless crystals of m. p. 125°C (XII), $C_{18}H_{20}O_6N_2$, and a compound corresponding to VIII, while that of 2-methoxy-3, 7-dibromotropone (XIII) gives colorless crystals of m. p. 115°C (XIV), $C_{13}H_{11}\cdot O_5Br$. The same reaction of 2-methoxy-3, 5, 7-tribromotropone (XV) gives colorless crystals of m. p. 146°C (XVI), $C_{18}H_{18}O_6N_2Br_2$, and of m. p. 217°C (XVII), $C_{11}H_5O_3NBr_2$.

The ultraviolet absorption spectra[*1] of III, VI, XII and XVI (Fig. 1) are similar to that of 2-amino-2-(cyano-ethoxycarbonylmethyl)-3-ethoxycarbonyl-α-benzopyran (XVIII) reported on in a previous paper[1]. The infrared absorption spectra[2] of these compounds showed the presence of amino, cyano and ester carbonyl groups and of an ester carbonyl group conjugated with an unsaturated bond. On the basis of these spectral data, it is assumed that III is the 8-bromo derivative, that VI is the 8-chloro derivative, that XII is the 8-methoxy derivative, and that XVI is the 5, 7-dibromo-8-methoxy derivative of XVIII.

Condensation of 3-bromosalicylaldehyde (XIX) and ethyl cyanoacetate in the presence of piperidine had given III, and the same reaction with 3-chlorosalicylaldehyde (XX) gave VI. These facts clearly indicate that III, VI, XII and XVI are all α-benzopyran derivatives.

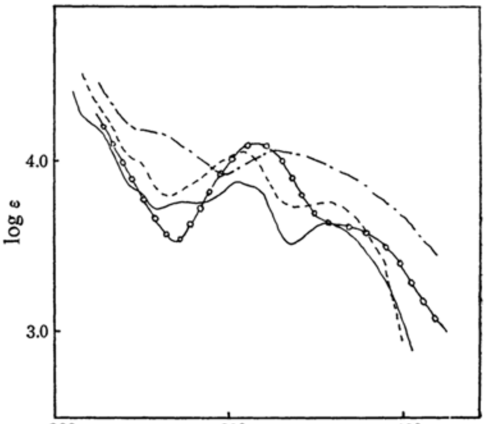

Fig. 1. Ultraviolet absorption spectra of III, VI, XII and XVI in methanol.
—— III : Y=log ε+0 ; ---- VI : Y=log ε +0.2 ; -○- XII : Y=log ε+0 ; - · - XVI : Y=log ε+0.

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1) S. Matsumura, This Bulletin, **34**, 995 (1961).

2) S. Matsumura, *Bull. Chem. Research Inst., Non-Aq. Solns., Tohoku Univ.*, **10**, 223 (1961).

[*1] The ultraviolet spectra were measured with a Hitachi EPU-2A spectrophotometer by Mr. H. Sato of this Institute, to whom the author is deeply indebted.

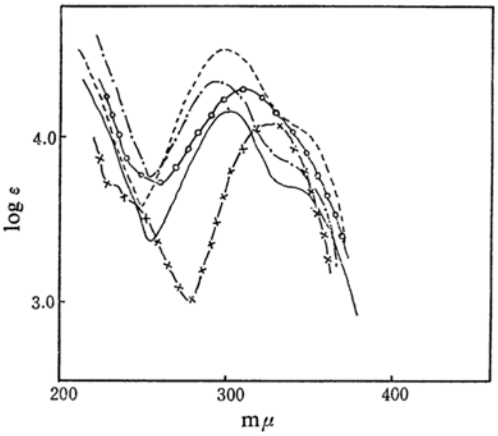

Fig. 2. Ultaviolet absorption spectra of IV, VII, X, XIV and XVII in methanol.
—— IV : Y=log ε+0 ; - · - VII : Y=log ε +0.2 ; ------ X : Y=log ε+0.4 ; -○- XIV : Y=log ε+0 ; -×- XVII : Y=log ε+0.

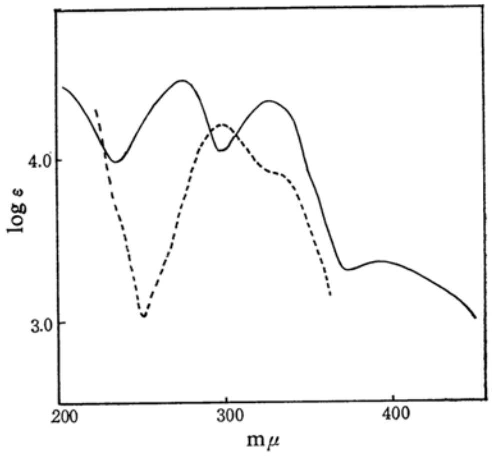

Fig. 3. Ultraviolet absorption spectra of VIII and XXIII in methanol.
—— VIII, ---- XXIII

The ultraviolet absorption spectra of IV, VII, X, XIV and XVII (Fig. 2) are similar to those coumarin derivatives. These compounds all have absorption bands in the region of 1760∼1735 cm^{-1} due to the unsaturated δ-lactonic carbonyl group in the coumarin ring. There is an absorption band due to the ester carbonyl group conjugated with an unsaturated bond in the region of 1710∼1690 cm^{-1} in IV, VII and XIV, while an absorption band of a carboxyl group is present at 2750 cm^{-1} in X, and that of a cyano group conjugated with an unsaturated bond at 2215 cm^{-1}, in XVII. These spectral evidences show that IV, VII and XIV are 8-bromo, 8-chloro, and 7-bromo-3-methoxy derivatives of 3-ethoxycarbonylcoumarin respectively, while X is 3-carboxy-8-bromocoumarin and XVII is 3-cyano-5, 7-dibromo-8-methoxycoumarin.

The heating of III with dilute hydrochloric acid for a short time converts it to IV, and a similar reaction of VI gives VII. The treatment of XII with hydrochloric acid gives 3-carboxy-8-methoxycoumarin (XXI), m. p. 172°C, while the treatment of XVI with hydrochloric acid affords 3-ethoxycarbonyl-5, 7-dibromo-8-methoxycoumarin (XXII), m. p. 187°C. XXII is also obtained by the treatment of XVII with absolute ethanol containing hydrochloric acid. On the basis of the ultraviolet spectrum of VIII (Fig. 3), this compound is assumed to be a coumarin derivative. The infrared spectrum of VIII indicates the presence of absorptions due to cyano- and carbonyl groups conjugated with an unsaturated bond and to a carbonyl group not conjugated with an unsaturated bond.

The hydrolysis of VIII with 6N hydrochloric acid gives a compound XXIII, m. p. 215°C, corresponding to the molecular formula of $C_{12}H_8O_6$. The ultraviolet spectrum of XXIII, as shown in Fig. 3, shows an absorption curve similar to that of 3-carboxycoumarin. The infrared spectrum of XXIII indicates the presence of a carboxyl and of a methylene group (1465 cm^{-1}). This spectral evidence shows that XXIII is 3-carboxy-8-carboxymethylcoumarin.

On the basis of the formation of 3-carboxy-8-carboxymethylcoumarin from VIII and the infrared absorption spectrum of VIII, VIII is assumed to be ethyl α-cyano-β-amino-γ-(3-ethoxycarbonylcoumarin-8-yl)-glutaconate.

Recently, the condensation reaction between 2, 4, 7-tribromotropone (XXIV) and II has been examined[3], and seven kinds of structurally unidentified compounds have been obtained; colorless crystals (XXV) of m. p. 177°C, yellow crystals (XXVI) of m. p. 214°C, brown crystals (XXVII) of m. p. 178°C, colorless crystals (XXVIII) of m. p. 155°C, yellow crystals (XXIX) of m. p. 141°C, pale yellow crystals (XXX) of m. p. 181°C, and orange crystals (XXXI) of m. p. above 340°C. From their analytical values, the molecular formula of $C_{17}H_{15}O_5N_2Br$ was given for XXVI, $C_{12}H_9O_3NBr_2$ for XXVII and XXX, and $C_{12}H_8O_3NBr_2Na$ for XXXI. Re-examination of these analytical values showed that the molecular formula of $C_{22}H_{21}\cdot O_8N_2Br$ would be more appropriate for XXVI than $C_{17}H_{15}O_5N_2Br$. No molecular formulae were given for XXV and XXVIII, but, from their analytical values, the formula of $C_{12}H_8\cdot O_4Br_2$ is now suggested for XXV and $C_{17}H_{16}\cdot O_5N_2Br_2$ for XXVIII. The ultraviolet absorption spectra[2] of XXVIII and XXIX are similar

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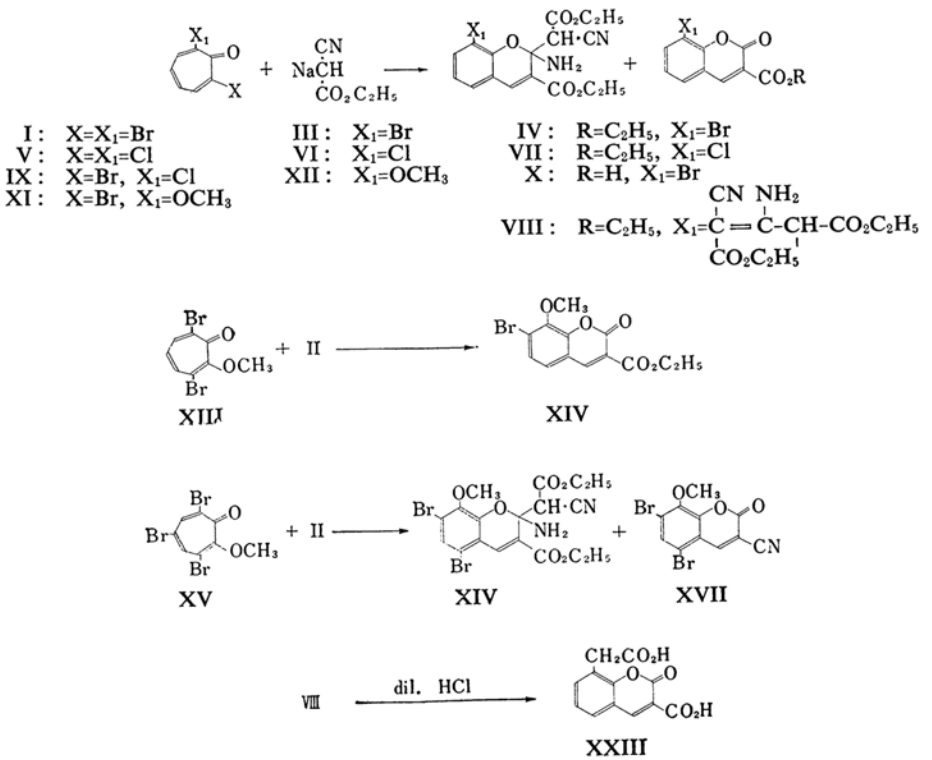
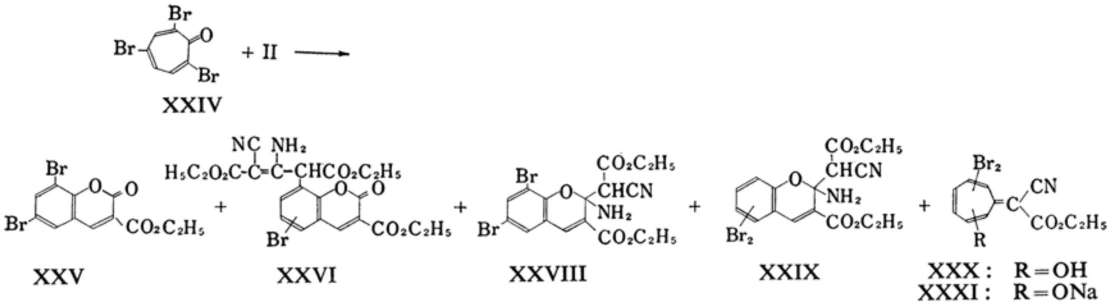
[3] H. Akino and S. Matsue, *Sci. Rep. Hirosaki Univ.*, **6**, 34 (1959).



Scheme 1.



Scheme 2.

to those of III and VI. The infrared spectra[3] of XXVIII and XXIX indicate the presence of cyano and ester carbonyl groups not conjugated with unsaturated bonds and of an ester carbonyl group conjugated with an unsaturated bond. This spectral evidence suggests that XXVIII and XXIX are α-benzopyran derivatives.

The condensation of 3, 5-dibromosalicylaldehyde (XXXII), obtained by the bromination of XIX, with ethyl cyanoacetate in the presence of piperidine affords XXVIII; this indicates that XXVIII is 6, 8-dibromo-2-amino-2-(cyano-ethoxycarbonylmethyl)-3-ethoxycarbonyl-α-benzopyran. The ultraviolet spectrum of XXV is similar to those of IV and VII. XXV is obtained by treatment of XXVIII with hydrochloric acid in ethanol. These facts show that XXV is 6,8-dibromo-3-ethoxycarbonylcoumarin.

The ultraviolet spectrum of XXVI is very similar to that of VIII, and the infrared spectrum of XXVI indicates the presence of amino and cyano, lactonic carbonyl, groups and of ester carbonyl groups conjugated with an unsaturated bond. Therefore, XXVI should be a 5- or 6-bromo derivative of VIII.

On the basis of a consideration of the ultraviolet and infrared absorption spectra, it is assumed that XXX and XXXI are heptafulvene derivatives. These reaction sequences are illustrated in Scheme 2.

Condensation of 2-halotropones substituted in the 7-position and II failed to indicate the formation of an azulene derivative; only rearrangement products were obtained.

Experimental*[2]

Reaction of 2,7-Dibromotropone (I) and Ethyl Sodiocyanoacetate (II).—A solution of 500 mg. of I dissolved in 20 ml. of dioxane was stirred into II, prepared from 90 mg. of metallic sodium, 3 ml. of absolute ethanol, and 500 mg. of ethyl cyanoacetate, under ice-cooling, the solution thereby became orange-red, and the colorless sodio compound changed into an orange-red precipitate. After the mixture was allowed to stand overnight at room temperature, the precipitate was collected by filtration and washed with ethanol, and the 400 mg. of colorless crystals that remained was recrystallized from ethanol. The easily soluble portion afforded 120 mg. of III as colorless prisms, m. p. 115~117°C.

Found: C, 50.13; H, 4.06; N, 6.65. Calcd. for $C_{17}H_{17}O_5N_2Br$: C, 49.87; H, 4.15; N, 6.84%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 307 (3.84), 360 (3.56).

The sparingly soluble portion afforded 80 mg. of IV as colorless scales, m. p. 149~150°C.

Found: C, 48.56; H, 3.21. Calcd. for $C_{12}H_9 \cdot O_4Br$: C, 48.48; H, 3.03%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 300 (4.14), 340 (3.68).

Formation of IV from III.—A solution of 50 mg. of III dissolved in 0.5 ml. of ethanol and with 0.2 ml. of 6 N hydrochloric acid added was heated on a water bath for 5 min., the solid thereby dissolved at once, and sparingly soluble needle crystals then separated out. Recrystallization of these crystals from ethanol gave 20 mg. of IV as colorless needles of m. p. 149~150°C.

Reaction of 2,7-Dichlorotropone (V) and II.—A solution of 500 mg. of V dissolved in 20 ml. of dehydrated dioxane was stirred, while being cooled by ice, into II, prepared from 140 mg. of sodium, 3 ml. of absolute ethanol, and 700 mg. of ethyl cyanoacetate, and the mixture was allowed to stand overnight at room temperature. The dioxane-ethanol mixture was evaporated at a reduced pressure, ethanol was added to the residue, and the precipitated orange-red crystals were repeatedly recrystallized from ethanol. The easily soluble portion afforded 160 mg. of VI as colorless scales, m. p. 122~123°C.

Found: C, 56.18; H, 4.56; N, 7.83. Calcd. for $C_{17}H_{17}O_5N_2Cl$: C, 56.03; H, 4.67; 7.69%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 305 (3.53), 355 (3.31).

The sparingly soluble portion afforded 80 mg. of VII as colorless needles, m. p. 145~146°C.

Found: C, 57.36; H, 3.28. Calcd. for $C_{12}H_9 \cdot O_4Cl$: C, 57.14; H, 3.57%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 296 (4.13), 340 (3.65).

The sparingly soluble portion also afforded 30 mg. of VIII as orange prisms, m. p. 151~152°C.

Found: C, 59.83; H, 5.29; N, 7.01. Calcd. for $C_{22}H_{22}O_8N_2$: C, 59.72; H, 5.01; N, 6.33%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 275 (4.48), 327 (4.35), 395 (3.35).

Formation of VII from VI.—A solution of 50 mg. of VI dissolved in 0.5 ml. of ethanol and with 0.2 ml. of 6 N hydrochloric acid added was warmed on a water bath for 5 min., and the colorless needle crystals that separated out were recrystallized from ethanol to give VII, m. p. 145~146°C.

Reaction of 2-Chloro-7-bromotropone (IX) and II.—A solution of 500 mg. of IX dissolved in 20 ml. of dioxane was stirred, while being cooled by ice, into II, prepared from 110 mg. of sodium, 3 ml. of absolute ethanol, and 550 mg. of ethyl cyanoacetate, and the mixture was treated as in the case of the reaction of V and II, affording 40 mg. of VI and 60 mg. of VII. The filtrate obtained after isolation of VI and VII was concentrated, the residue was dissolved in water, and the solution was neutralized with dilute nitric acid, from which 50 mg. of brown precipitate was obtained. Recrystallization of this precipitate from ethanol afforded 20 mg. of X as colorless crystals, m. p. 222~223°C (decomp.).

Found: C, 44.83; H, 1.89. Calcd. for $C_{10}H_5 \cdot O_4Br$: C, 44.60; H, 1.89%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 300 (4.13).

Reaction of 2-Methoxy-7-bromotropone (XI) and II.—A solution of 500 mg. of XI dissolved in 10 ml. of absolute ethanol was stirred, while being cooled by ice, into II, prepared from 100 mg. of sodium, 4 ml. of absolute ethanol, and 600 mg. of ethyl cyanoacetate; as a result the reaction started at once and the solution became reddish and clear. After the mixture had been left to stand overnight, the mixture was filtered and the filtrate was concentrated under reduced pressure. The tarry substance hereby formed was dissolved in benzene, the solvent was evaporated, and ethanol was added to the oily residue. The crystallized solid was recrystallized from ethanol, and 40 mg. of VIII, m. p. 151~152°C, was obtained. The recrystallization of the mother liquor afforded 340 mg. of XII as colorless prisms, m. p. 124~125°C.

Found (for XII): C, 60.57; H, 5.42; N, 7.83. Calcd. for $C_{18}H_{20}O_6N_2$: C, 59.99; H, 5.59; N, 7.77%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 316 (4.11), 360 (3.65).

Reaction of 2-Methoxy-3,7-Dibromotropone (XIII) and II.—A solution of 600 mg. of XIII dissolved in 15 ml. of dehydrated benzene was stirred, while being cooled by ice, into II, prepared from 100 mg. of sodium, 3 ml. of absolute ethanol, and 600 mg. of ethyl cyanoacetate, and the mixture was allowed to stand overnight at room temperature. The precipitate formed was collected and dissolved in 80 ml. of water, and the solution was neutralized with dilute nitric acid, producing 360 mg. of a greyish white precipitate. This precipitate was recrystallized first from benzene and then from ethanol to produce 260 mg. of XIV as colorless scales, m. p. 115~116°C.

Found: C, 47.34; H, 3.56. Calcd. for $C_{13}H_{11} \cdot O_5Br$: C, 47.70; H, 3.33%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 311 (4.29).

Reaction of 2-Methoxy-3,5,7-tribromotropone (XV) and II.—A solution of 500 mg. of XV dissolved in 10 ml. of absolute ethanol was stirred, while being cooled by ice, into II, prepared from 80 mg. of sodium, 3 ml. of absolute ethanol, and 400 mg. of ethyl cyanoacetate, and the mixture

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*[2] All the melting points are uncorrected.

was allowed to stand overnight at room temperature. The orange-red precipitate thereby formed was collected by filtration and recrystallized from ethanol to give 100 mg. of XVI as colorless scales, m. p. 146∼147°C.

Found: C, 42.03; H, 3.61; N, 5.86. Calcd. for $C_{18}H_{18}O_6N_2Br_2$: C, 41.69; H, 3.47; N, 5.43%.

UV $\lambda_{\max}^{\text{MeOH}}$ mμ (log ε): 266 (4.16), 333 (4.04).

Concentration of the filtrate precipitated colorless crystals which recrystallized from ethanol to produce 60 mg. of XVII as colorless prisms, m. p. 216∼217°C.

Found: C, 37.04; H, 1.36; N, 4.25. Calcd. for $C_{11}H_5O_3NBr_2$: C, 36.76; H, 1.39; N, 3.90%.

UV $\lambda_{\max}^{\text{MeOH}}$ mμ (log ε): 330 (4.07).

Synthesis of III.—One drop of piperidine was added to the solution of 100 mg. of 3-bromosalicylaldehyde (XIX) and 100 mg. of ethyl cyanoacetate dissolved in 0.2 ml. absolute ethanol; the solution here upon immediately became orange-yellow and prismatic crystals began to separate out. The crystals were collected and recrystallized from ethanol to give 120 mg. of III, m. p. 115∼117°C.

Synthesis of VI.—One drop of piperidine was added to a solution of 100 mg. of 3-chlorosalicylaldehyde (XX) and 100 mg. of ethyl cyanoacetate dissolved in 0.2 ml. of absolute ethanol; 150 mg. of VI, m. p. 122∼123°C, was obtained.

Reaction of XII with an Acid.—A solution of 100 mg. of XII dissolved in 1 ml. of ethanol and with 0.2 ml. of 6 N hydrochloric acid added was heated for 50 min., and the colorless crystals that separated out were recrystallized from ethanol to give 50 mg. of XXI, m. p. 171∼172°C.

Found: C, 60.31; H, 4.24. Calcd. for $C_{11}H_8O_5$: C, 60.00; H, 3.66%.

UV $\lambda_{\max}^{\text{MeOH}}$ mμ (log ε): 252 (3.89), 305 (4.15).

3-Ethoxycarbonyl-5, 7-dibromo-8-methoxycoumarin (XXII).—a) A solution of 100 mg. of XVI dissolved in 2 ml. of ethanol and with 0.3 ml. of 6 N hydrochloric acid added was heated on a water bath for 20 min.; the colorless crystals that separated out were recrystallized from ethanol to give 40 mg. of XXII, m. p. 186∼187°C.

Found: C, 38.20; H, 3.09. Calcd. for $C_{13}H_{10}O_5Br_2$: C, 38.42; H, 2.46%.

b) Hydrogen chloride gas was passed through the solution of 100 mg. of XVII dissolved in 3 ml. of absolute ethanol, and the solution was heated on a water bath for 5 hr. Ethanol was evaporated from the solution and the residual crystals were recrystallized from ethanol to give 80 mg. of XXII.

Reaction of VIII and an Acid.—A solution of 100 mg. of VIII dissolved in 6 ml. of ethanol and with 3 ml. of 3 N hydrochloric acid added was heated at 100∼120°C for 5 hr. Ethanol was evaporated from this solution, and the residual crystals were recrystallized from ethanol to give 40 mg. of XXIII as colorless crystals, m. p. 214∼215°C (decomp.).

Found: C, 57.27; H, 3.85. Calcd. for $C_{12}H_8O_6$: C, 58.07; H, 3.25%.

UV $\lambda_{\max}^{\text{MeOH}}$ mμ (log ε): 297 (4.12).

Reaction of 3,5-Dibromosalicylaldehyde (XXXII) and Ethyl Cyanoacetate.—One drop of piperidine was added to a solution of 50 mg. of XXXII and 50 mg. of ethyl cyanoacetate dissolved in 0.2 ml. of absolute ethanol. The solution thereby immediately colored orange-red. After the solution had been allowed to stand overnight, the colorless crystals that precipitated out were collected and recrystallized from ethanol to give 60 mg. of XXVIII as colorless prisms, m. p. 155∼156°C.

Found: C, 42.03; H, 3.56; N, 5.68. Calcd. for $C_{17}H_{16}O_5N_2Br_2$: C, 41.80; H, 3.28; N, 5.71%.

3-Ethoxycarbonyl-6,8-dibromocoumarin (XXV).—A solution of 100 mg. of XXVIII dissolved in 5 ml. of ethanol and with 0.3 ml. of 6 N hydrochloric acid added was heated on a water bath for 20 min., and the colorless crystals that separated out were recrystallized from ethanol to give 40 mg. of XXV, m. p. 176∼177°C.

Found: C, 38.49; H, 2.51. Calcd. for $C_{12}H_8O_4Br_2$: C, 38.30; H, 2.13%.

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