[Chem. Pharm. Bull. 22(4) 757—762 (1974)]

UDC 547.94.057 : 547.831.04 : 581.192

Experiments on the Synthesis of *dl*-Camptothecin. I. Attempted Synthesis of Potential Ring A-B-C Components

Tsutomu Sugasawa, Kazuyuki Sasakura, Tetsuro Hidaka, and Tatsuo Toyoda

Shionogi Research Laboratory, Shionogi & Co., Ltd.[1]

(Received July 19, 1973)

Attempted synthesis of 3-substituted (alkoxycarbonyl, hydroxymethyl or cyano)-2,3-dihydro-2-benzyl (acyl or alkoxycarbonyl)-1H-pyrrolo[3,4-*b*]quinolines (II), (III), and (VI) as potential ring A-B-C components for a total synthesis of *dl*-camptothecin (I) is described.

Many reports on synthetic studies of the plant antitumor agent, camptothecin (I)[2] and its analogs have already been published.[3] It is very interesting that seven research groups[4] have succeeded in total synthesis of I within the last two years and that each group has used a different synthetic approach involving interesting key reactions.

We wish to describe here our experimental results obtained in the course of a total synthesis of I.

It seemed to us that 3-substituted-2,3-dihydro-2-benzyl-1H-pyrrolo[3,4-*b*]quinolines (II) and III should be potential intermediates for the synthesis of I, for the following reasons. The C-3 of II should be suitable for annelation of the D ring, since it bonded to the α-position of the quinoline ring and is substituted by a alkoxycarbonyl group. In III the primary alcohol itself should be an appropriate substituent for the same purpose. Thus, methyl 3-methoxycarbonyl-α-bromo-2-quinolineacetate (IX), which was readily obtained from VIII,[5] was treated with benzylamine in the presence of triethylamine in dimethylformamide to give IV in good yield. Reduction of IV with lithium aluminum hydride in tetrahydrofuran did not give the desired III, but furnished the dihydroquinoline derivative XIV. The infrared (IR) spectrum of the product showed a ν_{max} at 1638 cm^{-1}, and the nuclear magnetic resonance (NMR) spectrum showed a signal for the newly formed C-9 methylene (2H, s, δ 3.64) and 4 aromatic proton signals (m, δ 6.5—7.2) instead of the quinoline proton signals (5H, m, δ 7.5—8.5) seen in the spectrum of IV. These data and the elemental analysis agree with structure XIV. Acetylation of XIV gave further evidence for its structure. Thus treatment of XIV with acetic anhydride in pyridine at room temperature afforded the acetate

1) Location: *Fukushima-ku, Osaka, 553, Japan.*

2) M.E. Wall, M.C. Wani, C.E. Cook, K.H. Palmer, A.T. Mcphail, and G.A. Sim, *J. Am. Chem. Soc.*, **88**, 3888 (1966).

3) All publications in this field: *a*) R. Volkmann, S. Danishefsky, J. Eggler, and D.M. Solomon, *J. Am. Chem. Soc.*, **93**, 5576 (1971); *b*) T. Sugasawa, T. Toyoda, and K. Sasakura, *Tetrahedron Letters*, **1972**, 5109. Thereafter additional references; *c*) T. Kametani, S. Takano, H. Terasawa, and H. Takeda, *Yakugaku Zasshi*, **92**, 868 (1972); *d*) G.R. Pettit, R.J. Quinn, T.H. Smith, P. Brown, C.C. Cheng, D.E. O'Brien, W. Haggerty, and O.L. Salerni, *J. Org. Chem.*, **37**, 2789 (1972); *e*) A.S. Kende, T.J. Bentley, R.W. Draper, J.K. Jenkins, M. Joyeux, and I. Kubo, *Tetrahedron Letters*, **1973**, 1307; *f*) A.I. Meyer, R.L. Nolen, E.W. Collington, R. Strickland, and T.A. Narwid, *J. Org. Chem.*, **38**, 1974 (1973).

4) *a*) G. Stork and A.G. Schultz, *J. Am. Chem. Soc.*, **93**, 4074 (1971); *b*) 3*a*,*b*); *c*) E. Winterfeldt, T. Korth, D. Pike, and M. Boch, *Angew. Chem.*, **84**, 265 (1972); M. Boch, T. Korth, J.M. Nelke, D. Pike, H, Radunz, and E. Winterfeldt, *Chem. Ber.*, **105**, 2126 (1972); *d*) M.C. Wani, H.F. Campbell, G.A. Brine, J.A. Kepler, M.E. Wall, and S.G. Levine, *J. Am. Chem. Soc.*, **94**, 3631 (1972); *e*) C. Tang and H. Rapoport, *ibid.*, **94**, 8615 (1972); *f*) 3*f*).

5) T. Sugasawa, T. Toyoda, K. Sasakura, and T. Hidaka, *Chem. Pharm. Bull.* (Tokyo), **19**, 1971 (1971).

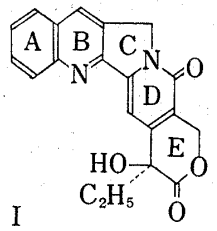
XV and V in a ratio of about 3.5: 1. The NMR spectrum of XV also indicated the C-9 methylene signal (s, 2H, δ 3.72). Compound V probably arose owing to susceptibility of XIV or XV to oxidation in the course of the reaction or during working-up. An analytically pure sample of XV could not be obtained even after repeated recrystallization and thin layer chromatography. Comparison of the acetyl signals in the NMR spectra of XV and V shows that the purest sample of XV so far obtained (mp 176—179°) contains *ca.* 11% of V. Results similar to that above have already been reported by two other group[6a,b] in connection with their attempts at synthesis of I.

The Borch method[7] (Meerwein reagent followed by sodium borohydride) did not give the desired product.

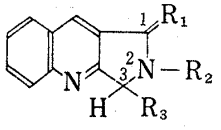
It therefore seemed necessary to initially convert the ester group of the C-3 alkoxycarbonylquinoline derivative to a carbinol group, if a compound of type II or III (R_2=H, acyl or benzyl) was to be obtained. In this connection, C.J. Ohnmacht, *et al.*[8] have recently shown that hydrogenation occurs on the quinoline ring rather than on the ester group, when a 3-alkoxycarbonylquinoline derivative is treated with sodium borohydride; and our obtaining XVII[9] (50% yield) on reduction of X is in accordance with their finding. However, we found that similar treatment of XI at room temperature gave XVIII in good yield (69%). The IR spectrum of XVII showed a ν_{max} at 3280 and 1640 cm^{-1} and its NMR spectrum contained a methylene signal coalesent with the methylester signal (5H, s, δ 3.72). Compound XVIII showed no methylester signal in either its IR or NMR spectra, and its NMR spectrum showed benzyl- (2H) and quinoline- (5H) protons at δ 4.84 and δ 7.35—8.1 respectively. These data confirm the structures of XVII and XVIII. The reduction of XII[5] with sodium borohydride was then tried to see if this would give a suitable precursor to II or III, but the hydrogenation occurred in an unfavourable direction to afford XIX (53%). Similar treatment of XIII[5] also gave the undesired XVI as the only isolable product. The physical data (see Experimental) for XIX and XVI satisfy their assigned structures. On the other hand, VIII was completely inert to reduction by sodium borohydride. It thus appeared that there is no consistency in the couse of the reduction of 3-alkoxycarbonylquinoline derivatives with sodium borohydride, so we were forced to abandon an approach involving conversion of a C-3 alkoxycarbonyl or acidamide substituted quinoline to a compound of the II or III type.

Next, we attempted to synthesize compound VI, a compound already having an unsubstituted C-1 position, by using the reaction developed by M. Hamana and his co-worker[10] in which the required carbon chain was successfully introduced at the α-position on the quinoline ring. Thus 3-acetylaminomethylquinoline-N-oxide (XXIII), prepared from XX and *m*-chloroperbenzoic acid, was treated with ethyl cyanoacetate and acetic anhydride to give XXIV (82%). That XXIV does not exist in the quinoline form, but in the tautomeric 1,2-dihydroquinolylidene form was fully substantiated by its spectral data, as already reported in references 11 and 12; namely the strong nitrile-(2195 cm^{-1}) and hydrogenbonded conjugate

6) *a*) M. Shamma and L. Novák, *Collection Czech. Chem. Commun.*, **35**, 3280 (1970); *b*) T. Tanaka, K. Mashimo, and M. Wagatsuma, *Tetrahedron Letters*, **1971**, 2803.
7) R.F. Borch, *Tetrahedron Letters*, **1968**, 61.
8) C.J. Ohnmacht, Jr., F. Davis, and R.E. Lutz, *J. Med. Chem.*, **14**, 17 (1971).
9) According to C.E. Kaslow and Wm.R. Clark (*J. Org. Chem.*, **18**, 55 (1953)) a white crystalline by-product (mp 137°) was obtained in considerable yield in addition to 3-quinolinemethanol, when 3-carbethoxyquinoline was reduced with lithium aluminum hydride at −50——20° in ether. They stated nothing about the structure of the by-product, but in view of their observations (the compound gave no urethane derivative) and our experimental result it is probably compound XVII. We found that reduction of X with lithium aluminum hydride in tetrahydrofuran gave 3-quinolinemethanol as main product (~72%) without any appreciable contamination by XVII (see Experimental).
10) M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.* (Tokyo), **11**, 415 (1963).
11) A.L. Borror and A.F. Haeberer, *J. Org. Chem.*, **30**, 243 (1965).
12) J.O. Baty, G. Johnes, and C. Moose, *J. Org. Chem.*, **34**, 3295 (1969).



I



II : $R_1=H_2$, $R_2=CH_2C_6H_5$, $R_3=COOCH_3$

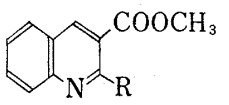
III : $R_1=H_2$, $R_2=CH_2C_6H_5$, $R_3=CH_2OH$

IV: $R_1=O$, $R_2=CH_2C_6H_5$, $R_3=COOCH_3$

V : $R_1=O$, $R_2=CH_2C_6H_5$, $R_3=CH_2OAc$

VI: $R_1=H_2$, $R_2=COCH_3$, $R_3=CN$

VII: $R_1=H_2$, $R_2=COOC_2H_5$, $R_3=H$



VIII: $R=CH_2COOCH_3$

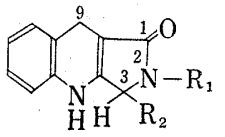
IX: $R=HCCOOCH_3$ (Br)

X : $R=H$

XI: $R=CH_3$

XII: $R=C(=NOH)-COOCH_3$

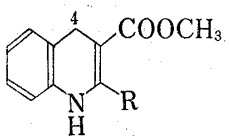
XIII: $R=HC(NHAc)-COOCH_3$



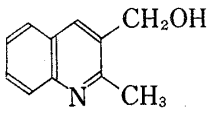
XIV: $R_1=CH_2C_6H_5$, $R_2=CH_2OH$

XV : $R_1=CH_2C_6H_5$, $R_2=CH_2OAc$

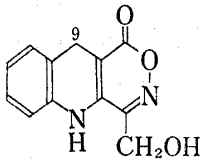
XVI: $R_1=Ac$, $R_2=COOCH_3$



XVII : R=H



XVIII



XIX

Chart 1

ester- absorption (1670 cm^{-1}) in the IR spectrum, the hydrogenbonded N-H signal (δ 14.7) in the NMR spectrum, and the characteristic ultraviolet (UV) absorption curve ascribable to the 1,2-dihydroquinolylidene chromophore (286 mμ (23900), 398 mμ (18500)). While hydrolysis of XXIV with potassium hydroxide or carbonate gave only unidentified products, hydrogenolysis of benzyl analog XXV with palladium-charcoal smoothly afforded XXI with simultaneous decarboxylation. Inspection of the spectral data of XXI (ν_{max} 2243 cm^{-1} (CN, weak), δ 4.46 (2H, s, CH_2) and λ_{max} 234 mμ (46000), 276 mμ (3500), 310 mμ (3300) and 318 mμ (3500)) shows that XXI exists in the quinoline form.[13] Bromination of XXI with bromine in acetic acid gave the monobromo compound XXII as pale brown needles, which were treated with sodium methoxide in methanol at room temperature in the expectation of obtaining the desired cyclization product VI. A solid which contained no bromine (negative Beilstein test) precipitate during the reaction, however, this was only slightly soluble in ordinary organic solvents and could not be purified. Attempted methylation of this crude material with sodium hydride and methyl iodide in dimethylformamide, a procedure which is considered to serve as model reaction for annelation of the carbon chain to form the D-E ring of *dl*-Camptothecin (I) and to simultaneously provide structure proof of the desired cyclization product, gave only unidentified products, and the mother liquor of the attempted cyclization reaction contained only tar.

An apparently simple synthesis of VI ($R_2=COOC_2H_5$ instead of $COCH_3$) would seem to be possible by condensation of 1-carbethoxy-2-cyano-3-pyrrolidone[14] (XXVI) with *o*-amino-

13) R. Mondelli and L. Merlini, *Tetrahedron*, **22**, 3253 (1966).
14) J. Blake, C.D. Willson, and H. Rapoport, *J. Am. Chem. Soc.*, **86**, 5297 (1964).

benzaldehyde. Under basic conditions, the conditions usually used in the Friedlander-synthesis, the desired product was not obtained, probably because of the lability and/or self-condensation of XXVI. It may be that the above condensation would be successful under acidic conditions, as applied recently by L.H. Zalkow, *et al.*[15] in their successful regioselective synthesis of VII from XXVII for the purpose of a total synthesis of I. However, we have not attempted this work, since we have completed a total synthesis of I by another route (see Part III).

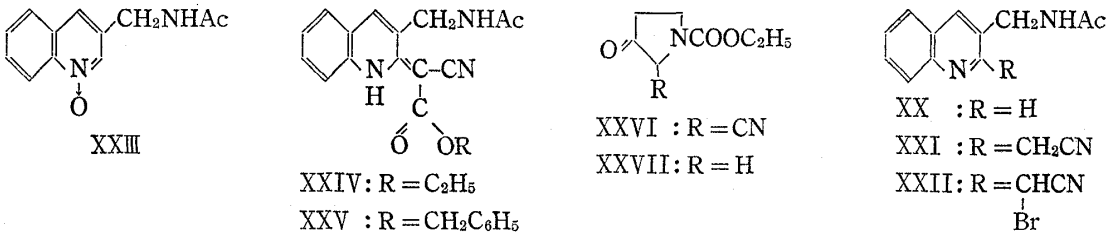


Chart 2

In view of the difficulties mentioned here, we were forced to abandon the attempt to synthesize a compound of the II, III or VI type as a potential intermediate for a total synthesis of I.

Experimental

General Methods——All melting points were determined on Yanagimoto Micromelting Apparatus and uncorrected. IR spectra were recorded by using a Koken DS-201B Spectrophotometer and UV spectra with Hitachi EPS-2 spectrometer. NMR spectra were taken on a Varian A-60 spectrometer, TMS serving as internal standard. The mass spectra were taken on a Hitachi RMU-6 mass spectrometer. Unless otherwise stated, the extracts were dried on anhydrous $MgSO_4$ or Na_2SO_4.

Bromination of VIII to IX——To a stirred solution of VIII (12 g, 46.3 mmoles) in AcOH (40 ml), Br_2 (2.51 ml, 48.6 mmoles) in AcOH (20 ml) was added portionsweise at room temperature and the solution stirred for a further 20 min. After concentration of the solution at reduced pressure, the residue was poured into ice-K_2CO_3 mixture and extracted with CH_2Cl_2–MeOH (1: 1). The organic layer was washed with H_2O, dried and evaporated to give brown syrup (16.7 g). Recrystallization of the residue from CH_2Cl_2–MeOH gave IX (14.8 g, 94%, mp 100—101°). *Anal.* Calcd. for $C_{14}H_{12}O_4NBr$: C, 49.72; H, 3.58; N, 4.14; Br, 23.63. Found: C, 49.89; H, 3.38; N, 4.09; Br, 23.23. NMR ($CDCl_3$) δ: 3.83 (3H, s), 3.99 (3H, s), 6.75 (1H, s, –CHBr–).

Cyclization of IX to IV with Benzylamine——To a stirred solution of IX (14.8 g, 43.7 mmoles) and $(Et)_3N$ (4.43 g, 43.7 mmoles) in DMF (175 ml), benzylamine (4.68 g, 43.7 mmoles) was added at room temperature and the solution was left for 100 hr. The crystals which separated were filtered off, washed successively with DMF and ether to give IV (11.6 g, mp 191—194°). Further IV (1.65 g, mp 187—191°) was obtained from the mother liquor, total yield 91%. Recrystallization from CH_2Cl_2–acetone gave an analytically pure sample (mp 190—193°). *Anal.* Calcd. for $C_{20}H_{16}O_3N_2$: C, 72.28; H, 4.58; N, 8.43. Found: C, 71.82; H, 4.83; N, 8.27. IR ν_{max}^{Nujol} cm^{-1}: 1745 and 1688. NMR ($CDCl_3$) δ: 3.71 (3H, s), 4.37 and 5.44 (2H, AB quartet, J_{AB}=15 Hz), 5.23 (1H, s, C-3 CH), 7.32 (5H, s), *ca.* 7.5—8.5 (5H).

$LiAlH_4$-Reduction of IV to XIV——To a stirred suspension of IV (187 mg) in THF (10 ml), $LiAlH_4$ (190 mg) was added portionsweise under stirring at room temperature. After being stirred for 1 hr the mixture was quenched with THF–H_2O (1: 1). The resulting inorganic salt was filtered off and washed repeatedly with warm $CHCl_3$ containing MeOH (*ca.* 3: 1). The combined filtrate was washed with H_2O, dried, and evaporated. The residue (126 mg) was recrystallized from CH_2Cl_2–acetone to give pure XIV (87 mg, 50%, mp 219—226°). *Anal.* Calcd. for $C_{19}H_{18}O_2N_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.12; H, 5.65; N, 9.26. IR ν_{max}^{Nujol} cm^{-1}: 3300, 3190, 1665 (sh), 1638, 1610 (sh). NMR (d_6-DMSO) δ: 3.64 (2H, s, C-9 CH_2), *ca.* 3.6—3.9 (3H), 4.19 and 4.95 (2H, AB quartet, J=16 Hz), 4.91 (1H, t, C-3 CH).

Acetylation of XIV to XV and V——A solution of XIV (0.26 g, 0.9 mmoles) and Ac_2O (0.17 ml, 1.8 mmoles) in pyridine (3 ml) was allowed to stand at room temperature for 20 hr. The solution was poured into ice-K_2CO_3 mixture and extracted with CH_2Cl_2–ether (1: 1). The organic layer was washed with H_2O, dried, and evaporated. The residue (297 mg) was recrystallized from CH_2Cl_2–MeOH to give a crystalline

15) L.H. Zalkow, J.B. Nabors, K. French, and S.C. Bisarya, *J. Chem. Soc.* (*C*), **1971**, 3551.

mixture of XV and V. The mixture was separated by TLC (Al_2O_3-GF, $CHCl_3$–EtOAc (2:1)) to give XV (158 mg) and V (46 mg), of which the former was isolated as the more polar fraction. A sample of XV was recrystallized from CH_2Cl_2–MeOH (mp 176—179°). NMR ($CDCl_3$) δ: 2.00 (3H, s), 3.72 (2H, s, C-9 CH_2), *ca.* 3.8—4.3 (3H), 3.72 and 5.02 (2H, AB quartet, J_{AB}=16 Hz), *ca.* 6.8—7.1 (4H), 7.22 (5H, s). Recrystallization from CH_2Cl_2–MeOH gave an analytically pure sample of V (mp 168 (sinter) 174—176°). *Anal.* Calcd. for $C_{21}H_{18}O_3N_2$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.54; H, 5.19; N, 7.91. NMR ($CDCl_3$) δ: 1.83 (3H, s), *ca.* 4.35—5.1 (3H), 4.45 and 5.45 (2H, AB quartet, J_{AB}=16 Hz), 7.31 (5H, s), *ca.* 7.5—8.4 (5H).

$NaBH_4$-Reduction——a) X to XVII: To a solution of X (100 mg) in THF (5 ml) was added a solution of $NaBH_4$ (50 mg) in H_2O (1 ml) under stirring at room temperature. A yellow emulsion was immediately formed. After being stirred for 1 hr the mixture was extracted with CH_2Cl_2, and the CH_2Cl_2 layer was washed with H_2O, dried, and concentrated. The resulting crystals (94 mg) were recrystallized from MeOH–ether to give pure XVII (42 mg, 50% yellow crystal, mp 136—139°). *Anal.* Calcd. for $C_{11}H_{11}O_2N$: C, 69.82; H, 5.86; N, 7.40. Found: C, 70.12; H, 5.74; N, 7.62. IR ν_{max}^{Nujol} cm^{-1}: 3280, 1660 (sh), 1640. NMR ($CDCl_3$) δ: 3.72 (5H, OCH_3 and C-4 CH_2), *ca.* 7.35—6.0 (6H).

b) XI to XVIII: To a solution of XI (865 mg) in THF (45 ml) was added a solution of $NaBH_4$ (430 mg) in H_2O (9 ml), and the mixture was stirred for 5 hr at room temperature. The solution was extracted with ether, the ether layer was washed with H_2O, dried, and concentrated. The residue (800 mg) was recrystallized from CH_2Cl_2–ether to give pure XVIII (510 mg, 69%, mp 158—159°). *Anal.* Calcd. for $C_{11}H_{11}ON$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.14; H, 6.19; N, 8.28. NMR ($CDCl_3$) δ: 2.68 (3H, s), 4.84 (2H, s, $-CH_2O-$), *ca.* 7.35—8.1 (5H).

c) XII to XIX: To a suspension of XII (1 g) in THF (40 ml), $NaBH_4$ (250 mg) was added under stirring at room temperature and the mixture was refluxed for 1 hr. After being cooled, the reaction mixture was extracted with $CHCl_3$–MeOH (3:1) and the organic layer was washed with H_2O, dried, and evaporated. The residue was recrystallized from $CHCl_3$–MeOH to give XIX (424 mg, 53%, mp 233—238°). *Anal.* Calcd. for $C_{12}H_{10}O_3N_2$: C, 62.60; H, 4.38; O, 20.85; N, 12.17. Found: C, 62.34; H, 4.44; O, 21.20; N, 11.77. IR ν_{max}^{Nujol} cm^{-1}: 3360, 3303, 1670, 1630, 1525, 1500. NMR (d_6-DMSO) δ: 3.78 (2H, s, C-9 CH_2), 4.53 (2H, s, $-CH_2O-$), *ca.* 6.9—7.2 (4H). Mass Spectrum *m/e*: 230 (M^+).

d) XIII to XVI: To a solution of XIII (100 mg) in THF (5 ml) and H_2O (1 ml), $NaBH_4$ (50 mg) was added portionsweise and the mixture was stirred for 30 min at room temperature. After adding H_2O, the mixture was extracted with $CHCl_3$–MeOH (3:1) and the organic layer washed with H_2O, dried, and evaporated. The residue (49 mg) was recrystallized from $CHCl_3$–MeOH to give XVI (37 mg, 40%, mp 285—287° (decomp.)). *Anal.* Calcd. for $C_{15}H_{14}O_4N_2$: C, 62.93; H, 4.93; O, 22.36; N, 9.79. Found: C, 62.83; H, 4.99; O, 21.37; N, 9.54. IR ν_{max}^{Nujol} cm^{-1}: 3223, 3120, 3050, 1770, 1679, 1652, 1540. NMR (d_6-DMSO) δ: 2.40 (3H, s), 3.64 (2H, s, C-9 CH_2), 3.72 (3H, s), 5.28 (1H, s, C-3 CH), *ca.* 7.0—7.1 (4H), *ca.* 9.6 (1H, disappeared by D_2O-addition). Mass Spectrum *m/e*: 286 (M^+).

Attempted Reduction of VIII——VIII (100 mg) was treated with $NaBH_4$ (50 mg) in THF (20 ml) and H_2O (2 ml) under refluxing and stirring for 1 hr. After usual work-up the starting material was quantitatively recovered. (TLC and IR).

Oxidation of XX to XXIII with *m*-Chloroperbenzoic Acid——To a solution of XX (5.0 g, 25 mmoles) in $CHCl_3$ (30 ml), *m*-chloroperbenzoic acid (6.24 g, 82.5%-purity, 30 mmoles) was added under ice-cooling and stirring and the solution was set aside for 20 hr. *m*-Chlorobenzoic acid which separated on standing was filtered off and washed with $CHCl_3$. The combined $CHCl_3$-solution was chromatographed, (220 g Al_2O_3 (Merck standardized)) and the eluate with $CHCl_3$ containing 2% MeOH was collected and concentrated. The residue (4.72 g) was recrystallized from CH_2Cl_2–MeOH to give XXIII (4.5 g, 83%, mp 191—193°). *Anal.* Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.76; H, 5.83; N, 12.98.

Reaction of XXIII with Ac_2O and Ethyl or Benzyl Cyanoacetate to give XXIV or XXV——To a mixture of XXIII (500 mg, 2.31 mmoles) and Ac_2O (0.26 ml, 2.8 mmoles), ethyl cyanoacetate (0.27 ml, 2.8 mmoles) was added at room temperature. An exothermic reaction occurred and a yellowish solid precipitated. After being kept for 20 hr at room temperature the solid was filtered and washed with MeOH and ether to give XXIV (590 mg, 82%, dp>280°). The product gave one spot on TLC (Silica GF, $CHCl_3$–MeOH 5:1). Recrystallization from CH_2Cl_2–MeOH gave yellow swollen crystals, which changed to yellow scales on drying at 60° under reduced pressure: dp>280°, hardly soluble in ordinary organic solvents. *Anal.* Calcd. for $C_{17}H_{17}O_3N_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.47; H, 5.38; N, 13.41. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3435, 2195, 1670, 1637, 1537. NMR ($CDCl_3$) δ: 1.38 (3H, t), 1.97 (3H, s), 4.32 (2H, q), 4.72 (2H, d, $-CH_2-$NH–), *ca.* 7.32—7.8 (4H), 8.22 (1H, s), 14.7 (1H). UV $\lambda_{max}^{95\%EtOH}$ mμ(ε): 286 (23900), 398 (18500).

Use of benzyl cyanoacetate in the above reaction gave XXV in 75% yield (dp>280°, CH_2Cl_2–acetone). *Anal.* Calcd. for $C_{22}H_{19}O_3N_3$: C, 70.76; H, 5.13; N, 11.25. Found: C, 70.47; H, 5.21; N, 11.44. IR ν_{max}^{Nujol} cm^{-1}: 3340, 2200, 1667, 1635, 1535.

Hydrogenolysis of XXV to XXI——XXV (500 mg) in DMF (200 ml) was reduced in the presence of 5% Pd-charcoal (400 mg 50% wet) for 6 hr. The apparently absorbed volume of H_2 was 1.76 times the theoretical amount. The catalyst was filtered off and washed with CH_2Cl_2. The resulting turbid filtrate was passed over a celite-layer and concentrated. The residue was recrystallized from CH_2Cl_2–MeOH to give XXI (281 mg, 92%, mp 179—182°). An analytically pure sample melted at 180—183°. *Anal.* Calcd.

for $C_{14}H_{13}ON_3$: C, 70.27; H, 5.48; N, 17.56. Found: C, 70.42; H, 5.28; N, 17.44. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 2243, 1680. NMR (d_6-DMSO) δ: 1.92 (3H, s), 4.46 (2H, d, $-C\underline{H}_2-NH-$), 4.46 (2H, s, $-CH_2-CN$), *ca.* 7.5—8.3 (6H). UV $\lambda_{max}^{95\%EtOH}$ mμ(ε): 234 (46000), 276 (3500), 310 (3300), 318 (3500).

Bromination of XXI to XXII——To a solution of XXI (2.05 g, 8.56 mmoles) in AcOH (50 ml), Br_2 (0.46 ml, 9.4 mmoles) was added portionsweise under ice-cooling and stirring. Soon after the addition of Br_2 a yellow solid precipitated. The mixture was stirred for 30 min, then AcOH was removed under reduced pressure at below 50°, and the residue was poured into ice-K_2CO_3 mixture. The solid was filtered off and washed with H_2O to give brown crude XXII (2.80 g, dp 156—158°). Recrystallization from CH_2Cl_2–MeOH gave an analytically pure sample (dp 160—164°). *Anal.* Calcd. for $C_{14}H_{12}ON_3Br$: C, 52.84; H, 3.80; N, 13.21; Br, 25.12. Found: C, 53.12; H, 3.68; N, 13.05; Br, 24.83. IR ν_{max}^{Nujol} cm^{-1}: 3277, 1647. NMR (d_6-DMSO) δ: 1.99 (3H, s), 4.54 (2H, d, $C\underline{H}_2-NH$), 6.78 (1H, s, $-CHBr-$), *ca.* 7.5—8.2 (5H).

$LiAlH_4$-Reduction of X to 3-Quinoline-Methanol——To a solution of X (1 g) in abs. THF (90 ml), $LiAlH_4$ (100 mg) was added potionsweise under stirring and ice-cooling. After being stirred for 30 min, additional three 50 mg-portions of $LiAlH_4$ was added in every 30 min under the same condition. The reaction mixture was quenched with acetone–H_2O (5: 1). The resulting inorganic salt was filtered off and washed with $CHCl_3$. Evaporation of the combined filtrate gave light-yellow oily residue, which was recrystallized from benzene–ligroin (3: 1) to give 3-quinoline methanol (610 mg, mp 82—84°, 72%). A TLC (silica gel, GF, $CHCl_3$-containing *ca.* 20% MeOH) of the mother liquor showed the formation of a small quantity of XVII.

Acknowledgement We thank Dr. A. Terui of this Laboratory for the helpful advice and discussion on the NMR interpretation.