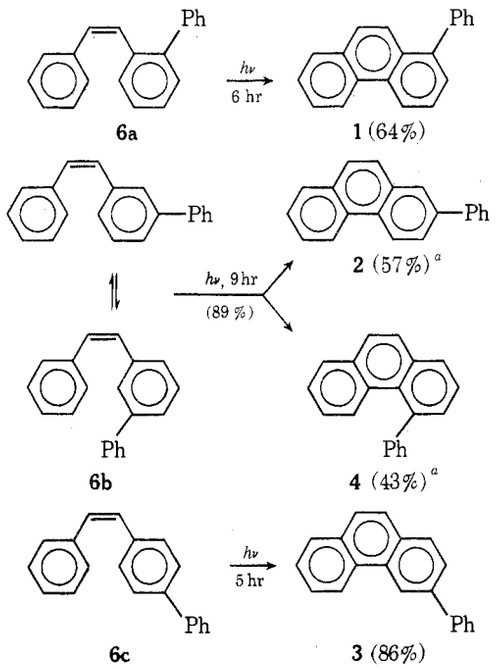
Scheme I



[a] Relative yields based on vpc analysis.

Experimental Section[10]

m-**Phenylstilbene (6b).** A solution of 10 g of KOH in water (150 ml) was added to cinnamic acid (22.84 g, 0.155 mol). The suspension was stirred mechanically until solution occurred. The solution was adjusted to pH 7 with 5% HCl, and cupric chloride dihydrate (8.5 g, 0.05 mol) was added. Acetone (495 ml) was added and the suspension stirred. To the reaction mixture was then added 50 ml of a diazotized solution of 3-aminobiphenyl hydrochloride (10.150 g, 0.0493 mol). The suspension was adjusted to pH 5 with dilute KOH and acetone (150 ml) was added, to maintain a 1:3 ratio of water to acetone. Stirring at room temperature was continued for 48 hr until evolution of nitrogen ceased. The suspension was steam distilled for 4 hr and the suspension remaining in the reaction vessel was made alkaline. The suspension was filtered under suction and the precipitate washed repeatedly with boiling benzene and discarded. The aqueous filtrate was extracted with hot benzene and the organic layers were combined, washed with water until neutral, dried (Na_2SO_4), and filtered. Evaporation of the solvent left an orange-brown residue which was chromatographed over neutral alumina (Woelm, activity grade I, 67.0 × 2.0 cm) using benzene as eluent (350 ml). The eluate was evaporated leaving a colorless solid: 4.73 g (37.5% yield based on amine hydrochloride); mp 100–101°. The uv spectrum (95% EtOH) showed maxima at 223, 228, 236, 297, and 308 nm (ε 17,600, 17,800, 16,700, 27,850, and 27,000).

Anal. Calcd for $C_{20}H_{16}$: C, 93.71; H, 6.29. Found: C, 93.75; H, 6.21.

The isomeric *o*- and *p*-phenylstilbenes were prepared in a similar manner in 6 and 35% yields, respectively.

2- and 4-Phenylphenanthrenes (2 and 4). The irradiation source was a 550-W Hanovia high-pressure mercury lamp housed in a water-cooled quartz immersion well. The reaction well was provided with a gas inlet tube and magnetic stirrer, and was fitted at the bottom with a stopcock to permit removal of aliquots during irradiation. A magnetically stirred solution of **6b** (1.28 g, 0.005 mol) and 0.064 g of iodine (2.5×10^{-4} mol) in 500 ml of benzene–cyclohexane (2:3, v/v) was irradiated. A slow stream of purified air was passed through the solution during the course of the reaction. The color of the solution turned gradually from purple to pale yellow at the end of the reaction. The required irradiation time was determined by following the progress of the reaction by glc. Aliquots (3 ml) taken at specified time intervals were shaken with 5% aqueous NaOH and the organic layer was separated, dried over $MgSO_4$, and filtered. The filtrate was concentrated to about 0.5 ml and injected into the gas chromatograph. Irradiation was continued for about 1 hr after the peak corresponding to **6b** was no longer detectable by glc. The solvent was removed *in vacuo* leaving 1.159 g (89% yield) of a mixture of **2** and **4** (57 and 43%, respectively, by glc). The mixture was chromatographed over neutral alumina (Woelm, activity grade I, 18.0 × 2.0 cm) using a hexane–benzene mixture (2:1, v/v) as eluent. The chromatogram was followed by uv light. The solvent was removed from the eluate leaving an oil which was dissolved in 25 ml of hot ethanol. On cooling 0.350 g of **2** (mp 195–197° (lit.[11] 196.6–197.2°)) deposited.

The ethanol was evaporated and the pale-yellow residue was chromatographed again (Woelm, neutral alumina, activity grade I, 35.0 × 2.0 cm) first using cyclohexane as eluent (450 ml) and then benzene (350 ml). The cyclohexane fraction, after removal of solvent, left an oil (0.405 g) which crystallized as colorless rods, **4**: mp 81.8–82.6° (lit.[4] 80–81.5°). The material showed a single peak in glc; its retention time was identical with that of an authentic sample prepared *via* Haworth synthesis.[5b]

The evaporated benzene fraction contained impure **2** (0.245 g), mp 180–185°.

Compounds **1** and **3** were prepared in a similar manner in the yields shown in Scheme I: **1**, mp 79.5–80.0° (lit.[4] 79.5–80.5°); **3**, mp 73° (lit.[12] 73°).

Acknowledgments. We wish to thank Professor M. S. Newman for a sample of 2-phenylphenanthrene. We are greatly indebted to Professor F. B. Mallory for manuscript copy in advance of publication.

Registry No.—**1**, 4325-76-2; **2**, 4325-77-3; **3**, 2903-83-5; **4**, 4325-78-4; **5a**, 52500-12-6; **5b**, 20893-76-9; **5c**, 4163-91-1; **6a**, 33506-75-1; **6b**, 52500-13-7; **6c**, 2039-69-2; cinnamic acid, 621-82-9.

References and Notes

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Synthesis and Biological Evaluation of De-*AB*-camptothecin

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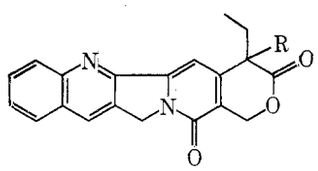
Received May 7, 1974

Recently, Rapoport and coworkers reported a route to analogs of the antitumor alkaloid camptothecin (**2**).[1] The Berkeley group synthesis,[2,3] patterned after the approach used in connection with its highly successful total synthesis,[4] involves a series of rearrangements, hydrogenolyses and dehydrogenations. Among the compounds reported were analogs[5] **3** and **4**.

The new synthesis of α-pyridones of diverse substitution pattern,[6] developed as part of our total synthesis,[7,8] allows for mounting the crucial D and E ring segment found in camptothecin, onto a preformed enamino ester of the type **6** in a very simple fashion. As part of a program aimed at establishing the minimum structural features required for camptothecin-like activity, we have undertaken the preparation and study of analogs where entire rings, found in the natural product, are deleted. In this connection, we have synthesized and evaluated compounds **3** and **4**.



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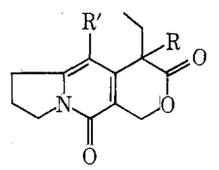
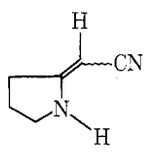
2, R = OH



3, R = R′ = H
4, R = OH, R′ = H
11, R = H, R′ = CO_2Me



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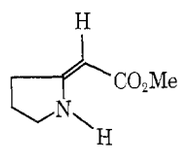

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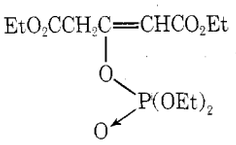

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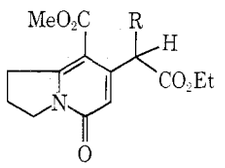

9, R = H
10, R = Et

Methanolysis of the readily available 2-cyanomethylenepyrrolidine (**5**)[9] gives the crystalline enamino ester **6**, mp 102–103.5°. The latter condenses smoothly with either[1,3] dicarbethoxyallene **7**[10] (method A) or its precursor enol phosphate **8**[10] (method B) to give pyridone **9**, mp 127–128°. Although method A is somewhat simpler in that no chromatography is required for purification, this factor does not justify the lower overall yield because of difficulties associated with the transformation of **8** → **7**.

Base-induced ethylation of **9** gave the alkylated pyridone **10**. With the nucleophilic 5 position of the pyridone blocked by the carbomethoxyl function, lactomethylation is forced to occur in the 3 position, affording the resultant lactone ester **11**. The structure of **11** follows from its mass spectrum, parent *m/e* 291, and its nmr spectrum in which the pyridone and ethyl ester proton resonances present in **10** have been eliminated. Without purification, **11** was converted into deoxy analog **3** through the action of concentrated HBr. Hydroxylation of the deoxy compound gave the desired de-*AB*-camptothecin **4**.

Compounds **3** and **4** were examined with respect to their performance as inhibitors of DNA and RNA synthesis. The efficiency of *dl*-**1** and *dl*-**2** as inhibitors of nucleic acid synthesis has already been established, and this property may well be crucial to the antitumor function of naturally occurring **2** (see ref 8 and bibliography), though this point has, by no means, been proved.[5f]

The de-AB analogs showed no discernible inhibition at the micromolar concentrations where *dl*-**1** and -**2** show 50% inhibition. For instance, for the case of **4**, 20% inhibition requires a concentration of 5×10^{-5} *M*.[11] Furthermore, compounds **3** (NSC 177364) and **4**[12] (NSC 174570) exhibited no meaningful activity in the N.C.I. L-1210 carcinoma screen at concentrations where camptothecin is quite active in control experiments.[13]

It would appear, on the basis of these studies and other information in the literature,[5b,d] that the AB portion may be more crucial to activity than was previously suspected. Studies directed toward this problem are in progress.

Experimental Section[14]

Preparation of 2-Carbomethoxymethylenepyrrolidine (6). Treatment of 8.5 g (0.0788 mol) of 2-cyanomethylenepyrrolidine (**5**)[9] with methanolic hydrogen chloride, according to the procedure of Horii[15] afforded 7.18 g (65%) of **6**, mp 88–95°. Chromatography of the mother liquors on 150 g of silica gel gave, after elution with 2:1 hexane–ethyl acetate, an additional 0.69 g (6.2%) of **6**. Several recrystallizations from ether–hexane afforded an analytical sample: mp 102–103.5°; λ_{max} ($CHCl_3$) 3375, 1650, 1590 cm^{-1}; δ ($CDCl_3$) 8.2–7.8 (~1 H, very broad), 4.53 (s, 1 H); 3.60, 3.53 (s + t, *J* = 7 Hz respectively, 5 H), 2.8–2.4 (m, 2 H), 2.4–1.8 (m, 2 H).

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85. Found: C, 59.66; H, 7.90.

Reaction of 6 with 1,3-Dicarbethoxyallene (7). Formation of 3-Carbomethoxymethyl-4-carbethoxy-1,6-cyclopentano-2-pyridone (9) (Method A). A solution of 1.15 g (0.0082 mol) of **6**, 1.513 g (0.0082 mol) of allene **7**,[10] and 16 drops of triethylamine in 8 ml of absolute ethanol was stirred at room temperature for 48 hr. The volatiles were removed *in vacuo*. Trituration of the residual solid with ether afforded 1.69 g (74%) of **9** as a white solid: mp 127–128°; λ_{max} ($CHCl_3$) 1720, 1700, 1650 cm^{-1}; δ ($CDCl_3$) 6.40 (s, 1 H), 4.35–3.95 (q + t, *J* = 7 Hz for each, 4 H), 3.78 (s, 5 H), 3.52 (t, *J* = 7 Hz, 2 H), 2.2 (quint, *J* = 7 Hz), 1.25 (t, *J* = 7 Hz, 3 H). Several recrystallizations from absolute ethanol afforded an analytical sample of **9**, mp 125–127°.

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14. Found: C, 60.13; H, 6.34.

Reaction of 6 with Enol Phosphate 8. Formation of Pyridone 9 (Method B). To a magnetically stirred solution of 0.141 g (0.001 mol) of **6** and 0.600 g (0.00177 mol) of enol phosphate **8** in ml of absolute ethanol was added *ca.* 0.3 ml of triethylamine. Stirring was continued for 48 hr at room temperature. The volatiles were removed *in vacuo*. Trituration of the residue afforded 0.150 g (54%) of **9**, mp 120–124°. Chromatography of the residue on silica gel and elution with 2:1 hexane–ethyl acetate gave an additional 0.073 g (26%) of **9**, mp 118–123°.

Preparation of the Ethylated Pyridone 10. To a slurry under N_2 of 1.62 g (0.00582 mol) of pyridone **9** in 25 ml of dry dimethoxyethane cooled in a Dry Ice–2-propanol bath was added, with stirring, 0.715 g (0.00638 mol) of potassium *tert*-butoxide (Alfa Inorganics). After 5 min 3.76 g (0.024 mol, 1.95 ml) of ethyl iodide was added and the reaction mixture was stirred for 2 hr in the cold. It was then allowed to warm to room temperature and stirred for 20 hr after which it was quenched by pouring it into 300 ml of water layered with 100 ml of methylene chloride. The aqueous layer was extracted with 2 × 100 ml of methylene chloride. The combined organic layers were washed with brine, dried over magnesium sulfate, and freed of solvent to afford 1.57 g (88%) of the ethylated pyridone **10** as a green-yellow oil, homogeneous to thin layer chromatography: δ ($CDCl_3$) 6.36 (s, 1 H), 3.8–4.2 (q + t, *J* = 7 Hz for each + m, 5 H), 3.67 (s, 3 H), 3.5–3.1 (m, 2 H), 2.4–1.4 (m, 5 H), 1.20 (t, *J* = 7 Hz, 3 H), 0.95 (t, *J* = 7 Hz, 3 H).

Reaction of Pyridone 10 with Paraformaldehyde. Formation Intermediate Lactone Ester 11. A thick-walled sealed tube containing 0.255 g (0.00083 mol) of the ethylated pyridone **10**, 0.120 g of paraformaldehyde, 1.5 ml of dioxane (undistilled), 3 drops of concentrated sulfuric acid, and 3 drops of water was heated at 104° for 22 hr. Upon cooling, the reaction mixture was poured into 50 ml of water and extracted with 1 × 50 plus 2 × 25 ml of methylene chloride. The combined organic extracts were washed with brine, dried over magnesium sulfate, and freed of solvent to afford 0.261 g of a yellow oil containing the tricyclic lactone **11** (*m/e* 291) which was used, as such, in the next step.

Preparation of De-*AB*-deoxycamptothecin (3). A mixture of 0.261 g of the crude **11** just described and 7.5 ml of aqueous hydrobromic acid was heated at reflux under nitrogen for 18 hr (oil bath at 115°). It was then poured into 50 ml of water and 50 ml of methylene chloride and the layers were separated. The aqueous one was extracted with 2 × 20 ml of methylene chloride. The combined organic layers were extracted with brine, dried over magnesium sulfate, and freed of solvent to afford 0.150 g of a crude partially crys-

talline oil: λ_{max} (KBr) 1730, 1658, 1592, 1580 cm^{-1}; δ ($CDCl_3$) 5.93 (s, 1 H), 5.25 (broadened S, 2 H), 4.08 (t, J = 8 Hz, 2 H), 3.48–2.85 (m, 3 H), 2.45–1.62 (m, 4 H), 0.95 (t, J = 8 Hz, 3 H). Chromatography on 12 g of silica gel eluting with chloroform afforded 0.089 g (46% based on starting **10**[16]) of **3** as a white solid, mp 145–148° (lit.[2] 149–150°).

Preparation of De-*AB*-camptothecin (4). A solution of 0.190 g (0.000815 mol) of deoxy **3** at 0.200 g (0.0018 mol) of potassium *tert*-butoxide in 40 ml of methanol was allowed to stir at room temperature for 10 min prior to the addition of 10.15 ml of a solution of 1 ml of 30% hydrogen peroxide in 20 ml of ether dried over Na_2SO_4. The resulting solution was stirred for 26 hr at room temperature. The reaction mixture was then acidified with methanolic hydrochloric acid and freed of volatiles *in vacuo*. The residue was triturated with 3 × 20 ml of methylene chloride. The combined methylene chloride extracts were dried over anhydrous magnesium sulfate and freed of solvent of afford 0.191 g of a yellow oil. Crystallization from ethanol afforded 0.126 g of a white solid which, from its nmr spectrum, was judged to contain *ca.* 80% of the desired analog **4** and 20% of the starting deoxy **3**. This material was dissolved in 20 ml of methanol and treated as described above with 0.097 g (0.000865 mol) of potassium *tert*-butoxide and 5 ml of a solution of 1 ml of 30% H_2O_2 in 20 ml of anhydrous ether dried over sodium sulfate. Upon work-up, there was obtained 0.125 g of a yellow oil whose nmr spectrum indicated it to be almost pure **4**. Chromatography on 15 g of silica gel, after chloroform elution afforded 0.088 g (43%) of analog **4** as a white solid, mp 172–182°. Two recrystallizations from ethanol afforded the analog **4** as a white solid: mp 176–179° (reported[2] mp 175–177°); λ_{max} (KBr) 3401, 1748, 1730, 1647, 1582; δ ($CDCl_3$) 6.45 (s, 1 H), 5.75–4.95 (AB quartet, 2 H), 4.25–4.03 [t + s (OH), 3 H], 3.30–3.05 (t, 2 H), 2.5–1.6 (quintet + quartet, 4 H), 1.10–0.85 (t, 2 H).

Acknowledgments. This research was supported by U. S. Public Health Service Grant No. CA 12107-09. Nmr spectra were obtained on instrumentation supported by R.R.-00292-07.

Registry No.—**3,** 43083-10-9; **4,** 40163-27-7; **5,** 13939-73-6; **6,** 36625-47-5; **7,** 52358-42-6; **8,** 52358-43-7; **9,** 52358-44-8; **10,** 52358-45-9; **11,** 52358-46-0; paraformaldehyde, 30525-89-4.

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(12) This was assigned to the sample first submitted by Professor Rapoport.
(13) We wish to thank Dr. Robert Engle, National Cancer Institute, National Service Center, Drug Development Brand, Bethesda, Md., for expediting these studies.
(14) Melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer Model 247 spectrophotomer. Nmr spectra were measured on a Varian Associates T-60 spectrometer with tetramethylsilane as the internal standard. Combustion analysis were performed by Galbraith Laboratories, Knoxville, Tenn.
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The Chemistry of 2-Alkoxy-3,4-dihydro-2*H*-pyrans. II. Addition of Dimethyl Acetylenedicarboxylate to 2-Alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans

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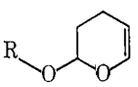
Received May 29, 1974

The introduction of an alkoxy group at the 2 position of 3,4-dihydro-2*H*-pyran (**1**) drastically alters the chemistry of the title compounds, 2-alkoxy-3,4-dihydro-2*H*-pyrans (**2**), as compared to the parent compound, 3,4-dihydro-2*H*-

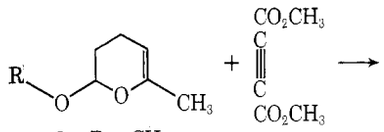
1



2

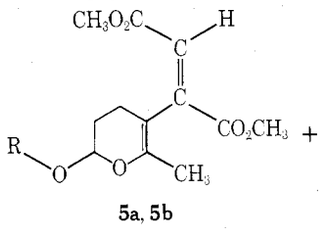
pyran (**1**). This can be most dramatically appreciated by comparing the addition of tetracyanoethylene,[1] condensation with benzenesulfonyl azide,[2] and oxidation by *m*-chloroperbenzoic acid,[3,4] with 3,4-dihydro-2*H*-pyran (**1**) and 2-alkoxy-3,4-dihydro-2H-pyrans (**2**).[5] Herein we wish to report yet another unusual reaction of the title pyrans with dimethyl acetylenedicarboxylate.

Refluxing a toluene solution of 2-methoxy-6-methyl-3,4-dihydro-2*H*-pyran (**3a**) and dimethyl acetylenedicarboxylate (**4**) for 65 hr afforded a mixture of 2-methoxy-5-(dimethylfumaryl)-6-methyl-3,4-dihydro-2*H*-pyran (**5a**)[6] and dimethyl 2-acetyl-3-methoxycyclohex-6-ene-1,2-dicarboxylate (**6a**) in a ratio of 1:1 (glpc). Similar results were obtained with 2-ethoxy-6-methyl-3,4-dihydro-2*H*-pyran (**3b**).

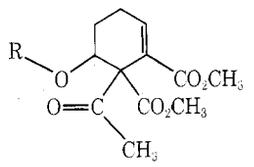


3a, R = CH_3
b, R = C_2H_5

4



5a, 5b



6a, 6b

The assigned structures of the two products are consistent with the spectral data and composition analyses. The isolated yields are presumably low owing to the lability of 2-alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans.[7]

The above reactions might best be described as involving the intermediacy of zwitterion **7,** analogous to intermediates invoked in enamine chemistry,[8] which can lead to product **5** by proton transfer or to the cyclobutene intermediate **8** by cyclization. The cyclobutene intermediate **8,** similar to that proposed as intermediates in reactions of ketene diethyl acetal[9] and enamines[8b,10] with acetylenic esters, can subsequently rearrange to **6.** Frequent monitoring (glpc) of the reaction indicated that no stable intermediate accumulated, and resubjecting products **5** and **6** to the conditions confirmed that each is a true end product of the reaction.