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Ring Contraction Reactions of Methyl Quinoline 1-Oxide 5-Carboxylates *via* the Corresponding Benz[*d*]-1,3-oxazepines.[1,2] A Facile Synthesis of Methyl Indole 4-Carboxylate and Its Derivatives

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A new synthetic method of the 4-substituted indoles from 5-substituted quinoline 1-oxides was developed. The method involves a photochemical ring enlargement of the N-oxides to benz[*d*]-1,3-oxazepines and subsequent ring contraction to these indoles under thermal or photochemical conditions.

An interesting ring contraction of the 6-alkoxycarbonyl-2-cyanobenz[*d*]-1,3-oxazepine to 5-aminoisocoumarins and their ring transformation to the 4-alkoxycarbonylindoles were also disclosed.

Keywords——indole synthesis; photochemical reaction; ring transformation; ring contraction; 4-substituted indoles; 5-aminoisocoumarin derivatives

In view of the marked propensity of benz[*d*]-1,3-oxazepines readily obtainable from quinoline 1-oxides upon irradiation to give the indole derivatives either under thermal[4] or photochemical condition,[5] we have investigated the ring contraction reactions of the oxazepines having an alkoxycarbonyl function at the 6-position as a direct route to 4-substituted indoles. The results reported in this paper demonstrate that the ring enlargement of quinoline 1-oxides having a carbon unit at the 5-position to the oxazepines followed by the ring contraction reactions provides a mild, simple, and versatile entry to the indoles substituted at the 4-position.

Two N-oxides (IIIa and IIIb) were used in the present study. The N-oxide (IIIa) was synthesized by the usual N-oxidation reaction of methyl quinoline 5-carboxylate (IIa). It should be noted that this carboxylate is especially fitted for the starting material for a preparative experiment, because Skraup reaction of *m*-aminobenzoic acid with glycerol under the usual conditions resulted regioselectively in the formation of quinoline 5-carboxylic acid (Ia) and practically none of its isomer (quinoline 7-carboxylic acid) was obtained.[6] The other N-oxide (IIIb) was obtained from IIIa in *ca.* 80% overall yield by the Reissert reaction followed by N-oxidation.

1) This paper forms part XXXII of "Studies on the N-Oxides of π-Deficient N-Heteroaromatics." Part XXXI: C. Kaneko, A. Yamamoto, and M. Gomi, *Heterocycles*, **12**, 227 (1979). This also forms part VII of "Studies on the Oxazepine Derivatives." Part VI: C. Kaneko, S. Kawai, and M. Somei, *Chem. Lett.*, **1978**, 1281.

2) Presented at the 98th Annual Meeting of Pharmaceutical Society of Japan, Okayama, April 1978, Abstracts of papers, p. 221.

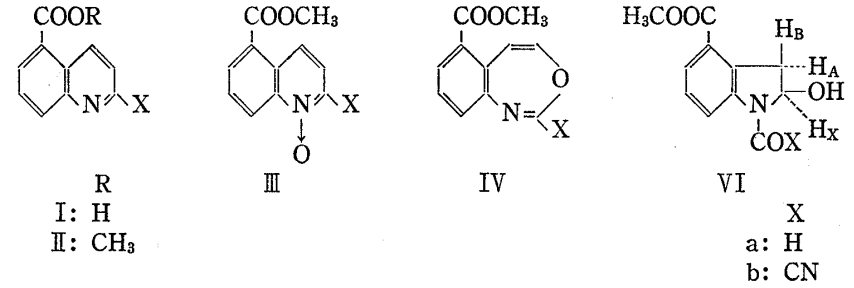
3) Location: *13-1, Takara-machi, Kanazawa 920, Japan.*

4) The ring contraction reactions of the oxazepines to indole derivatives under solvolytic conditions were summarized in the following reviews; *a*) C. Kaneko, *Yuki Gosei Kagaku Kyokai Shi* (*J. Syn. Org. Chem. Japan*), **26**, 758 (1968); *b*) M. Ishikawa and C. Kaneko, *Kagaku no Ryoiki*, **Suppl. 92**, 149 (1970); *c*) G.G. Spence, E.C. Taylor, and O. Buchardt, *Chem. Rev.*, **1970**, 231; *d*) F. Bellamy and J. Streith, *Heterocycles*, **4**, 1391 (1976).

5) For leading references, see; *a*) C. Kaneko and R. Kitamura, *Heterocycles*, **1977**, 111; *b*) *Idem*, *ibid.*, **1977**, 117; *c*) R. Kitamura, H. Fujii, K. Hashiba, M. Somei, and C. Kaneko, *Tetrahedron Lett.*, **1977**, 2911.

6) L. Bradford, T.J. Elliott, and F.M. Rowe, *J. Chem. Soc.*, **1947**, 433.

The N-oxide (IIIa) was irradiated in acetone by 400 W high pressure mercury arc lamp through a Pyrex filter under nitrogen until the N-oxide disappeared completely. The reaction mixture, after evaporation of the solvent under a reduced pressure, was chromatographed on silica gel to give the indolinol (VIa) and methyl 2-quinolone 5-carboxylate (V) in 41 and 33% yields, together with a very small amount (*ca.* 1%) of the deoxygenated product (IIa). The structure of the former product (VIa) was deduced from its nuclear magnetic resonance spectrum (NMR) which showed two singlet signals of methyl (δ: 3.86, 3H) and formyl groups (δ: 8.65, 1H) and an ABX pattern due to three protons on C-2 and C-3: δ_A=3.23, δ_B=3.60, δ_X=5.88 with J_{AB}=19.0, J_{BX}=7.0, and J_{AX}=1.9 Hz. The final confirmation for the structure of VIa was provided by its conversion to methyl indole 4-carboxylate (VIII).[7] Thus, the treatment of VIa with trifluoroacetic acid resulted in the formation of methyl 1-formylindole 4-carboxylate (VII) which gave VIII by a mild alkaline hydrolysis in a quantitative yield from VIa. From the results of photolyses of quinoline 1-oxides having no or an alkyl substituent at the 2-position in an aprotic solvent,[4] the formation of the indolinol (VIa) can be explained by assuming an initial formation of the oxazepine (IVa) and its subsequent hydrolysis by moisture during the purification stage.



Under an identical irradiation condition with that of IIIa, the N-oxide (IIIb) afforded the oxazepine (IVb) as a stable crystalline compound in 94% yield along with a trace of the quinoline (IIb). As reminiscent of the photolyses of 2-cyanoquinoline 1-oxides,[4] none of the carbostyril derivatives was obtained. In the NMR spectrum of IVb, the olefinic protons appeared as an AB quartet centered at δ 6.16 and 6.94 with J=6.3 Hz. When this oxazepine (IVb) was refluxed in aqueous dioxane (1:1 v/v) for 2 days, the same indole (VIII) was obtained in 68% yield as an only isolable product. The formation of VIII from IVb is explained by the mechanism shown in Chart 1 and this mechanism not only accounts for

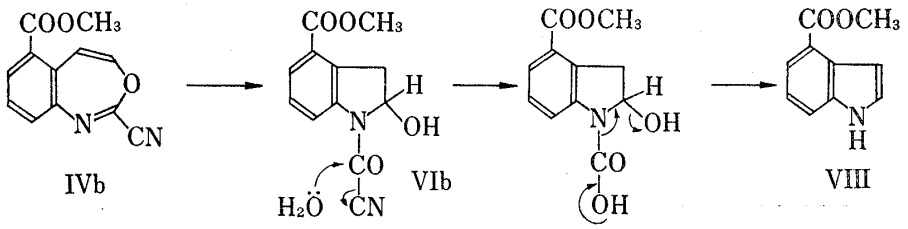


Chart 1

the formation of the same indole from IVa (*vide supra*) but also is in good accordance with the observed ring transformation reactions of IVb with nucleophiles as described below. Thus, by refluxing of IVb in methanol or in ethanol, 5-aminoisocoumarin derivatives (IX: R=CH_3 and CH_2CH_3) were formed in very high yields, respectively. The structure of these isocoumarins was determined from both infrared (IR) [2225, 1720—1730, 1650—1655 cm^{-1}] and NMR spectra (for IX (R=CH_3): the C-3 proton appeared as a doublet (δ: 6.53; J=6

7) E. Hardegger and H. Corrodi, *Helv. Chim. Acta*, 37, 1826 (1954).

Hz), that of C-8 as a doublet of doublets (J=7.0 and 1.5 Hz) at 8.20, and the other three ring protons in the region of 7.2—7.6). The compound IVb also reacted with aqueous methylamine in ether at room temperature to give rise the N-substituted indolinol (XI)[8] in 71% yield, whose structure was again deduced from its spectral data (see Experimental).

The formation of these ring contraction products (IX and XI) is explainable by assuming an initial attack of the nucleophile at the 2-position of the oxazepine (IVb) followed by the ring opening and subsequent cyclization as depicted in Chart 2.

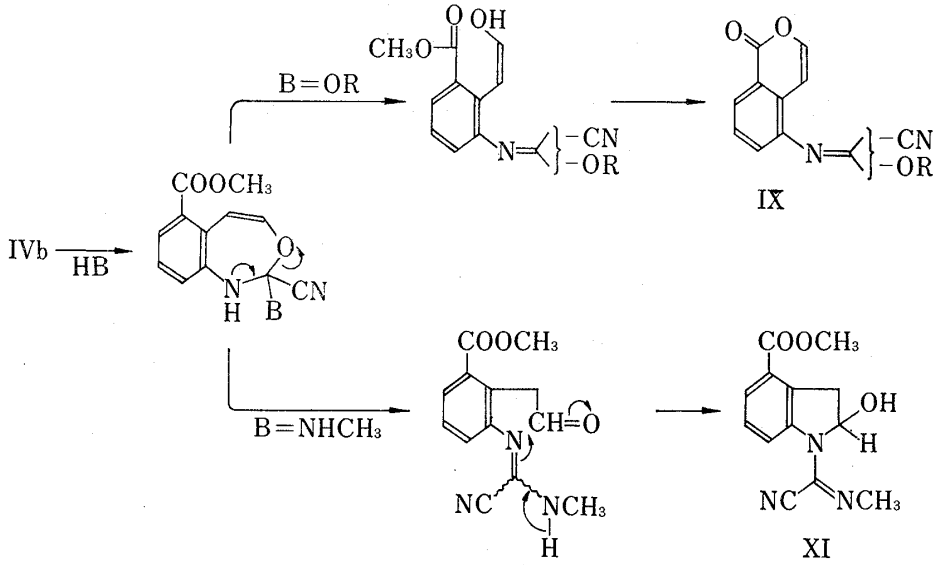


Chart 2

Though at present, a detailed mechanism for the existing regioselectivity in each ring closure reaction is uncertain,[9] an almost quantitative formation of the isocoumarins (IX) in an alcohol is remarkable. These isocoumarins were readily transformed in good yields to the indole (VIII) by the treatment with concd. hydrochloric acid in refluxing methanol. Since an intermediacy of 5-aminoisocoumarin (X) was clearly ascertained by its isolation when these isocoumarins (IX) were treated with methanol containing a small amount of 10% hydrochloric acid at room temperature for 20 hr, the mechanism shown in Chart 3 can be

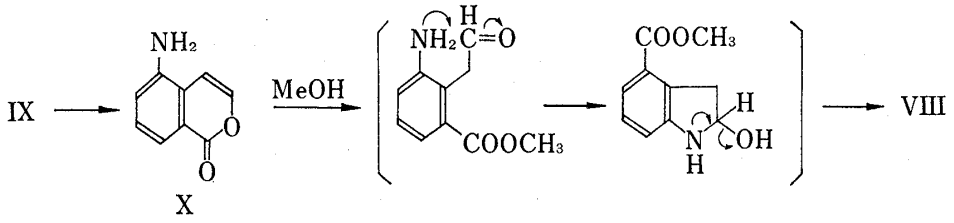
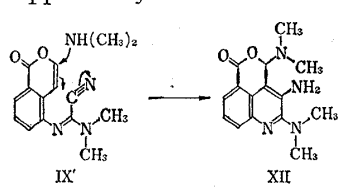


Chart 3

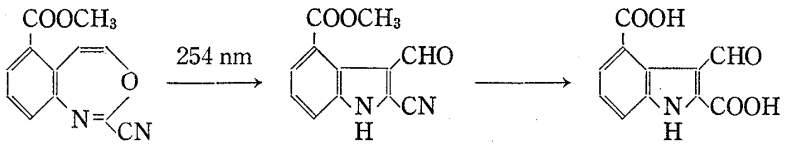
8) A similar addition product to XI was obtained from 6-cyanodibenz[*d*,*f*]-1,3-oxazepine by treatment with methylamine under a comparable condition: C. Kaneko, R. Hayashi, M. Yamamori, K. Tokumura, and M. Itoh, *Chem. Pharm. Bull.* (Tokyo), **26**, 2508 (1978).

9) Treatment of IVb with dimethylamine instead of methylamine led to the predominant formation of XII obviously arisen from the corresponding isocoumarin (IX′) by the pathway indicated below and the yield of XI-type product decreased appreciably.



proposed as a reasonable one. A quite similar mechanism including a cleavage of the lactone ring and subsequent cyclization of the resulted oxo-amine was proposed by Ames *et al.*[10] for the formation of 2-substituted indole 4-carboxylic acid from 3-alkyl-5-aminoisocoumarins by alkaline hydrolysis followed by acidification.

Finally, photochemical ring contraction reaction of IVb was examined. Though this oxazepine (IVb) was stable to the irradiation whose wavelength was longer than 300 nm as most of the related oxazepines,[5] photolysis of IVb in acetonitrile by the same light source without a Pyrex filter was found to give methyl 3-formyl-2-cyanoindole 4-carboxylate (XIII) in 70% yield.[11] The structure of XIII was deduced from its spectral properties as well as its conversion to the indole dicarboxylic acid (XIV) by alkaline hydrolysis. Since the N-oxide



(IIIb) also afforded the same indole (XIII) under the same irradiation condition, it is obvious that the photochemical indole formation from quinoline 1-oxides *via* the oxazepine species[5,11] can also be applied to the N-oxides having a substituent at the 5-position.

With these results, the present reactions (ring enlargement of 5-substituted quinoline 1-oxide to the oxazepine and its ring contraction either under solvolytic or under photochemical conditions) promise to be widely applicable for the preparation of various 4-substituted indoles, whose syntheses were rather tedious.[12]

Experimental

All melting points were determined in a capillary tube and are uncorrected. IR spectra were determined with a JASCO-IRA-2 spectrometer, UV spectra with a Hitachi Model 323 spectrometer, NMR spectra with a JEOL-JNM-C-60H spectrometer and the chemical shifts are in δ-units with coupling constants in Hz. Mass spectra (MS) were recorded on a JEOL-JNM-01SG spectrometer using in all cases a direct sample insertion into the ion source. For spectroscopic data, the following abbreviations are used: d=doublet, d-d, doublet of doublets, m=multiplet, s=singlet, sh=shoulder peak, and t=triplet. Merck silica gel GF_{254} was used for the preparative thin-layer chromatography (prep. TLC).

Photolyses were carried out in an immersion apparatus equipped with 400W Toshiba high-pressure mercury lamp with or without a Pyrex filter and cooled internally with running water. Irradiation was runned in argon or nitrogen under stirring.

Quinoline 5-Carboxylic Acid (Ia)——The acid (Ia: mp>300°, UV λ_{max}^{MeOH} nm: 215.5, 285.0, 318.5) was prepared in *ca.* 30% yield from Skraup reaction of *m*-aminobenzoic acid with glycerol by the reported procedure.[6]

Methyl Quinoline 5-Carboxylate (IIa)——a) Methylation of the Acid (Ia) with Methanol in the Presence of Sulfuric Acid: To a solution of 2.44 g of the acid (Ia) in 80 ml of methanol was added 3 ml of conc. sulfuric acid in small portions. After refluxing for 16 hr, the reaction mixture was concentrated under a reduced pressure to *ca.* 1/3 volume. After the addition of 60 ml of ice water, the mixture was made alkaline by K_2CO_3

10) E. Ames and O. Riheiro, *J. Chem. Soc. Perkin I*, **1976**, 1073.

11) It should be noted that the oxazepines, formally categorized as 6,7-disubstituted benz[*d*]-1,3-oxazepines, derived from benzo[*f*]quinoline 1-oxides did not give the corresponding ring contraction products under any photochemical condition: C. Kaneko, A. Yamamoto, and R. Kitamura, the 97th Annual Meeting of Pharmaceutical Society of Japan (Tokyo, April, 1977), Abstracts of Papers, II, p. 54.

12) A convenient synthetic method of 4-substituted and 3,4-disubstituted indoles from readily available 5-nitroisoquinoline *via* 4-methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]isoquinoline as a key intermediate was recently accomplished by Somei *et al.*: M. Somei, K. Hashiba, F. Yamada, T. Maekawa, T. Kimata, and C. Kaneko, *Chemistry Lett.*, **1978**, 1245; M. Somei, F. Yamada, and C. Kaneko, *ibid.*, **1978**, 1249. The references cited in these two papers surveyed the previously reported synthetic methods of 4-substituted indole derivatives.

and extracted with CH_2Cl_2. After drying over Na_2SO_4, the solvent was removed. The residue was chromatographed by a short column of silica gel (10 g). The fractions eluted with hexane–ether (3: 1 v/v) were collected and recrystallized from hexane to give the ester (IIa: 2.07 g, 78%), mp 51—52°, UV λ_{max}^{MeOH} nm: 217.0, 283.0, 308.0, 321.0. MS *m/e*: 187 (M^+). NMR ($CDCl_3$): 4.03 (3H, s), 7.5—7.85 (2H, m), 8.3 (2H, m), 8.98 (1H, m), 9.37 (1H, m).

b) Methylation of Ia *via* the Acid Chloride: The acid (Ia: 4 g) was refluxed for 1 hr in 10 ml of thionyl chloride. After the addition of 50 ml of benzene, the mixture was evaporated under a reduced pressure. The solution resulted by the addition of 30 ml of methanol to the residue was refluxed for 30 min. After evaporation under a reduced pressure, the residue was basified with 10% aq. Na_2CO_3 and extracted with CH_2Cl_2. After dried over $MgSO_4$ and concentration, the residue was chromatographed on silica gel as described in a) to afford 3.8 g (88%) of the ester (IIa), mp 51—52°.

Methyl Quinoline 1-Oxide 5-Carboxylate (IIIa)——The ester (IIa: 5.27 g) was dissolved in 50 ml of AcOH. After the addition of 6 ml of 30% H_2O_2, the mixture was warmed on the water bath at 80° for 3 hr. After cooling and the addition of 5 ml of the H_2O_2 solution, the reaction mixture was again warmed at 80° for further 4 hr. After the repeated addition of water (each 80 ml) following by concentration to the original volume under a reduced pressure (three times), the residue was basified by K_2CO_3 and extracted with CH_2Cl_2. The residue obtained by evaporation of the solvent (dried over $MgSO_4$) was chromatographed on silica gel. The fractions eluted with ether were collected to give 4.43 g (77.5%) of the N-oxide (IIIa) as an oil which solidified slowly upon standing, mp 83—87° [picrate, mp 158—161° (recrystallized from MeOH)]. UV λ_{max}^{MeOH} nm: 226.5, 244.0, 346.0. NMR ($CDCl_3$): 4.00 (3H, s), 7.2—7.9 (2H, m), 8.2—8.6 (2H, m), 8.8—9.1 (2H, m).

Methyl 2-Cyanoquinoline 5-Carboxylate (IIb)——The N-oxides (IIIa: 3.4 g) was dissolved in 50 ml of water containing 1.95 g of KCN. To this mixture was added 4.1 ml of benzoyl chloride in small portions under stirring with an external cooling. After the addition, the mixture was kept stirring for 1 hr under ice-cooling. The resulting precipitate was collected by filtration and washed thoroughly with 5% aq. Na_2CO_3 and finally with water. After drying in a desiccator, the crude product was recrystallized from CH_2Cl_2–methanol to give 3.06 g (86%) of methyl 2-cyanoquinoline 5-carboxylate (IIb), mp 153—154°. UV λ_{max}^{MeOH} nm: 216.5, 234.5, 300.0, 321.5, 335.5. MS *m/e*: 212 (M^+), 181, 153, 126. NMR ($CDCl_3$): 4.05 (3H, s), 7.83 (1H, d, J=8.9), 7.91 (1H, m), 8.25—8.53 (2H, m), 9.59 (1H, d, J=8.9).

Methyl 2-Cyanoquinoline 1-Oxide 5-Carboxylate (IIIb)——A solution of the quinoline (IIb; 996 mg) in 16 ml of AcOH and 1.5 ml of 30% H_2O_2 was warmed on a water bath (*ca.* 85°) for 4 hr. After the addition of 1.5 ml of the peroxide solution, the mixture was heated for further 3 hr under the same condition. After cooling, the precipitate was collected by filtration, washed thoroughly with water, and dried in a desiccator. The addition of water to the concentrated filtrate afforded further amounts of the N-oxide. The combined crude N-oxide was recrystallized from hexane–acetone to give 0.97 g (90.5%) of methyl 2-cyanoquinoline 1-oxide 5-carboxylate (IIIb), mp 189—191°. UV λ_{max}^{MeOH} nm (log ε): 243.0 (4.64), 273.0 (4.19), 335.0 (3.66), 378.0 (3.70). IR ν_{max}^{KBr} cm^{-1}: 2235, 1710, 1265. MS *m/e*: 228 (M^+), 212, 197, 181, 169, 153, 126. NMR ($CDCl_3$): 4.05 (3H, s), 7.63 (1H, d, J=9.4), 7.83 (1H, d-d, J=7.5 and 8.8), 8.45 (1H, d–d, J=7.5 and 1.2), 8.95 (2H, m). *Anal.* Calcd. for $C_{12}H_8N_2O_3$: C, 63.16; H, 3.53; N, 12.28. Found: C, 63.41; H, 3.45; N, 12.30.

Irradiation of IIIa in Acetone——A solution of IIIa (281 mg; the sample was dried *in vacuo* at 50° for 5 hr before use) in 300 ml of acetone was irradiated by 400W high-pressure mercury lamp with a Pyrex filter for 10 min. After evaporation of the solvent under a reduced pressure, the residue was chromatographed on silica gel (10 g). Elution with hexane–ether (2: 1 v/v) gave a small amount (3 mg, 1%) of the deoxygenated product (IIa). Elution with hexane–ether (1: 2 v/v) afforded, after recrystallization from acetone, 126 mg (41%) of VIa, mp 172—173°. UV λ_{max}^{MeOH} nm (log ε): 227.0 (4.48), 308.0 (3.56). IR ν_{max}^{KBr} cm^{-1}: 3420, 1709, 1646. MS *m/e*: 221 (M^+), 203, 175, 144, 116. NMR (DMSO-d_6): complex signals of an ABX pattern centered at 3.23, 3.60 and 5.88 (3H; see the text for detailed analysis), 3.86 (3H, s), 6.74 (1H, s, disappeared by the addition of D_2O), 7.3—8.2 (3H, m), 8.65 (1H, s). *Anal.* Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.86; H, 4.98; N, 6.30.

Elution with MeOH–CH_2Cl_2 (5: 95 v/v) gave 92 mg (33%) of methyl 2-quinolone 5-carboxylate (V), mp 251—254° (recrystallized from MeOH). MS *m/e*: 203 (M^+), 172. UV λ_{max}^{MeOH} nm: 228.0, 273.5, 340.0. NMR (DMSO-d_6): 3.98 (3H, s), 6.57 (1H, d, J=10), 7.4—7.7 (3H, m), 8.55 (1H, d, J=10).

Dehydration of VIa to Methyl 1-Formylindole 4-Carboxylate (VII)——The compound (VIa: 66 mg) was dissolved in 1 ml of CF_3COOH and the mixture was kept stirring for 1 hr at room temperature. After evaporation of the solvent under a reduced pressure, the residue was basified with 5% aq. K_2CO_3 and extracted with CH_2Cl_2. After drying with $MgSO_4$ and evaporation of the solvent, the residue was chromatographed on silica gel (5 g) using hexane–ether (3: 1 v/v) as the eluent to give 54 mg (89%) of VII (recrystallized from hexane–ether), mp 111.5—113°. IR ν_{max}^{KBr} cm^{-1}: 1715 (broad). UV λ_{max}^{MeOH} nm (log ε): 247.5 (4.25), 287.0 (4.15). MS *m/e*: 203 (M^+), 172, 144. NMR ($CDCl_3$): 3.93 (3H, s), 7.1—7.5 (3H, m), 7.90 (1H, d-d, J=7.5 and 1.1), 8.35 (1H, b.s, $W_{1/2}$=14), 9.32 (1H, s). *Anal.* Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.01; H, 4.31; N, 7.07.

Hydrolysis of VII to Methyl Indole 4-Carboxylate (VIII)——The compound (VII: 26 mg) was suspended in a mixture of 1 ml of methanol and 5 ml of 10% aq. $NaHCO_3$. The mixture was heated on a boiling water bath for 5 min. After cooling, the product was extracted with CH_2Cl_2 and dried over Na_2SO_4. Evaporation

of the solvent afforded 18 mg (80%) of methyl indole 4-carboxylate (VIII: recrystallized from ether–hexane), mp 64—65° (lit. mp 64—65°,[7,13] and 69.5—70.5[14]). UV λ_{max}^{MeOH} nm: 229, 314. NMR ($CDCl_3$): 3.98 (3H, s), 7.14—7.34 (3H, m), 7.55 (1H, m), 7.89 (1H, m), 8.48 (1H, s, NH: disappeared by the addition of D_2O).[15]

Irradiation of Methyl 2-Cyanoquinoline 1-Oxide 5-Carboxylate (IIIb) in Acetone——A solution of IIIb (836 mg) in 500 ml of acetone was irradiated by 400W high-pressure mercury lamp with a Pyrex filter for 18 min. After evaporation of the solvent under a reduced pressure, the residue was chromatographed on silica gel (45 g). Elution with hexane–ether (3: 1 v/v) gave, added to a very small amount of the deoxygenated product (IIb: *ca.* 5 mg), a crystalline fraction which was recrystallized from hexane–ether to afford 786 mg (94%) of methyl 2-cyanobenz[*d*]-1,3-oxazepine 6-carboxylate (IVb) as yellow needles, mp 109—110°. UV $\lambda_{max}^{CH_3CN}$ nm (log ε): 247.5 (4.36), 321.0 (3.43). IR ν_{max}^{KBr} cm^{-1}: 2235, 1717, 1656, 1276, 776. MS *m/e*: 228 (M^+), 200, 197, 169, 141, 114. NMR ($CDCl_3$): 3.91 (3H, s), 6.16 (1H, d, J=6.3), 6.94 (1H, d, J=6.3), an A_2B pattern: δ_A=7.38 and δ_B=7.84 with J_{AB}=5.8 (3H). *Anal.* Calcd. for $C_{12}H_8N_2O_3$: C, 63.16; H, 3.53; N, 12.28. Found: C, 62.92; H, 3.29; N, 12.43.

Refluxing of the Oxazepine (IVb) in Aqueous Dioxane——The oxazepine (IVb; 46 mg) was dissolved in 20 ml of aq. dioxane (1: 1 v/v) and the mixture was refluxed until the consumption of IVb was complete (44 hr). The CH_2Cl_2 extract was dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (4 g) with hexane–ether (3: 1 v/v) as an eluent to give 23 mg (65%) of methyl indole 4-carboxylate (VIII), mp 64—65° (recrystallized from ether–hexane).

Reaction of the Oxazepine (IVb) with Ethanol——The oxazepine (IVb, 220 mg) was refluxed for 30 min in 50 ml of ab. ethanol. After evaporation of the solvent, the residue was chromatographed on silica gel (15 g) with hexane–ether (1: 1 v/v) as an eluent to give 228 mg (97%) of the isocoumarin (IX: R=Et), mp 114.5—115.5°. IR ν_{max}^{KBr} cm^{-1}: 2235. UV λ_{max}^{MeOH} nm (log ε): 224.0 (4.26), 237.0 (4.25, sh), 244.5 (4.29), 250.5 (4.29), 320.0 (3.70). MS *m/e*: 242 (M^+), 187, 159. NMR ($CDCl_3$): 1.41 (3H, t, J=7.0), 4.42 (2H, q, J=7.0), 6.44 (1H, b.d, J=5.8), 7.1—7.6 (3H, m), 8.16 (1H, d-d, J=7.2 and 1.5). *Anal.* Calcd. for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.57. Found: C, 64.69; H, 4.08; N, 11.20.

Conversion of the Oxazepine (IVb) to 5-Aminoisocoumarin (X)——i) Reaction of IVb with Methanol: The oxazepine (IVb, 55 mg) was refluxed in 25 ml of methanol for 3 hr. The preparative TLC of the residue on silica gel plate (developing solvent: hexane–ether 1: 2 v/v) afforded 45 mg (82%) of IX (R=CH_3) which was recrystallized from CH_2Cl_2–hexane, mp 132—133°. IR ν_{max}^{KBr} cm^{-1}: 2235. UV λ_{max}^{MeOH} nm (log ε): 224.0 (4.27), 238.0 (4.26, sh), 250.5 (4.29), 320.0 (3.71). MS *m/e*: 228 (M^+), 185. NMR ($CDCl_3$): 4.09 (3H, s), 6.53 (1H, d, J=6.0), 7.3—7.7 (3H, m), 8.20 (1H, d-d, J=7.0 and 1.5). *Anal.* Calcd. for $C_{12}H_8N_2O_3$: C, 63.16; H, 3.53; N, 12.28. Found: C, 63.05; H, 3.43; N, 12.39.

ii) Formation of 5-Aminoisocoumarin (X): The compound (IX: R=CH_3, 13.2 mg) was dissolved in 10 ml of methanol containing 20 drops of 10% HCl and the mixture was kept standing at room temperature for 30 hr. The residue after evaporation of the solvent under a reduced pressure was basified with K_2CO_3 and the mixture was extracted with CH_2Cl_2 and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was recrystallized from methanol to give 7.5 mg (80%) of 5-aminoisocoumarin (X), mp 189.5—191°. UV λ_{max}^{MeOH} nm (log ε): 216.5 (3.04), 236.0 (3.27), 243.5 (3.31), 275.0 (3.00), 359.5 (2.69); $\lambda_{max}^{10\%HCl\text{-}MeOH}$ nm: 228.0, 242.0, 257.0, 275.5, 321.0. IR ν_{max}^{KBr} cm^{-1}: 3380, 3320, 1707. MS *m/e*: 161 (M^+), 133, 104. NMR (DMSO-d_6): 5.73 (2H, b.s, NH_2: disappeared by the addition of D_2O), 6.8—7.5 (5H, m). *Anal.* Calcd. for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.19; H, 4.30; N, 8.73.

Hydrolysis of IX (R=Et) to Methyl Indole 4-Carboxylate (VIII)——The compound (IX: R=Et, 110 mg) was dissolved in 13 ml of methanol. After the addition of 3 ml of 20% HCl, the mixture was refluxed for 20 hr. After evaporation of methanol under a reduced pressure, 10 ml of water was added to the residue and the whole was extracted with CH_2Cl_2 and dried over Na_2SO_4. The residue obtained by evaporation of the solvent was chromatographed on silica gel (5 g) with hexane–ether (3: 1 v/v) as an eluent. The fraction obtained, after recrystallization from ether–hexane, gave 29 mg (36.5%) of VIII, mp 64—65°. The aqueous layer afforded after basification and extraction with CH_2Cl_2, 11 mg (15%) of 5-aminoisocoumarin (X), mp 188—190° (recrystallized from MeOH).

Reaction of the Oxazepine (IVb) with Methylamine——The oxazepine (IVb, 104 mg) was dissolved in ether containing 0.3 ml of 40% aq. CH_3NH_2 and the mixture was kept standing for 1 hr at room temperature. The residue obtained after evaporation of the solvent was recrystallized from methanol to give 67 mg of XI. The mother liquor was evaporated and the residue was separated by prep. TLC on silica gel plate to give 6 mg (8%) of VIII, mp 63—65° and 16 mg of XI. The compound (XI) obtained in 70% yield was recrystallized from methanol, mp 128—130°. UV λ_{max}^{MeOH} nm: 224, 299. IR ν_{max}^{KBr} cm^{-1}: 3430, 1686. MS *m/e*: 259 (M^+), 241, 216, 200, 67. NMR (acetone-d_6): a complex ABX pattern with δ_A=3.4, δ_B=3.64 and δ_X=6.0 (3H; J_{AX}=

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15) Though the references 7, 13 and 14 did not describe the NMR of VIII, our NMR was almost identical in the ring-proton region with that of ethyl indole 4-carboxylate prepared by the method of Somei and Natsume: M. Somei and M. Natsume, *Tetrahedron Lett.*, 1973, 2451.

19.0, $J_{BX}=6.5$ and $J_{AX}=1.8$), 3.45 (3H, s), 3.83 (3H, s), 5.61 (1H, b.s, OH), 7.19 (1H, m), 7.48 (1H, m), 8.15 (1H, m).

Reaction of the Oxazepine (IVb) with Dimethylamine——The oxazepine (IVb, 89 mg) was dissolved in 8 ml of ether containing 0.4 ml of 50% aq. dimethylamine and the mixture was left standing overnight. After evaporation under a reduced pressure, the products were separated by chromatography on silica gel (5 g).

Elution with hexane–ether (8: 1 v/v) afforded 27 mg (24%) of XII, mp 125—141°. MS *m/e*: 286 (M^+), 241, 212, 185. NMR ($CDCl_3$): 2.46 (6H, s), 2.91 (6H, s), 5.10 (2H, b.s, $-NH_2$), 6.30 (1H, s), 7.40 (1H, m), 7.8—8.2 (2H, m).

Elution with hexane-ether (1: 1 v/v) afforded 8 mg (9%) of the isocoumarin derivative of the type IX ($N(Me)_2$ instead of OR in the formula IX), mp 168.5—169.5° (recrystallized from ether–hexane). IR ν_{max}^{KBr} cm^{-1}: 2235, 1727, 1620. MS *m/e*: 241 (M^+), 197, 184, 170. UV λ_{max}^{MeOH} nm: 239, 267.5, 326. NMR ($CDCl_3$): 3.24 (6H, s), 6.60 (1H, d, $J=5.8$), 7.1—7.5 (3H, m), 8.01 (1H, m). *Anal.* Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.66; H, 4.56; N, 17.31.

Photochemical Ring Contraction of IVb to Methyl 2-Cyano-3-formylindole 4-Carboxylate (XIII)——The oxazepine (IVb, 421 mg) in 500 ml of acetonitrile was irradiated by 400W high-pressure mercury lamp for 8 hr. After evaporation of the solvent under a reduced pressure, the residue was chromatographed on silica gel (40 g) with ether–hexane (1: 1 v/v) as an eluent. The fraction thus eluted was recrystallized from methanol to give 294 mg (70%) of XIII, mp 235° (dec.). IR ν_{max}^{KBr} cm^{-1}: 2235, 1727, 1646, 1135. UV λ_{max}^{MeOH} nm (log ε): 224.0 (4.61), 254.5 (3.87), 316.0 (4.20), MS *m/e*: 228 (M^+), 213, 169, 141, 114. NMR (DMSO-d_6): 3.97 (3H, s), 7.50 (1H, d-d, $J=6.8$ and 7.4), 7.82—8.0 (2H, m), 10.47 (1H, s). *Anal.* Calcd. for $C_{12}H_8N_2O_3$: C, 63.16; H, 3.53; N, 12.28. Found: C, 63.16; H, 3.33; N, 11.99.

Hydrolysis of XIII to the Dicarboxylic Acid (XIV)——The indole (XIII, 185 mg) in a mixture of 13 ml of methanol and 30 ml of 10% aq. NaOH was refluxed on a boiling water bath for 7 hr. After cooling, the mixture was acidified by the addition of conc. HCl. After standing for 1 hr, the precipitate appeared was collected by filtration to give 150 mg of the diacid. The filtrate after evaporation of methanol was extracted with ether to give further amounts of the diacid. The combined diacid (166 mg, 87.5%) was recrystallized from methanol to give a pure sample (XIV), mp 250° (dec.). UV λ_{max}^{MeOH} nm: 224.5, 319. IR ν_{max}^{KBr} cm^{-1}: 1710—1675, 2250—3250, 3425. MS *m/e*: 233 (M^+), 215, 187, 143. NMR (DMSO-d_6): 7.3—7.8 (3H, m), 10.47 (1H, s), CHO), 12.89 (1H, s; disappeared by the addition of D_2O).

An attempted decarboxylation by refluxing of XIV in a mixture of methanol and 10% HCl for 10 hr was failed and the starting material was recovered unchanged.

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