cant amounts of d or f bonding (such as the heavy alkalies and alkaline earths), are in progress.

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Received July 3, 1972

Synthesis of Some DE and CDE Ring Analogs of Camptothecin

Sir:

Since the isolation and structure determination of the antitumor alkaloid camptothecin (**1**) in 1966,[1] several syntheses have been developed.[2a-d] The α-hydroxylactone functionality present in the E ring is an absolute requirement[3] for antitumor activity, and at present only one synthetic analog of camptothecin containing this E ring structure is known.[4] We now present the synthesis of several DE and CDE ring analogs.

Our synthetic procedure is broadly applicable and consists essentially of three stages. First, a nipecotic acid is subjected to the methylene lactam rearrangement,[5] giving the corresponding 3-methylene-2-piperidone. Second, this methylene lactam is converted to the dihydropyridone–primary allylic alcohol, and the acetic acid residue is introduced *via* Claisen rearrangement. Third, this 4-substituted 3-methylene-2-piperidone is again converted to a primary allylic alcohol, dehydrogenated, lactonized, and oxidized to give the fused pyridone–hydroxylactone. Examples of this overall process, with variations, are given below.

Nicotinic acid was converted to glycol **5a** (82%) *via* **2a**, **3a**, and **4a** as described.[5] Acetylation with acetic anhydride–pyridine at room temperature gave the monoacetate **6a** (mp 105–106°, 95%)[6] from which the 5,6-dihydropyridone **7a** (70%) was obtained by successive dehydration ($SOCl_2$–pyridine) and deacetylation (K_2CO_3–aqueous CH_3OH). Introduction of the lactone ring carbon atoms was accomplished by Claisen rearrangement.[7] Thus, allylic alcohol **7a**, excess trimethyl orthobutyrate,[8] and a catalytic amount of propionic acid at 145°, 3 hr, led to methylene lactam **9a** (96%) as a mixture of diastereomers. Allylic oxidation of **9a** with selenium dioxide[9] in refluxing toluene gave a mixture of tertiary alcohols which was converted into dihydropyridone **10a** (69%) by heating in acetic acid–acetic anhydride (catalytic H_2SO_4, 135–140°, 3 hr).

Although dehydrogenation of **10a** proceeded poorly with both lead tetraacetate in acetic acid[2a] and DDQ in boiling *p*-dioxane,[4] bromopyridone **11a** was prepared in 96% yield from **10a** with 200 mol % of NBS in CCl_4 (AIBN initiation, 8 min). Lactonization of **11a** in 2 *N* H_2SO_4–monoglyme at 50° (20 hr) gave lactone **13a** (100%). Removal of the bromine was cleanly effected (97%) by dehalogenation with H_2–Pd/C–Et_3N.[10] The resulting lactone **14a** (mp 91–92°) was converted to the camptothecin analog **15a** (mp 176–177°, 68%) by oxidation[11] with oxygen and alkali in the presence of triethyl phosphite.

6-Methoxycarbonylnicotinic acid,[12] successively treated with $SOCl_2$ (reflux, 2 hr) and benzyl alcohol (benzene–pyridine, 15 hr), gave the 2-methyl 5-benzyl diester[13] which on hydrogenation as hydrochloride in ethanol over PtO_2 followed by substitution of 10% Pd/C and addition of excess formaldehyde gave the hydrochloride of ester acid **2b** (62% overall). Rearrangement[5] of **2b** in acetic anhydride–K_2CO_3 gave methylene lactam **3b** (85%). Treatment of **3b** with MCPA[5] gave epoxide **4b** (98%) which was converted in refluxing HOAc, 24 hr, to the hydroxy acetate **6b** (60%).[14] Dehydration with $SOCl_2$–pyridine (55%) followed by deacetylation (K_2CO_3–CH_3OH) gave the allylic alcohol **7b** which was subjected to Claisen rearrangement and selenium dioxide oxidation as described above to effect the transformation to **10b**. NBS–CCl_4 converted **10b** directly to pyridone **12b** (60%). The desired camptothecin analog **15b** (mp 152–153°) was obtained by one-step lactonization–oxidation of **12b** with K_2CO_3 in oxygenated methanol, while deoxylactone **14b** resulted when oxygen was excluded.

3-Cyano-6-phenyl-2-pyridone,[15] heated with $C_6H_5POCl_2$[16] at 180°, 4 hr, gave 2-chloro-3-cyano-6-phenylpyridine which was dehalogenated (71%) in DMF with H_2–Pd/C–Et_3N. Hydrolysis[17] to the acid[18] and esterification gave methyl 6-phenylnicotinate[19] in 83%

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

(2) (a) G. Stork and A. G. Schultz, *ibid.*, **93**, 4074 (1971); (b) R. Volkmann, S. Danishefsky, J. Eggler, and D. M. Solomon, *ibid.*, **93**, 5576 (1971); (c) M. C. Wani, H. F. Campbell, G. A. Brine, J. A. Kepler, and M. E. Wall, *ibid.*, **94**, 3631 (1972); (d) E. Winterfeld, T. Korth, D. Pike, and M. Boch, *Angew. Chem.*, **84**, 265 (1972).

(3) M. E. Wall, 4th International Symposium on the Biochemistry and Physiology of Alkaloids, Halle, DDR, June 25–28, 1969; *Abh. Deut. Akad. Wiss. Berlin*, 46 (1971).

(4) M. E. Wall, H. F. Campbell, M. C. Wani, and S. G. Levine, *J. Amer. Chem. Soc.*, **94**, 3632 (1972).

(5) M. L. Rueppel and H. Rapoport, *ibid.*, **94**, 3877 (1972).

(6) All new compounds were characterized as to purity by tlc or gc, and spectral data (ir, nmr, and uv where appropriate) support the assigned structures. Elemental compositions were established by high-resolution mass spectra, combustion analyses, or both.

(7) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Peterson, *J. Amer. Chem. Soc.*, **92**, 741 (1970).

(8) S. M. McElvain and C. L. Aldridge, *ibid.*, **75**, 3987 (1953).

(9) U. T. Bhalerao and H. Rapoport, *ibid.*, **93**, 4835 (1971).

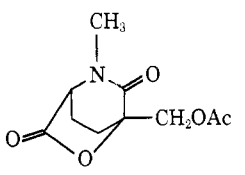
(10) J. W. Wilt and E. Vasiliauskas, *J. Org. Chem.*, **37**, 1467 (1972).

(11) J. N. Gardner, F. E. Carlon, and O. Gnoj, *ibid.*, **33**, 3294 (1968).

(12) K. Isagawa, M. Kawai, and Y. Fushizaka, *Nippon Kagaku Zasshi*, **88**, 553 (1967).

(13) L. Thunus and M. Dejardin-Duchene, *J. Pharm. Belg.*, **24**, 3 (1969).

(14) The principal by-product in this acetylation is the lactone i.



i

(15) C. Barat, *J. Indian Chem. Soc.*, **8**, 801 (1931).

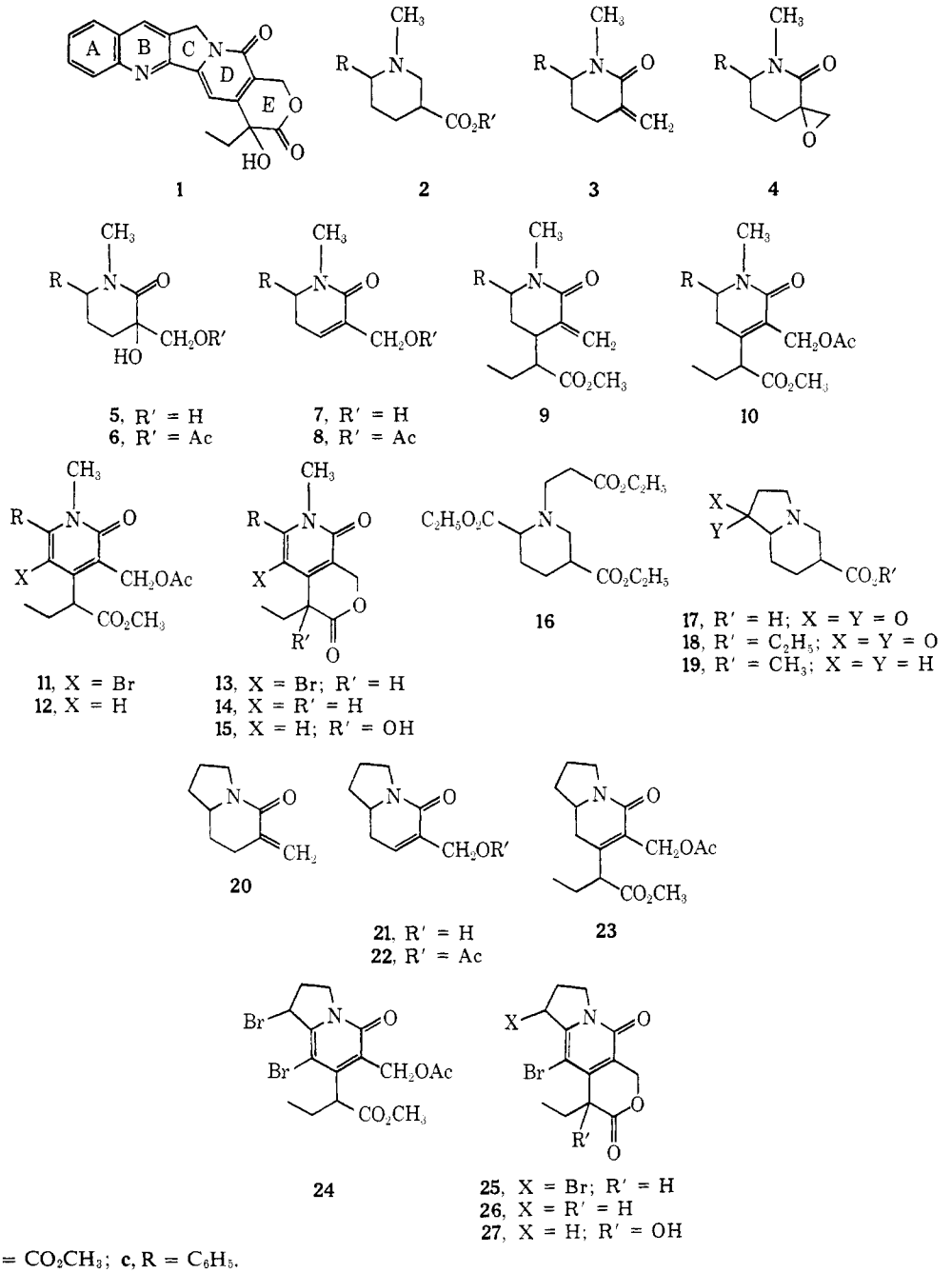
(16) M. M. Robison, *J. Amer. Chem. Soc.*, **80**, 5481 (1958).

(17) S. M. McElvain and M. A. Goese, *ibid.*, **65**, 2233 (1943).

(18) R. A. Abramovitch, G. C. Sang, and A. D. Notation, *Can. J. Chem.*, **38**, 761 (1960).

(19) F. Bordin, F. Baccichetti, and G. Fattori, *Ann. Chim. (Rome)*, **55**, 882 (1965).

Chart I[a]



[a] **a**, R = H; **b**, R = CO_2CH_3; **c**, R = C_6H_5.

yield from pyridone. Heating this methyl ester with methyl *p*-toluenesulfonate (110°, 2 hr) gave the quaternary salt which was hydrogenated (ethanol–PtO_2) to ester **2c**.[20] Hydrolysis (NaOH, aqueous CH_3OH) and acetic anhydride rearrangement[5] gave methylene lactam **3c** (85%). The conversion of **3c** to the desired camptothecin analog **15c** (mp 170–171°) was accomplished using the same procedures as in the **a** series (see Chart I), omitting the catalytic debromination since, as with **10b**, NBS–CCl_4 aromatization of **10c** gave no bromopyridone.

Synthesis of a CDE ring analog of camptothecin began with diethyl piperidine-2,5-dicarboxylate,[21] which was alkylated with ethyl 3-bromopropionate to give the triester **16** (bp 124–126° (0.03 mm), 75%). Dieckmann cyclization[22] followed by hydrolysis and decarboxylation (6 *N* HCl, 105°, 5 hr) led quantitatively to the hydrochloride of **17**, characterized as ethyl ester **18**, and gc showed the expected mixture of two isomers. Hydrogenation of **17** in aqueous HCl over PtO_2 resulted in hydrogenolysis[23] and, after esterification (HCl–CH_3OH), gave bicyclic amine **19** (55%). Hydrolysis followed by rearrangement[5] in acetic anhydride afforded methylene lactam **20** (mp 43–45°, 69%) which was converted to allylic alcohol **21** in 55% yield by oxidation with selenium dioxide in acetic acid (100°, 4 hr), giving **22**, followed by deacetylation with K_2CO_3–aqueous CH_3OH.

Transformation of alcohol **21** into dihydropyridone **23** followed the same procedure and gave comparable

(20) W. K. Chang and L. A. Walter, *J. Med. Chem.*, **14**, 1011 (1971).
(21) S. de Groot and J. Strating, *Recl. Trav. Chim. Pays-Bas*, **80**, 944 (1961).
(22) J. Blake, C. D. Wilson, and H. Rapoport, *J. Amer. Chem. Soc.*, **86**, 5293 (1964).
(23) C. P. Rader, G. E. Wicks, Jr., R. L. Young, Jr., and H. S. Aaron, *J. Org. Chem.*, **29**, 2252 (1964).

yields to the **a** series analog. Reaction of **23** with NBS–CCl_4 afforded the dibromide **24** which was lactonized to **25** (mp 175–176°) with aqueous H_2SO_4–monoglyme. Catalytic dehalogenation[10] followed by chromatography gave two fractions; the major product was bromopyridone **26** (mp 169–170°) and the minor product was the debromo analog of **26**. Finally, oxidation of each as described for the **a** series gave the CDE ring analog **27** (mp 195–197°) and debromo-**27** (mp 175–177°).

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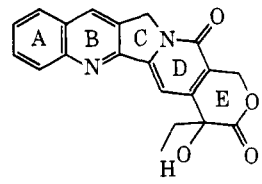
A Total Synthesis of *dl*-Camptothecin

Sir:

The initial report of potent antileukemic and antitumor activity of the novel alkaloid camptothecin (**1**), whose isolation and structure determination were reported[1] in 1966, has been followed by several total syntheses of this important compound.[2] Recently, there was reported[3] from this laboratory a broadly applicable synthesis of a series of analogs of camptothecin containing the fused pyridone–lactone DE ring system of the parent alkaloid. We now wish to present an extension of this synthetic procedure to the total synthesis of *dl*-camptothecin.

The previously reported syntheses[2] involved formation of the pyridone D ring *via* cyclization followed by elaborations on the pyridone ring, generally effected through Michael-type additions either before or after D ring formation. The route we are presenting has the pyridone D ring intrinsically built into the starting material, pyridine-2,5-dicarboxylic acid. Subsequent methylene lactam rearrangement of a nipecotic acid[4] gives the desired piperidone. The main feature of our synthesis is a facile series of alternate rearrangement–oxidation reactions, proceeding in good yields and culminating in a practical preparation of *dl*-camptothecin.

The bicyclic keto acid **2**, obtained[3] in 85% yield from pyridine-2,5-dicarboxylic acid, was reduced by sodium borohydride in methanol–water (0°, 18 hr) to the hydroxy amino acid **3**,[5] obtained in 86% yield after purification by ion exchange. α-Methylene lactam rearrangement[4] in acetic anhydride (145°, 2.5 hr) gave, after chromatography on silica gel, an 84% yield of the piperidone acetate **4** as a mixture of isomers. This mixture was subjected to SeO_2 oxidation in glacial acetic acid (70°, 1 hr), and chromatography gave a 58% yield of the allylic diacetate **6**. Hydrolysis of this diacetate **6** in anhydrous methanol–K_2CO_3 (20°, 30 min) to the diol **7**, *m/e* 183, was achieved quantitatively.



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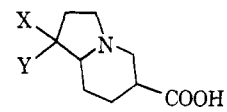
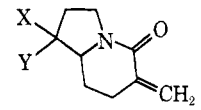
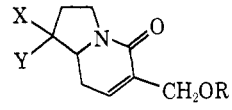


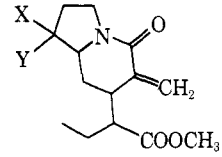
2, X,Y = O
3, X = H; Y = OH



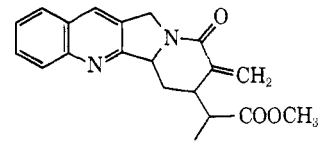
4, X = H; Y = $OCOCH_3$
5, X,Y = O



6, X = H; Y = $OCOCH_3$; R = $COCH_3$
7, X = H; Y = OH; R = H



8, X = H; Y = $OCOC_3H_7$
9, X = H; Y = OH
10, X,Y = O



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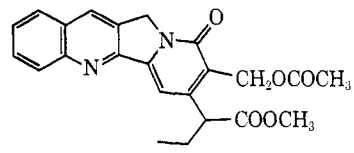

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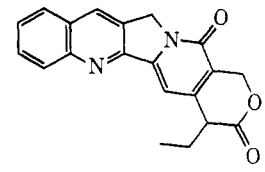

13

Introduction of the α-butyrate side chain was accomplished by Claisen rearrangement,[6] utilizing diol **7** and excess trimethyl orthobutyrate with a catalytic amount of propionic acid at 145° for 3 hr. The crude reaction mixture was distributed between methylene chloride and dilute aqueous hydrochloric acid and evaporation of the methylene chloride phase gave a 75% yield of material containing the α-butyrate side chain. This material was a mixture of the free alcohol **9** and its butyrate ester **8**. Treatment with anhydrous K_2CO_3 in methanol (20°, 1 hr) and chromatography on silica gel with 5% methanol–chloroform gave the alcohol **9**, obtained as a mixture of isomers in 100% yield.

To introduce the AB ring system it was now necessary to oxidize the alcohol **9** to ketone **10** in preparation for a Friedlander quinoline synthesis. This was effected by oxidation of the alcohol **9** with dicyclohexylcarbodiimide in DMSO with a catalytic amount of phosphoric acid[7] (20°, 30 hr) giving, after chromatography,

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

(2) (a) G. Stork and A. G. Schultz, *ibid.*, **93**, 4074 (1971); (b) R. Volkmann, S. Danishefsky, J. Eggler, and D. M. Solomon, *ibid.*, **93**, 5576 (1971); (c) M. C. Wani, H. F. Campbell, G. A. Brine, J. A. Kepler, and M. E. Wall, *ibid.*, **94**, 3631 (1972); (d) M. Boch, T. Korth, J. M. Nelke, D. Pike, H. Radunz, and E. Winterfeldt, *Chem. Ber.*, **105**, 2126 (1972).

(3) J. J. Plattner, R. D. Gless, and H. Rapoport, *J. Amer. Chem. Soc.*, **94**, 8613 (1972).

(4) M. L. Rueppel and H. Rapoport, *J. Amer. Chem. Soc.*, **94**, 3877 (1972).

(5) All new compounds were characterized as to purity by tlc or gc, and their ir and nmr spectra support the assigned structures. Elemental compositions were established by high-resolution mass spectra, combustion analyses, or both. A number of compounds were obtained as isomeric mixtures, but these were not separated since they converged after compound **11**.

(6) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Peterson, *J. Amer. Chem. Soc.*, **92**, 741 (1970).

(7) K. E. Pfitzner and J. G. Moffatt, *ibid.*, **85**, 3027 (1963).