Total Synthesis of Camptothecin. I. Synthesis of Ethyl 8-(α-Chlorobutyryloxymethyl)-7,9-dioxo-7,8,9,11-tetrahydroindolizino[1,2-*a*]quinoline-8-carboxylate and Related Tetracyclic Compounds (1)

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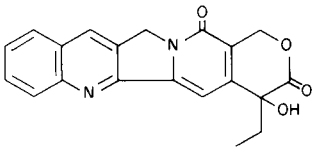
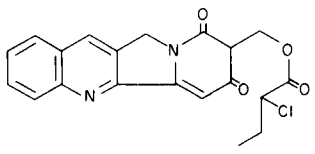
A practical synthesis of the 8-ethoxycarbonyl-8-hydroxymethyl-7,9-dioxo-7,8,9,11-tetrahydroindolizino[1,2-*a*]quinoline ester of α-chlorobutyric acid, a tetracyclic intermediate for the total synthesis of the alkaloid camptothecin, was prepared from the anil of *o*-aminobenzaldehyde in six steps. Preparative procedures of other related tetracyclic compounds are also reported.

The unique structure (2,3) and the antineoplastic activity (2,4-9) of camptothecin (I), an alkaloid isolated from the Chinese tree *Camptotheca acuminata* Decne. (fam. *Nyssaceae*), have interested many investigators in searching for synthetic approaches (10-15) to this pentacyclic compound. A practical synthetic procedure for the preparation of ethyl 8-(α-chlorobutyryloxymethyl)-7,9-dioxo-7,8,9,11-tetrahydroindolizino[1,2-*b*]quinoline-8-carboxylate (II) and related compounds are reported in this communication.



I



II

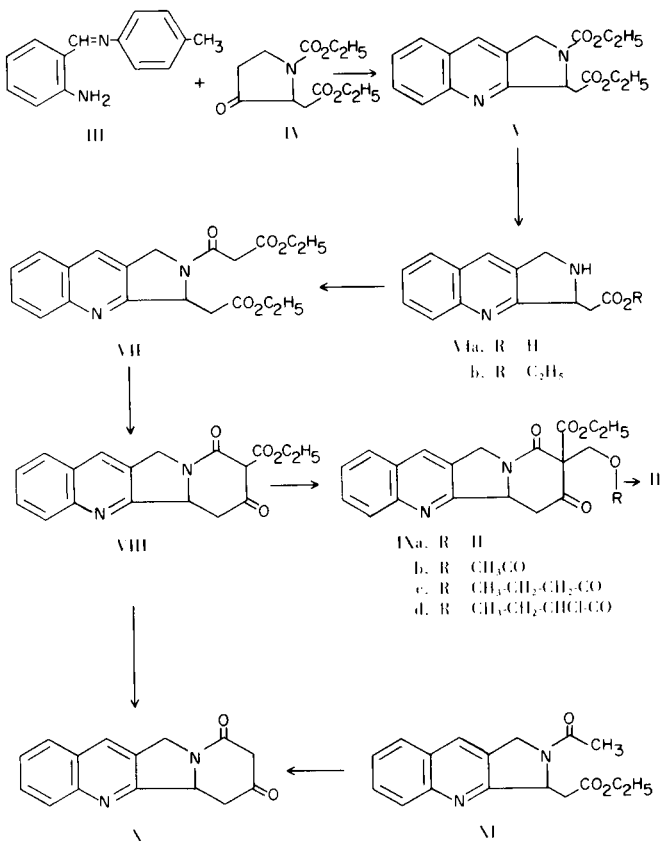
Condensation of *N*-(2-aminobenzylidene)-*p*-toluidine (III) (16) with ethyl *N*-ethoxycarbonyl-3-pyrrolidinone-2-acetate (IV) (17) in toluene in the presence of *p*-toluenesulfonic acid yielded ethyl 2-ethoxycarbonyl-1,3-dihydro-2*H*-pyrrolo[3,4-*b*]quinoline-3-acetate (V), m.p. 111-113°. Compound V was refluxed with hydriodic acid to give, after neutralization, the free acid VIa, m.p. 248-250° dec. Esterification of VIa afforded the dihydrochloride salt of the corresponding ester VIb, m.p. 210° dec.

The diester VII, m.p. 96-98°, was readily obtained by condensation of VIb and the monoethyl ester of malonic acid in chloroform in the presence of *N,N'*-dicyclohexylcarbodiimide. Dieckmann cyclization of compound VII gave the tetracyclic ethyl 7,9-dioxo-5b,6,7,8,9,11-hexahydroindolizino[1,2-*b*]quinoline-8-carboxylate (VIII), m.p. 194.5-196°. The yield was quite high in each of the aforementioned steps. Some were nearly quantitative.

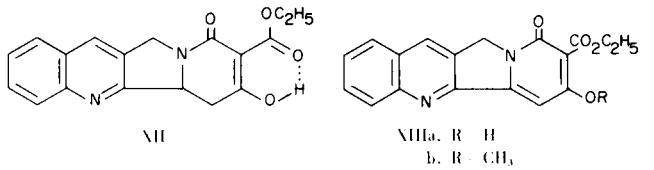
The introduction of a functional side chain for the construction of the lactone ring of camptothecin was carried out as follows: treatment of compound VIII with 40% formaldehyde in the presence of potassium bicarbonate yielded ethyl 8-hydroxymethyl-7,9-dioxo-5b,6,7,8,9,11-hexahydroindolizino[1,2-*b*]quinoline-8-carboxylate (IXa), m.p. 196-199° dec. Esterification of IXa with acetic anhydride, butyric anhydride, and α-chlorobutyryl chloride gave the corresponding acetyl (IXb), butyryl (IXc), and α-chlorobutyryl (IXd) esters, respectively. On the other hand, prolonged stirring resulted in the formation of ethyl 8-(α-chlorobutyryloxymethyl)-7,9-dioxo-7,8,9,11-tetrahydroindolizino[1,2-*b*]quinoline-8-carboxylate (II), m.p. 140-142°, from IXa and α-chlorobutyryl chloride.

Decarboxylation of the ester VIII was achieved in hot aqueous acetic acid to give 7,9-dioxo-5b,6,7,8,9,11-hexahydro[1,2-*b*]quinoline (X), m.p. 222-224°. Compound X was also obtained by Dieckmann cyclization of ethyl 2-acetyl-1,3-dihydro-2*H*-pyrrolo[3,4-*b*]quinoline-3-acetate (XI). The latter, m.p. 145-147°, was prepared by condensation of VIb and glacial acetic acid with *N,N'*-dicyclohexylcarbodiimide in benzene in a similar fashion to that used for the preparation of the diester VII.

It is noteworthy that the infrared absorption spectra of ethyl 7,9-dioxo-5b,6,7,8,9,11-hexahydroindolizino[1,2-*b*]-quinoline-8-carboxylate (VIII) do not exhibit bands corresponding to the keto- and the ester-carbonyl groups. Absorption bands at 1650 (broad, overlapping >CO-N< and enolic C=O bands), 1590, 1500 and 1250 cm^{-1} suggest that the compound exists predominantly in the intramolecularly hydrogen-bonded enol form XII. Enolization



of β-keto esters has been studied in detail (18,19). The presence of the amide carbonyl group evidently enhances the enolization to such an extent that there is practically no keto form present. NMR spectra of this compound also indicate the presence of enolic hydroxyl group. Hence compound VIII (XII) was readily oxidized by means of



nitrous acid (20,21) at room temperature to the corresponding aromatized compound XIIIa, m.p. > 350°. The latter was methylated in chloroform with diazomethane to give ethyl 7-methoxy-9-oxoindolizino[1,2-*b*]quinoline-8-carboxylate (XIIIb), m.p. 257-257.5°, in almost quantitative yield.

The infrared absorption spectra of 7,9-dioxo-5b,6,7-8,9,11-hexahydroindolizino[1,2-*b*]quinoline (X), the decarboxylated product of VIII, show that although this compound is not predominantly in its enolized form, it is nevertheless in equilibrium with the latter, as expected. The ultraviolet absorption spectra of XIIIb bear a striking resemblance to those of camptothecin.

EXPERIMENTAL

All melting points were taken on a Thomas-Hoover melting point apparatus. The ultraviolet absorption spectra were determined with a Beckman DK-2 spectrophotometer, the infrared spectra were taken with a Perkin-Elmer Infracord, the NMR data were acquired with a Varian A-60 High Resolution NMR spectrometer, and the mass spectra data were obtained with a Varian Mat CH-4B Mass Spectrometer.

Ethyl 2-Ethoxycarbonyl-1,3-dihydro-2*H*-pyrrolo[3,4-*b*]quinoline-3-acetate (V).

This compound was prepared previously by the base-catalyzed condensation of *o*-aminobenzaldehyde and ethyl *N*-ethoxycarbonyl-3-pyrrolidine-2-acetate (IV) in less than 30% yield (8). Following is a practical, large scale synthetic procedure. A solution of 630 g. (3 moles) of *N*-(2-aminobenzylidene)-*p*-toluidine (III), 730 g. (3 moles) of IV, 15 g. of *p*-toluenesulfonic acid in 3 liters of toluene was heated under reflux, with mechanical stirring, until no additional water was collected (Dean-Stark apparatus; 3-4 hours reflux). The reaction mixture was filtered while hot to remove a small amount of insoluble solid. The filtrate was evaporated *in vacuo* to remove most of the solvent. It was then cooled to 0° and to this was added 750 ml. of ether. The desired product, which precipitated from the mixture, was collected by filtration, washed with ether and dried to give 775 g. (76.3% yield) of V, m.p. 108-110°. An analytical sample was prepared by recrystallization from ethyl acetate, m.p. 111-113°; ν max 1750 (ester carbonyl), 1675 cm^{-1} (amide carbonyl).

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 66.10; H, 5.92; N, 8.66.

1,3-Dihydro-2*H*-pyrrolo[3,4-*b*]quinoline-3-acetic Acid (VIa).

A solution of 560 g. (1.7 moles) of V in 2.4 liters of 57% hydriodic acid was refluxed, with stirring, for 53 hours. At the end of this period most product precipitated from the hot solution as the dihydriodide salt. The reaction mixture was cooled and the orange solid collected by filtration. It was washed with acetone, ether and dried *in vacuo* to give 610 g. of solid. An additional 50 g. of solid was obtained by evaporation of the filtrate. The combined solids were dissolved in 3 liters of water. The *p*H of the solution was adjusted to slightly above 7 with dilute sodium hydroxide, then acidified to *p*H 6 with glacial acetic acid to insure complete precipitation of the amino acid VIa. The product was collected by filtration, washed successively with water, ethanol and ether, and dried at 90° under reduced pressure to give 346 g. (87.3% yield) of VIa, m.p. 240-245° dec. An analytical sample was prepared by recrystallization from aqueous ethanol, m.p. 248-250° dec.

Anal. Calcd. for $C_{13}H_{12}N_2O_2 \cdot \frac{1}{4}H_2O$: C, 67.08; H, 5.41; N, 12.04. Found: C, 67.09; H, 5.29; N, 11.90.

Ethyl 1,3-Dihydro-2*H*-pyrrolo[3,4-*b*]quinoline-3-acetate (VIb).

A slow stream of dry hydrogen chloride was bubbled through a refluxing suspension of 83 g. (0.36 mole) of VIa and 500 ml. of absolute ethanol, with stirring. The solid gradually dissolved and soon the dihydrochloride salt of the esterified product started to precipitate from the hot reaction mixture. After 7 hours the

mixture was cooled and the solid collected by filtration. It was washed with ethanol, ether and dried *in vacuo* to give 117 g. (99.5% yield) of VIb as the dihydrochloride salt which was pure enough for the following reaction. An analytical sample was prepared by recrystallization from 95% ethanol, m.p. 210° dec. Its free base melted at 60-61°; ν max 1735 cm^{-1} (ester carbonyl).

Anal. Calcd. for $C_{15}H_{16}N_2O_2 \cdot 2HCl$: C, 54.72; H, 5.51; N, 8.51. Found: C, 55.12; H, 5.66; N, 8.41.

Ethyl 2-Carbethoxyacetyl-1,3-dihydro-2*H*-pyrrolo[3,4-*b*]quinoline-3-acetate (VII).

To a solution of 165 g. (0.5 mole) of VIb and 1.2 liters of water in a 5 liter three-necked flask fitted with a mechanical stirrer was added, with vigorous stirring at 0°, 1 liter of chloroform followed by dropwise addition of a solution of 40 g. (1 mole) of sodium hydroxide in 125 ml. of water. The reaction mixture was stirred vigorously for an additional 30 minutes after the addition. The chloroform layer was then separated, dried over anhydrous magnesium sulfate, and filtered into a 3 liter three-necked flask fitted with a dropping funnel, a mechanical stirrer and a condenser attached to a drying tube. To the solution was added 103 g. (0.5 mole) of *N,N'*-dicyclohexylcarbodiimide with stirring. A solution of 66 g. (0.5 mole) of the monoethyl ester of malonic acid in 100 ml. of chloroform was added dropwise, with vigorous stirring, at room temperature over a period of 2 hours, during which time *N,N'*-dicyclohexylurea precipitated. The reaction mixture was filtered, the urea was washed with a small amount of chloroform, and the combined chloroform solutions evaporated *in vacuo*. Additional urea precipitated from the oily residue. This was again separated by filtration. The filtrate was then added to 400 ml. of hexane, and the product precipitated. It was collected by filtration, washed with hexane, and dried *in vacuo* to give 165 g. (89% yield) of VII as a white solid, m.p. 92-95°. An analytical sample was prepared by recrystallization from ethyl acetate, m.p. 96-98°; ν max 1725 (ester carbonyl), 1640 cm^{-1} (amide carbonyl); δ (deuteriochloroform): 1.05 (3H, *t*, CH_3), 1.28 (3H, *t*, CH_3), 3.40 (2H, *d*, J = 4 cps, CH_2CO), 3.49 (2H, *s*, Ar-CH_2-N<), 3.95 (2H, *q*, CO_2CH_2-), 4.28 (2H, *q*, CO_2CH_2-), 5.01 (2H, *s*, $COCH_2CO$), 5.54 (1H, *t*, J = 4 cps, N-CH<), 7.50-8.30 (5H, *m*, aro-H).

Anal. Calcd. for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.84; H, 6.25; N, 7.78.

Ethyl 7,9-Dioxo-5b,6,7,8,9,11-hexahydroindolino[1,2-*d*]quinoline-8-carboxylate (VIII).

To an ethanol solution of sodium ethoxide (prepared by dissolving 12 g. of sodium in 750 ml. of absolute ethanol) was added, with vigorous stirring at room temperature, 185 g. (0.5 mole) of VII. The mixture was refluxed with stirring for 4 hours under anhydrous conditions. It was then cooled and acidified with dilute hydrochloric acid to *p*H 1. The precipitate was collected by filtration and washed thoroughly with water and ethanol. It was dried at 80° *in vacuo* to give 141 g. (87% yield) of VIII, m.p. 185-190° dec. An analytical sample was prepared by recrystallization from aqueous ethanol, m.p. 194.5-196° dec.; ν max 1650 (broad, overlapping of amide and chelated carbonyl groups), 1590 (C=C), 1500, 1250 cm^{-1} (C=C-O-); λ max (*p*H 1) 239 (ϵ, 59,300), 325 nm (ϵ, 10,100); λ max (*p*H 11) 233 (ϵ, 41,000), 271 (ϵ, 13,300), 320 nm (ϵ, 7,200); δ (deuteriochloroform) 14.2 (enol-H).

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 67.00; H, 4.77; N, 8.58.

Ethyl 8-Hydroxymethyl-7,9-dioxo-5b,6,7,8,9,11-hexahydroindolizino[1,2-*b*]quinoline-8-carboxylate (IXa).

To a solution of 16.2 g. (0.05 mole) of VIII in 350 ml. of dichloromethane was added, with stirring, 0.5 g. of powdered potassium bicarbonate and 6 g. of 40% formaldehyde. Stirring was continued at room temperature for 20 hours during which time the product gradually precipitated. The solid was collected by filtration, washed successively with 5% acetic acid, 95% ethanol and ether, and air dried to yield 15 g. of crude product, m.p. 180-185° dec. It was dissolved in 500 ml. of warm glacial acetic acid, diluted with 500 ml. of water and chilled at 5° for 18 hours. The resulting white crystals were collected by filtration, washed with water and 95% ethanol, and dried at 40° *in vacuo* to give 10 g. (57% yield) m.p. 196-199° dec.; ν max 1755 (ester C=O), 1725 (carbonyl), 1650 cm^{-1} (amide C=O).

Anal. Calcd. for $C_{19}H_{18}N_2O_5$ (354.37): C, 64.40; H, 5.12; N, 7.91. Found: C, 64.66; H, 5.36; N, 7.76; m/e: 354.

Ethyl 8-Acetoxymethyl-7,9-dioxo-5b,6,7,8,9,11-hexahydroindolizino[1,2-*b*]quinoline-8-carboxylate (IXb).

A mixture of 1.2 g. of IXa, 10 ml. of glacial acetic acid, 10 ml. of acetic anhydride, and 0.65 g. of *p*-toluenesulfonic acid was stirred at room temperature until a clear solution resulted. The solution was allowed to stand at room temperature for 20 hours and poured onto *ca.* 300 g. of crushed ice. The precipitated white solid was collected by filtration, washed thoroughly with water and air dried. It was recrystallized from benzene to give 1 g. (74.5% yield) of analytically pure product, m.p. 118-120°; ν max 1755 (ester C=O), 1725 (C=O), 1650 cm^{-1} (amide C=O); δ (deuteriochloroform): 1.20 (3H, *t*, CH_3), 2.00 (3H, *t*, $COCH_3$), 3.05 (1H, *q*, J_{AX} = 13 cps, J_{AB} = 15 cps, CH_A-CO), 3.68 (1H, *q*, J_{BX} = 3 cps, J_{AB} = 15 cps, CH_B-CO), 4.23 (2H, *q*, CO_2CH_2), 4.68-5.60 (5H, *m*, >N-CH_X, -CH_2-N<, -CH_2-O-), 7.70-8.25 (5H, *m*, aro-H).

Anal. Calcd. for $C_{21}H_{20}N_2O_6$ (396.41): C, 63.63; H, 5.09; N, 7.07. Found: C, 63.60; H, 4.85; N, 7.11; m/e: 396.

Ethyl 8-Butyryloxymethyl-7,9-dioxo-5b,6,7,8,9,11-hexahydroindolizino[1,2-*b*]quinoline-8-carboxylate (IXc).

A mixture of 1.2 g. of IXa, 10 ml. of butyric acid, 10 ml. of butyric anhydride and 0.7 g. *p*-toluenesulfonic acid was stirred at room temperature for 3 hours. The clear solution was allowed to stand at room temperature for 24 hours and poured onto *ca.* 200 g. of crushed ice. The resulting aqueous mixture was neutralized with dilute sodium bicarbonate. The oily product was separated and the aqueous solution extracted twice with 100 ml. of chloroform. The combined oil and chloroform extract was dried over anhydrous magnesium sulfate, filtered, and evaporated. The resulting oil was triturated with hexane and chilled overnight. The resulting solid was collected and recrystallized from a mixture of benzene and hexane to give 0.65 g. of product, m.p. 127-128.5°; ν max 1750 (ester C=O), 1725 (C=O), 1650 cm^{-1} (amide C=O).

Anal. Calcd. for $C_{23}H_{24}N_2O_6$ (424.46): C, 65.08; H, 5.70; N, 6.60. Found: C, 65.00; H, 5.66; N, 6.59; m/e: 424.

Ethyl 8-(α-Chlorobutyryloxymethyl)-7,9-dioxo-5b,6,7,8,9,11-hexahydroindolizino[1,2-*b*]quinoline-8-carboxylate (IXd).

To a partial solution of 2 g. of IXa in 5 ml. of dry pyridine and 30 ml. of dimethylformamide was added, with stirring at 0°, 2 ml. of α-chlorobutyryl chloride. The reaction mixture was then allowed to stir at room temperature for 6 hours and the resulting solution was poured into 200 ml. of iced water. The precipitated product was collected by filtration, washed successively with water, ethanol and hexane to give 1.2 g. of analytically pure

product, m.p. 156-158°; ν max 1755 (ester C=O), 1725 (C=O), 1650 cm^{-1} (amide C=O); λ max (*p*H 1) 239 (ε, 68,700), 323 nm (ε, 22,900); λ max (*p*H 11) 320 nm (ε, 23,000); δ (deuteriochloroform): 1.00 (3H, *t*, CH_3), 1.22 (3H, *t*, CH_3), 1.58-2.10 (3H, *m*, N-CH, N-CH_2), 2.88-3.90 (2H, *m*, CH_2-CO), 4.22 (2H, *q*, ≥C-CH_2-O-), 4.23 (1H, *m*, CHCl), 5.01 (2H, *d*, J = 4 cps, CH_2), 5.18-5.60 (2H, *m*, CH_2), 7.70-8.25 (5H, *m*, aro-H).

Anal. Calcd. for $C_{23}H_{23}ClN_2O_6$: C, 60.20; H, 5.05; N, 6.10. Found: C, 60.08; H, 4.98; N, 6.20.

Ethyl 8-(α-Chlorobutyryloxymethyl)-7,9-dioxo-7,8,9,11-tetrahydroindolizino[1,2-*b*]quinoline-8-carboxylate (II).

To a partial solution of 4 g. of IXa, 10 ml. of dry pyridine and 35 ml. of dimethylformamide was added dropwise, at 0° with stirring, 4 ml. of α-chlorobutyryl chloride. The reaction mixture, which was excluded from moisture but not from air, was allowed to warm up gradually to room temperature and stirring was continued for an additional 18 hours. The resulting solution was poured into 300 ml. of iced water whereupon the product precipitated. It was collected by filtration, washed well with water, and recrystallized from ethanol to give 2 g. of yellow prisms, m.p. 140-142°; ν max 1755 (ester C=O), 1700 (C=O), 1640 (amide C=O); λ max (*p*H 1) 258 (ε, 27,000), 320 (ε, 12,000), 378 nm (ε, 15,600); λ max (*p*H 11) 247 (ε, 50,200), 358 nm (ε, 17,300); δ (deuteriochloroform): 0.89 (3H, *t*, CH_3), 1.23 (3H, *t*, CH_3), 1.58-2.10 (2H, *m*, CH_2), 4.20 (1H, *m*, CH), 4.25 (2H, *q*, CH_2), 5.07 (2H, *s*, CH_2-O-), 5.24 (2H, *s*, CH_2-N≤), 6.75 (1H, *s*, aro-H), 7.80-8.25 (5H, *m*, aro-H).

7,9-Dioxo-5b,6,7,8,9,11-hexahydroindolizino[1,2-*b*]quinoline (X).

A mixture of 7.5 g. (0.023 mole) of VIII and 100 ml. of 50% acetic acid was refluxed with stirring for 2 hours. The clear reaction solution was evaporated under reduced pressure and the resulting slurry was neutralized with dilute sodium carbonate. The solid was collected by filtration, washed thoroughly with water and then with ethanol and ether, and dried at 80° *in vacuo* to give 4.5 g. (77.2% yield) of white solid, m.p. 215-220° dec. An analytical sample was prepared by recrystallization from ethanol, m.p. 222-224° dec.; ν max 3400 (enol), 1720 (C=O), 1650 (amide C=O), 1250 cm^{-1} (C=C-O-); λ max (*p*H 1) 230 (ε, 44,000), 305 (ε, 5,500), 319 nm (ε, 7,100); λ max (*p*H 11) 231 (ε, 40,800), 279 (ε, 13,600), 305 (ε, 10,100), 318 nm (ε, 7,600).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.77; N, 11.11. Found: C, 71.16; H, 4.59; N, 11.08.

Compound X was also prepared by direct cyclization of ethyl 2-acetyl-1,3-dihydro-2*H*-pyrrolo[3,4-*b*]quinoline-3-acetate (XI): to a solution of 44.7 g. of XI (m.p. 145-147°) in 450 ml. of dry toluene was added, with stirring, 1 ml. of absolute ethanol followed by 7 g. of 57% sodium hydride in mineral oil. The mixture was refluxed with stirring under anhydrous conditions for 20 hours. The resulting solid was collected by filtration and redissolved in 50 ml. of water. The aqueous solution was neutralized with glacial acetic acid and extracted with 3 x 50 ml. of chloroform. The chloroform extract was dried and evaporated, and the residue was recrystallized from 2-methoxyethanol to give 10.8 g. of solid, m.p. 222-224°. The product was found to be identical with that prepared by the aforementioned method.

Ethyl 7-Hydroxy-9-oxoindolizino[1,2-*b*]quinoline-8-carboxylate (XIIIa).

To a stirred partial solution of 13 g. (0.04 mole) of VIII (XII) in 110 ml. of glacial acetic acid was added dropwise, at room temperature, a solution of 6 g. of sodium nitrite in 10 ml. of water. After the addition was complete, the reaction mixture was stirred for an additional 24 hours. It was then chilled, the precipitated product was collected by filtration and washed successively with water, ethanol and ether. The product was dried *in vacuo* to give 9.1 g. (70.5% yield) of an off-white solid, m.p. > 350°. An analytical sample (white needles, m.p. > 350°) was prepared by recrystallization from glacial acetic acid; ν max 1665 (chelated ester), 1625 (amide C=O), 1250 cm^{-1} (C=C-O-); δ (trifluoroacetic acid) 1.16 (3H, *t*, CH_3), 4.40 (2H, *q*, CO_2CH_2), 5.44 (2H, *s*, CH_2N≤), 7.66-7.98 (6H, *m*, aro-H), 9.00 (1H, *s*, aro-OH).

Anal. Calcd. for $C_{18}H_{14}N_2O_4$ (322.33): C, 67.07; H, 4.38; N, 8.69. Found: C, 67.41; H, 4.07; N, 8.85; m/e: 322.

Ethyl 7-Methoxy-9-oxoindolizino[1,2-*b*]quinoline-8-carboxylate (XIIIb).

To a solution of 0.5 g. of XIIIa in 280 ml. of chloroform was added an ethereal solution of diazomethane (*ca.* 2.8 g. of diazomethane in 300 ml. of ether, prepared (*cf.* ref. 22,23) as follows: to 150 ml. of ether in a new Erlenmeyer flask placed behind a shield in the hood was added 30 ml. of 40% potassium hydroxide. The mixture was cooled to 5° and, with cooling and occasional shaking, was added 10 g. of finely powdered *N*-nitroso-*N*-methylurea. The diazomethane was dissolved in the upper ether layer as it was being formed. After 30 minutes the deep yellow ether was decanted into the reaction mixture, additional 150 ml. of ether was added to the diazomethane-generating flask and the yellow ether layer was again added to the reaction mixture by decantation). The resulting solution was allowed to stand at room temperature for 16 hours. It was then evaporated in a hood with a stream of air to dryness. The resulting yellow solid was recrystallized from 125 ml. of acetone to give 0.44 g. (84.6% yield) of light yellow crystals, m.p. 257-257.5°. Larger scale (2.5 g.) runs gave XIIIb in near quantitative yields; ν max 1725 (ester C=O), 1640 (amide C=O), 1600 (C=C), 1250 cm^{-1} (C=C-O-); λ max (*p*H 1) 252 (ε, 30,300), 394 nm (ε, 18,200); λ max (*p*H 11) 250 (ε, 36,000), 353 (ε, 23,500), 365 nm (ε, 23,000).

Anal. Calcd. for $C_{19}H_{16}N_2O_4$ (336.35): C, 67.85; H, 4.79; N, 8.33. Found: C, 67.56; H, 5.02; N, 8.21; m/e: 336.

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