Cyclization Reactions of 1,2-Bis(2-cyanophenyl)propionitriles. II. Synthesis of 5-Amino-4,7-dimethoxy-11*H*-indeno[1,2-*c*]isoquinolin-11-one[1)]

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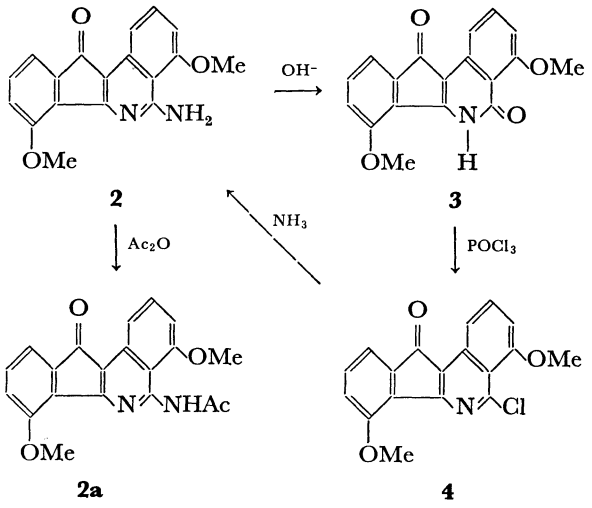
The structure of 5-amino-4,7-dimethoxy-11*H*-indeno-[1,2-*c*]isoquinolin-11-one (**2**) derived by the degradation of the "red pigment" has been confirmed by synthesis. 5,6-Dihydro-4,7-dimethoxy-11*H*-indeno[1,2-*c*]-isoquinoline-5,11-dione (**3**) obtained from **2** was used as a relay compound. This was first converted into **2** by chlorination with phosphorus oxychloride and treatment with ammonia. Subsequently **3** was synthesized from 2-(2-carboxy-3-methoxyphenyl)-4-methoxyindane-1,3-dione (**13**) *via* 4,7-dimethoxy-11*H*-indeno[1,2-*c*]isocoumarin-11-one (**12**).

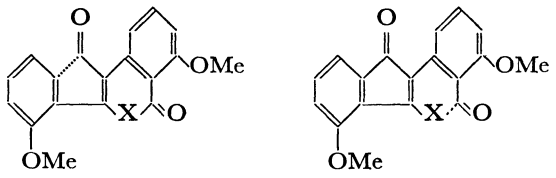
In a previous paper[1)] it was reported that a red pigment **1**, $C_{22}H_{19}N_3O_4$ is obtained in a good yield by the base catalyzed cyclization of 1,2-bis(2-cyano-3-methoxyphenyl)propionitrile in the presence of diethyl carbonate, and its treatment with alkaline hydrogen peroxide leads to the formation of an oxidation product, $C_{18}H_{14}N_2O_3$. We have deduced the structure 5-amino-4,7-dimethoxy-11*H*-indeno-[1,2-*c*]isoquinolin-11-one (**2**) for this compound from spectral and chemical evidences. The crucial role of this assignment in the structure elucidation of **1** led us to confirm the structure of **2** unequivocally by synthesis.

For the synthetic route to **2** it would be reasonable to pass through 5,6-dihydro-4,7-dimethoxy-11*H*-indeno-[1,2-*c*]isoquinoline-5,11-dione (**3**), obtained from **2** by alkaline hydrolysis. Partial synthesis of **2** from **3** was studied first. Treatment of **3** with phosphorus oxychloride at refluxing temperature provided an orange-red colored substance **4**. Since its infrared spectrum revealed the disappearance of the lactam group in **3** and the retainment of the indenone carbonyl group (1705 cm^{-1}), **4** was proved to be the expected chloride, 5-chloro-4,7-dimethoxy-1*H*-indeno[1,2-*c*]isoquinolin-11-one. This was heated with ammonia in ethanol in a sealed tube at 150 °C for 14 hr. The product thus obtained was identified as **3** and the divided acetate as **2a** by comparison of their infrared spectra with those of authentic specimens, mixed thin layer chromatography and mixed melting point determination. These transformations met our first aim and at the same time verified the presumed structural relationship between **2** and **3**.[1)]



Scheme 1

In principle two ways of ring closure as depicted in **5a** and **5b** are conceivable for the construction of 5,6-dihydro-11*H*-indeno[1,2-*c*]isoquinoline-5,11-dione (**5**, X=NH) or 5,6-dihydro-11*H*-indeno[1,2-c]isocoumarin-11-one (**5**, X=O) system. The latter system is convertible to the former by treatment with ammonia.[2)]



5a **5b**

Since 4-carboxy-8-methoxy-3-(2-methoxyphenyl)isocarbostyril necessary in route **5a** seemed to be more easily accessible, the synthetic approach in this direction was investigated first. The condensation of 2-cyano-3-methoxyphenylacetonitrile (**6**)[3)] with 2-methoxybenzoyl chloride (**7**) with sodium hydride yielded the product **9**, $C_{26}H_{20}N_2O_5$. The spectral data revealed that **9** was the product, which arose through the enol-benzoylation of once-formed 1-(2-cyano-3-methoxyphenyl)-1-(2-methoxybenzoyl)acetonitrile (**8**). Thus the reaction mixture of the above condensation was directly treated with 40% hydrogen bromide in glacial acetic acid at 70 °C to provide the desired isocoumarin **10**. Treatment of **10** with ammonia at 150 °C in a sealed tube afforded the carbostyril **11**. All attempts to hydrolyse **11** to **12** including treatment with alkaline hydrogen peroxide or the refluxing with potassium hydroxide in ethylene glycol were unsuccessful. The resistance of the cyano group in **11** to hydrolysis remains unclarified.

The synthesis of **2** by way of route **5b** was investigated subsequently. We undertook to prepare 4,7-dimethoxyindenoisocoumarin-11-one (**12**) first. Indenoisocoumarin-11-one (**15**) was synthesized by the dehydrative cyclization of 2-(2-carboxyphenyl)indane-1,3-dione (**14**) by Pailer *et al.*[4)] and we examined the synthesis of **12a** by this method though the cyclizations in two directions would be possible in the intermediate, 2-(2-carboxy-3-methoxyphenyl)-4-methoxyindane-1,3-dione (**13**). The reaction of 6-methoxyphthalaldehydic acid (**16**)[5)] and 7-methoxyphthalide (**17**)[6)] with sodium

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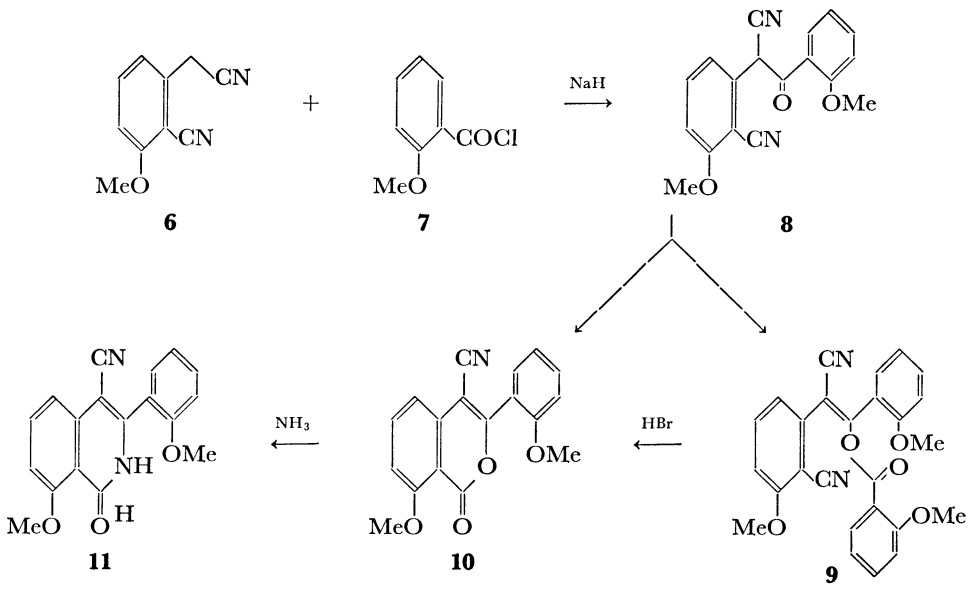
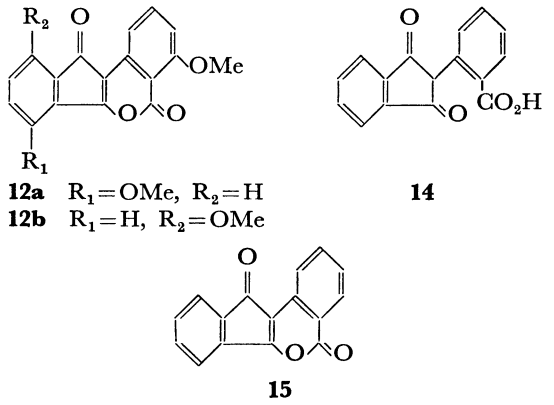
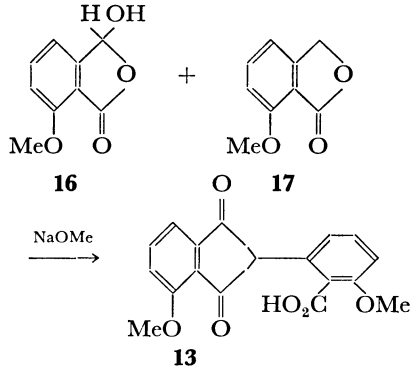


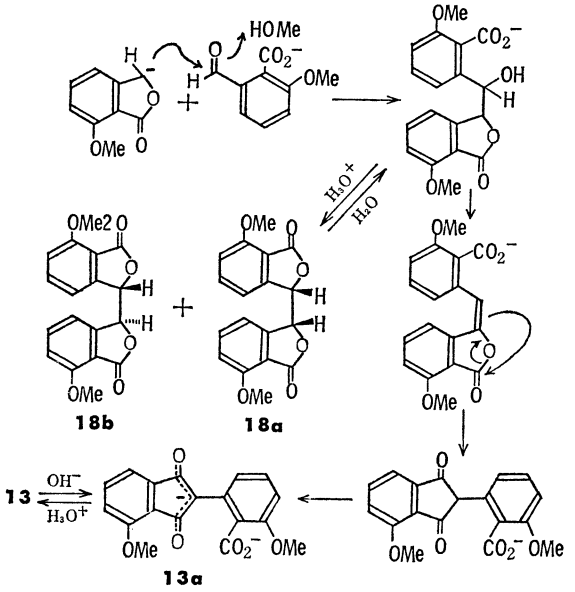
Scheme 2.



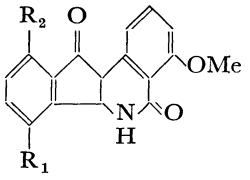
methoxide gave 2-(2-carboxy-3-methoxyphenyl)-4-methoxyindane-1,3-dione (**13**) accompanied by a mixture of the diastereomeric hydrodiphthalyls **18a** and **18b** which were separable by chromatography on a silica gel column. **18a** was more easily eluted on the chromatography than **18b**. Inspection of the models shows that the diastereomeric protons in the *dl*-form would be more susceptible to the shielding anisotropy of the β-phenyl groups in comparison to the *meso*-form in which such effect would be negligible. Thus the methine proton of **18a** resonates at lower filed than that of **18b**, and **18a** could tentatively be assigned to the *meso*-form and the latter to the *dl*-form. The hydrodiphthalyls **18a** and **18b**, when treated again with excess sodium methoxide, provide the indanedione **13** which yields a red anion **13a** by treatment with base which on heating gradually turns red above 216 °C. When **13** was heated with acetic anhydride, two kinds of colored products were obtained; a reddish orange compound **12a**, mp 287 °C, ν_{max} 1770 and 1705 cm^{-1}; a yellowish orange compound **12b**, mp 247—247.5 °C, ν_{max} 1760 and 1710 cm^{-1}. Since both compounds have the same molecular composition $C_{18}H_{12}O_5$ and exhibit similar carbonyl bands due to lactonic and ketonic groups in the IR spectra, they represent the 11-oxoindenoisocoumarin isomers formed by the cyclization of **13** in two possible directions. However, it could not be said for the products which were which of the two isomers. On treatment of **12a** and **12b** with ethanolic ammonia at 120 °C for 12 hr both



Scheme 3.



Scheme 4.



19a R=OMe, R_2=H
19b R_1=H, R=OMe

compounds afforded the same products **19a** and **19b** in different ratios, 2.3 : 1 and 1 : 4, respectively. The result suggests that the isocoumarins **12a** and **12b** yield mainly the corresponding isocarbostyrils **19a** and **19b** respectively, though some equilibrium may exist between the isomers during the course of reaction. Actually **19a** was found to be identical with **3** from a comparison of their IR spectra and Tlc, and the mixed melting point determination. The structure of **19b** was verified by elemental analyses and the appearance of the absorption bands at 3100—2600 (broad, lactam), 1705 (ketone) and 1650 cm^{-1} (lactam) in its IR spectrum.

Comparison of NH stretching bands of the lactam groupings in **19a** and **19b** provides important information on the differentiation of both compounds. The NH band in **19a** is observed as a sharp peak at 3380 cm^{-1} owing to the obstruction for the formation of intermolecular hydrogen bond, whereas **19b** exhibits the bonded broad absorption without such hindrance. The contrast in NH stretching bands in **19a** and **19b** rationalizes our assumption made on the assignment of structure **3** for the oxidation product of the "red pigment".[1] The structures of **19a** and **19b** are thus delineated as shown and the formulas **12a** and **12b** are given to the parent isocoumarin isomers. Thus as a matter of course **19a** has to be identical with **3** and this was found to be the case.

In conclusion, the synthesis of **2** has been accomplished using **3** as a relay compound and the structure of **2** has been determined unambiguously.

Experimental[1]

*Conversion of 5,6-Dihydro-4,7-dimethoxy-11H-indeno[1,2c]isoquinoline-5,11-dione (**3**) into 5-Chloro-4,7-dimethoxy-11H-indeno-[1,2-c]isoquinolin-11-one (**2**).* **3** (298 mg) was heated with phosphorus oxychloride (10 ml) under refluxing for 2 hr. After cooling the reaction mixture was poured into ice-water and the resulting reddish orange precipitate was filtered, dried and chromatographed on a silica gel column (10 g). Elution with benzene-chloroform (1 : 1) gave reddish orange crystals (105 mg) which on recrystallization from chloroform gave pure **4**, mp 266—267 °C; λ_{max}^{EtOH} 217 (ε 34700), 273(49600), 358(1820), 394(450) and 460 nm(160); ν_{max} 1705 cm^{-1} (>CO). Found: C, 66.33; H, 3.70; N, 4.26%. Calcd for $C_{18}H_{12}ClNO_3$: C, 66.37; H, 3.71; N, 4.30%.

*Treatment of 5-Chloro-4,7-dimethoxy-11H-indeno[1,2-c]isoquinolin-11-one (**4**) with Ammonia.* **4** (130 mg) was heated with saturated ethanolic ammonia solution (18 ml) in a sealed tube at 150 °C for 22 hr. The red colored product, precipitated on cooling, was collected by filtration (110 mg) and recrystallized from chloroform-ethanol to yield 5-amino-4,7-dimethoxy-11*H*-indeno[2,2-*c*]isoquinolin-11-one (**2**), mp 289—290 °C. The IR spectrum of this product was superimposable with that of an authentic sample derived from the red pigment **1**.[1] The result of mixed melting point determination and tlc also corroborated the identity of both compounds. The derived acetate **2a**, mp 270—273 °C, was found to be identical with the one obtained previously.[1]

*Condensation of 2-Cyano-3-methoxyphenylacetonitrile (**6**) with 2-Methoxybenzoyl Chloride (**7**).* 2-Methoxybenzoyl chloride (**7**) (9.00 g) was added to a cooled solution of sodium salt of the acetonitrile **6**, prepared by the addition of **6** (6.75 g) to a mixture of sodium hydride (50% oil-coated, 1.99 g) and dry tetrahydrofuran (200 ml) and the mixture was stirred at room temperature for 2 hr. The reaction mixture was poured into water (400 ml) and the product was extracted with benzene. The organic layer was washed successively with 5% $NaHCO_3$ and water, and then dried over anhyd. Na_2SO_4. Evaporation of the solvent left a gummy residue (*ca.* 14 g), which was then warmed with a mixture of glacial acetic acid (7 ml) and 40% hydrobromic acid (18 ml) at 70 °C for 30 min. After cooling the mixture was poured into ice-water and the product was extracted with chloroform. The extract was washed with 5% $NaHCO_3$ and dried. Evaporation of the solvent provided a solid residue (*ca.* 10 g), which, on crystallization from chloroform-methanol yielded crude 4-cyano-8-methoxy-3-(2-methoxyphenyl)isocoumarin **10**, mp 205—227 °C (3.25 g). Further recrystallization from acetic acid afforded pure **10**, mp 236—237 °C; λ_{max}^{EtOH} 212 (ε 24600), 256(13300) and 342 nm (11800); ν_{max}^{EtOH} 2230 (–CN), 1765 (>CO) and 1755 cm^{-1} (>CO); $\delta^{CF_3CO_2H}$ 4.00 (3H, s, $-OCH_3$), 4.11 (3H, s, $-OCH_3$) and 7.03—8.15 (7H, m, ArOH). Found: C, 70.12; H, 4.33; N, 4.54%. Calcd for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26; N, 4.56%. Crystallization of the gummy residue from chloroform-ether, without treatment with HBr-AcOH, gave the enol benzoate **9** as needles, mp 155—156 °C; ν_{max} 2225 (–CN) and 1745 cm^{-1} (>CO); δ^{CDCl_3} 3.53 (3H, s, $-OCH_3$), 3.85 (3H, s, $-OCH_3$), 3.90 (3H, s, $-OCH_3$) and 6.65—8.20 (11H, m, ArOH). Found: C, 70.82; H, 4.77; N, 6.39%. Calcd for $C_{26}H_{20}N_2O_5$: C, 70.90; H, 4.58; N, 6.36%.

*4-Cyano-8-methoxy-3-(2-methoxyphenyl)isocarbostyril (**11**).* The isocoumarin **10** (200 mg) was treated with saturated ethanolic ammonia solution (15 ml) in a sealed tube at 150 °C for 5 hr. The product (92 mg) precipitated on cooling was collected by filtration. Recrystallization from methanol gave **11**, mp 304—306 °C; ν_{max} 3160 (>NH), 2230 (–CN) and 1670 cm^{-1} (>CO); δ^{CDCl_3} 3.96 (3H, s, $-OCH_3$), 4.38 (3H, s, $-OCH_3$) and 7.11—8.35 (7H, m, ArOH). Found: C, 70.28; H, 4.67; N, 8.88%. Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15%.

*Condensation of 7-Methoxyphthalide (**17**) and 6-Methoxyphthalaldehydic Acid (**16**).* **17** (500 mg) was dissolved in a solution of sodium methoxide in methanol (prepared from 103 mg of sodium and 25 ml of abs. methanol) and then **16** (738 mg) was added under nitrogen atmosphere. After the mixture was refluxed for 2.5 hr, the solvent was evaporated *in vacuo* from the reddish reaction mixture. The concentrated mixture was poured into ice-water (50 ml), acidified with 1M H_2SO_4 and then extracted with chloroform. Evaporation of the solvent from the washed and dried organic layer provided colorless gummy residue (1.08 g), which was treated with hot ethanol (40 ml). The insoluble material turned out to be the mixture of the diastereomers **18a** and **18b**, and was separated by chromatography on a silca gel column. Elution with benzene-chloroform (1 : 1) afforded first **18a** and then **18b** in a ratio of 1 : 1. **18a** was crystallized from a mixture of chloroform and ethanol: mp 277—278 °C (dec.); ν_{max} 1705 cm^{-1} (>CO); $\delta^{CF_3CO_2H}$ 4.00 (6H,

s, 2-OCH_3) and 6.20 (2H, s, 2-$CO_2CH\langle$). **18b** was crystallized from chloroform: mp 286—286.5 °C; ν_{max} 1770 (sh.) and 1760 cm^{-1} ($\rangle CO$); $\delta^{CF_3CO_2H}$ 4.06 (6H, s, 2-OCH_3) and 6.00 (2H, s, 2-$CO_2CH\langle$). Saturated aq. $NaHCO_3$ was added to the ethanolic solution obtained in the above treatment. The red alkaline solution was, after washing with chloroform, acidified by the addition of 1M H_2SO_4 and extracted with chloroform. The organic layer was washed with water and dried. Evaporation of the solvent yielded an oil (80 mg), which on trituration with ether furnished 4-methoxy-2-(2-carboxy-3-methoxyphenyl)indane-1,3-dione (36 mg): mp 220—222 °C (from ethanol, turned red at (**13**), *ca.* 216 °C); ν_{max} 3260 (broad, $-CO_2H$), 1740 (weak, $\rangle CO$) and 1710 cm^{-1} (strong, $-CO_2H$). When both **18a** (50 mg) and **18b** (50 mg) were treated with excess sodium methoxide in methanone, the indane-1,3-dione **13** was obtained in the yields of 17 mg and 38 mg, respectively.

*Dehydrative Cyclization of 4-Methoxy-2-(2-carboxy-2-methoxyphenyl)indane-1,3-dione (**13**).* The indane-1,3-dione **13** (100 mg) was heated with acetic anhydride (5 ml) on a water bath (90 °C) for 30 min. The solution became red and finally gave a reddish precipitate. The reaction mixture was poured into ice-water and the precipitated product was recrystallized from acetic acid to afford **12a** as reddish orange needles (40 mg): mp 287 °C; λ_{max}^{EtOH} 214 (ε 31800), 236 (31000), 259 (sh., 34400), 266 (44500), 278 (sh., 17300), 354 (14700) and 456 nm (3300); ν_{max} 1770 (lactone) and 1705 cm^{-1} (ketone). Found: C, 69.78; H, 4.01%. Calcd for $C_{18}H_{12}O_5$: C, 70.13; H, 3.92%. After removal of the solvent from the mother liquor of the recrystallization, the residue was recrystallized successively from benzene and acetic acid to yield **12b** as yellowish orange needles (33 mg): mp 247—247.5 °C; λ_{max}^{EtOH} 236 (ε 38700), 254 (39500), 261 (60900), 273 (sh., 18700), 352 (16800) and 430 nm (3200); ν_{max} 1760 (lactone) and 1710 cm^{-1} (ketone). Found: C, 70.10; H, 3.97%. Calcd for $C_{18}H_{12}O_5$: C, 70.13; H, 3.92%.

*Ammonia Treatment of 4,7-Dimethoxy- (**19a**) and 4,10-Dimethoxy-11H-indeno[1,2-c]isocoumarin-11-one (**19b**).* The reddish orange isomer **12a** (50 mg) was heated with saturated ethanolic ammonia in a sealed tube at 120 °C for 12 hr. After cooling the reaction mixture was poured into water and the red colored product, collected by filtration, was chromatographed on a silica gel column (2 g). Elution with chloroform afforded first the orange colored product **19a** (25 mg) and then the yellow colored isomer **19b** (11 mg). The former is more soluble in common organic solvents than the latter. When the yellow isomer **12b** was treated with ammonia in the same way as **12a**, **19a** and **19b** were obtained on fractional crystallization from chloroform in 11 mg and 44 mg yields, respectively. **19a**, mp 29.5 °C, recrystallized from a mixture of chloroform and ethanol, was identical with **3** obtained previously by the degradation of the "red pigment"[1] in the IR spectra, tlc and mixed melting point determination. Found: C, 70.15; H, 4.22; N, 4.70%. Calcd for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26; N, 4.56%. The yellow isomer **19b** was recrystallized from acetic acid: mp>300 °C; λ_{max}^{EtOH} 232 (ε 32400), 264 (36900), 290 (19700), 348 (20600), 368 (13300) and 450 nm (2500); ν_{max} 3100—2600 (broad, lactam NH), 1705 (ketone) and 1650 (lactam carbonyl) cm^{-1}. Found: C, 70.29; H, 4.33; N, 4.68%. Calcd for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26; N, 4.56%.

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