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Experiments on the Synthesis of *dl*-Camptothecin. III.[1] Total Synthesis of *dl*-Camptothecin[2]

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dl-Camptothecin (XXX) and two epimeric N-formyl-1,2,6,7-tetrahydrocamptothecins (XXIIIa, b) have been synthesized from 3-oxo-1H-pyrrolo[3,4-*b*]quinoline IIIa by using following two key reactions. 1) An intramolecular aldol condensation of the imido-ester (VIIIb→IXb). 2) Vilsmeier reaction on a 4-methoxy-2-pyridone ring (XVIb→XVII) followed by nucleophilic attack of a malonate carbanion onto the formyl-pyridone ring (XVII→XVIII).

We have described in Part I[4] of this series that attempts to obtain $3R_1$ (R_1: methoxycarbonyl, hydroxymethyl, or cyano) 2,3-dihydro-$2R_2$ (R_2: benzyl, acetyl or ethoxycarbonyl)-1H-pyrrolo[3,4-*b*]quinoline (II) for application as an intermediate for the total synthesis of camptothecin (I) failed. In the present work we tried to use 3-ethoxy-1H-pyrrolo[3,4-*b*]-quinoline (IV) prepared from IIIa with Meerwein reagent in 52% yield. The starting material IIIa was generated (65%) by reduction of V[5] with Raney Nickel more conveniently than by the method[6] previously reported. Starting from IV, a synthesis of the compound (VIb) was attempted by condensation of a crotonate moiety at the C-3 position of IV followed by con-

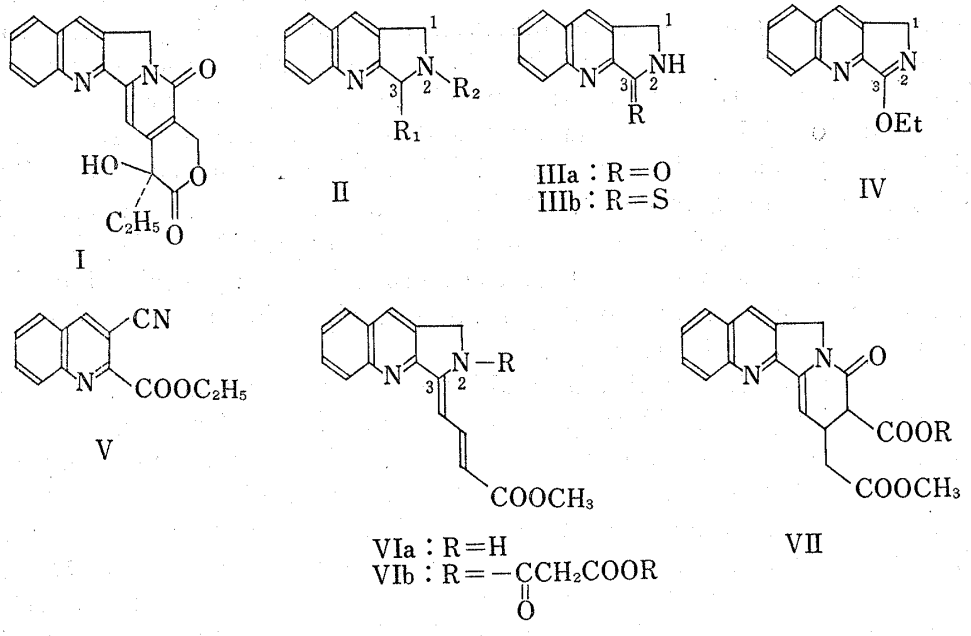


Chart 1

1) Part II: T. Sugasawa, K. Sasakura, and T. Toyoda, *Chem. Pharm. Bull.* (Tokyo), 22, 763 (1974).
2) Presented at the 16th Symposium on the Chemistry of Natural Products, October, 1972, Osaka. Preliminary Communication: T. Sugasawa, T. Toyoda, and K. Sasakura, *Tetrahedron Letters*, 1972, 5109.
3) Location: *Fukushima-ku, Osaka*, 553, *Japan*.
4) T. Sugasawa, K. Sasakura, H. Hidaka, and T. Toyoda, *Chem. Pharm. Bull.* (Tokyo), 22, 757 (1974).
5) R.F. Borch, C.V. Grundzinskas, D.A. Peterson, and L.D. Weber, *J. Org. Chem.*, 37, 1141 (1972).
6) T. Sugasawa, T. Toyoda, K. Sasakura, and T. Hidaka, *Chem. Pharm. Bull.* (Tokyo), 19, 1971 (1971).

nection of malonate at the N-2 position. This attempt was based on the expectation that VIb may cyclize to a compound with ABCD rings bearing carbon chains as an E ring precursor (VII), provided that VIb has a favourable molecular geometry for the intramolecular Michael addition. However, the reaction of IV with the Reformatsky-reagent of methyl ω-bromocrotonate or with Grignard-reagent of propargyl bromide gave only an unidentified mixture. In order to make use of the sulfide contraction method developed by A. Eschenmoser, *et al.*[7] condensation of IIIb[6] with ω-bromocrotonaldehyde-diacetate[8] was tried, but again affording only an intractable mixture.

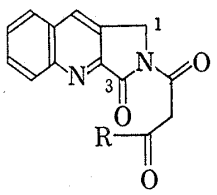
On the other hand, we have reported the synthesis of the D-E ring analog of I from 4-methoxy-2(1H)-pyridone in the preceding paper.[1] Utilization of this method for the total synthesis of I required compounds of the IX-type, which contain the 4-hydroxy- or alkoxyl-2(1H)-pyridone moiety as the D ring. For this purpose we planed the synthesis of IXa from VIIIa prepared from IIIa, by assuming that the imido-carbonyl group at C-3 of VIIIa, being located at the α-position of the quinoline ring, is sufficiently activated to undergo the cyclodehydration by intramolecular aldol condensation. Treatment of IIIa with diketene in the presence of methyl magnesium iodide or thallous ethoxide gave VIIIa (72 and 41%). The nuclear magnetic resonance (NMR) spectrum in deuterochloroform and trifluoroacetic acid showed that VIIIa exists as a keto-enol tautomeric mixture in a ratio of *ca.* 4: 1 (see Experimental). Attempted cyclization of VIIIa to IXa under basic conditions (dianion formation by sodium hydride and *n*-butyl lithium,[9] or sodium hydride in hexamethylphosphoric triamide) gave rise only to cleavage of the imido group, regenerating IIIa accompanied by recovered VIIIa. Use of acid or Lewis acid (*p*-toluenesulfonic acid, boron trifluoride etherate or titanium tetrachloride) as condensation reagent resulted in the recovery of VIIIa. To promote the acidity of the methyl group of VIIIa, IIIa was heated in diethyl acetonedicarboxylate to give VIIIb (95%), its NMR spectrum in deuterochloroform and trifluoroacetic acid also showing a keto-enol tautomeric mixture in a ratio of *ca.* 4 to 1 (see Experimental). However, a similarly discouraging result was observed in the attempted cyclization to IXb from VIIIb. These results showed the necessity of somewhat milder reaction conditions. Use of ammonium acetate in acetic acid led to an undesired compound (Xa) containing a pyrimidone ring in 87% yield from VIIIa. Similar treatment of VIIIb gave a possible precursor (XI or its double bond tautomer and their geometrical isomer) to Xb on the basis of its elemental analysis and IR spectrum (3400 cm^{-1}). Although further attempt to obtain Xb was not made, novel sequence from lactam to 6-substituted 4 keto pyrimidone *via* β-keto imido functionality was incidentally suggested. That the method is also applicable for aliphatic acid amide has been shown by treatment of 2-pyrrolidinone with diketene followed by ammonium acetate in acetic acid to afford XII (67%).

Next, cyclization to IXa or IXb was tried by the enamine method. While heating VIIIa in acetonitrile containing pyrrolidine gave the enamine XIIIa (or its geometrical isomer) in 46% yield as a sole product, similar treatment of VIIIb followed by thin-layer chromatographic purification afforded the enamine XIIIb (or its double bond tautomer and their geometrical isomer, 19%) and a compound of mp 281—282° (decomp.) (44%) as a more polar fraction. The mass spectrum of the latter showed its molecular ion peak at 322 and the IR spectrum contained a band at 1655 cm^{-1} ascribable to pyridone. In the NMR spectrum, instead of disappearance of the methylene-proton signals of VIIIb, the proton signal at C-16[10] was observed at δ 6.97 as a singlet (trifluoroacetic acid). The UV-absorption curve resembled that of I (see Experimental). The corresponding methyl ether (IXc) prepared by treatment with dimethyl sulfate and pottasium carbonate in refluxing acetone had a singlet of the C-16

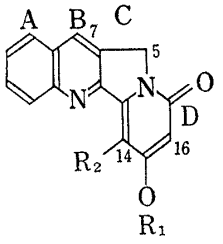
7) M. Roth, P. Dubs, E. Götschi, and A. Eshenmoser, *Helv. Chim. Acta*, **54**, 710 (1971).
8) H. Schmidt and E. Grob, *Helv. Chim. Acta*, **32**, 77 (1949).
9) S.N. Huckin and Larry Weiler, *Tetrahedron Letters*, **1971**, 4835.
10) Numbering assigned by M. Shamma, *Experientia*, **24**, 107 (1968).

proton signal at δ 6.49 (deutero-chloroform and trifluoroacetic acid). These data strongly suggested that the structure IXb could be assigned to the compound of mp 281—282° (decomp.). To test, whether IXb was generated *via* XIIIb, the isolated XIIIb was further heated for several hours in acetonitrile with or without pyrrolidine, but XIIIb was recovered in quantitative yield. Fearing that the double bond of XIIIb might be localized at an unfavourable position for the cyclization, XIIIb was treated in acetonitrile with pyrrolidine and acetic acid in order to bring it in equilibrium with the tautomeric form. XIIIb was again recovered quantitatively. Moreover IXb was obtained by treatment of VIIIb with triethylamine in stead of pyrrolidine albeit in low yield (28%). These data show that IXb was not formed *via* enamine XIIIb, but directly *via* the ammonium enolate of VIIIb.

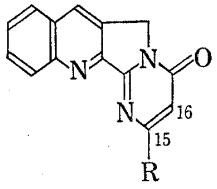
In order to improve the yield of IXb, and considering the above result, VIIIb was similarly treated with piperidine instead of pyrrolidine in view of the sluggishness of formation of corresponding enamines.[11] Indeed, IXb was obtained in high yield (89%) without any coformation of piperidine enamine of VIIIb. Although T.A. Bryson[12] had pointed out the inadequacy of the sequence by cyclodehydration of a compound of type VIII to one of type IX in his attempted total synthesis of camptothecin, we have realized the intended route by using VIIIb and piperidine as the condensation reagent.



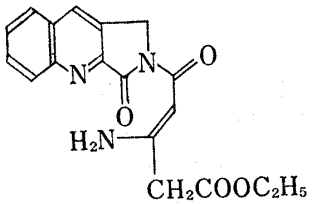
VIIIa : R=CH_3
VIIIb : R=$CH_2COOC_2H_5$



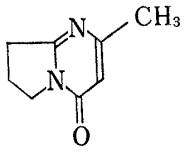
IXa : R_1=R_2=H
IXb : R_1=H, R_2=$COOC_2H_5$
IXc : R_1=CH_3, R_2=$COOC_2H_5$
IXd : R_1=CH_3, R_2=H



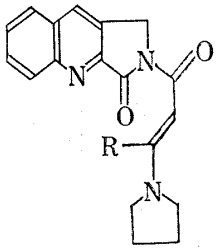
Xa : R=CH_3
Xb : R=$CH_2COOC_2H_5$



XI



XII



XIIIa : R=CH_3
XIIIb : R=$CH_2COOC_2H_5$

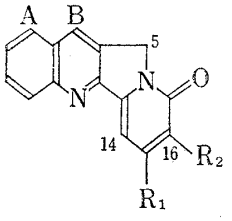
Chart 2

Hydrolysis of IXb with concomitant decarboxylation was effected by heating with conc. hydrochloric acid in a glass tube at 150° giving IXa (94%), which was methylated to the desired compound (IXd) (87%). Its NMR spectrum showed C-16 and C-14 proton signals

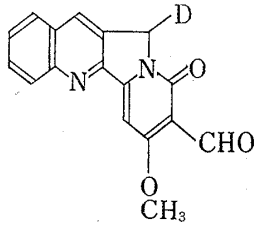
11) J. Szmuszkovicz, "Advances in Organic Chemistry: Methods and Results," Vol. 4, Interscience Publishers, New York, 1963, p. 11.
12) T.A. Bryson, Dissertation Abstr. Intern., 31, No. 8, 4567-B—4568-B (1971).

as doublets with *meta*-coupling constants (2 Hz) at δ 6.63 and 7.71 respectively (deuterochloroform and trifluoroacetic acid). The assignment of each proton is deduced from comparison of the NMR spectra of IXc and IXd. Treatment of IXd with excess of Vilsmeier reagent at room temperature gave XIVa in 82% yield. That the aldehyde group was introduced at the desired C-16 position was inferred from the fact that in the NMR spectrum the C-14-proton signal remained at δ 7.84 (deuterochloroform and trifluoroacetic acid), although the formyl-proton signal was not observed because it coalesced with that of trifluoroacetic acid. An attempt to obtain XV from XIVa, analogously to 1-methyl-3-formyl-4-methoxy-2(1H)-pyridone (Part II) by treatment with di-*tert*-butyl sodiomalonate unfortunately failed, giving only an intractable mixture. The acidity of the C-5 methylene of XIVa were thought to be responsible for the failure, and to ascertain this the acidities of the C-5 methylene groups of IXd and XIVa were compared with that of di-*tert*-butyl malonate by deuterium exchange. Thus XIVa was treated with di-*tert*-butyl sodiomalonate in dioxane and quenched with a mixture of deutero-acetic acid and deuteroxide. The NMR- and mass spectroscopic analysis of the product showed that it consisted of a *ca.* 1:1-mixture of XIVa and XIVb.

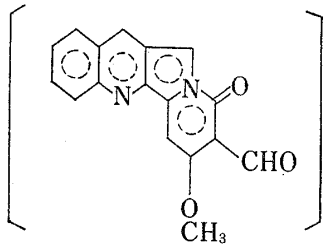
Similar treatment of IXd gave only the starting material without deuterium incorporation. These experiments indicate that XIVa has approximately comparable acidity with di-*tert*-butyl malonate, whereas IXd is far less acidic than the former. This may be rationalized by assuming that the anion of XIVa (XIVc) containing 18-π electron is further stabilized by the aldehyde group at C-16. The resulting deep blue anion (XIVc) probably led to an unfavourable course during the heating of the reaction mixture.



IXd : R_1=OCH_3, R_2=H
XIVa : R_1=OCH_3, R_2=CHO
XV : R_1=$CH(COOtBu)_2$, R_2=CHO



XIVb



XIVc

Chart 3

In order to avoid anion formation at the C-5 position of XIVa, hydrogenation of the B-ring of XIVa was desired, to give a compound of XVII-type having a structure which seemed to posess a better analogy to the model compound (Part II) for annelation of the E-ring.

Thus IXd was reduced with Adams-catalyst in methanol-dioxane containing hydrochloric acid to give amorphous N-tetrahydroquinoline-pyridone XVIa. Direct formylation afforded XVIb in 80% yield. The mass spectrum (M+, 296), ν_{max} at 1660 cm^{-1} (N-CHO) and disappearance of λ_{max} at 350—360 mμ of the starting material, confirmed the structure of XVIb. The configuration of the B-C ring-juncture was not determined. Vilsmeier reaction of XVIb gave XVII (76%), the proton signal of C-14 remaining at 6.51 δ in the NMR-spectrum. Treatment of XVII with di-*tert*-butyl sodiomalonate in dioxane afforded, as expected, XVIII in 64% crude yield. The NMR-spectrum contained signals of the mono-substituted di-*tert*-butyl malonate at 1.50 (18H) and 5.58 δ (1H) instead of that of a methoxy group of XVII. The singlet of the formyl group at C-16 remained at 10.29 δ. These data verified that the structure was that bearing the side chain desired as E-ring precursor.

The problem of introduction of the malonate moiety to the D-ring now being solved, the total synthesis of *dl*-camptothecin XXX could be achieved by a route quite analogous to that

for the model compound (Part II) followed by dehydrogenation to regenerate the quinoline nucleus. Thus sodium borohydride reduction of XVIII gave XIX, which was cyclized to the N-formyl lactone XX by treatment with trifluoroacetic acid in 68% over-all yield. The NMR spectrum showed signals of the methylene protons of C-17 and C-20 at 5.31 and 3.68 δ respectively. Ethylation of XX with sodium hydride and ethyl iodide in dimethylformamide gave diethyl lactone XXII (12%) and the desired monoethyl lactone XXI (45%) (an epimeric mixture) besides the starting material (28%) after thin-layer chromatographic separation. Although the methine-proton signal at C-20 of XXI was not clearly observed in the NMR spectrum, the intensity of the proton signals of each group and the elemental analysis indicated the assigned structure. Treatment of XXI in methanol solution with an oxygen-stream in the presence of cupric acetate and triethylamine smoothly gave an epimeric mixture XXIII, which was separated by thin-layer chromatography into XXIIIa (24%) and XXIIIb (35%). Each isomer gave satisfactory physical data, thus furnishing two epimer of N-formyl-(1,2,6,7)-tetrahydro-camptothecin, though their relative configurations were not determined.

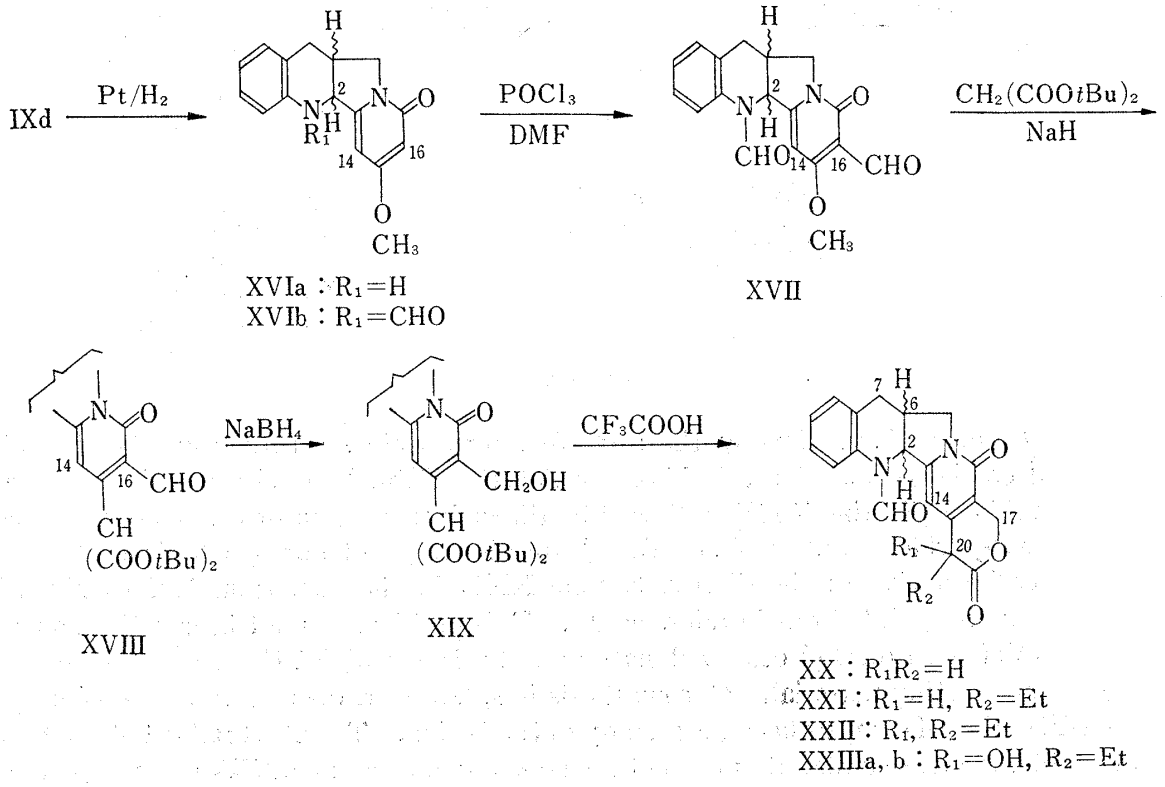
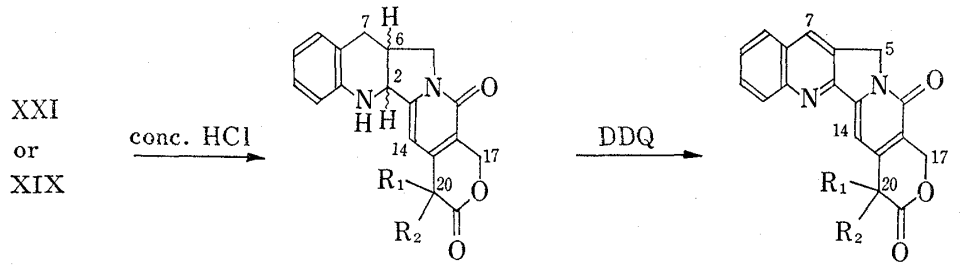


Chart 4

dl-Camptothecin XXX was obtained by the following sequence. Crude epimeric mixture of XXI was deformylated by treatment with conc. hydrochloric acid to give XXIV, which was directly oxygenated with oxygen to afford an epimeric mixture of XXV analogously to the preparation of XXIII from XXI. Dehydrogenation of the resulting crude XXV with dichlorodicyanoquinone gave *dl*-camptothecin XXX in 35% over-all yield from XXI. The IR spectrum in chloroform (1 mm-cell) and the low-resolution mass spectrum of XXX were completely superimposable with those of natural camptothecin.[13] The thin-layer chromatographic properties (chloroform–methanol (20: 1) and chloroform–ethyl acetate–methanol (12: 6: 1)) of both compounds were also identical.

13) The authors are very grateful to Dr. Monroe E. Wall of the Research Triangle Institute, N. C. for kindly providing us with a sample of authentic natural camptothecin.

Alternatively XXX was obtained from XIX by the following sequence. Treatment of XIX with conc. hydrochloric acid gave crude XXVI, which was dehydrogenated with dichlorodicyanoquinone to afford lactone XXVII. The physical data coincided with the description of Winterfeldt, *et al.*[14] Our experiment to obtain XXX from XXVII was as follows. Ethylation of XXVII, analogous to the production of XXI from XX, gave diethyl lactone XXIX (13%), the desired monoethyl lactone XXVIII (25%), and the starting material (15%). Recrystallization of the XXVIII-fraction gave *dl*-desoxycamptothecin (mp 258—264° (decomp.)).[15] Oxygenation of crude XXVIII as above furnished *dl*-camptothecin (XXX) in 8% over-all yield from XXVII. It is obvious that the latter sequence is far less favourable for the preparation of XXX, mainly because of the poor solubility of XXVII in solvents suitable for alkylation.



XXIV : R_1=H, R_2=Et
XXV : R_1=OH, R_2=Et
XXVI : R_1, R_2=H

XXVII : R_1, R_2=H
XXVIII : R_1=H, R_2=Et
XXIX : R_1, R_2=Et
XXX : R_1=OH, R_2=Et

Chart 5

In conclusion, we have thus synthesized *dl*-camptothecin starting from IIIa by using internal aldol condensation of the imido-ester (VIIIb→IXb), Vilsmeier reaction on the 4-methoxy-2-pyridone (XVIb→XVII), followed by direct introduction of the malonate moiety onto the formyl-pyridone (XVII→XVIII). A disadvantage of our synthetic route is the unavoidable co-formation of the diethyl lactone XXII in the step from XX to XXI. A similar fact was also pointed out in reference 14. This problem has not been solved, as both reaction of XVII with diethyl ethylmalonate and ethylation of XVIII led to the complete recovery of the starting material. Our synthesis has, however, opened up the possibility of unique modification of camptothecin, especially in the B-ring. The alkyl radical of the E-ring is also variable, whereas similar alteration of the poorly soluble lactone XXVII is not practical.

Experimental

General procedure see Part II.[1]

Reductive Cyclization of V to IIIa——V was prepared according to Borch, *et al.*[5] with a little modification—A mixture of anthranyl aldehyde (1.21 g, 10 mmoles) and ethyl 3-cyano-3-sodiopyruvate (2.44 g, 15 mmoles) in AcOH (15 ml) containing *p*-TsOH·H_2O (190 mg, 1 mmole) was stirred at 70° under N_2 atmosphere for 2 hr. After being cooled, the solution was slightly basified by slow addition of 15% NH_4OH under stirring and ice-cooling. The resulting precipitate was extracted with ether, the organic layer was washed with H_2O, dried, and evaporated. The residue was recrystallized with MeOH to give V (892 mg, mp 133—135°, 39%). A solution of V (19.2 g) in MeOH (1.5 l) and dioxane (600 ml) was shaken with Raney-Ni (60 ml) in the presence of liq. NH_3 (18 ml) under H_2 atmosphere. The H_2-absorption ceased after consumption of the theoretical volume (*ca.* 3.8 l) within 3 hr. The catalyst was filtered off and washed with CH_2Cl_2–MeOH (3 : 1) repeatedly. Concentration of the combined filtrate gave IIIa (10.1 g, 65%).

14) M. Boch, T. Korth, J.M. Nelke, D. Pike, H. Radunz, and E. Winterfeldt, *Chem. Ber.*, **105**, 2126 (1972).
15) R. Volkmann, S. Danishefsky, J. Eggler, and D.M. Solomon, *J. Am. Chem. Soc.*, **93**, 4074 (1971).

mp 280—283° (decomp.).

IV from IIIa with Meerwein Reagent——To a stirred suspension of IIIa (500 mg, 2.72 mmoles) in $CHCl_3$ (40 ml, washed twice with 2N Na_2CO_3, dried over $CaCl_2$ then P_2O_5, and distilled.) was added a solution of triethyloxonium fluoroborate (2.6 g, 11.6 mmoles) in CH_2Cl_2 (20 ml purified as above) over 20 min under N_2 atmosphere at room temperature. The nearly clear solution was stirred for 1 hr. Ice and 1N Na_2CO_3 were added to the solution which was then extracted with $CHCl_3$. The $CHCl_3$-solution was washed with H_2O, dried, and evaporated. The residue was triturated with ether and the ether solution was evaporated. The residue was dissolved in benzene and the benzene solution was passed through an Al_2O_3-layer (10 g). The collected benzene-eluate (200 ml) was evaporated and the residue was recrystallized from ether and petrol-ether to give IV (300 mg, mp 138—140°, 52%). *Anal.* Calcd. for $C_{13}H_{12}ON_2$: C, 73.56; H, 5.70; O, 7.54; N, 13.20. Found: C, 73.49; H, 5.82; O, 7.99; N, 13.28. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1618, 1603, 1580. NMR ($CDCl_3$) δ: 1.53 (3H, t, J=7 Hz), 4.65 (2H, q, J=7 Hz), 4.72 (2H, s).

VIIIa from IIIa and Diketene——i) With CH_3MgI: To a stirred suspension of IIIa (2 g, 11 mmoles) in DMF (30 ml) was added a CH_3MgI–ether-solution (containing 13 mmoles of the Grignard reagent in 8 ml of ether) over 30 min under ice-cooling and N_2 atmosphere. The resulting clear solution was stirred for a further 10 min at room temperature. To this stirred solution was added a solution of diketene (1.2 g, 15.5 mmoles) in ether (2 ml) under ice-cooling and the solution was stirred for 1 hr at room temperature. Ice was added and the resulting precipitate was filtered off and washed with acetone followed by petrol-ether to give a yellow solid (2.7 g). This was suspended in dil. AcOH and extracted with $CHCl_3$–MeOH (3: 1). The usual work-up gave a white crystalline residue, which was recrystallized from $CHCl_3$–MeOH–acetone to give VIIIa (1.77 g, mp sintered at 230°, 270—280° (decomp.)). From the mother liquor of the yellow solid additional VIIIa (0.33 g) was obtained by the same treatment. Total yield, 72%. *Anal.* Calcd. for $C_{15}H_{12}O_3N_2$: C, 67.15; H, 4.51; O, 17.89; N, 10.44. Found: C, 66.91; H, 4.54; O, 17.63; N, 10.22. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1747, 1729, 1703. NMR ($CDCl_3$+CF_3COOH) δ: 2.12 (0.6H, s, $C\underline{H}_3$–C(OH)=CH), 2.38 (2.4H, s, H_3C–C=O), 4.29 (1.6H, s, –$COCH_2$–), 5.16 (2H, s, C–1–CH_2), 6.67 (0.2H, s, –C(OH)=C$\underline{H}$–). Mass Spectrum m/e: 268 (M^+).

ii) With TlOEt: To a stirred suspension of IIIa (50 mg, 0.27 mmole) in DMF (4 ml) was added a solution of TlOEt (88 mg, 0.35 mmole) in benzene (2.1 ml) under N_2 atmosphere at room temperature, and the suspension was stirred for 1 hr. Diketene (35 mg, 4.05 mmoles) was then added to this suspension and it was stirred for 1 hr under the same conditions. The precipitate was filtered off, suspended in dil-AcOH, and extracted with $CHCl_3$–MeOH (3: 1). The usual work-up gave a residue (50 mg), which was recrystallized from $CHCl_3$–ether to give VIIIa (20 mg, 41%).

VIIIb from IIIa——A suspension of IIIa (3 g) in diethyl acetonedicarboxylate (60 ml) was heated under stirring at 160—165° (bath temperature) at reduced pressure (15—20 mmHg) for 2 hr. Cooling the solution and filtration of the resulting precipitate followed by washing with acetone and ether gave VIIIb (4.39 g). Concentration of the filtrate gave further VIIIb (0.34 g, TLC one spot). Total yield 95%. An analytically pure sample (mp 186—187°) was obtained by recrystallization from $CHCl_3$–MeOH. *Anal.* Calcd. for $C_{18}H_{16}O_5N_2$: C, 63.52; H, 4.74; O, 23.51; N, 8.23. Found: C, 63.43; H, 4.73; O, 23.30; N, 8.16. IR ν_{max}^{Nujol} cm^{-1}: 1751, 1740, 1721, 1700. NMR ($CDCl_3$+CF_3COOH) δ: 1.28 (3H, t, J=7 Hz), 3.42 (0.4H, s, $C\underline{H}_2$(COOEt)C(OH)=CH–), 3.73 (1.6H, s, –CO–$C\underline{H}_2$–COOEt), 4.23 (2H, q, J=7 Hz), 4.38 (1.6H, s, –CO–$C\underline{H}_2$–CO), 5.05 (2H, s, C-1-CH_2), 6.95 (0.2H, s, CH_2(COOEt)C(OH)=C$\underline{H}$–). Mass Spectrum m/e: 340 (M^+).

Xa from VIIIa——A stirred suspension of VIIIa (100 mg, 0.37 mmoles) in toluene (7 ml) and AcOH (0.6 ml) was refluxed for 2 hr in the presence of dried $AcONH_4$ (60 mg, 0.74 mmoles) with a water separator filled with molecular-sieves. After being cooled, the reaction mixture was poured into water and extracted with $CHCl_3$. The residue (85 mg) obtained after the usual work-up was recrystallized from MeOH–$CHCl_3$ (3: 1) to give Xa (81 mg, mp>290° (decomp.), 87%). *Anal.* Calcd. for $C_{15}H_{11}ON_3$: C, 72.27; H, 4.45; N, 16.86. Found: C, 72.22; H, 4.40; N, 17.30. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1675. NMR ($CDCl_3$) δ: 2.53 (3H, d, J=1 Hz, C-15-CH_3), 5.19 (2H, s), 6.39 (1H, q, J=1 Hz, C-16-H). Mass Spectrum m/e: 249 (M^+).

XI from VIIIb——A suspension of VIIIb (50 mg) in toluene (3 ml) and AcOH (0.3 ml) was terated with $AcONH_4$ (17 mg) analogously as above. After being cooled, the resulting crystals were filtered off and dissolved in $CHCl_3$–MeOH (3: 1). The solution was washed with sat. NaCl–H_2O, dried and evaporated. The resulting residue was recrystallized from MeOH–acetone to give XI (20 mg, mp 233—234° (decomp.)). *Anal.* Calcd. for $C_{18}H_{17}O_4N_3$: N, 12.38. Found: N, 12.03. IR ν_{max}^{Nujol} cm^{-1}: 3400, 1730.[16]

XII from 2-Pyrrolidone——A solution of 2-pyrrolidinone (8 g) and diketene (8 g) in toluene (20 ml) was refluxed for 20 hr. After removal of the solvent, the residue was distilled at 0.5 mmHg. The second fraction, boiling at 108—113°, was collected to give N-acetoacetyl-2-pyrrolidone (10.4 g). IR ν_{max}^{film} cm^{-1}: 1730, 1685. NMR ($CDCl_3$) δ: 2.24 (3H, s, CH_3CO), 4.00 (2H, s, CO–CH_2–CO). A stirred solution of N-acetoacetyl-2-pyrrolidone (623 mg) in benzene (10 ml) and AcOH (3 ml) was refluxed with dried $AcONH_4$ as above for 6 hr. After being cooled, the solution was poured onto ice-water, and extracted with CH_2Cl_2. Evaporation of the dried extract gave a hygroscopic crystalline residue (422 mg), which afforded picrate

16) IR-spectra were taken on a JASCO-IRS spectrometer.

(935 mg, 67%) on treatment with picric acid in ether. Recrystallization from CH_3OH gave pure XII picrate, mp 159—160°. *Anal.* Calcd. for $C_{14}H_{13}O_8N_5$: C, 44.33; H, 3.45; N, 18.47. Found: C, 44.41; H, 3.78; N, 18.41. The free base was recrystallized from ether, mp 69—73° (hygroscopic). *Anal.* Calcd. for $C_8H_{10}ON_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.95; H, 6.84; N, 18.29. NMR ($CDCl_3$) δ: 2.1—2.5 (2H), 2.28 (3H, d, J=1 Hz, $-CH_3$), 3.0—3.3 (2H), 4.0—4.3 (2H), 6.08 (1H, q, J=1 Hz, -CH).

XIIIa from VIIIa——A stirred suspension of VIIIa (200 mg, 0.75 mmoles) in CH_3CN (15 ml) was refluxed for 4.5 hr in the presence of pyrrolidine (230 mg, 2.3 mmoles) in benzene (5 ml) with a water separator filled with molecular-sieve. The solvent was removed and the resulting residue was recrystallized from CH_2Cl_2–MeOH to give XIIIa (148 mg, mp 265—267°, 62%). *Anal.* Calcd. for $C_{19}H_{19}O_2N_3$: C, 71.01; H, 5.96; N, 13.08. Found: C, 70.77; H, 6.04; N, 12.95. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1630. NMR ($CDCl_3$) δ: 2.00 (4H, m), 2.61 (3H, s, $C\underline{H}_3$–C=CH), 3.50 (4H, m), 5.01 (2H, s), 6.55 (1H, s, –CO–C<u>H</u>=C).

IXb and XIIIb from VIIIb with Pyrrolidine——A stirred suspension of VIIIb (90 mg, 0.26 mmoles) in CH_3CN (7 ml) was refluxed in the presence of pyrrolidine (23 mg, 0.32 mmoles) for 1.5 hr. The reaction mixture was cooled to *ca.* 30—40° and the crystals were filtered off to give nearly pure IXb (37 mg). The concentrated residue from the filtrate was purified by TLC (solvent-system $CHCl_3$–MeOH=3: 1) to afford additional IXb (13 mg), XIIIb (18 mg, 17%) and IIIa (8 mg, 16%). Total yield of IXb, 59%. Recrystallization from $CHCl_3$–MeOH gave pure IXb, mp 281—282° (decomp.). *Anal.* Calcd. for $C_{18}H_{14}O_4N_2$: C, 67.07; H, 4.38; O, 19.86; N, 8.69. Found: C, 66.91; H, 4.58; O, 19.74; N, 8.65. IR ν_{max}^{Nujol} cm^{-1}: 3140, 1728, 1655. NMR (CF_3COOH) δ: 1.72 (3H, t, J=7 Hz), 5.05 (2H, q, J=7 Hz), 5.90 (2H, s, C-5-CH_2), 6.97 (1H, s, C-16-H). UV λ_{max}^{EtOH} mμ(ε): 245 (55,000), 250 (57,500), 269 (12,100), 355 (18,500) (shoulder), 362 (19,000). Mass Spectrum *m/e*: 322 (M^+). Recrystallization of XIIIb from $CHCl_3$–MeOH gave pure XIIIb, mp 248—249°. *Anal.* Calcd. for $C_{22}H_{23}O_4N_3$: C, 67.16; H, 5.89; O, 16.27; N, 10.68. Found: C, 67.22; H, 5.59; O, 16.12; N, 10.57. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1630, 1555 (broad). NMR ($CDCl_3$) δ: 1.30 (3H, t, J= 7 Hz), 2.00 (4H, m), 3.50 (4H, m), 4.24 (2H, s, =C–C<u>H</u>$_2$–COOEt), 4.24 (2H, q, J=7 Hz), 4.98 (2H, s), 6.69 (1H, s, CO–CH=C–N), 7.58—8.42 (5H, m).

IXb from VIIIb with Piperidine——A stirred suspension of VIIIb (31.5 g, 92.7 mmoles) in CH_3CN (2.6 l) was refluxed for 4 hr in the presence of piperidine (9.58 ml, 97.4 mmoles). Within 20 min the reaction mixture became a clear solution and in a further 30 min precipitation of pale yellow crystals began. After the mixture had been cooled the crystals were filtered off and washed with CH_3CN and ether to give pure IXb (24.4 g). Concentration of the combined filtrate gave additional IXb (2.0 g). mp 281—282° (decomp.). Total yield 89%.

IXb from VIIIb with Triethylamine——VIIIb (50 mg) was treated analogously with $(Et)_3N$ (16 mg) in CH_3CN (5 ml) for 5 hr. Separated crystals were filtered off to give IXb (13 mg, 28%). From the filtrate, VIIIb (31 mg, 62%) was recovered.

Attempted Cyclization of XIIIb to IXb——A solution of XIIIb (300 mg) in CH_3CN (3.5 ml) was refluxed for 5 hr. TLC check showed the presence of only XIIIb. Pyrrolidine (2.7 ml) was added to the solution, which was further refluxed for 4.5 hr. In another run, a solution of XIIIb (17 mg) in CH_3CN (2 ml) was refluxed for 5 hr with CH_3CN-solution (1 ml) containing pyrrolidine (3.7 mg, 0.05 mmole) and AcOH (3.1 mg, 0.05 mmole). In both cases XIIIb was quantitatively recovered.

IXc from IXb——A stirred suspension of IXb (1 g, 3.1 mmoles) in acetone (80 ml) containing dimethyl sulfate (785 mg, 6.2 mmoles) and K_2CO_3 (860 mg, 6.2 mmoles) was refluxed for 2 hr. After the mixture had been cooled, the precipitate was filtered off, suspended in H_2O, and extracted with $CHCl_3$–MeOH (3: 1). The concentrated residue of the organic layer was recrystallized from CH_3OH to give IXc (0.53 g). The filtrate of the separated precipitate was concentrated and the residue was treated analogusly to the precipitate to give additional IXc (0.39 g). Total yield 89%. Recrystallization from MeOH gave an analytically pure sample, mp 262—263°. *Anal.* Calcd. for $C_{19}H_{16}O_4N_2$: C, 67.85; H, 4.80; O, 19.03; N, 8.33. Found: C, 67.56; H, 4.91; O, 18.76; N, 8.33. IR ν_{max}^{Nujol} cm^{-1}: 1732, 1667. NMR ($CDCl_3$+CF_3COOH) δ: 1.48 (3H, t, J=7 Hz), 3.98 (3H, s, OCH_3), 4.66 (2H, q, J=7 Hz), 5.16 (2H, s, C-5-CH_2), 6.49 (1H, s, C-16-H), 7.60—8.40 (5H, m).

IXa from IXb——IXb (13.1 g) was heated at 160° with conc. HCl (300 ml) in a glass tube for 15 hr. After the mixture had been cooled, the crystals which separated were filtered and washed with H_2O to give the HCl-salt of IXa. This was suspended in H_2O, neutralized with AcONa, and extracted with $CHCl_3$–MeOH (3: 1) repeatedly. Concentration of the organic layer gave IXa (9.54 g, 94%). Recrystallization from $CHCl_3$–MeOH gave an analytically pure sample, mp>300°. *Anal.* Calcd. for $C_{15}H_{10}O_2N_2$: C, 71.99; H, 4.03; O, 12.79; N, 11.20. Found: C, 71.81; H, 4.28; O, 12.95; N, 11.07. IR ν_{max}^{Nujol} cm^{-1}: 2500 (broad), 1950—1850 (broad), 1665, 1648. NMR (CF_3COOH) δ: 5.92 (2H, s), 7.20 (1H, broad s, C-16-H), 8.12—8.60 (5H, m, containing C-14-H), 9.52 (1H, s, C-7-H). Mass Spectrum *m/e*: 250 (M^+).

IXd from IXa——A stirred suspension of IXa (4 g, 1.6 mmoles) in acetone (320 ml) was refluxed with dimethyl sulfate (4 g, 3.2 mmoles) and K_2CO_3 (4.4 g, 3.2 mmoles) for 7 hr. After the mixture had been cooled, the precipitate which separated was filtered off and treated analogously to IXc from IXb. The residue was recrystallized from CH_3OH to give IXd (3.65 g, 87%, mp 280—283° (decomp.)). *Anal.* Calcd. for $C_{16}H_{12}O_2N_2$: C, 72.71; H, 4.58; O, 12.11; N, 10.60. Found: C, 72.72; H, 4.61; O, 12.65; N, 10.89. IR ν_{max}^{Nujol} cm^{-1}: 1678. NMR ($CDCl_3$+CF_3COOH) δ: 4.00 (3H, s, OCH_3), 5.51 (2H, s, C-5-CH_2), 6.63 (1H, d, J=

2 Hz, C-16-H), 7.71 (1H, d, J=2 Hz, C-14-H), 7.87—8.55 (4H, m), 8.92 (1H, s, C-7-H). UV $\lambda_{max}^{95\%EtOH}$ mμ(ε): 214 (42,400), 249 (36,500), 349 (14,500) (shoulder), 360 (16,600). Mass Spectrum *m/e*: 264 (M^+).

XIVa from IXd——Vilsmeier-reagent prepared by stirring a mixture of $POCl_3$ (2.9 g, 18.9 mmoles) and DMF (6 ml) for 1 hr at 60° was added to a stirred suspension of IXd (500 mg, 1.89 mmoles) in DMF (100 ml) under ice-cooling and the mixture was stirred for 16 hr at room temperature to give a deep brown solution. This was added dropwise to ice-H_2O and neutralized with AcONa. The precipitate which separated was filtered, washed with H_2O, acetone, and ether successively. Recrystallization from CH_3OH–$CHCl_3$ gave XIVa (468 mg, 82%). An analytically pure sample melts at 249—252° (decomp.). *Anal.* Calcd. for $C_{17}H_{12}O_3N_2 \cdot 2/3H_2O$: C, 67.10; H, 4.41; N, 9.20. Found: C, 67.05; H, 4.36; N, 8.86. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1677, 1655. NMR ($CDCl_3$+CF_3COOD) δ: 4.24 (3H, s), 5.56 (2H, s), 7.84 (1H, s, C-14-H), 7.95—9.05 (5H, m). Mass Spectrum *m/e*: 292 (M^+).

Deuterium-exchange of XIVa to XIVb——To a stirred solution of di-*tert*-butyl malonate (163 mg, 0.69 mmoles) in dioxane (6 ml), NaH (33 mg, 0.69 mmoles) was added and the mixture was stirred for 30 min under N_2 at room temperature. To this solution, XIVa (170 mg, 0.53 mmoles) was added and the mixture was stirred for 30 min at the above condition. A deep greenish blue color immediately developed. The reaction mixture was quenched by adding a mixture of CD_3COOD and D_2O (0.2 ml respectively). The mixture was diluted with ice-H_2O and extracted with $CHCl_3$–MeOH (3: 1). The residue from the organic layer was dissolved in $CHCl_3$ containing 1% MeOH and passed through a silica-gel layer (3 g). The fraction containing XIVb was collected and evaporated. The resulting residue was recrystallized from $CHCl_3$–MeOH to give a mixture of XIVa and XIVb (32 mg, 19%, mp 249—253° (decomp.)). NMR ($CDCl_3$+CF_3-COOD) δ: 4.28 (3H, s, OCH_3), 5.65 (1.5H, s, C-5-CH_2). The mass spectrum (70 eV, direct inlet system at 205°) indicated the presence of the isotopic species d_0 (*m/e*: 292) *ca.* 50%, and d_1 (*m/e*: 293) *ca.* 50%.

Attempted Deuteration of IXd——IXd (100 mg, 0.38 mmoles) was similarly treated with a solution of di-*tert*-butyl malonate (106 mg, 0.49 mmoles) and NaH (22 mg, 0.49 mmoles) in dioxane (4 ml) for 1 hr. No deep coloration was observed during the reaction. Analogous work-up to XIVb from XIVa gave IXd (93 mg, mp 280—282° (decomp.)). The NMR and mass spectra of the product indicated no deuterium incorporation.

Reduction of IXd to XVIb *via* XVIa——A solution of IXd (800 mg) in a mixture of dioxane (120 ml), MeOH (90 ml) and H_2O (60 ml) containing 0.5N HCl (90 ml) was shaken under H_2 with Adams-catalyst prepared from PtO_2 (150 mg) in MeOH (60 ml). H_2-Absorption (186 ml, theoretical amount: 147 ml for 2 moles H_2) ceased within 40 min. After separation of the catalyst, the filtrate was alkalized with 2N NaOH and extracted with $CHCl_3$.

Concentration of the organic layer gave XVIa (830 mg) as an amorphous residue. XVIa was refluxed in 98% HCOOH (3 ml) for 30 min under a N_2-stream. The concentrated residue was recrystallized from acetone–CH_2Cl_2 to give XVIb (714 mg, 80%, mp 212—216° (decomp.)). An analytically pure sample melts at 219—220° (decomp.). *Anal.* Calcd. for $C_{17}H_{16}O_3N_2$: C, 68.90; H, 5.44; O, 16.20; N, 9.45. Found: C, 68.97; H, 5.49; O, 16.13; N, 9.16. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660. UV $\lambda_{max}^{95\%EtOH}$ mμ(ε): 236 (11,400), 282 (6,880). NMR ($CDCl_3$) δ: 3.70 (3H, s), 5.72 (1H, d, J=3 Hz, C-16-H), 6.09 (1H, d of d, J=10 and 1 Hz, C-2-H), 6.26 (1H, d of d, J=3 and 1 Hz, C-14-H), 6.88—7.30 (4H, m), 8.60 (1H, s, N-C<u>H</u>O). Mass Spectrum *m/e*: 296 (M^+).

XVII from XVIb——Vilsmeier-reagent prepared by stirring $POCl_3$ (2.01 g, 13.2 mmoles) and DMF (9 ml) for 45 min at 55° was added to a stirred solution of XVIb (2.6 g, 8.8 mmoles) in DMF (45 ml) under ice-cooling and N_2 atmosphere. The solution was stirred for 2 hr at 60°. After being cooled, the solution was poured into ice-H_2O, neutralized with AcONa, and extracted with $CHCl_3$–MeOH (3: 1). Concentration of the organic layer gave XVII (2.16 g, 76%, mp 274—277° (decomp.)). An analytically pure sample melts at 275—277° (decomp.). *Anal.* Calcd.for $C_{18}H_{16}O_4N_2$: C, 66.66; H, 4.97; O, 19.73; N, 8.64. Found: C, 66.42; H, 5.09; O, 19.98; N, 8.43. IR ν_{max}^{Nujol} cm^{-1}: 1670, 1645. NMR ($CDCl_3$–CD_3OD (3: 1)) δ: 3.99 (3H, s), 6.17 (1H, d, J=10 Hz, C-2-H), 6.51 (1H, broad s, C-14-H), 6.95—7.36 (4H, m), 8.60 (1H, s, N-CHO), 10.12 (1H, s, C-16-C<u>H</u>O). Mass Spectrum *m/e*: 324 (M^+).

XVIII from XVII——To a stirred solution of di-*tert*-butyl malonate (2.26 g, 10.4 mmoles) in dioxane (68 ml). NaH (455 mg, 10.4 mmoles) was added and the mixture was stirred for 30 min at room temperature under N_2 atmosphere. XVII (2.6 g, 8.03 mmoles) was then added to the solution and the mixture was refluxed for 3.5 hr. After the mixture had been cooled the precipitate which separated during the reaction (sodium salt of XVIII) was filtered off and washed with dioxane. The precipitate was then treated with ice-AcOH and extracted with $CHCl_3$. Concentration of the organic layer gave amorphous XVIII (2.6 g, crude yield 64%. TLC, nearly one spot). A portion of XVIII was purified by TLC (solvent-system $CHCl_3$–MeOH (10: 1)). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1723, 1679, 1650. NMR ($CDCl_3$) δ: 1.50 (18H, s), 5.58 (1H, s, <u>H</u>-C=($COOtBu$)$_2$), 6.18 (1H, d, J=10 Hz, C-2-H), 6.70 (1H, broad s, C-14-H), 6.88—7.33 (4H, m), 8.65 (1H, s, N-CHO), 10.29 (1H, s, C-16-CHO).

XIX from XVIII——To a stirred solution of XVIII (1.8 g, 3.54 mmoles) in CH_3OH (100 ml), H_2O (4.7 ml) and AcOH (212 mg, 3.54 mmoles), was added $NaBH_4$ (269 mg, 7.08 mmoles) portionsweise under ice-cooling. The mixture was stirred for 20 min at room temperature. The solution was poured in ice-AcOH and extracted with $CHCl_3$. Concentration of the organic layer and recrystallization of the resulting residue

from CH_3OH gave XIX (1.37 g, 63%, mp 195—199°). Further recrystallization from acetone–CH_2Cl_2 gave an analytically pure sample, mp 196—197°. *Anal.* Calcd. for $C_{28}H_{34}O_7N_2$: C, 65.86; H, 6.71; O, 21.94; N, 5.49. Found: C, 65.66; H, 6.54; O, 21.65; N, 5.45. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1746, 1660. NMR ($CDCl_3$) δ: 1.49 (18H, s), 6.14 (1H, d, J=10 Hz), 6.71 (1H, broad s), 4.52 (2H, s, C$\underline{H}_2$–OH), 4.65 (1H, s, $\underline{H}$–C=(COO*t*Bu)$_2$), 6.84—7.32 (4H, m), 8.55 (1H, s).

XX from XIX——A solution of XIX (1.63 g) in CF_3COOH (12 ml) was refluxed for 30 min. The solvent was removed and the resulting residue was recrystallized from CH_3OH to give XX (1.04 g, 98%, mp 258—260° (decomp.)). An analytically pure sample melts at 260—262° (decomp.). *Anal.* Calcd. for $C_{19}H_{16}O_4N_2$: C, 67.85; H, 4.80; O, 19.03; N, 8.33. Found: C, 67.82; H, 4.96; O, 18.83; N, 8.43. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1662. NMR ($CDCl_3$+CF_3COOH) δ: 3.68 (2H, s, C-20-C$\underline{H}_2$), 5.31 (2H, s, C-17-C$\underline{H}_2$), 6.25 (1H, d, J=10 Hz, C-2-H), 6.77 (1H, s, C-14-H), 6.92—7.47 (4H, m), 8.66 (1H, s, N–CHO).

XXI and XXII from XX——To a stirred solution of XX (530 mg, 1.57 moles) in DMF (32 ml), NaH (82 mg, 1.88 mmoles) was added under ice-cooling and N_2 atmosphere. After the mixture had been stirred for 40 min, EtI (492 mg, 3.14 mmoles) was added and the solution was stirred for a further 30 min under the above conditions. The solution was poured into ice-AcOH and extracted with $CHCl_3$–MeOH (3: 1). The residue from the extract was separated by TLC (solvent-system: $CHCl_3$–AcOEt–MeOH (12: 6: 1)) to give XXII (73 mg, 12%), XXI (256 mg, 45%), and XX (147 mg, 28%) as the most polar fraction. Recrystallization of XXII from CH_3OH gave an analytically pure sample, mp 277—282° (decomp). *Anal.* Calcd. for $C_{23}H_{24}O_4N_2$: C, 70.39; H, 6.16; O, 16.31; N, 7.14. Found: C, 70.22; H, 6.34; O, 16.58; N, 6.96. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1731, 1665. NMR ($CDCl_3$) δ: 0.60 and 0.75 (6H, two t, J=7 Hz), 1.5—2.5 (4H, m), 5.18 (2H, s), 6.18 (1H, d, J=10 Hz), 6.40 (1H, s), 8.57 (1H, s). Recrystallization of XXI from MeOH gave a diastereoisomeric mixture of XXI, mp 192—195°. *Anal.* Calcd. for $C_{21}H_{20}O_4N_2$: C, 69.21; H, 5.53; N, 7.69. Found: C, 69.24; H, 5.37; N, 7.60. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1788, 1726, 1674, 1650. NMR ($CDCl_3$) δ: 0.95 and 1.00 (3H, t, J=7 Hz), 5.21 and 5.25 (2H, s), 6.15 (1H, d, J=10 Hz), 6.41 (1H, broad s), 8.60 (1H, s).

XXIIIa,b from XXI——A stream of O_2 was passed through a slightly cloudy solution of a diastereoisomeric mixture of crude XXI (147 mg, 0.40 mmoles), $Cu(OAc)_2 \cdot H_2O$ (16 mg, 0.08 mmoles), and $(Et)_3N$ (81.6 mg, 0.81 mmoles) in CH_3OH (10 ml) for 30 min at room temperature. CH_3OH was removed at room temperature and the residue was treated with ice-AcOH and extracted with $CHCl_3$. The residue (168 mg) from the extract was separated by TLC (solvent-system: $CHCl_3$–MeOH (20: 1)) to give XXIIIa (37 mg, 24%) and XXIIIb (53 mg, 35%). Recrystallization of XXIIIa from CH_3OH gave an analytically pure sample, mp 248—249° (decomp.). *Anal.* Calcd. for $C_{21}H_{20}O_5N_2$: C, 66.38; H, 5.30; O, 21.03; N, 7.37. Found: C, 66.33; H, 5.12; O, 21.18; N, 7.09. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540, 1740, 1665, 1155. NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7 Hz), 1.75 (2H, q, J=7 Hz), 5.06 and 5.46 (2H, AB quartet, J_{AB}=16 Hz, C-17-CH_2), 6.23 (1H, d, J=10 Hz, C-2-H), 6.83 (1H, broad s, C-14-H), 6.92—7.31 (4H, m), 8.60 (1H, s, N–CHO). Mass Spectrum *m/e*: 380 (M^+). Recrystallization of XXIIIb from MeOH–ether gave an analytically pure sample, mp 249—251° (decomp.). *Anal.* Calcd. for $C_{21}H_{20}O_5N_2$: C, 66.38; H, 5.30; O, 21.03; N, 7.37. Found: C, 66.36; H, 5.22; O, 21.13; N, 7.17. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530, 1740, 1675, 1658, 1155. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7 Hz), 1.72 (2H, q, J=7 Hz), 5.02 and 5.42 (2H, AB quartet, J_{AB}=16 Hz, C-17-CH_2), 6.24 (1H, d, J=10 Hz, C-2-H), 6.81 (1H, broad s, C-14-H), 6.90—7.34 (4H, m), 8.60 (1H, s, N–CHO). Mass Spectrum *m/e*: 380 (M^+).

***dl*-Camptothecin from XXI *via* XXIV and XXV**——A solution of crude XXI (314 mg, 0.86 mmoles) in conc. HCl (0.4 ml) was allowed to stand for 16 hr at room temperature. The solution was treated with ice-AcONa and extracted with $CHCl_3$. Concentration of the extract gave an amorphous diastereoisomeric mixture of XXIV (284 mg, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460, 1660, 1743). An O_2 stream was passed through a solution of crude XXIV (234 mg) in MeOH (10 ml), in the presence of $Cu(OAc)_2 \cdot H_2O$ (28 mg, 0.14 mmoles) and $(Et)_3N$ (210 mg, 2.09 mmoles) for 30 min at room temperature. Analogous work-up to that used in the preparation of XXIIIa,b from XXI gave an amorphous diastereoisomeric mixture of XXV (252 mg, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530, 3420, 1748, 1660, 1156).[16] To a solution of crude XXV (129 mg, 0.37 mmoles) in dioxane (14 ml), DDQ (188 mg, 0.83 mmoles) was added and the mixture was refluxed for 1 hr under stirring. The solvent was removed and the resulting residue was suspended in $CHCl_3$ containing 1% MeOH and chromatographed (silica-gel 5 g, each fraction containing 10 ml $CHCl_3$–MeOH (99: 1)). Fractions 5—10 were collected and concentrated. The residue was recrystallized to give *dl*-camptothecin (XXX) (44 mg, 35% from XXI, mp 274—275° (decomp.)). Further recrystallization gave an analytically pure sample, mp 276—278° (decomp.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540 (OH), 1742 (lactone C=O), 1660 (pyridone C=O), 1601 (aromatic C=C), 1155 (C–O) (1 mm-cell). IR ν_{max}^{KBr} cm^{-1}: 3420 (broad, OH), 3260 (shoulder, OH), 1755 (lactone C=O), 1647 (pyridone C=O), 1613, 1583 (aromatic C=C), 1157 (C–O). Mass Spectrum *m/e*: 348 (M^+).

XXVII from XIX *via* XXVI——A solution of XIX (288 mg, 0.57 mmoles) in conc. HCl (0.3 ml) was allowed to stand at room temperature for 16 hr. Analogous work-up to that used in the preparation of XXIV from XXI gave an amorphous residue (XXVI, 213 mg, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 1747,[16] NMR ($CDCl_3$+CF_3COOH) δ: 3.65 (2H, s), 5.16 (2H, s)).[17] To a solution of crude XXVI (213 mg) in dioxane, DDQ (257

17) NMR spectra were taken on a Varian T-60 spectrometer.

mg, 1.13 mmoles) was added and the mixture was refluxed for 2 hr under stirring. The concentrated residue was suspended in $CHCl_3$ containing 1% CH_3OH and passed through a Al_2O_3-layer (acidic, grade I). Eluate (~400 ml) was concentrated to give XXVII (78 mg, 46% from XIX, nearly one spot on TLC). Recrystallization from MeOH–$CHCl_3$ gave an analytically pure sample, mp>275° (decomp.). *Anal.* Calcd. for $C_{18}H_{12}O_2N_3$: C, 71.04; H, 3.98; N, 9.21. Found: C, 71.22; H, 3.79; N, 9.51. IR ν_{max}^{Nujol} cm^{-1}: 1747, 1736, 1660. UV $\lambda_{max}^{95\%EtOH}$ $m\mu(\varepsilon)$: 218 (42,100), 254 (31,400), 288 (6,030), 361 (20,500), 370 (20,100) (shoulder). NMR ($CDCl_3+CF_3COOH$) δ: 3.95 (2H, s, C-20-CH_2), 5.59 (2H, s, C-17-CH_2), 5.65 (2H, s, C-5-CH_2), 7.85 (1H, s, C-14-H), 7.96—8.44 (4H, m), 9.15 (1H, s, C-7-H). Mass Spectrum *m/e*: 304 (M^+).

XXVIII and XXIX from XXVII——To a solution of XXVII (33 mg, 0.11 mmoles) in DMF (15 ml), NaH (6 mg, 0.13 mmoles) was added and a mixture was stirred for 10 min under N_2 atmosphere at room temperature. EtI (65 mg, 0.42 mmoles) was added and the solution was stirred for 4 hr under the above conditions. The solution was poured into ice-AcOH and extracted with $CHCl_3$–MeOH (3: 1). The residue from the extract was separated by TLC (solvent-system 20: 1) to give XXIX (5 mg, 13%), XXVIII (9 mg, 25%), and XXVII (5 mg, 15%) as the most polar fraction. Recrystallization of XXIX from MeOH gave an analytically pure sample of XXIX, mp 283—296° (decomp.). *Anal.* Calcd. for $C_{22}H_{20}O_3N_2$: C, 73.31; H, 5.59; O, 13.32; N, 7.77. Found: C, 73.45; H, 5.40; O, 13.57; N, 7.79. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1732, 1661. NMR ($CDCl_3$) δ: 0.83 (6H, t, J=7 Hz), 1.70—2.55 (4H, m), 5.32 (2H, d, J=1 Hz, C-17-CH_2), 5.46 (2H, s, C-5-CH_2), 7.25 (1H, s, C-14-H), 7.50—8.42 (5H, m). Recrystallization of XXVIII from MeOH gave an analytically pure sample of XXVIII, mp 258—264° (decomp.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745, 1664.[16] NMR ($CDCl_3$) δ: 1.08 (3H, t, J=7 Hz), 1.80—2.36 (2H, m), 3.62 (1H, t, J=7 Hz C-20-H), 5.29 (2H, broad s), 5.49 (4H, broad s, C-5-CH_2 and C-17-CH_2), 7.18 (1H, s).[17]

***dl*-Camptothecin (XXX) from XXVIII**——An O_2-stream was passed through a slightly cloudy solution of XXVIII (8 mg, 0.02 mmoles), $Cu(OAc)_2 \cdot H_2O$ (6 mg, 0.03 mmoles), and $(Et)_3N$ (0.5 ml) in DMF (2 ml) and MeOH (6 ml) for 20 min at room temperature. The solution was poured into H_2O and extracted with $CHCl_3$. The residue from the extract was purified by TLC (solvent-system: $CHCl_3$–MeOH (20: 1) to give XXX (3 mg, 36%). Recrystallization from MeOH–CH_2Cl_2 gave pure XXX, mp 276—278° (decomp.).

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