[Chem. Pharm. Bull. 22(4) 763—770 (1974)]

UDC 547.94.057 : 581.192

Experiments on the Synthesis of *dl*-Camptothecin. II.[1] Synthesis of a D-E Ring Analog of Camptothecin and a Total Synthesis of Ricinine[2]

Tsutomu Sugasawa, Kazuyuki Sasakura, and Tatsuo Toyoda

Shionogi Research Laboratory, Shionogi & Co., Ltd.[3]

(Received July 19, 1973)

A D–E ring analog (XX) of camptothecin (I) was synthesized from 4-methoxy-1-methyl-2(1H)-pyridone by using Vilsmeier reaction followed by nucleophilic direct introduction of di-*tert*-butyl malonate onto the pyridone ring, ethylation and hydroxylation.

That the α-hydroxylactone functionality present in the E ring is an absolute requirement for antitumor activity of camptothecin (I)[4] has prompted many synthetic chemists to attempt to synthesize D-E ring analogs of I. Three successful examples[5] have so far been published in preliminary form, their syntheses using widely differing key reactions. Other approaches have also been suggested.[6]

We describe here our method in detail. The method is quite simple and consists essentially of two steps. First, the Vilsmeier reaction (phosphorus oxychloride in dimethylformamide) is applied to 4-alkoxy-1-methyl-2(1H)-pyridones (IV, V, and VI) to give the required 3-formyl substituted pyridones (VIII, IX, and X) with complete regioselectivity. Secondly, nucleophilic direct introduction of a malonate moiety is made at the C-4 position of the formyl pyridone. In this way a pyridone ring bearing the carbon chain necessary for formation of the δ-lactone of the E ring is easily obtained. It is here that our method is different from previous approaches,[5a,b] where oxidative aromatization of a piperidone bearing a carbon chain as E ring-precursor is necessary.

Whereas electrophilic substitution of 1-alkyl-2(1H)-pyridone gives a mixture of C-3 and C-5 substituted derivatives with the latter predominating,[7a–c] nitration and bromination of 4-hydroxy-2(1H)-pyridone provide exclusively C-3 substituted derivatives.[7d] Considering the Vilsmeier reagent as a weaker electrophile, we first applied it to II, but the reaction gave 3-formyl-4-chloropyridone (VII) in only poor yield (5%), along with 4-chloropyridone (III) (22%). Next, the reaction was tried on 4-alkoxy-1-methyl-2(1H)-pyridones (IV, V, and VI), having stronger electron releasing group at C-4. The desired 3-formyl derivatives (VIII, IX, and X) were formed in good yield (Table I). The nuclear magnetic resonance (NMR)

1) Part I: T. Sugasawa, K. Sasakura, T. Hidaka, and T. Toyoda, *Chem. Pharm. Bull.* (Tokyo), **22**, 757 (1974).
2) Presented partially at the 21st Annual Kinki Local Meeting of the Pharmaceutical Society of Japan, November, 1971, Osaka.
3) Location: *Fukushima-ku, Osaka, 553, Japan.*
4) M.E. Wall, 4th International Symposium on the Biochemistry and Physiology of Alkaloids, Halle, DDR, June 25—28, 1969. *Abh. Deut. Akad. Wiss. Berlin*, **1971**, 46.
5) *a*) M.C. Wani, H.F. Campbell, G.A. Brine, J.A. Kepler, and M.E. Wall, *J. Am. Chem. Soc.*, **94**, 3632 (1972); *b*) J.J. Plattner, R.D. Gless, and H. Rapoport, *ibid.*, **94**, 8613 (1972); *c*) T. Sugasawa, T. Toyoda, and K. Sasakura, *Tetrahedron Letters*, **1972**, 5109.
6) *a*) R.H. Wood, P.G. Hofman, V.S. Waravdekar, and H.B. Wood, Jr., "Abstr. Papers, Am. Chem. Soc.," No. 162, ORGN 88, (1971); *b*) C.V. Grudzinskas, "Dissertation Abst. Intern. B32," No. 3, 1971, p. 1449.
7) *a*) H. Meislich, "Pyridine and its derivatives. Part III," ed. by E. Klingsberg, Interscience Publishers, New York, N. Y., 1962, pp. 659—673; *b*) H. Tomisawa, Y. Kobayashi, H. Hongo, and R. Fujita, *Chem. Pharm. Bull.* (Tokyo), **18**, 932 (1970); *c*) H. Tomisawa, H. Hongo, H. Kato, and H. Fujita, *ibid.*, **19**, 2414 (1971); *d*) R.A. Abramovitich and J.G. Saha, "Advance in Heterocyclic Chemistry," Vol. IV, ed. by A.R. Katritzky and A.J. Boulton, Academic Press, New York, N. Y., 1966, pp. 253—265.

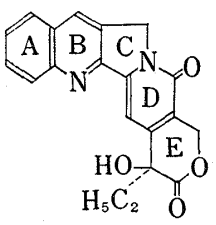
spectra of the products showed signals (δ, *ca.* 6 (1H, d) and 7.5 (1H, d)) with *ortho* coupling constants J=7—8 Hz, affording unequivocal structure proof. No C-5 substituted isomeric formyl pyridones were formed as in nitration and bromination,[7d] the carbon atom between the C=O and C-OR groups being the most reactive in the molecules. It is rather surprising that on the prolonged reaction VII was obtained as the main product from VI in stead of X (see Table I). To check whether the primary product (X) was converted to VII in the course of reaction, X was subjected to the reaction for 17 hr. However, VII was isolated only in 3% yield, together with recovered starting material (74%). Thus the course of the formation of VII remains unclear. A low yield (3%) of VII was also obtained by chlorination of XI prepared by hydrogenolysis of X.

Oximation of VIII with concomitant dehydration was effected by warming with hydroxylamine hydrochloride and sodium acetate in acetic acid, giving ricinine XII; an alkaloid of Ricinus Communis L.[8] Though the direct comparison with the natural product was not done, the structure was confirmed by the physical data (mp 201—202°, and ν_{max} 2220 cm^{-1}).

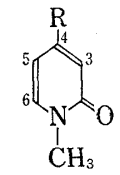
Table I. Vilsmeier Reaction on 4-Hydroxy- or Alkoxy-1-methyl-2(1H)-pyridone

Starting material	II	IV	V	VI	X
Product	VII	VIII	IX	X[a]	X
Yield %	5	73	73	67	74
	III			X[b]	VII
	22			23	3
				VII[b]	
				39	

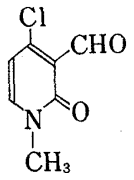
a) reaction time 2.5 hr
b) reaction time 17 hr



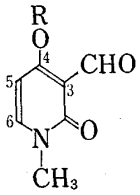
I



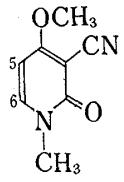
II : R=OH
III : R=Cl
IV : R=OCH_3
V : R=OC_2H_5
VI : R=$OCH_2C_6H_5$



VII



VIII : R=CH_3
IX : R=C_2H_5
X : R=$CH_2C_6H_5$
XI : R=H



XII

Chart 1

The carbon chain required for subsequent ring closure to give the E ring was introduced by nucleophilic addition of diethyl malonate at C-4 of VIII with simultaneous elimination of CH_3OH, the position being activated by the C-3 formyl group. Thus, VIII was converted to XIII (33%), on being refluxed with diethyl malonate and sodium hydride in dimethoxyethane or potassium *tert*-butylate in dioxane. The infrared (IR) spectrum of XIII showed ν_{max} 1745 and 1733 cm^{-1}. The NMR spectrum indicated proton signals of monosubstituted diethyl malonate (δ 1.27 (6H, t, J=7 Hz), 4.22 (4H, q, J=7 Hz), and 6.00 (1H, s)), instead of those of the methoxy group of VIII, and the aldehyde-proton signal appeared as a singlet at δ 10.5. These data agree with the structure XIII. A second product (XV) was isolated as a less polar fraction, its physical data (ν_{max} 3200, 1720, and 1650 cm^{-1}, δ 1.41 (3H, t), 1.43

8) See ref. 7*a*), pp. 715—719.

(3H, t), 4.47 (4H, q), 9.02 (1H, s), and 11.7 (1H, s, exchangeable by D_2O-addition, (M^+) 319) confirming the isocarbostyril structure. The formation of XV can be rationalized as aldol condensation of a further molecule of diethyl malonate with XIII followed by base-catalyzed Dieckmann-cyclization and elimination of an ethoxycarbonyl group. Thus the yield of the desired XIII was not satisfactorily. However, similar reaction of VIII with di-*tert*-butyl malonate afforded XIV (86%) as the sole product (TLC-check), the bulkiness of the di-*tert*-butyl group precluding secondary reaction. The NMR spectrum of the product contained signals of *tert*-butyl-, methine-, and aldehyde-protons (δ 1.47, 5.76, and 10.45), confirming the assigned structure XIV. A few examples of the nucleophilic attack of malonate carbanion on π-deficient heteroaromatic nuclei are precedent,[9a-e] but that on the π-rich pyridone ring has not been reported.

Sodium borohydride reduction of XIV gave XVI (76%, δ 4.62 (2H, s)), which was converted smoothly to the pyridone-lactone (XVII, 82%) on being refluxed in trifluoroacetic acid, by decarboxylation and lactonization. The physical data of the product (ν_{max} 1743 cm^{-1}, δ 3.52 (2H, broad s), and 5.36 (2H, broad s)) satisfy the structure XVII. The over-all yield of XVII amounts to *ca.* 53% from VIII.

Ethylation of the lactone ring was effected by treatment of XVII with ethyl bromide and sodium hydride in dimethylformamide, affording the desired monoethyl compound XVIII (43%) accompanied with diethyl compound XIX (17%) and the starting material XVII (16%), after thin layer chromatographic separation. In the NMR spectra of XVIII and XIX, the intensity of their ethyl-proton signals were consistent respectively with each structure and the methine-proton signal of XVIII was observed at δ *ca.* 3.4 as a triplet-like multiplet. To avoid co-formation of the undesired XIX, reaction of VIII with ethyldiethyl malonate instead of diethyl malonate and ethylation of the sodium salt of XIV with ethyl bromide were attempted. In both case, however, only the starting material was recovered.

The monoethyl product XVIII underwent hydroxylation to give XX (46%), on being treated with oxygen in the presence of triethylamine and cupric acetate, conditions similar to those used by H.C. Volger and W. Brackman[10] for the oxidation of unsaturated carbonyl compounds. XX had mp 182—183°, ν_{max} 3536 cm^{-1} and 223 (M^+), and other physical data also coincided completely with the assigned structure. The synthesis of XX has been reported recently by H. Rapoport, *et al.*[5b] after our work had been completed.

In an experiment (see Experimental, b) on the ethylation of XVII it was shown that compound XX is already formed to some extent (10%) in this step, suggesting that XVIII is considerably susceptible to oxygen. This observation led to the conjecture, that the co-formation of XIX may be avoided to some extent, if the ethylation is carried out in the presence of oxygen.

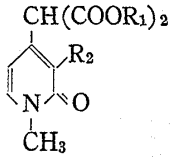
In order to improve the last two steps (ethylation and hydroxylation), a synthesis of α-ketolactone XXI was attempted, with the idea that this might be transformed to XX with ethyl magnesium halogenide. Thus XVII was treated with sodium nitrite in acetic acid and water to give XXII (63%). The IR spectrum showed absorptions of a strongly bonded hydroxyl group (*ca.* 2600—2300 cm^{-1}) and a lactone group (1740 cm^{-1}). The NMR spectrum indicates disappearance of the methylene-proton signal at δ 3.52 of XVII. Attempted cleavage of XXII to XXI[11a] with excess isoamyl nitrite gave only unidentified products. The reductive

9) *a*) H.E. Mertel, "Pyridine and its Derivatives. Part II," ed. by H. Klingsbery, Interscience Publischers, New York, N. Y., 1962, p. 356; *b*) A.R. Katritzky and J.M. Lagowski, "The Principles of Heterocyclic Chemistry," Academic Press, New York, N. Y., 1967, p. 46; *c*) T.M. Mishina and L.S. Efros, *Zh. Obshch. Khim.*, **32**, 2217 (1962); *d*) D. Farquhar and D. Leaver, *Chem. Commun.*, **1969**, 24; *e*) G.H. Cooper and R.L. Rickard, *J. Chem. Soc., C*, **1971**, 772.

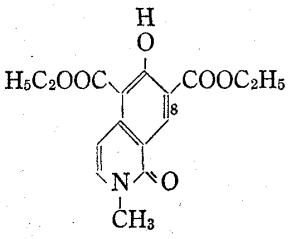
10) H.C. Volger and W. Brackman, *Rec. Trav. Chim.*, **84**, 579 (1965).

11) *a*) L.S. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley and Sons, Inc., Vol. I, p. 1098; *b*) *ibid.*, Vol. II, p. 63.

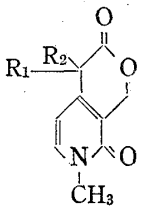
cleavage of XXII to XXI *via* an imine with titanium trichloride[12] was also unsuccessful. The reaction of XVII with isoamyl nitrite in hydrochloric acid and methanol gave XXIII (23%); the formation of which can be rationalized by assuming a benzylic acid rearrangement of the initially formed α-ketolactone XXI followed by intervention of methanol. The NMR spectrum of XXIII showed two methoxy signals as singlets at δ 3.20 and 3.78 respectively. The mass spectrum showed a molecular ion peak at 239. These data agree with the structure proposed. Attempted conversion of XXIII to XXI by acid treatment failed. Attempt to obtain XXI from XVII with ceric ammonium nitrate, a mild oxidizing reagent for a benzylic position,[11b] gave XXIV as the only isolable product. The molecular ion peak (165) and the IR absorption of the five membered lactone (1790 cm^{-1}) confirm the structure XXIV. These results show that compound XXI is too unstable to isolate, the molecule rapidly rearranging with decarbonylation to the five membered ring.



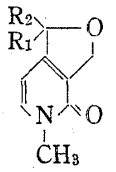
XIII : $R_1=C_2H_5$, R_2=CHO
XIV : R_1=*t*-Bu, R_2=CHO
XVI : R_1=*t*-Bu, $R_2=CH_2OH$



XV



XVII : $R_1=R_2$=H
XVIII : $R_1=C_2H_5$, R_2=H
XIX : $R_1=R_2=C_2H_5$
XX : $R_1=C_2H_5$, R_2=OH
XXI : R_1, R_2=O
XXII : R_1, R_2=NOH



XXIII : $R_1=OCH_3$, $R_2=COOCH_3$
XXIV : R_1, R_2=O

Chart 2

Experimental

General Methods——For details of the measurement of melting point, IR, ultraviolet (UV), NMR, and mass spectra, and the washing of extracts, see Experimental of the Part I.[1] Unless otherwise stated, column chromatography was on silica gel (act II, mesh 0.05—0.2 mm) and thin-layer chromatography (TLC) on silica gel GF. Sodium hydride coated with oil (55%) was used and washed 3 times with benzene before use.

Preparation of 4-Alkoxy-1-methyl-2(1H)-pyridone (IV,[13] V,[14] VI)——These compounds were prepared according to a method described in the literature.[14] An example VI is as follows: 4-Benzyloxypyridine-1-oxide[15] (7.6 g) was refluxed in Ac_2O (30 ml) for 20 hr. After concentration of the reaction mixture at reduced pressure, Ac_2O was removed by co-distillation with benzene. The residue (*ca.* 10 g) was dissolved in benzene (400 ml) and the solution was allowed to stand with Al_2O_3 (300 g, act. II) for 50 hr. The Al_2O_3 layer was washed with benzene, then with $CHCl_3$–MeOH (3 : 1). Evaporation of $CHCl_3$–MeOH extract gave crystalline residue (4.5 g), which was decolorized with char coal in MeOH and recrystallized to give 4-benzyloxy-2(1H)-pyridone (2.93 g, mp 197—203°, 39%). An analytically pure sample melts at 202—204°. *Anal.* Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.52; N, 6.96. Found: C, 71.64; H, 5.54; N, 6.96. To a solution of 4-benzyloxy-2(1H)-pyridone (1.87 g) in CH_3OH (80 ml) and 2 N NaOH (9.3 ml, 18.6 mmoles), dimethyl sulfate (1.73 ml, 18.6 mmoles) was added under stirring and ice-cooling. After being kept for 20 hr at room temperature, CH_3OH was removed and the residue was poured into an ice-K_2CO_3 mixture and extracted with $CHCl_3$. The $CHCl_3$-layer was washed with H_2O, dried, and evaporated. The residue was recrystallized from CH_2Cl_2–acetone to give VI (1.59 g, mp 91—99°, 89%). An analytically pure sample melts at 97—99°. *Anal.* Calcd. for $C_{13}H_{13}O_2N$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.34; H, 6.13; N, 6.40. NMR ($CDCl_3$) δ: 3.46 (3H, s), 4.97 (2H, s), *ca.* 5.9 (2H, m), *ca.* 7.1 (1H, m), 7.34 (5H, s). IV and V were obtained

12) G.H. Timms and E. Wildsmith, *Tetrahedron Letters*, **1971**, 195.
13) H.J. Den Hertog and D.J. Buurman, *Rec. Trav. Chim.*, **75**, 257 (1956).
14) K. Igarashi, [*C.A.*, **48**, 738*i* (1954)].
15) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Company, 1967, p. 380.

analogously as hygroscopic crystals in *ca.* 40% yield from the corresponding 4-alkoxypyridine-1-oxide.

Hydrogenolysis of VI to II[13]——A solution of VI (500 mg) in dioxane (35 ml) was shaken with 5% palladium charcoal (200 mg, 50% wet) under hydrogen. The theoretical amount of H_2 (58 ml) was absorbed within 2 hr. The mixture was filtered through a celite to remove the catalyst and, the filtrate was concentrated at reduced pressure. The residue (278 mg) was recrystallized from MeOH to give II (252 mg, mp 168—172°, 87%).

Vilsmeier Reaction, Conversions of II to III and VII——To the Vilsmeier reagent prepared by stirring a mixture of $POCl_3$ (0.1 ml, 1.05 mmoles) and DMF (0.1 ml) for 1 hr at 60°, a solution of II (100 mg, 0.8 mmoles) in $CHCl_3$ (3 ml) was added and the solution was refluxed for 2 hr. After being cooled, the reaction mixture was poured onto ice, stirred for 1 hr, made alkaline with 10% NH_4OH, and extracted with $CHCl_3$. The $CHCl_3$-layer was washed with sat. NaCl–H_2O, dried and evaporated. The residue (48 mg) was separated by TLC (solvent system, cyclohexane–AcOEt–AcOH (5: 5: 2)) to give III (25 mg) and VII (9 mg). The picrate of III was recrystallized from CH_3OH, mp 127—134°. *Anal.* Calcd. for $C_{12}H_{19}O_8N_4Cl$: C, 38.67; H, 2.43; N, 15.04. Found: C, 38.91; H, 2.66; N, 15.19. NMR of III ($CDCl_3$) δ: 3.49 (3H, s), 6.17 (1H, d of d, J=7 Hz and J=2 Hz, C-5 H), 6.58 (1H, d, J=2 Hz, C-3 H), 7.24 (1H, d, J=7 Hz, C-6 H). Recrystallization of VII from acetone–ether gave analytically pure VII, mp 138—140°. *Anal.* Calcd. for $C_7H_6O_2NCl$: C, 49.00; H, 3.53; N, 8.16. Found: C, 49.45; H, 3.61; N, 8.66. NMR ($CDCl_3$) δ: 3.56 (3H, s), 6.27 (1H, d, J=7 Hz), 7.48 (1H, d, J=7 Hz), 10.3 (1H, s CHO).

Conversion of IV to VIII——To the Vilsmeier reagent prepared by stirring $POCl_3$ (4.0 ml, 42 mmoles) and DMF (4.0 ml) for 1 hr at 60°, a solution of IV (4.5 g, 32 mmoles) in $CHCl_3$ (20 ml) was added and the solution was refluxed for 20 hr. Work-up as above gave a crystalline residue (4.4 g), which was recrystallized from CH_2Cl_2–acetone to give VIII (3.92 g, mp 152—158°, 73%). An analytically pure sample melts at 159—160°. *Anal.* Calcd. for $C_8H_9O_3N$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.68; H, 5.53; N, 8.28. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1678, 1655. NMR ($CDCl_3$) δ: 3.56 (3H, s, NCH_3), 4.00 (3H, s, OCH_3), 6.09 (1H, d, J=8 Hz, C-5 H), 7.63 (1H, d, J=8 Hz, C-6 H), 10.39 (1H, s, CHO).

Conversion of V to IX——To the Vilsmeier reagent prepared from $POCl_3$ (0.4 ml, 4.2 mmoles) and DMF (0.4 ml), a solution of V (500 mg, 3.3 mmoles) in DMF (1 ml) was added, and the solution was stirred for 1.5 hr at 55°. Work-up as above gave a crystalline residue (463 mg), which was recrystallized from MeOH and ether to give IX (407 mg, mp 123—125°, 73%). *Anal.* Calcd. for $C_9H_{11}O_3N$: C, 59.66; H, 6.12; O, 26.49; N, 7.73. Found: C, 60.04; H, 6.25; O, 26.09; N, 7.82. NMR ($CDCl_3$) δ: 1.46 (3H, t), 3.50 (3H, s), 4.22 (2H, q), 6.06 (1H, d, J=8 Hz), 7.59 (1H, d, J=8 Hz), 10.3 (1H, s, CHO).

Conversion of VI to X and VII——To the Vilsmeier-reagent prepared from $POCl_3$ (0.28 ml, 3.0 mmoles) and DMF (0.28 ml), a solution of VI (500 mg, 2.3 mmoles) was added and stirred for 2.5 hr at 60°. Work-up gave a crystalline residue (504 mg), which was recrystallized from acetone–ether to give X (380 mg, mp 144—147°, 67%). An analytically pure sample melts at 147—148°. *Anal.* Calcd. for $C_{14}H_{13}O_3N$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.21; H, 5.39; N, 5.62. NMR ($CDCl_3$) δ: 3.49 (3H, s), 5.27 (2H, s, $-CH_2-$), 6.07 (1H, d, J=8 Hz), 7.38 (5H, s), 7.48 (1H, d, J=8 Hz), 10.4 (1H, s, CHO). The above experiment was also carried out with the reaction time prolonged to 17 hr. After being cooled, the solution was poured in K_2CO_3-ice water and the resulting precipitate was filtered off and washed with H_2O. The dried precipitate (107 mg, mp 146—148°) was pure X (mixed melting point and TLC). The combined filtrate was extracted with $CHCl_3$ and the $CHCl_3$-layer was washed with sat. NaCl–H_2O, dried, and evaporated. The residue (283 mg) was recrystallized from CH_2Cl_2–acetone to give VII (106 mg, mp 132—136°). The residue (402 mg) from the mother liquor was separated by TLC (solvent system; cyclohexane–AcOEt–AcOH (5: 5: 2)) to afford VII (62 mg) and X (34 mg), the latter being the more polar fraction. Recrystallization of the fractions from CH_2Cl_2–acetone gave VII (49 mg, mp 138—139°) and X (21 mg, mp 145—148°) respectively. Total yield: VII, 39%, X, 23%.

Attempted Conversion of X to VII——A solution of X (200 mg, 0.82 mmole) in DMF (1 ml) was allowed to stand for 17 hr at 60° with Vilsmeier reagent prepared from $POCl_3$ (0.1 ml, 10.4 mmoles) and DMF (0.1 ml). Work-up gave a crystalline residue (197 mg), which was recrystallized from CH_2Cl_2–acetone to give recovered X (130 mg, mp 144—150°). TLC (as above) of the residue from the mother liquor gave VII (8 mg) and further X (28 mg). Recrystallization of the fractions from CH_2Cl_2–acetone gave VII (4 mg, mp 137—139°) and X (19 mg, mp 144—147°). Total yield: VII, 3%, X, 74%.

Hydrogenolysis of X to XI——A solution of X (300 mg) in dioxane (15 ml) was shaken with 5% palladium-charcoal (120 mg, 50% wet) under hydrogen. Hydrogen absorption (37 ml, theoretical amount 31 ml) ceased within 20 min. After usual work-up, the crystalline residue (220 mg) was recrystallized from acetone to give XI (166 mg, mp 160—163°, 88%). An analytically pure sample melts at 162—163°. *Anal.* Calcd. for $C_7H_7O_3N$: C, 54.90; H, 4.61; N, 9.15. Found: C, 55.19; H, 4.71; N, 9.26. IR ν_{max}^{Nujol} cm^{-1}: 2600—2300, 1660, 1635, 1570. NMR ($CDCl_3$) δ: 3.49 (3H, s), 5.92 (1H, d, J=8 Hz), 7.42 (1H, d, J=8 Hz), 10.2 (1H, s, CHO), 13.7 (1H, exchangeable with D_2O).

Conversion of XI to VII by Vilsmeier-reagent——To a Vilsmeier-reagent prepared by stirring $POCl_3$ (0.08 ml, 0.85 mmole) with DMF (0.08 ml) for 1 hr at 60°, a solution of XI (100 mg, 0.65 mmole) in $CHCl_3$ (3 ml) was added and the solution was refluxed for 2 hr. After being cooled the solution was poured into

K_2CO_3-ice mixture, stirred for 1 hr and extracted with $CHCl_3$. The $CHCl_3$-layer gave a residue (46 mg) which on TLC (solvent-system; $CHCl_3$–AcOEt–MeOH (12: 6: 1)) afforded VII (4 mg). The aqueous-layer was acidified with AcOH and concentrated to dryness. The residue was dissolved in warm $CHCl_3$ and the solution was passed through a silica-gel layer (2 g). Evaporation of the eluent (100 ml, $CHCl_3$) gave recovered XI (22 mg, mp 163—166°).

Ricinine (XII) from VIII——To a solution of VIII (100 mg, 0.6 mmole) in AcOH (2 ml) was added $NH_2OH \cdot HCl$ (50 mg, 0.7 mmole) and NaOAc (69 mg, 0.8 mmole) and the mixture was refluxed under stirring for 3 hr. After being cooled, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$–MeOH (3: 1). The residue (69 mg) from the organic layer was recrystallized from $CHCl_3$–MeOH to give XII (52 mg, mp 195—197°, 53%). Further recrystallization afforded pure XII (mp 201—202°) (authentic sample, mp 201.5° [7]). IR ν_{max}^{Nujol} cm^{-1}: 2220, 1658, 1635, 1637, 1540, 1140. NMR ($CDCl_3$) δ: 3.40 (3H, s, NCH_3), 3.76 (3H, s, OCH_3), 6.12 (1H, d, J=8 Hz, C-5 H), 7.78 (1H, d, J=8 Hz, C-6 H).

Reaction of VIII with Diethyl Malonate to give XIII and XV——a) With *t*-BuOK in Dioxane: To a solution of VIII (2.1 g, 12.5 mmoles) and diethyl malonate (2.28 ml, 15 mmoles) in dioxane (30 ml) was added *t*-BuOK (1.69 g, 15 mmoles) and the mixture was refluxed under stirring and N_2 atmosphere for 2 hr. A deep brown precipitate appeared, soon after heating was begun. After being cooled, the reaction mixture was poured into ice-AcOH, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with sat. NaCl–H_2O, dried, and evaporated. The residue was separated by TLC (solvent system; $CHCl_3$–AcOEt–MeOH (12: 6: 1)) to give XV, (570 mg) and XIII (1.0 g) as the more polar fraction. The XV-fraction was recrystallized from CH_2Cl_2–acetone to give XV (470 mg, mp 159—161°, 13%). *Anal.* Calcd. for $C_{16}H_{17}O_6N$: C, 60.18; H, 5.37; N, 4.39. Found: C, 60.24; H, 5.37; N, 4.47. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200 (broad), 1720, 1678, 1650, 1630. NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7 Hz), 1.43 (3H, t, J=7 Hz), 3.56 (3H, s), 4.47 (4H, q, J=7 Hz), 6.51 (1H, d, J=8 Hz), 7.14 (1H, d, J=8 Hz), 9.02 (1H, s, C-8 H), 11.7 (1H, s, exchangeable with D_2O). UV $\lambda_{max}^{95\%EtOH}$ mμ(ε): 229 (28400), 284 (15800), 334 (12200). Mass Spectrum *m/e*: 319 (M^+).

The XIII-fraction was recrystallized from ether to give XIII (527 mg, mp 77—79°, 14%). *Anal.* Calcd. for $C_{14}H_{17}O_6N$: C, 56.94; H, 5.80; N, 4.74. Found: C, 57.04; H, 5.94; N, 4.79. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745, 1733, 1633, 1653. NMR ($CDCl_3$) δ: 1.27 (6H, t, J=7 Hz), 3.57 (3H, s), 4.22 (4H, q, J=7 Hz), 6.00 (1H, s, –CH–), 6.32 (1H, d, J=8 Hz), 7.53 (1H, d, J=8 Hz), 10.5 (1H, s, CHO).

b) With NaH in Dimethoxyethane: To a stirred solution of diethyl malonate (3.3 ml, 21.8 mmoles) and NaH (955 mg, 21.8 mmoles) in dimethoxyethane (55 ml), VIII (3.05 g, 18.2 mmoles) was added under N_2 atmosphere, and the solution was refluxed for 2 hr. The mixture was cooled and the precipitate was removed by filtration and washed with dimethoxyethane. The precipitate was treated with ice-AcOH then extracted with $CHCl_3$. The $CHCl_3$-layer was washed with sat. NaCl–H_2O, dried, and evaporated. The residue (2.64 g) was dissolved in $CHCl_3$ and the solution was passed through a silica gel layer (25 g). Evaporation of the collected eluate (*ca.* 1 liter $CHCl_3$) gave a mixture (1.8 g) consisting mainly of XIII. The filtrate from the reaction mixture was evaporated and the residue was treated in the same way as the precipitate from the reaction. The eluate with $CHCl_3$ (800 ml) yielded 1 g of residue. Further purification of each fraction by a combination of column- and thin-layer- (solvent system see (a)) chromatography followed by recrystallization gave XV (30 mg, <1%) and XIII (1.75 g, 33%).

Conversion of VIII to XIV with Di-*tert*-butyl Malonate——To a stirred solution of di-*tert*-butyl malonate (777 mg, 3.6 mmoles) and NaH (156 mg, 3.6 mmoles) in dimethoxyethane (5 ml), VIII (500 mg, 3.0 mmoles) was added under N_2 atmosphere, and the mixture was refluxed for 1 hr. The mixture was cooled, and the precipitate was separated by filtration and washed with dimethoxyethane. The precipitate was treated with ice-AcOH and extracted with $CHCl_3$. The $CHCl_3$-layer was washed with sat. NaCl–H_2O, dried, and evaporated to give crude XIV (903 mg, mp 100—112°, 86%, TLC, one spot), which was used in the subsequent conversion to XVI without further purification. An analytically pure sample melts at 118—121° after recrystallization from ether. *Anal.* Calcd. for $C_{18}H_{25}O_6N$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.79; H, 7.18; N, 4.10. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (shoulder), 1725, 1680, 1650. NMR ($CDCl_3$) δ: 1.47 (18H, s), 3.57 (3H, s), 5.76 (1H, s, –CH–), 6.39 (1H, d, J=8 Hz), 7.53 (1H, d, J=8 Hz), 10.45 (1H, s).

$NaBH_4$-reduction of XIV to XVI——To a stirred solution of XIV (0.81 g, 2.3 mmoles) in dioxane (10 ml), H_2O (1 ml), and AcOH (0.13 ml, 2.3 mmoles), was added $NaBH_4$ (87 mg, 2.3 mmoles) portionsweise under ice-cooling. The mixture was stirred for 30 min at room temperature, then additional $NaBH_4$ (44 mg, 1.2 mmoles) was added and the solution was stirred for a further 30 min. The solution was poured into ice-AcOH and extracted with $CHCl_3$. The $CHCl_3$-layer was washed with sat. NaCl–H_2O, dried, and evaporated. The residue (730 mg) was washed with acetone–ether to give XVI (362 mg, mp 136—138°). Concentration of the mother liquor gave further XVI (251 mg, mp 130—136°). Total yield: 76%. An analytically pure sample melts at 137—139° after recrystallization from acetone–ether. *Anal.* Calcd. for $C_{18}H_{27}O_6N$: C, 61.17; H, 7.70; N, 3.96. Found: C, 61.39; H, 7.69; N, 4.14. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 1740 (shoulder), 1725, 1646. NMR ($CDCl_3$) δ: 1.46 (18H, s), 3.53 (3H, s), 4.62 (2H, s, $-CH_2O-$), 4.71 (1H, s, –CH–), 6.40 (1H, d, J=8 Hz), 7.22 (1H, d, J=8 Hz).

Lactonization of XVI to XVII with CF_3COOH——A solution of XVI (545 mg) in CF_3COOH (5 ml) was refluxed for 1 hr. The solvent was removed by co-distillation with benzene and a solution of the resulting

residue in $CHCl_3$ (600 ml) was passed through a silica gel layer (5 g). Elution with $CHCl_3$-containing 1% MeOH, and concentration of the combined eluates gave XVII (245 mg), which was recrystallized from CH_2Cl_2–acetone to give pure XVII (225 mg, mp 180—182°, 82%). *Anal.* Calcd. for $C_9H_9O_3N$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.13; H, 5.12; N, 7.73. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1743, 1663. NMR ($CDCl_3$) δ: 3.52 (2H, broad s, $-CH_2CO-$), 3.56 (3H, s), 5.36 (2H, broad s, $-CH_2O-$), 6.05 (1H, d, $J=8$ Hz), 7.31 (1H, d, $J=8$ Hz).

Ethylation of XVII to XVIII and XIX——a) To a stirred solution of XVII (300 mg, 1.67 mmoles) in DMF (5 ml) was added NaH (88 mg, 2.0 mmoles) under ice-cooling and N_2-atmosphere. After the mixture had been stirred for 20 min. EtBr (0.15 ml, 2.0 mmoles) was added and the solution was stirred for a further 3 hr under the above conditions. The solution was poured into ice-AcOH and extracted with $CHCl_3$. The residue (366 mg) from the extract was separated by TLC (solvent system; $CHCl_3$–MeOH (10: 1)) to give XIX (66 mg, 17%), XVIII (148 mg, 43%), and recovered XVII (49 mg, 17%) as the most polar fraction. Analytically pure XIX was obtained by recrystallization from ether, mp 93—99°. *Anal.* Calcd. for $C_{13}H_{17}O_3N$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.20; H, 7.24; N, 6.14. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1660, 1600. NMR ($CDCl_3$) δ: 0.75 (6H, t, $J=7$ Hz, $CH_3\times2$), 1.5—2.5 (4H, m, $CH_2\times2$), 3.56 (3H, s), 5.30 (2H, s), 6.08 (1H, d, $J=8$ Hz), 7.33 (1H, d, $J=8$ Hz). An analytically pure sample of XVIII was obtained by recrystallization from acetone–ether, mp 100—102°. *Anal.* Calcd. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.48; H, 6.30; N, 6.82. Mass Spectrum *m/e*: 207 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1660, 1603. NMR ($CDCl_3$) δ: 1.00 (3H, t, $J=7$ Hz, CH_3-), 1.72—2.20 (2H, m, $-CH_2-$), 3.4 (1H, m, $-CH-$), 3.55 (3H, s), 5.32 (2H, broad s), 6.03 (1H, d, $J=8$ Hz), 7.30 (1H, d, $J=8$ Hz).

b) To a stirred solution of XVII (1.35 g, 7.53 mmoles) in DMF (25 ml), NaH (394 mg, 9.0 mmoles) was added at 0° under N_2 atmosphere. The mixture was stirred for 20 min, then EtI (7.3 ml, 9.0 mmoles) was added portionsweise over 5 min at −45——55° and the solution was stirred for 5 hr at this temperature. Work-up as in (a) gave XIX (381 mg, 22%), XVIII (167 mg, 11%) and a mixed fraction of recovered XVII and further oxidized XX (520 mg). The mixed fraction was further separated by TLC (solvent system; $CHCl_3$–AcOEt–MeOH (12: 6: 1)) to give XX (161 mg, mp 177—182°, 10%), and XVII (187 mg, mp 172—179°, 14%) as the more polar fraction. XX was identified with an authentic sample prepared by oxygenation of XVIII (see next).

Oxygenation of XVIII to XX——A stream of oxygen was passed through a slightly cloudy solution of XVIII (100 mg), $Cu(OAc)_2\cdot H_2O$ (10 mg) and $(Et)_3N$ (0.5 ml) in 99% EtOH (10 ml) for 5 hr at 0°, and then for a further 30 min at room temperature. The reaction mixture was concentrated, and the residue was dissolved in $CHCl_3$. The $CHCl_3$-layer was washed with H_2O and filtered through a celite layer. The filtrate was concentrated and passed through a silica gel (2 g) layer. Evaporation of the $CHCl_3$-eluate (100 ml) gave crude XX (71 mg), which was recrystallized from CH_2Cl_2–acetone to give XX (49 mg, mp 179—180°, 46%). An analytically pure sample melts at 182—183°. *Anal.* Calcd. for $C_{11}H_{13}O_4N$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.14; H, 6.04; H, 6.37. Mass Spectrum *m/e*: 223 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3635, 1741, 1659, 1603, 1155. NMR ($CDCl_3$) δ: 0.97 (3H, t, $J=7$ Hz, CH_3-), 1.64—2.00 (2H, m, $-CH_2-$), 3.58 (3H, s, NCH_3), 3.80 (1H, s, exchangeable with D_2O), 5.14 and 5.55 (2H, AB quartet, $J=16$ Hz, $-CH_2O-$), 6.51 (1H, d, $J=7$ Hz), 7.40 (1H, d, $J=7$ Hz).

Oximation of XVII to XXII——To a stirred solution of XVII (100 mg, 0.56 mmole) in AcOH–H_2O (*ca.* 3: 2, 2 ml) was added 5 portions of $NaNO_2$ (42 mg, total 5.5 mmoles) at 30 min intervals at room temperature. The mixture was then stirred for a further 1 hr. The solvent was concentrated at reduced pressure and the precipitate was filtered and washed with H_2O. The precipitate (92 mg) was washed with MeOH to give XXII (74 mg, dp 207—210°, 64%). Further trituration with $CHCl_3$–MeOH gave an analytically pure sample (dp 208—213°). *Anal.* Calcd. for $C_9H_8O_4N_2$: C, 51.92; H, 3.87; N, 13.46. Found: C, 51.74; H, 4.02; N, 13.22. Mass Spectrum *m/e*: 208 (M^+), IR ν_{max}^{Nujol} cm^{-1}: 2600—2300, 1740, 1630, 1570. NMR ($CDCl_3+CF_3COOH$) δ: 3.75 (3H, s), 5.57 (2H, s), *ca.* 7.7 (2H).

Conversion of XVII to XXIII——To a stirred suspension of XVII (50 mg, 0.28 mmoles) in CH_3OH (1 ml) was added conc. HCl (0.1 ml) and isoamyl nitrite (0.06 ml, 0.42 mmoles) and the solution was allowed to stand at room temperature for 20 hr. The solution was poured into ice-H_2O and extracted with $CHCl_3$. The $CHCl_3$-layer was washed with sat. NaCl–H_2O, dried and evaporated. The residue (68 mg) was separated by TLC (solvent system; cyclohexane–AcOEt–AcOH (5: 5: 2)) to give XXIII (15 mg, oil, 22%), and recovered XVII (17 mg, 33%) as the more polar fraction. XXIII: Mass Spectrum *m/e*: 239 (M^+). IR ν_{max}^{film} cm^{-1}: 1740, 1660, 1610, 1560. NMR ($CDCl_3$) δ: 3.20 (3H, s), 3.60 (3H, s), 3.78 (3H, s), 5.12 (2H, s), 6.32 (1H, d, $J=8$ Hz), 7.40 (1H, d, $J=8$ Hz).

Conversion of XVII to XXIV——To a stirred solution of XVII (300 mg, 1.67 mmoles) in AcOH–H_2O (9: 1, 15 ml) was added $(NH_4)_2Ce(NO_3)_6$ (3.67 g, 6.7 mmoles) and the mixture was stirred for 1.5 hr at 70—80°. The reaction mixture was concentrated to dryness after addition of $(Et)_3N$ (for neutralization of liberated HNO_3) and the residue was extracted with $CHCl_3$ in a soxhlet apparatus. The $CHCl_3$-extract (413 mg) was recrystallized from acetone–ether to give crude XXIV (68 mg, 25%). An analytically pure sample was obtained by passing a solution of the crude product in $CHCl_3$ containing 1% MeOH, through a silica-gel (900 mg) column, followed by recrystallization; mp 199—200° (decomp.). *Anal.* Calcd. for $C_8H_7O_3N$: C, 58.18; H, 4.27; N, 8.48. Found: C, 57.84; H, 4.31; N, 8.73. Mass Spectrum *m/e*: 165 (M^+). IR ν_{max}^{Nujol}

cm^{-1}: 1785, 1680 (shoulder), 1670. NMR ($CDCl_3+CF_3COOH$) δ: 3.85 (3H, s), 5.45 (2H, s), 7.15 (1H, d, $J=8$ Hz), 7.80 (1H, d, $J=8$ Hz).

Acknowledgement We thank Dr. M. Narisada of this laboratory for his helpful advice and discussion.