A New Synthesis of Dibenzo[*b*,*g*][1,5]naphthyridine-6,12(5*H*,11*H*)dione (Epindolidione)

C. K. Kim and C. A. Maggiulli

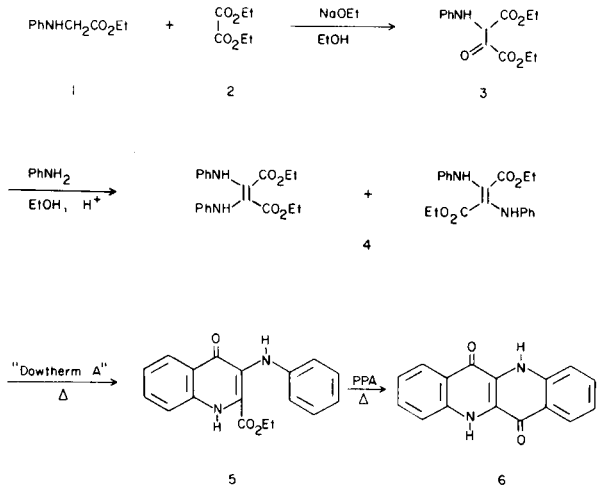
Organic Process Development, Building 303,
Kodak Park, Eastman Kodak Company, Rochester, New York 14650

Received June 5, 1979

A new convenient synthesis of dibenzo[*b*,*g*][1,5]naphthyridine-6,12(5*H*,11*H*)dione starting from *N*-phenylglycine ethyl ester is described. Ester condensation of *N*-phenylglycine ethyl ester with diethyl oxalate followed by reaction with aniline under acid catalysis gave a mixture of diethyl dianilinomaleate and diethyl dianilinofumarate in 54% yield. Upon heating this mixture in a high-boiling inert solvent, 3-anilino-2-ethoxycarbonyl-4-quinolone was obtained in 72% yield. Final ring closure of the quinolone derivative using polyphosphoric acid gave the epindolidione.

J. Heterocyclic Chem., **16**, 1651 (1979).

Dibenzo[*b*,*g*][1,5]naphthyridine-6,12(5*H*,11*H*)dione (**6**) is a yellow pigment which possesses good properties of lightfastness and tinctorial strength. The name of epindolidione for this compound was first used by Ainley and Robinson (1) who synthesized the 2,8-dimethyl derivative of **6** from 2-chloro-2′-amino-5′-methylacetophenone in order to compare its properties with those of indigo, a structural isomer **6**. Subsequently, this synthesis was applied to the preparation of the parent compound **6** (2). In addition, three other synthetic routes to epindolidione and its derivatives have been reported. The first synthesis starting from dihydroxyfumaric acid afforded epindolidione (**6**) and some symmetrically substituted derivatives (3,4). The second method involved a condensation reaction of 3-amino-4-quinolone with *o*-bromobenzoic acid (3). The third route using substituted anilines and diethyl oxalacetate gave some unsymmetrically substituted epindolidiones (4). We wish to report here a new convenient synthesis of epindolidione (**6**) using a readily available starting material. The new synthesis can be easily extended to the synthesis of some symmetrically substituted epindolidiones. The starting material, *N*-phenylglycine ethyl ester (**1**), is commercially available or easily obtained by the reaction of aniline with ethyl chloroacetate. Ester condensation of *N*-phenylglycine ethyl ester (**1**) with diethyl oxalate (**2**) using sodium ethoxide in ethanol yielded diethyl anilinooxalacetate (**3**) as a viscous oil which was used directly in the next step without purification. Thus, the crude anilinooxalacetate (**3**) reacted with aniline in the presence of a catalytic amount of concentrated hydrochloric acid in ethanol to give a mixture of diethyl dianilinomaleate and diethyl dianilinofumarate (**4**) in 54% overall yield from the *N*-phenylglycine ethyl ester. The nature of the mixture **4** was apparent from its tlc, ir, and proton nmr analyses. The tlc shows two distinctive spots with approximately equal intensity. The ir spectrum of **4** shows triple bands (3360, 3330, and 3290 cm^{-1}) at the N-H stretching region, another set of triple bands (1725, 1680, and 1655 cm^{-1}) at the carbonyl stretching region, and two strong absorptions (1600 and 1570 cm^{-1}) at the aromatic and olefinic double-bond stretching region. The bands in each region seem to be a combination of doublets due to a mixture of two isomers. The nmr spectrum exhibits ethyl protons as two triplets (at 1.00 and 1.16δ) and two quartets (at 4.07 and 4.18δ), and aromatic protons as a multiplet (between 6.70 and 7.40δ). Integration under the two triplets indicates that it is an approximately 55:45 mixture of two isomers. These observations were confirmed by separation of two isomers by preparative thin layer chromatography. From a 500 mg. sample of the mixture **4**, 220 mg. of a high Rf (0.60) compound and 180 mg. of a low Rf (0.30) compound were obtained. The ir spectrum of the high Rf compound showed the N-H absorption at 3360 and 3270 cm^{-1}, the carbonyl bands at 1725 and 1655 cm^{-1}, and strong bands at 1600 and 1585 cm^{-1} in the aromatic and olefinic double-bond stretching region. The ir of the low Rf compound exhibited the N-H stretching at 3330 and 3290 cm^{-1}, the carbonyl bands at 1725 and 1680 cm^{-1},



0022-152X/79/081651-03$02.25

and a strong band at 1570 cm^{-1} with two shoulders at 1600 and 1590 cm^{-1} in the aromatic and olefinic double-bond stretching region. The triplet and quartet for the ethyl groups in the nmr spectrum is located at δ 1.00 and 4.07 for the high Rf compound, and δ 1.16 and 4.18 for the low Rf compound, respectively. The low Rf compound was tentatively assigned as diethyl dianilinomaleate based on the following observations: (i) the maleate is more polar and thus may move slower than the fumarate in the tlc; and (ii) the ir spectrum of the low Rf compound shows a strong band at 1570 cm^{-1} assignable to the olefinic double-bond stretching vibration as would be expected of the maleate structure. According to selection rules (5), the fumarate isomer should show little or no absorption in this region as is clear from the ir of the high Rf compound.

The formation of the mixture **4** was contrary to the results of condensation reaction of dimethyl dihydroxyfumarate with anilines, which gave only maleate derivatives (3). However, it was not necessary to separate the mixture since the next step in the synthesis was a Conrad-Limpach cyclization (6a-c) which required heating the substrates in a high-boiling inert solvent. At a higher temperature the maleate in the mixture was expected to rearrange to its *trans* isomer and thus the mixture became mainly the fumarate, which cyclized to the quinolone derivative **5**. On the other hand, the reaction involved the intramolecular cyclization which was favored at higher dilution and thus the mode of addition of the substrates was important. The best yield of quinolone **5** was obtained by slow addition of a solution of the mixture **4** in "Dowtherm A" (phenyl ether-biphenyl eutectic) to the same solvent under reflux. In this reaction the mixture of maleate and fumarate actually had an advantage over a single isomer because the former had better solubility and required much less amount of solvent. A typical yield of quinolone **5** was 72% after purification by recrystallization from ethanol. The final ring closure of the quinolone **5** to the epindolidione (**6**) using polyphosphoric acid was accomplished by following a procedure similar to that described by earlier workers (3). The quality of final products obtained by the new synthesis was the same as that of products obtained by existing methods. Although the last two steps in the new synthesis are similar to those of a known procedure (3), the new synthesis has several unique advantages over the known methods as already mentioned, and appeared to be the most practical method for manufacturing the yellow pigments.

We gratefully acknowledge the help of Dr. A. D. Debboli of Industrial Laboratory, Kodak Park, Eastman Kodak Company, for obtaining spectra and analyses.

EXPERIMENTAL

Melting points were determined using a Mel-Temp and are uncorrected. Infrared spectra were recorded on a Beckman 4220 spectrophotometer and nmr spectra were obtained on a Varian T-60 spectrometer using TMS as an internal standard. Mass spectra were obtained on an AEI MS-9 mass spectrometer. Tlc's were done on silica gel plates. Elemental analyses were done by Analytical Sciences Division, Research Laboratories, Eastman Kodak Company, Rochester, New York.

Mixture of Diethyl Dianilinomaleate and Diethyl Dianilinofumarate (**4**).

In a 2-l. three-necked flask equipped with a mechanical stirrer and a reflux condenser bearing a calcium chloride drying tube was placed 500 ml. of absolute ethyl alcohol, to which 71.4 g. (1.05 moles) of sodium ethoxide was added with stirring. When all of the sodium ethoxide had dissolved, the temperature rose to 50-55°, and 146.1 g. (1.0 mole) of diethyl oxalate was added at once, followed by 179.2 g. (1.0 mole) of *N*-phenylglycine ethyl ester. The mixture was stirred at 25° for 16-20 hours.

The solvent was removed by distillation under reduced pressure. To the residual gum was added 750 ml. of water and 71 ml. (1.25 moles) of glacial acetic acid with vigorous stirring. It is desirable to ensure the complete break-up of the gum to an orange oil at this point. The stirrer was stopped when 600 ml. of toluene was added. The mixture was stirred gently for a few seconds and allowed to stand for a few minutes. Vigorous stirring at this stage can cause severe emulsion problems. The stirring and standing was repeated twice, then the mixture was allowed to separate into layers. It usually required 0.5-1 hour to obtain the clear aqueous layer and the red turbid toluene layer with some gelatinous material at the interface. The aqueous layer was separated and extracted with toluene (2 × 200 ml.). The combined toluene extracts were filtered through a Super-cel pad and the filtrate was washed with water (600 ml.) and evaporated to dryness under reduced pressure keeping the pot temperature at 60-70° to give 245 g. (88%) of the crude product diethyl anilinooxalacetate, as a red oil.

A mixture of the above crude product, 84 g. (0.9 mole) of aniline, and 8.5 ml. of concentrated hydrochloric acid in 750 ml. of absolute ethyl alcohol was heated under reflux for 3 hours. The red solution was allowed to cool under running cold water (5-10°) without stirring overnight then further cooled to −10° in an ice-salt bath with slow stirring. The first crop of pale yellow crystals was collected and washed with a minimum amount of cold ethyl alcohol (about 100 ml.) to remove the red color. After drying in a vacuum oven at 40°, the product weighed 181 g. The second crop (12 g.) was obtained by concentrating the mother liquor to 150 ml. under reduced pressure and cooling. The total yield of diethyl dianilinomaleate and -fumarate mixture, melting at 90-95°, was 193 g., which was 54% (overall yield based on the *N*-phenylglycine ethyl ester) of the theoretical amount of 354.4 g.; ir (potassium bromide): 3360, 3330, 3290, 1725, 1680, 1655, 1600, and 1570 cm^{-1}; nmr (deuteriochloroform): δ 1.00 and 1.16 (each t, 6H, -CH_3), 4.07 and 4.18 (each q, 4H, -CH_2-), and 6.70, 7.40 (m, 12H, aromatic *H* and -N*H*-); ms: m/e 354 (M^+).

Separation of the Mixture (**4**).

A solution of 500 mg. of the mixture (**4**) in acetone was applied on three preparative thin layer chromatography plates coated with solica gel (20 × 20 cm, thickness 2 mm) and eluted with 3 parts of ethyl ether and 2 parts of hexane. The upper band centered at Rf = 0.60 was collected and extracted with 10% methanol in chloroform. The solvent was evaporated and the residual yellow solid was crystallized from ethanol to give 220 mg. of pale yellow needles, m.p. 104-105°; ir (potassium bromide): 3360, 3270, 1725, 1655, 1600, 1585 cm^{-1}; nmr (deuteriochloroform): δ 1.00 (t, 6H, -CH_3), 4.07 (q, 4H, -CH_2-), and 6.70-7.40 (m, 12H, aromatic *H* and -N*H*-); ms: m/e 354 (M^+).

Anal. Calcd. for $C_{20}H_{22}N_2O_4$: C, 67.8; H, 6.3; N, 7.9. Found: C, 67.3; H, 6,6; N, 7.9.

The lower band centered at Rf = 0.30 was collected and treated similarly as described above to give 180 mg. of pale yellow crystals, m.p. 118-119°; ir (potassium bromide): 3330, 3290, 1725, 1680, 1600 (sh), 1590 (sh), 1570 cm^{-1}; nmr (deuteriochloroform): δ 1.16 (t, 6H, -CH_3), 4.18 (q, 4H, -CH_2-), 5.80 (broad s, 2H, -N*H*-), and 6.70∿7.40 (m, 10H, aromatic *H*); ms: m/e 354 (M^+).

Anal. Calcd. for $C_{20}H_{22}N_2O_4$: C, 67.8; H, 6.3; N, 7.9. Found: C, 67.6; H, 6.8; N, 7.7.

3-Anilino-2-ethoxycarbonyl-4-quinolone (**5**).

In a 2-l., four-necked flask, equipped with a stirrer, thermometer, addition funnel, and a Dean-Stark tube with a reflux condenser, was placed 700 ml. of "Dowtherm A" (phenyl ether-biphenyl eutectic) and heated to boiling. To this solvent under gentle reflux (260-265°) was added a hot (80-100°) solution of 183 g. (0.516 moles) of the diethyl dianilinomaleate and -fumarate mixture (**4**) in 300 ml. of the "Dowtherm A" over a period of 30 minutes. After completion of the addition, heating under reflux was continued for another 15 minutes. A mixture of ethyl alcohol and "Dowtherm A" was collected in the Dean-Stark tube. The solution was cooled to room temperature with occasional stirring and then allowed to stand at room temperature overnight. The precipitated dark yellow crystalline product was collected and washed well with hexane until the filtrate was colorless. After drying in a vacuum oven at 60°, the product (m.p. 181-183°) weighed 132 g.

The purification was accomplished by dissolving the crude product in 5-l. of hot ethyl alcohol, adding 40 g. of decolorizing carbon, and heating the mixture with stirring under reflux for 15 minutes. The hot solution was filtered through a Super-cel pad. The red colored filtrate was concentrated to a volume of 3-l. by distillation under reduced pressure and then chilled under running cold water (5-10°) for 3 hours.

The first crop (108 g.) of bright yellow needles was collected by filtration. The filtrate was further concentrated under reduced pressure to a volume of 400 ml., again chilled, and the second crop (7 g.) collected and washed with cold ethyl alcohol. The total yield of purified 3-anilino-2-ethoxycarbonyl-4-quinolone, melting at 182-183°, was 115 g., which is 72% of the theoretical amount of 159 g.; ir (potassium bromide): 3350, 3260, 1695, 1620 (sh), 1600 (sh), 1570 cm^{-1}; nmr (DMSO-d_6): δ 1.00 (t, 3H, -C*H*$_3$), 4.08 (q, 2H, -C*H*$_2$-), and 6.50 ∿ 8.20 (m, 9H, aromatic *H*); ms: m/e 308 (M^+).

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.1; H, 5.2; N, 9.1. Found: C, 70.0; H, 5.5; N, 9.2.

Dibenzo[*b,g*][1,5]naphthyridine-6,12(5*H*,11*H*)dione (**6**).

In a 250 ml. flask was placed 12 g. (38.9 mmoles) of the 3-anilino-2-ethoxycarbonyl-4-quinolone (**5**) and 120 g. of polyphosphoric acid. The mixture was heated slowly with stirring to 150° over the period of 1 hour and stirred for another 2 hours keeping the temperature at 145-150°. The mixture was then cooled to about 50° and an ice-water mixture was added slowly maintaining the temperature at 50-60° until the vigorous hydrolysis reaction had ceased, after which an excess of water was added to fill the flask to capacity. The mixture was stirred vigorously until the acid complex was completely broken-up and transferred to 2-l. flask. The mixture was diluted with 1.5 l. of water and stirred for 1 hour. The yellow product was collected on a sintered glass funnel (medium or fine) and washed with water until the washings were neutral. The wet cake was reslurried in 1-l. of water and allowed to stand overnight. At this point, the water solution should be neutral. If the water was still slightly acidic, a few drops of ammonium hydroxide was added until the *p*H is 7. The product was collected and washed with water, and dried in a vacuum oven at 60°. There was obtained 8.5 g. of fine bright yellow powder, which is 83% of the theoretical amount of 10.2 g. The ir and mass spectra were identical with those of an authentic sample of epindolidione prepared by the dihydroxyfumaric acid method (3).

REFERENCES AND NOTES

(1) A. D. Ainley and R. Robinson, *J. Chem. Soc.*, 1508 (1934).

(2) H. de Diesbach, A. Schurch, and G. Cavin, *Helv. Chim. Acta*, **31**, 716 (1948).

(3) E. E. Jaffe and H. Matrick, *J. Org. Chem.*, **33**, 4004 (1968).

(4) G. R. Aldridge, E. E. Jaffe, and H. Matrick, U. S. Patent 3,334,102 (1967); *Chem. Abstr.*, **67**, 109632S (1967).

(5) F. A. Miller in "Organic Chemistry," Vol. III, H. Gilman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 131 and 132.

(6a) M. Conrad and L. Limpach, *Ber.*, **20**, 1944 (1887); *ibid.*, **21**, 521 (1888); (b) R. C. Elderfield in "Heterocyclic Compounds," R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 1; (c) R. H. Reitsema, *Chem. Rev.*, **43**, 43 (1948).