through a thick bed of silica gel and subsequent recrystallization from ether, the desired benzoquinone diimine (**1h**) was obtained in a pure state: mp 110–112 °C; ^{1}H NMR ($CDCl_3$) δ 4.09 (s, 2), 6.97 (dd, J_{AB} = 10 Hz, 1), 7.16 (d, J_{AX} = 2 Hz, 1), 8.12 (d, J_{AB} = 10 Hz, 1), 7.50–8.16 (m, 5); IR ($CHCl_3$) 1690, 1590, 1450 cm^{-1}; UV (EtOH) 265 nm (ϵ 9000).

Preparation of 2′-Methyl-4′-(2-bromo-2-methylpropionamido)benzenesulfonanilide (Reduced 6). To a rapidly stirred suspension of 5.2 g (20 mmol) of 2′-methyl-4′-aminobenzenesulfonanilide (**3a**) and 2.0 g (20 mmol) of finely divided, anhydrous sodium carbonate in 300 mL of chloroform (dry, ethanol removed) was added dropwise 3.5 mL (20 mmol, 4.6 g) of 2-bromo-2-methylpropionyl bromide (Eastman Kodak) dissolved in 10 mL of chloroform. After stirring at room temperature for 3 h, 30 mL of 2 N hydrochloric acid was added, and the reaction mixture was transferred to a separatory funnel. After addition of additional 100 mL of chloroform and another 100 mL of 2 N hydrochloric acid, the layers were separated. The chloroform solution was subsequently washed with saturated potassium bicarbonate solution (1 × 100 mL) and saturated sodium chloride solution (1 × 100 mL) and then dried over anhydrous sodium sulfate. Removal of the solvent in vacuo provided 8.0 g (95%) of a semisolid material that solidified upon standing. Recrystallization of this material from ethyl acetate and petroleum ether provided the desired product in a pure state: mp 138–140 °C; NMR (acetone-d_6) δ 1.93 (s, 3), 2.01 (s, 6), 7.06 (d, J = 9 Hz, 1), 7.30–7.83 (m, 7), 8.3 (br s, 1), 9.0 (br s, 1); NMR ($CDCl_3$) δ 1.93 (s, 3), 2.10 (s, 6), 7.1–7.8 (m, 8). IR ($CHCl_3$) 3380, 1680, 1165 cm^{-1}; UV (EtOH) 265 nm (ϵ 14 000); MS, m/e 412 and 410 ($M^+ - C_6H_5SO_2$, 1:1).

Preparation of 2-Methyl-N^1-(phenylsulfonyl)-N^4-(2-bromo-2-methylpropionyl)benzoquinone Diimine (6). To 6.8 g (16.5 mmol) of 2′-methyl-4′-(2-bromo-2-methylpropionamido)benzenesulfonanilide (described above) dissolved in 75 mL of chloroform (dry, ethanol removed) was added all at once 8.0 g (17 mmol) of dry, finely divided lead tetraacetate with rapid stirring. After stirring at room temperature for 30 min, the insoluble lead salts were removed by filtration. The filtrate volume was reduced to approximately 50 mL, and petroleum ether (90–100 °C), approximately 25 mL, was added until the solution clouded. Cooling on dry ice induced crystallization of the desired product as bright yellow crystals. Subsequent crops were obtained by reducing the volume of the mother liquor (total yield 5.9 g, 85%). Recrystallization from ether by cooling on dry ice provided pure benzoquinone diimine **6**: mp 128–130 °C; NMR ($CDCl_3$) δ 2.01 (s, 6), 2.06 (d, J = 1 Hz, 3), 6.8–7.1 (m, 2), 7.4–8.15 (m, 6); IR ($CHCl_3$) 1683, 1590 cm^{-1}; UV (EtOH) 275 nm (ϵ 15 000).

Preparation of 2-(Bromoacetamido)-N^4-(bromoacetyl)naphthoquinone Imine (7). To 2.1 g (10 mmol) of 2-amino-N^4-naphthoquinone iminium hydrochloride (prepared according to Fieser's method[6]) suspended in dry acetonitrile along with 4.8 g (30 mmol) of sodium bromoacetate was added dropwise 2.3 mL (4.0 g, 23 mmol) of bromoacetyl bromide (Aldrich). The orange-red suspension was stirred at room temperature for 72 h, after which time the red solid material was removed by filtration. Refrigeration of the filtrate induced formation of a bright yellow crystalline product. Subsequent addition of water to the acetonitrile mother liquor yielded additional crystalline product (total product recovered, 1.4 g, 33%). Recrystallization of this product from hot ethyl acetate provided pure naphthoquinone imine **7**: mp 187–188.5 °C; NMR (acetonitrile-d_3) δ 4.13 (s, 2), 4.29 (s, 2), 7.67–8.33 (m, 5); IR (KBr) 1690, 1650, 1580, 1490, 1320 cm^{-1}; MS, m/E 412, 414, 416 (M^+, ratio approximately 1:2:1), 214 (base).

Registry No. **1a**, 62442-86-8; **1b**, 62442-88-0; **1c**, 86785-28-6; **1d**, 86785-29-7; **1f**, 86785-30-0; **1g**, 86785-31-1; **1h**, 86785-32-2; **2a**, 86785-33-3; **2b**, 1829-81-8; **2c**, 86802-67-7; **2d**, 65680-53-7; **2e**, 86785-34-4; **3a**, 86785-35-5; **3b**, 5466-91-1; **3c**, 86785-36-6; **3d**, 82565-49-9; **3e**, 86785-37-7; **4a**, 86785-38-8; **4b**, 86822-01-7; **4c**, 86785-39-9; **4d**, 27022-75-9; **4e**, 86785-40-2; **4f**, 86785-41-3; **4g**, 86785-42-4; **4h**, 86785-43-5; **5a**, 21226-32-4; **5b**, 86802-68-8; **6**, 86785-44-6; **7**, 86785-45-7; benzenesulfonyl chloride, 98-09-9; 2-methyl-4-nitroaniline, 99-52-5; bromoacetyl bromide, 598-21-0; 4′-aminobenzenesulfonanilide hydrochloride, 86785-46-8; sodium bromoacetate, 1068-52-6; 2-cyano-3-acetoxy-N'-(phenylsulfonyl)-N^4-(bromoacetyl)benzoquinone diimine, 4377-73-5; 2′-cyano-3′-acetoxy-4′-(bromoacetamido)benzenesulfonanilide, 86785-47-9; 2-bromo-2-methylpropionyl bromide, 20769-85-1; 2′-methyl-4′-(2-bromo-2-methylpropionamido)benzenesulfonanilide, 86785-48-0; 2-amino-N^4-naphthoquinone iminum hydrochloride, 5438-85-7.

Studies on the Syntheses of Heterocyclic Compounds and Natural Products. 1000. Double Enamine Annelation of 3,4-Dihydro-1-methyl-β-carboline and Isoquinoline Derivatives with 6-Methyl-2-pyrone-3,5-dicarboxylates and Its Application for the Synthesis of (±)-Camptothecin†

Masataka Ihara, Kazuharu Noguchi, Tatsushi Ohsawa, and Keiichiro Fukumoto

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Tetsuji Kametani*

Institute of Medicinal Chemistry, Hoshi University, Ebara, 2-4-41, Shinagawa-ku, Tokyo 142, Japan

Received January 4, 1983

6-Methyl-2-pyrone-3,5-dicarboxylates **8** and **9** were prepared by the reaction of dimethyl (methoxymethylene)malonate and acetoacetates in the presence of sodium hydride followed by an acid treatment. Reaction of the pyrones **8** and **9** with 3,4-dihydro-1-methylisoquinolines **10** and **11** and β-carboline (**16**) produced the tetra- (**14** and **15**) and pentacyclic compounds (**17** and **18**) by a double annelation. 14-(*tert*-Butoxycarbonyl)-12b,2-(epoxyetheno)-1,2,3,6,7,12b-hexahydro-3-(methoxycarbonyl)-13-methylindolo[2,3-*a*]quinolizidin-4-one (**18**), prepared by the above double enamine annelation method, was converted into the acetate **34** which previously had been transformed into (±)-camptothecin (**1a**) in two steps.

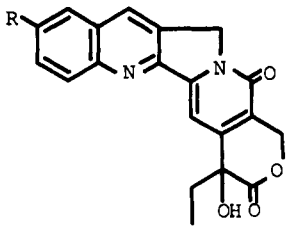
Utilizing the enamine character of 1-methyl-3,4-dihydroisoquinolines and 1-methyl-3,4-dihydro-β-carbolines, we developed an efficient synthesis of benzo- and indolo[*a*]quinolizidine derivatives by reactions with α,β-unsaturated esters.[1] Application of this method led us to the

† Part 999: Fukumoto, K.; Chihiro, M.; Ihara, M.; Kametani, T.; Honda, T. *J. Chem. Soc., Perkin Trans. 1*, in press.

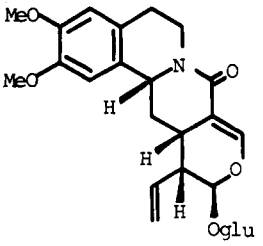
(1) Kametani, T.; Terasawa, H.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2547.

0022-3263/83/1948-3150$01.50/0

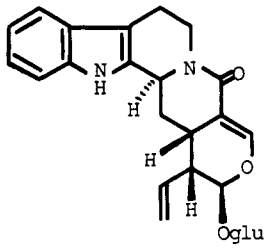
Chart I



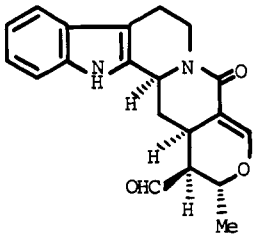
(1a) R= H
(1b) R=OH



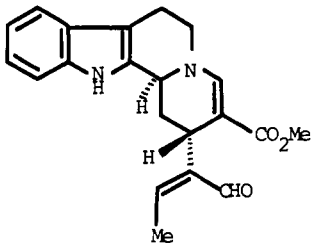
(2)



(3)



(4)



(5)

total syntheses of some ipecac and indole alkaloids.[2] Recently Palmisano and his co-workers extended this annelation for the synthesis of (±)-dephancheine.[3] We now have investigated other Michael acceptors which would act as more effective precursors for the synthesis of a variety of alkaloids. In our previous synthesis of camptothecin (**1a**) the introduction of the ethyl group at the C_{20} position had some problems and resulted in poor yield. Therefore we designed a reaction with 6-methyl-2-pyrone-3,5-dicarboxylates possessing all the needed eight carbon atoms, since it was expected that the 4-position of the pyrone would be electron-deficient enough for the attack of ambident nucleophiles and that the annelation would give potential intermediates for the synthesis of alangiside (**2**),[4] strictosamide (**3**),[5] naucleidinal (**4**),[6] and vallesiachotamin (**5**)[7] as well as camptothecin (**1a**)[7] (Chart I). The reaction gave an unexpected double annelation, yielding quinolizidines having an epoxyetheno bridge. (±)-Camptothecin was synthesized from the product as described in this paper.

Double Enamine Annelation with Pyrones

Pyrone derivatives were prepared by a modification of Crombie's method.[8] Dimethyl (methoxymethylene)-malonate (**6**) was reacted with alkyl acetoacetate in the presence of sodium hydride in benzene, and the crude product was treated with *p*-toluenesulfonic acid in benzene to give the desired 2-pyrones **8** and **9**. The cyclization had proceeded through the Michael adduct **7**.

It was observed that the pyrones were very reactive toward enamines. When pyrone **8** was treated with 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (**10**) at room temperature in acetonitrile, both starting materials disappeared quickly, and two products were detected by TLC analysis. Furthermore, the more polar product changed gradually into the less polar product. Thus, after reaction for 12 h at the same temperature, followed by short-column purification, a crystalline product (mp 126–127 °C) was obtained in 82.5 % yield. The tetracyclic structure **14** was assigned to it on the basis of the following spectral data. The UV spectrum (MeOH; 230, 240, and 280 nm) indicated the presence of a tetrahydroisoquinoline moiety, and the mass spectrum (*m/e* 444, M^+) and the microanalysis supported the molecular formula $C_{23}H_{17}NO_8$. In the IR spectrum ($CHCl_3$) three carbonyl absorptions were observed at 1728, 1700, and 1645 cm^{-1} and the NMR spectrum ($CDCl_3$) showed three *O*-methyl groups at 3.73, 3.87, and 3.89 ppm, one *O*-ethyl group at 4.23 and 1.32 ppm, and one *C*-methyl group at 2.28 ppm. The relative stereochemistry of H_2 and H_3 was assumed to be the thermodynamically stable trans form. Reaction of the pyrone **8** with phenethylisoquinoline **11** produced quantitatively the corresponding product **15** (mp 74–75 °C), whose H_1 stereochemistry remained unknown (see Scheme I). It was assumed that the carbonyl group in the dihydropyrone ring of the Michael adduct **12** is more electrophilic than the two ester groups, and the ring closure of the resulting zwitter ion (**13**) affords the tetracyclic compounds.

On treatment of 3,4-dihydro-1-methyl-β-carboline (**16**) with the pyrones **8** and **9** under the same reaction conditions the pentacyclic compounds **17** and **18** were obtained in 54.6% and 65.3% yields, respectively.

(2) (a) Synthesis of (±)-emetine and (±)-dihydroprotoemetine: Kametani, T.; Suzuki, Y.; Terasawa, H.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 1211. (b) (±)-Tubulosine and (±)-deoxytubulosine: Kametani, T.; Suzuki, Y.; Ihara, M. *Can. J. Chem.* **1979**, *57*, 1679. (c) (±)-Camptothecin and (±)-10-methoxycamptothecin: Kametani, T.; Ohsawa, T.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1563 and references cited therein. (d) (±)-Dihydrocorynantheol, (±)-corynantheine, and (±)-ajmalicine: Kametani, T.; Kanaya, N.; Hino, H.; Huang, S.; Ihara, M. *Ibid.* **1981**, 3168.

(3) (a) Calabi, L.; Danieli, B.; Lesma, G.; Palmisano, G. *Tetrahedron Lett.* **1982**, *23*, 2139. (b) Woodward synthesized sempervirine from 1,4-dimethyl-β-carboline and isopropoxymethylenecyclohexanone: Woodward, R. B.; McLamore, W. M. *J. Am. Chem. Soc.* **1949**, *71*, 379.

(4) Burnett, A. R.; Knowles, G. D.; Battersby, A. R. *Chem. Commun.* **1971**, 904.

(5) Brown, R. T.; Chapple, C. L.; Lansford, A. G. *Phytochemistry* **1977**, *16*, 1619.

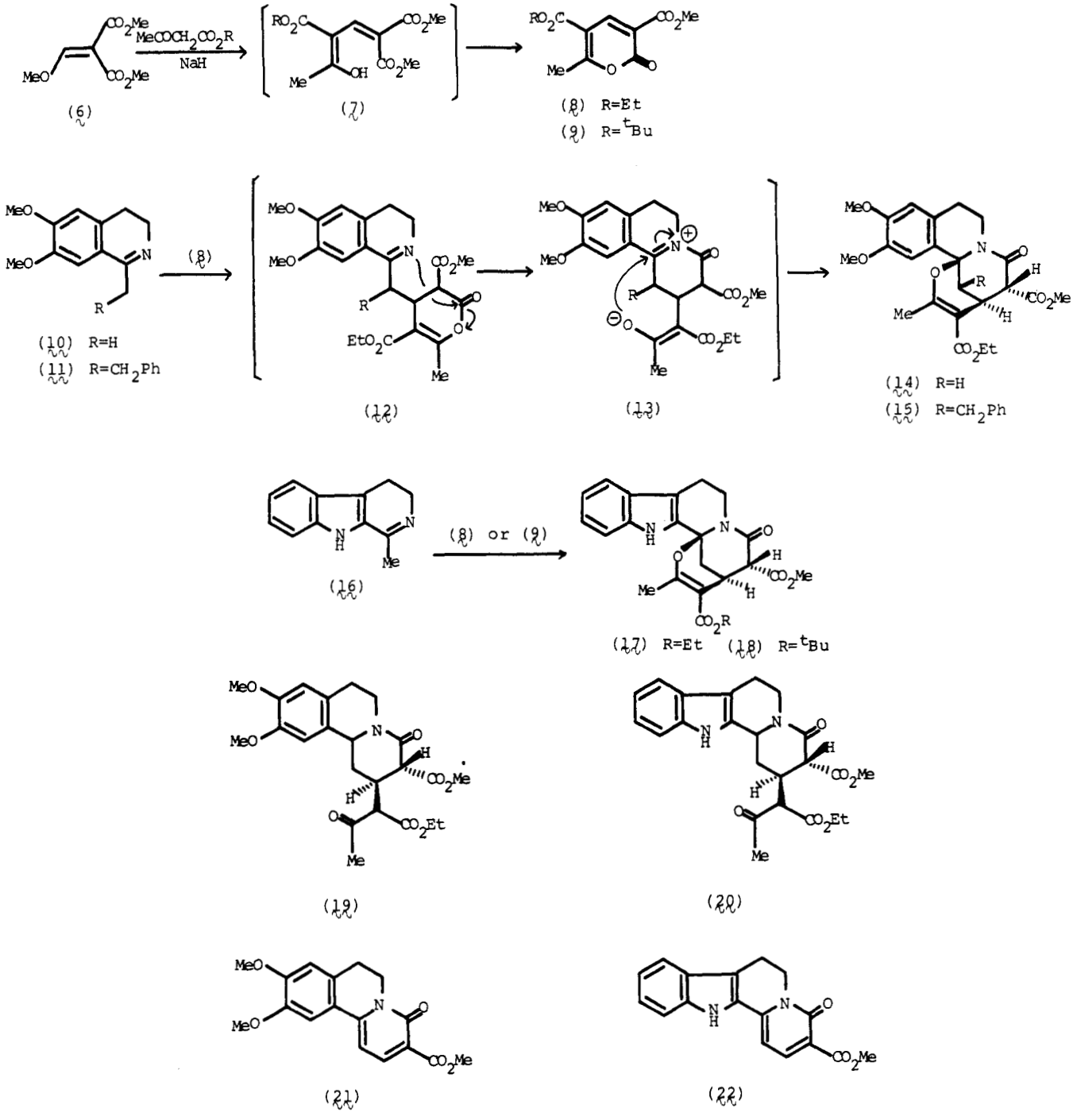
(6) Hotellier, F.; Delaveau, P.; Pousset, J.-L. *Phytochemistry* **1980**, *19*, 1884.

(7) De Silva, K. T. D.; Smith, G. N.; Warren, K. E. H. *Chem. Commun.* **1971**, 905.

(8) Crombie, L.; Eskins, M.; Games, D. E.; Loader, C. *J. Chem. Soc., Perkin Trans. 1* **1979**, 478.

(9) Lane, C. F. *Synthesis* **1975**, 135.

Scheme I



The epoxyetheno bridge was cleaved easily by the action of hydrogen chloride, and the imine formed was reduced with sodium cyanoborohydride[10] at pH 3. By this procedure the compounds **14** and **17** were converted into the β-keto esters **19** and **20** in 92.5% and 81.6% yields, respectively.

The NMR spectra of the products indicated them to be mixtures of stereoisomers or keto–enol tautomers, although they were homogeneous on TLC. On treatment of the β-keto ester **19** and **20** with *p*-toluenesulfonic acid retro-Michael reaction accompanied by dehydrogenation occurred to give 6,7-dihydro-3-(methoxycarbonyl)-quinolizin-4-one derivatives **21** and **22**.[2]

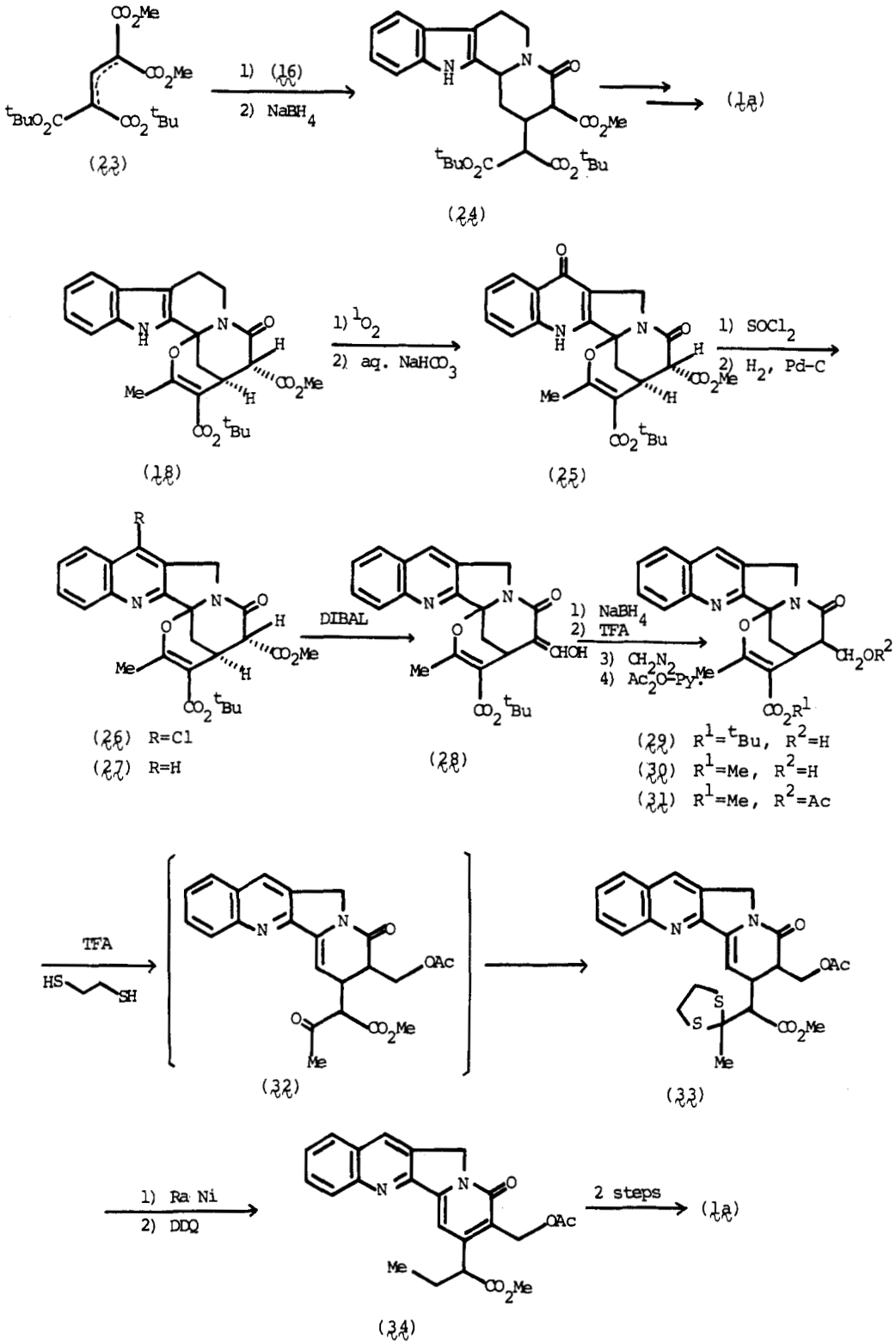
It was expected that the above procedure would provide a useful synthetic method for the aforementioned alkaloids, were the ester groups protected properly. Hence a synthesis of camptothecin was investigated, starting with the *tert*-butyl ester **18**.

Synthesis of (±)-Camptothecin

We had synthesized earlier (±)-camptothecin (**1a**) from the indolo[*a*]quinolizidine **24** by the application of Winterfeldt's method,[10] the starting material having been prepared by the condensation of unsaturated ester **23** with 1-methyl-β-carboline (**16**), followed by a reduction with sodium borohydride.[2] The racemate of 10-hydroxycamptothecin (**1b**), a potential antitumor agent,[11] also was

(10) Boch, M.; Korth, T.; Nelke, J. M.; Pike, D.; Randunz, H.; Winterfeldt, E. *Chem. Ber.* **1972**, *105*, 2126. Winterfeldt, E.; Korth, T.; Pike, D.; Boch, M. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 289. Krohn, K.; Winterfeldt, E. *Chem. Ber.* **1975**, *108*, 3030.

Scheme II



synthesized by this method.[11] The present double annelation product, however, was a more desirable intermediate than the indolo[*a*]quinolizidine, because all the carbon atoms required for the synthesis of camptothecin are present in the compound.

Both pentacyclic ester **18** and the reductively opened compound could be used as the synthetic intermediate. Since the transformation of the pentacyclic compound **18** into camptothecin seemed to be difficult, **18** was converted into the quinoline derivative by a singlet oxygen reaction and a subsequent base treatment.[2] The photooxygenation of **18** was carried out at 20–25 °C for 15 h by irradiation with a halogen lamp under oxygen bubbling in the presence of Rose Bengal in a methanol–methylene chloride. The resulting mixture was treated for 2 days with aqueous sodium bicarbonate solution at ambient temperature to give the quinolone **25** [mass spectrum, *m/e* 466 (M^+); UV (MeOH) λ_{max} 243, 320, 333 nm; IR ($CHCl_3$) ν_{max} 1740, 1640 cm^{-1}] in 60.2% overall yield. Treatment of **25** with thionyl

(11) Wani, M. C.; Ronmand, P. E.; Lindley, J. T.; Wall, M. E. *J. Med. Chem.* **1980**, *23*, 554.

chloride in dimethylformamide at 0 °C gave, in 91% yield, the chloride **26**, which was dechlorinated by using palladium–charcoal under a hydrogen atmosphere to afford the quinoline **27** in 80.6% yield (Scheme II).

The methyl ester of **27** was reduced selectively at -65 to -60 °C with diisobutylaluminum hydride[12] in dimethoxyethane, in 83.1% yield, to the hydroxymethylene compound **28**, which was reduced with sodium borohydride. Two stereoisomeric alcohols **29**, separable by column chromatography, were obtained in 98.2% yield. Since more severe conditions were required for the opening the epoxyetheno bridge than that of the indole derivative described in the preceding section, the *tert*-butyl ester was converted preliminarily into a methyl ester (**31**). Reaction of the chromatographically more polar alcohol **29** with trifluoroacetic acid at room temperature for 15 min, followed by esterification of the resulting carboxylic acid with diazomethane, furnished **30** in 98% yield. After acetylation with acetic anhydride and pyridine, the acetate **31**, obtained in 94% yield, was subjected to the ring-opening reaction.

Refluxing **31** with trifluoroacetic acid formed β-keto ester **32**, as shown by NMR spectroscopy (H_1 doublet at 6.30 ppm). However, a retro-Michael reaction expelling the acetoacetate moiety occurred to a considerable extent. Therefore, a mixture of **31** and ethanedithiol in trifluoroacetic acid was heated for 2 h under reflux to produce the thioketal **33** as a steroisomeric mixture in 57.7% yield. When the less polar epimer of the alcohol **29** was subjected to the above reactions under the same conditions, the retro-Michael reaction took place exclusively, even though the ring-opening reaction was carried out in the presence of ethanedithiol.

The thioketal ester **33** was treated with Raney nickel in ethanol for 2 h. The desulfurized compound, obtained in 57.4% yield, was dehydrogenated by refluxing with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in benzene for 10 min, affording the acetate **34** in 54.1% yield, mp 176–179.5 °C (lit.[13] mp 171–178 °C), whose UV (MeOH) and NMR ($CDCl_3$) spectra were consistent with those reported.[13] The acetate has been converted earlier into (±)-camptothecin (**1a**) in two steps by Rapoport.[13] Thus a biomimetic synthesis of (±)-camptothecin has been accomplished, and the double annelation of pyrone derivatives provided a useful method of synthesis of several ipecac and indole alkaloids.[14]

Experimental Section

UV spectra were measured with a Hitachi 124 spectrophotometer, IR spectra with a Hitachi 260-10 spectrophotometer, and NMR spectra with JEOL-PMX-60 and JEOL-PS-100 spectrometers. Ordinary mass spectra were obtained with a Hitachi M-52G, while FD and accurate mass spectra were taken with a JEOL JMS-01SG-2 spectrometer.

5-(Ethoxycarbonyl)-3-(methoxycarbonyl)-6-methyl-2-pyrone (8). To a suspension of 60% NaH (0.48 g, 12 mmol) in dry benzene (50 mL) was added a solution of ethyl acetoacetate (1.3 g, 10 mmol) in dry benzene (5 mL) dropwise at 0 °C, and the mixture was stirred for 30 min at room temperature. A solution of dimethyl (methoxymethylene)malonate (**6**; 1.74 g, 10 mmol) in dry benzene (5 mL) was then added, and the resulting mixture was stirred for 3 h at room temperature. On cooling, the reaction mixture was acidified with 10% HCl, washed with H_2O and brine, and dried over Na_2SO_4. Evaporation of the solvent afforded an oily residue, which was, without purification, dissolved in benzene (20 mL). After addition of *p*-TsOH (0.1 g), the mixture was stirred for 24 h at room temperature. The reaction mixture was washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated to afford an oily residue, which was subjected to silica gel chromatography. Elution with benzene–Me_2CO (49:1 v/v) gave a powder, which was recrystallized from benzene–*n*-hexane to afford **8**: 0.284 g (11.8%); colorless needles; mp 89–90 °C; IR ($CHCl_3$) 1760, 1720, 1605 cm^{-1}; NMR ($CDCl_3$) δ 1.37 (3 H, t, J = 7 Hz, CH_2CH_3), 2.72 (3 H, s, 6-Me), 3.90 (3 H, s, OMe), 4.34 (2 H, q, J = 7 Hz, CH_2CH_3), 8.70 (1 H, s, 4-H); mass spectrum, m/e 240 (M^+). Anal. Calcd for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04. Found: C, 55.17; H, 4.93.

5-(*tert*-Butoxycarbonyl)-3-(methoxycarbonyl)-6-methyl-2-pyrone (8). To a suspension of 60% NaH (2.88 g, 72 mmol) in dry benzene (200 mL) was dropwise added a solution of *tert*-butyl acetoacetate (9.5 g, 60 mmol) in dry benzene (20 mL) at 0 °C. After the mixture was stirred for 30 min at room temperature, a solution of dimethyl (methoxymethylene)malonate (**6**; 10.4 g, 60 mmol) in dry benzene (20 mL) was dropwise added at room temperature, and the mixture was stirred for 3 h. The same workup followed by treatment with *p*-TsOH as above gave the pyrone **9**: 4.53 g (28.2%); colorless needles; mp 116–117 °C; UV (MeOH) 210, 247, 325 nm; IR ($CHCl_3$) 1775, 1760, 1715, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.53 (9 H, s, *t*-Bu), 2.70 (3 H, s, 6-Me), 3.90 (3 H, s, OMe), 8.57 (1 H, s, 4-H); mass spectrum, m/e 268 (M^+). Anal. Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 5.97. Found: C, 57.94; H, 5.96.

11b,2-(Epoxyetheno)-13-(ethoxycarbonyl)-1,2,3,6,7,11b-hexahydro-3-(methoxycarbonyl)-12-methylbenzo[*a*]quinolizin-4-one (14). A solution of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (**10**; 85.5 mg, 0.417 mmol) and the pyrone **8** (100 mg, 0.417 mmol) in CH_3CN (10 mL) was stirred for 14 h at room temperature. After evaporation of the solvent, the residue was chromatographed on silica gel. Elution with chloroform afforded **14**: 153 mg (82.5%); powder; mp 126–127 °C; UV (MeOH) 230, 240, 280 nm; IR ($CHCl_3$) 1728, 1700, 1645 cm^{-1}; NMR ($CDCl_3$) δ 1.32 (3 H, *t*, J = 7 Hz, CH_2CH_3), 2.28 (3 H, s, 12-Me), 3.73, 3.87 and 3.89 (each 3 H, each s, 3OMe), 4.23 (2 H, q, J = 7 Hz, CH_2CH_3), 4.68–4.92 (1 H, m, 6-H), 6.66 and 6.80 (each 1 H, each s, 9- and 11-H); mass spectrum, m/e 445 (M^+). Anal. Calcd for $C_{23}H_{27}NO_8$: C, 62.01; H, 6.11; N, 3.14. Found: C, 61.82; H, 5.99; N, 2.86.

1-Benzyl-11b,2-(epoxyetheno)-13-(ethoxycarbonyl)-1,2,3,4,6,7,11b-heptahydro-3-(methoxycarbonyl)-12-methylbenzo[*a*]quinolizin-4-one (15). 3,4-Dihydro-1-phenethyl-6,7-dimethoxyisoquinoline (**11**; 130 mg, 0.417 mmol) was treated for 14 h with the pyrone **8** (100 mg, 0.417 mmol) in CH_3CN (10 mL) as above to give **15**: 230 mg (100%); powder; mp 74–75 °C; IR ($CHCl_3$) 1745, 1705, 1660, 1635 cm^{-1}; NMR ($CDCl_3$) δ 1.20 (3 H, *t*, J = 7 Hz, CH_2CH_3), 2.27 (3 H, s, 12-Me), 3.63, 3.73, 3.87 (each 3 H, each s, 3OMe), 4.70–5.13 (1 H, m, 6-H), 6.58 (2 H, s, 9- and 11-H), 6.73–7.27 (5 H, m, 5 Ar H); mass spectrum, m/e 535 (M^+). Anal. Calcd for $C_{30}H_{33}NO_8$: C, 67.27; H, 6.21; N, 2.62. Found: C, 67.53; H, 6.14; N, 2.35.

12b,2-(Epoxyetheno)-14-(ethoxycarbonyl)-1,2,3,4,6,7,12b-heptahydro-3-(methoxycarbonyl)-13-methylindolo[2,3-*a*]quinolizin-4-one (17). 3,4-Dihydro-1-methyl-β-carboline (**16**; 154 mg, 0.834 mmol) was reacted for 14 h with the pyrone **8** (200 mg, 0.834 mmol) in CH_3CN (15 mL) as above to afford **18**: 193 mg (54.6%); colorless needles; mp 139–140 °C; IR ($CHCl_3$) 1730, 1700, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (3 H, *t*, J = 7 Hz, CH_2CH_3), 2.25 (3 H, s, 13-Me), 3.67 (3 H, s, OMe), 4.33 (2 H, J = 7 Hz, CH_2CH_3), 5.00 (1 H, m, 6-H), 6.78–7.66 (4 H, m, 4 Ar H), 8.53 (1 H, br s, NH); mass spectrum, m/e 424 (M^+). Anal. Calcd for $C_{23}H_{24}H_2O_6 \cdot 0.25H_2O$: C, 64.40; H, 5.76; N, 6.53. Found: C, 64.19; H, 5.70; N, 6.41.

14-(*tert*-Butoxycarbonyl)-12b,2-(epoxyetheno)-1,2,3,4,6,7,12b-heptahydro-3-(methoxycarbonyl)-13-methylindolo[2,3-*a*]quinolizin-4-one (18). A solution of 3,4-dihydro-1-methyl-β-carboline (**16**; 350 mg, 1.87 mmol) and the pyrone *tert*-butyl ester **9** (500 mg, 1.87 mmol) in CH_3CN (20 mL) was stirred for 14 h at room temperature. After evaporation of the solvent, the residue was chromatographed on silica gel. Elution with benzene–Me_2CO (49:1 v/v) afforded **18**: 555 mg (65.3 %); colorless needles; mp 164–166 °C; UV (MeOH) 220, 268 nm; IR

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($CHCl_3$) 1740, 1700, 1655 cm^{-1}; NMR ($CDCl_3$) δ 1.53 (9 H, s, *t*-Bu), 2.23 (3 H, s, 13-Me), 3.70 (3 H, s, OMe), 4.70–5.20 (1 H, m, 6-H), 7.17–7.43 (4 H, m, 4 Ar H), 8.05 (1 H, br s, NH); mass spectrum, *m/e* 452 (M^+). Anal. Calcd for $C_{25}H_{28}N_2O_6$: C, 65.05; H, 6.33; N, 6.07. Found: C, 65.20; H, 6.25; N, 6.02.

2-[1-(Ethoxycarbonyl)-2-oxopropyl]-1,2,3,4,6,7,11b-heptahydro-4-(methoxycarbonyl)-9,10-dimethoxybenzo[*a*]quinolizin-4-one (19). To a solution of the tetracyclic compound **14** (100 mg, 0.225 mmol) in MeOH (20 mL) was added $NaBH_3CN$ (141 mg, 2.25 mmol) and a trace of methyl orange. HCl–MeOH (7:100 w/v) was added at room temperature to the stirring mixture to maintain the red color. After 14 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$, which was extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to afford a residue, which was subjected to chromatography on silica gel. Elution with $CHCl_3$ gave the β-keto ester **19**: 93 mg (92.5%); syrup; IR ($CHCl_3$) 1740, 1720 (sh), 1638 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (3 H, *t*, *J* = 7 Hz, CH_2CH_3), 3.80 (3 H, s, OMe), 3.84 (6 H, s, 2OMe), 4.50–4.93 (2 H, m, 6-H_2), 6.59 (2 H, s, 2 Ar H); mass spectrum, *m/e* 447 (M^+); exact mass calcd for $C_{23}H_{29}NO_8$ 447.1893, found 447.1923.

2-[1-(Ethoxycarbonyl)-2-oxopropyl]-1,2,3,4,6,7,12b-heptahydro-4-(methoxycarbonyl)indolo[2,3-*a*]quinolizin-4-one (20). To a mixture of the pentacyclic compound **17** (100 mg, 0.236 mmol), $NaBH_3CN$ (149 mg, 2.36 mmol), and a trace of methyl orange in MeOH (20 mL) was added HCl–MeOH (7:100 w/v) at room temperature to maintain the red color. After 2 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$. After extraction with $CHCl_3$, the extract was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was subjected to chromatography on silica gel, eluting with $CHCl_3$ to afford **20** (82 mg, 81.6%) as a stereoisomeric mixture: IR ($CHCl_3$) 1735, 1720 (sh), 1635 cm^{-1}; NMR ($CDCl_3$) δ 2.21 (3 H, s, COMe), 3.80 (3 H, s, OMe); mass spectrum, *m/e* 426 (M^+); exact mass for calcd for $C_{23}H_{26}N_2O_6$ 426.1790, found 426.1790.

14-(*tert*-Butoxycarbonyl)-12b,2-(epoxyetheno)-1,2,3,12b-tetrahydro-3-(methoxycarbonyl)-13-methyl-6*H*-indolizino[1,2-*b*]quinoline-4,7-dione (25). A solution of **18** (3.77 g, 8.34 mmol) and Rose Bengal (100 mg) in a mixture of MeOH (100 mL) and CH_2Cl_2 (50 mL) was irradiated with a 500-W halogen lamp through a Pyrex filter for 15 h in a current of O_2 at 20–25 °C. After addition of saturated aqueous $NaHCO_3$ (50 mL), the mixture was stirred for 2 days at room temperature and then concentrated in vacuo. The residual solution was diluted with CH_2Cl_2 and washed with H_2O and brine. The CH_2Cl_2 extract was dried over Na_2SO_4 and evaporated to give a residue, which was chromatographed on silica gel. Elution with $CHCl_3$–MeOH (49:1 v/v) afforded the indolizinoquinolone **25**: 2.34 g (60.2%); colorless powder; mp >300 °C; UV (MeOH) 215, 243, 320, 333 nm; IR ($CHCl_3$) 1740, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.53 (9 H, s, *t*-Bu), 2.21 (3 H, s, 13-Me), 3.73 (3 H, s, OMe), 4.66 and 4.90 (each 1 H, each d, *J* = 15 Hz, 6-H_2), 7.35–7.80 (3 H m, 3 Ar H), 8.33 (1 H, d, *J* = 15 Hz, 8-H); mass spectrum, *m/e* 466 (M^+), exact mass calcd for $C_{25}H_{26}N_2O_7$ 466.1739, found 466.1704.

14-(*tert*-Butoxycarbonyl)-7-chloro-12b,2-(epoxyetheno)-1,2,3,12b-tetrahydro-3-(methoxycarbonyl)-13-methyl-6*H*-indolizino[2,3-*b*]quinolin-4-one (26). To a solution of the quinolone **25** (1 g, 2.15 mmol) in dry DMF (25 mL) was added $SOCl_2$ (1.5 mL) under ice-cooling. The mixture was stirred at 0 °C for 30 min and then poured into saturated aqueous $NaHCO_3$ under cooling with ice. After extraction with benzene, the extract was washed with brine, dried over Na_2SO_4, and evaporated to give a powder, which was recrystallized from benzene–*n*-hexane to afford the chloride **26**: 0.948 g (91.2%); colorless needles; mp 211–212 °C; UV (MeOH) 210, 234, 307, 322 nm; IR ($CHCl_3$) 1725, 1695, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.58 (9 H, s, *t*-Bu), 2.21 (3 H, s, 13-Me), 3.75 (3 H, s, OMe), 4.73 and 5.30 (each 1 H, each d, *J* = 16 Hz, 6-H_2), 7.60–8.40 (4 H, m, 4 Ar H); mass spectrum, *m/e* 484 (M^+). Anal. Calcd for $C_{25}H_{25}N_2O_6Cl$: C, 61.92; H, 5.20; N, 5.78. Found: C, 61.90; H, 5.39; N, 5.47.

14-(*tert*-Butoxycarbonyl)-12b,2-(epoxyetheno)-1,2,3,12b-tetrahydro-3-(methoxycarbonyl)-13-methyl-6*H*-indolizino[1,2-*b*]quinolin-4-one (27). A mixture of the chloride **26** (647 mg, 1.34 mmol) and 10% Pd/C (100 mg) in a mixture of MeOH (50 mL) and AcOEt (20 mL) was stirred for 48 h under a H_2 atmosphere. The catalyst was removed by filtration, and the filtrate was evaporated to give a residue, which was chromatographed on silica gel. Elution with benzene–Me_2CO (49:1 v/v) afforded a powder, which was recrystallized from MeOH to give the indolizinoquinoline **27**: 483 mg (80.2%); colorless needles; mp 216–217 °C dec; UV (MeOH) 212, 237, 307, 322 nm; IR ($CHCl_3$) 1735, 1700, 1660, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.54 (9 H, s, *t*-Bu), 2.21 (3 H, s, 13-Me), 3.74 (3 H, s, OMe), 4.75 and 5.26 (each 1 H, each d, *J* = 16 Hz, 6-H_2), 7.55–8.40 (5 H, m, 5 Ar H); mass spectrum, *m/e* 450 (M^+). Anal. Calcd for $C_{25}H_{26}N_2O_6$: C, 66.65; H, 5.82; N, 6.22. Found: C, 66.47; H, 5.75, N, 6.17.

14-(*tert*-Butoxycarbonyl)-12b,2-(epoxyetheno)-1,2,3,12b-tetrahydro-3-(hydroxymethylene)-13-methyl-6*H*-indolizino[1,2-*b*]quinolin-4-one (28). To a solution of the above diester **27** (1 g, 2.22 mmol) in dry DME (40 mL) was dropwise added a 25 w/vol % solution of DIBAL in toluene (6.4 mL) at -60 to -65 °C, and the mixture was further stirred for 1 h at the same temperature under a N_2 atmosphere. The reaction mixture was then poured into 10% HCl and extracted with benzene. The extract was washed with H_2O and brine, dried over Na_2SO_4, and evaporated. The residue was purified by chromatography on silica gel. Elution with benzene–Me_2CO (99:1 v/v) afforded a powder, which was recrystallized from MeOH to give **28**: 776 mg (83.1%); colorless needles; mp 202 °C dec; IR ($CHCl_3$) 1695, 1645, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.53 (9 H, s, *t*-Bu), 2.17 (3 H, s, 13-Me), 4.73 and 5.30 (each 1 H, each d, *J* = 16 Hz, 6-H_2), 7.50–8.30 (5 H, m, 5 Ar H); mass spectrum, *m/e* 420 (M^+). Anal. Calcd for $C_{24}H_{24}N_2O_5 \cdot 0.5H_2O$: C, 67.12; H, 5.87; N, 6.52. Found: C, 67.43; H, 5.80; N, 6.35.

14-(*tert*-Butoxycarbonyl)-12b,2-(epoxyetheno)-1,2,3,12b-tetrahydro-3-(hydroxymethyl)-13-methyl-6*H*-indolizino[1,2-*b*]quinolin-4-one (29). To a suspension of the above hydroxymethylene **28** (300 mg, 0.71 mmol) in MeOH (50 mL) was added $NaBH_4$ (30 mg) in portions under ice cooling. The mixture was stirred for additional 15 min at room temperature before evaporation. The residue was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ layer was dried over Na_2SO_4 and evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with benzene–Me_2CO (96:4 to 95:5 v/v) affforded a powder which was recrystallized from MeOH to give one epimer of the alcohol **29a**: 150 mg (49.8%); colorless needles; mp 209–211 °C; IR ($CHCl_3$) 3450, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (9 H, s, *t*-Bu), 2.18 (3 H, s, 13-Me), 4.68 and 5.13 (each 1 H, each d, *J* = 16 Hz, 6-H_2), 7.50–8.30 (5 H, m, 5 Ar H); mass spectrum, *m/e* 422 (M^+). Anal. Calcd for $C_{24}H_{26}N_2O_5 \cdot 0.5H_2O$: C, 66.80; H, 6.31; N, 6.49. Found: C, 66.53; H, 6.12; N, 6.39.

Further elution with benzene–Me_2CO (94:6 to 93:7 v/v) afforded a powder. Recrystallization from MeOH gave the epimer **29b**: 146 mg (48.4%); colorless needles; mp 193–194 °C; IR ($CHCl_3$) 3400, 1695, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.53 (9 H, s, *t*-Bu), 2.20 (3 H, s, 13-Me), 3.92 (2 H, d, *J* = 6 Hz, CH_2OH), 4.68 and 5.25 (each 1 H, each d, *J* = 16 Hz, 6-H_2), 7.50–8.30 (5 H, m, 5 Ar H); mass spectrum, *m/e* 422 (M^+). Anal. Calcd for $C_{24}H_{26}N_2O_5 \cdot 0.5H_2O$: C, 66.80; H, 6.31; N, 6.49. Found: C, 67.00; H, 6.20; N, 6.56.

12b,2-(Epoxyetheno)-1,2,3,12b-tetrahydro-3-(hydroxymethyl)-14-(methoxycarbonyl)-13-methyl-6*H*-indolizino[1,2-*b*]quinolin-4-one (30). The above polar alcohol **29b** (320 mg, 0.758 mmol) was dissolved in CF_3CO_2H (3 mL), and the mixture was stirred for 15 min at room temperature. After evaporation of the solvent at 30 °C, the residue was dissolved in a mixture of $CHCl_3$ (10 mL) and MeOH (20 mL). Excess ethereal CH_2N_2 was added, and the resulting mixture was stirred for 12 min, before evaporation of the solvents and the excess reagent. The residue was chromatographed on silica gel, eluting with $CHCl_3$–MeOH (49:1 v/v) to afford a powder. Recrystallization from MeOH gave the methyl ester **30b**: 285 mg (99.4%); colorless pillars; mp 194.5–196 °C; IR ($CDCl_3$) 3400, 1700, 1630 cm^{-1}; NMR ($CDCl_3$) δ 2.22 (3 H, s, 13-Me), 3.77 (3 H, s, OMe), 3.92 (2 H, d, *J* = 6 Hz, CH_2OH), 4.68 and 5.24 (each 1 H, each d, *J* = 16 Hz, 6-H_2), 7.50–8.36 (5 H, m, 5 Ar H); mass spectrum, *m/e* 380 (M^+). Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.30; H, 5.30; N, 7.37. Found: C, 65.87; H, 5.34; N, 7.23.

By the same procedure, the less polar alcohol **29a** (160 mg) was converted to the corresponding methyl ester (**30**): 118 mg (81.9%); mp 214–215 °C; IR ($CHCl_3$) 3400, 1700 (sh), 1640 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (3 H, s, 13-Me), 3.63 (2 H, m, CH_2OH), 4.68 and

5.15 (each 1 H, d, J = 16 Hz, 6-H_2), 7.50–8.30 (5 H, m, 5 Ar H); mass spectrum, m/e 380 (M^+). Anal. Calcd for $C_{21}H_{20}N_2O_5 \cdot 0.5H_2O$: C, 64.77; H, 5.44; N, 7.19. Found: C, 64.74; H, 5.30; N, 7.08.

3-(Acetoxymethyl)-12b,2-(epoxyetheno)-1,2,3,12b-tetrahydro-14-(methoxycarbonyl)-13-methyl-6*H*-indolizino[1,2-*b*]quinolin-4-one (31). A solution of the above methyl ester (**30b**, 100 mg, 0.265 mmol) and Ac_2O (0.5 mL) in pyridine (0.5 mL) was stirred for 2 h at 50 °C. The reaction mixture was poured into aqueous $NaHCO_3$ and then extracted with benzene. After the extract was dried over Na_2SO_4, evaporation of the solvent gave a crystalline mass, which was recrystallized from MeOH to afford the acetate **31b**: 104 mg (93.6%); colorless needles; mp 200–202.5 °C; IR ($CHCl_3$) 1725, 1700, 1655, 1620 cm^{-1}; NMR ($CDCl_3$) δ 2.03 (3 H, s, Ac), 2.20 (3 H, s, 13-Me), 3.70 (3 H, s, OMe), 4.51 (2 H, d, J = 6 Hz, CH_2OAc), 4.73 and 5.20 (each 1 H, each d, J = 16 Hz, 6-H_2), 7.56–8.33 (5 H, m, 5 Ar H); mass spectrum, m/e 422 (M^+). Anal. Calcd for $C_{23}H_{22}N_2O_6 \cdot 0.75H_2O$: C, 63.37; H, 5.43; N, 6.43. Found: C, 63.72; H, 5.23; N, 6.41.

The epimer **30a** (100 mg) was converted, by the same procedure, to the corresponding acetate **31b**: 102 mg (93.0%); mp 194–195 °C; IR ($CHCl_3$) 1725, 1700, 1660, 1620 cm^{-1}; NMR ($CDCl_3$) δ 2.05 (3 H, s, Ac), 2.18 (3 H, s, 13-Me), 3.70 (3 H, s, OMe), 4.73 and 5.20 (each 1 H, each d, J = 16 Hz, 6-H_2), 7.45–8.30 (5 H, m, 5 Ar H); mass spectrum, m/e 422 (M^+). Anal. Calcd for $C_{23}H_{22}N_2O_6 \cdot 0.75H_2O$: C, 63.37; H, 5.43; N, 6.43. Found: C, 63.12; H, 5.13; N, 6.32.

3-(Acetoxymethyl)-1,2,3,12b-tetrahydro-2-[1-(methoxycarbonyl)-2,2-(ethylenedithio)propyl]-6*H*-indolizino[1,2-*b*]quinolin-4-one (33). To a solution of the acetate **31b** (100 mg, 0.238 mmol) in CF_3CO_2H (3 mL) was added ethanedithiol (0.5 mL), and the mixture was refluxed for 2 h. After evaporation of the reagents, the residue was chromatographed on silica gel. Elution with benzene–Me_2CO (26:1 v/v) afforded the thioketal **33**: 70 mg (57.7%); syrup; IR ($CHCl_3$) 1725, 1650 cm^{-1}; NMR ($CDCl_3$) δ 4.90 (2 H, s, 6-H_2), 6.27 (1 H, d, J = 4.5 Hz, 1-H); mass spectrum, m/e 498 (M^+).

3-(Acetoxymethyl)-2-[1-(methoxycarbonyl)propyl]-6*H*-indolizino[1,2-*b*]quinolin-4-one (34). A mixture of the thioketal **33** (65 mg, 0.127 mmol) and W-2 Raney Ni (1.3 g) in EtOH (10 mL) was refluxed for 2 h. After filtration, the filtrate was evaporated, and the residue was chromatographed on silica gel. Elution with benzene–Me_2CO (19:1 v/v) afforded a syrup (30 mg), which was dissolved in benzene (5 mL). After addition of DDQ (46 mg, 0.2 mmol), the mixture was refluxed for 10 min and then poured into aqueous $NaHCO_3$. Extraction with benzene, followed by washing with H_2O, drying over Na_2SO_4, the evaporation of the solvent, gave a residue, which was chromatographed on silica gel. Elution with $CHCl_3$ afforded a powder, which was recrystallized from $CHCl_3$–*n*-hexane to give 34: 14 mg (31.3% from **33**); mp 176–179.5 °C (lit.[13] mp 171–178 °C); UV and NMR spectra were identical with reported ones.[13]

Acknowledgment. A part of this work was financially supported by Grant-in-Aid for Special Project Research "Biomimetic Chemistry" from the Ministry of Education, Science and Culture, which is greatly acknowledged. We thank K. Kawamura, Y. Kobayashi, E. Kurosawa, K. Mushiake, and K. Koike for microanalyses, for spectral measurements, and for preparation of the manuscript.

Registry No. **1**, 31456-25-4; **8**, 83913-71-7; **9**, 83919-99-7; **10**, 4721-98-6; **11**, 81305-67-1; **14**, 83913-50-2; **15**, 86708-49-8; **16**, 525-41-7; **17**, 83913-48-8; **18**, 83913-49-9; **19**, 86708-50-1; **20**, 86668-35-1; **25**, 83983-61-3; **26**, 83983-62-4; **27**, 83983-63-5; **28**, 83983-64-6; **29** isomer 1, 83983-65-7; **29** isomer 2, 84025-94-5; **30** isomer 1, 86708-51-2; **30** isomer 2, 86708-52-3; **31** isomer 1, 86708-53-4; **31** isomer 2, 86708-54-5; **33**, 83983-70-4; **34**, 86668-36-2; ethyl acetoacetate, 141-97-9; dimethyl (methoxymethylene)-malonate, 22398-14-7; *tert*-butyl acetoacetate, 1694-31-1.

Silica Gel Mediated Photoisomerization of Retinal Isomers and Comparisons with Other Forms of Environmental Perturbation

Mary E. Zawadzki and Arthur B. Ellis*

Department of Chemistry, University of Wisconsin—Madison, Madison, Wisconsin 53706

Received February 8, 1983

The electronic spectra and photoreactivity of slurries of retinal isomers, prepared by adsorbing the isomers onto wet silica gel and suspending the support in cyclohexane, have been investigated. Adsorption of 9-*cis*-, 11-*cis*-, 13-*cis*-, and *all-trans*-retinal is accompanied by an ~3000-cm^{-1} red shift of their lowest energy absorption band maxima relative to their band positions in homogeneous cyclohexane solution. Irradiation of the slurries at 514.5 nm, a wavelength inefficiently absorbed in the absence of silica gel, leads to reasonably efficient photoisomerization of each of these isomers. Prolonged photolysis yields a mixture of the four isomers that is photostationary with respect to relative concentrations and richest in 11-*cis*-retinal, which constitutes ~35% of this mixture. Although small quantities of other isomers are present, the photostationary composition of the heterogeneous photolysate can be predicted with reasonable accuracy from the relative absorptivities and primary photoprocesses of the four principal isomers comprising the photolysate. Comparisons with primary photoprocesses reported for retinal isomers in polar and nonpolar solvents reveal that adsorption onto silica gel can result in novel patterns of photoisomerization. Complementary comparisons are made with the electronic spectra and photoreactivity of adducts formed in hydrocarbon solution from retinal isomers and a lanthanide β-diketonate complex. The excited-state properties of these various retinal-based systems highlight the importance of environment in controlling photoreactivity. Steric and electronic factors that may contribute to the observed features of silica gel mediated photoisomerization are discussed in this context.

The perturbation of electronic structure and excited-state reactivity through changes in environment is well established for molecular species. Although solvent and temperature have traditionally been used to elicit these effects,[1] recent studies have demonstrated that adduct formation and adsorption onto silica gel can also profoundly influence the excited-state properties of a substrate. Examples of systems for which adduct-mediated photochemistry has been reported include the Lewis acid/Lewis base combinations of BF_3/3,4,6,6-tetramethyl-2,4-cyclohexadienone,[2] $EtAlCl_2$/α,β-unsaturated

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