Experimental Section

General. Melting points were taken on a Kofler hot stage apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 727 spectrometer. NMR spectra were determined on a Varian HA-100 spectrometer using Me_4Si as an internal standard. Analytical gas chromatography was carried out on a Fisher Series 4800 gas chromatograph with a flame ionization detector, using a 6 ft × 0.125 in. column packed with 6% SE-30 in 90–100 mesh Chromosorb W. Microanalyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Allyl aryl ethers were prepared by reaction of either 1-chloro-3-methyl-2-butene or geranyl bromide[13] with the corresponding phenols in the presence of K_2CO_3 in either acetone or DMF and purified by silica gel chromatography.

The following is a typical procedure for Claisen rearrangement.

Rearrangement of 5-Quinolinyl Geranyl Ether. A magnetically stirred mixture of 1.0 g of 5-quinolinyl geranyl ether (**1d**), 1.0 g of KOAc, and 15 ml of Ac_2O was heated at 160 °C (bath temperature) in a heavy-walled sealed tube for 3.5 h in an argon atmosphere. The cooled mixture was poured into 35 ml of distilled water and stirred vigorously for 0.5 h. The resulting aqueous solution was extracted with two 150-ml portions of ether. The combined ether extracts were washed with saturated $NaHCO_3$ solution until the washings were basic. The resulting organic fraction was washed with 50 ml of saturated NaCl solution, dried over $MgSO_4$, and ether evaporated. After filtration through silica gel (15 g; EtOAc/hexane 1/2) the residue (1.098 g) was crystallized from pentane to give 814 mg of **2d** as tan crystals. Purification of the mother liquor by preparative layer chromatography (20 × 20 × 0.25 cm silica gel plate; EtOAc/hexane 1/1) yielded an additional 63 mg of **2d.** After one recrystallization from pentane **2d** was obtained as small plates: mp 73–75 °C; ir (CH_2Cl_2) 1760, 1200 cm^{-1}; NMR ($CDCl_3$) δ 1.48 (s, 3, CH_3), 1.50 (s, 3, CH_3), 1.62 (s, 3, CH_3), 2.34 (s, 3, $OCOCH_3$), 1.7–2.3 (m, 4, CH_2CH_2), ~5.1 (m, 3, $C{=}CH_2$, $C{=}CH$), 6.16 (dd, 1, J = 10, 18 Hz, $CH{=}CH_2$), 7.2–8.9 (m, 5, aromatic).

Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.91; H, 7.66; N, 4.37.

***o*-(1,1-Dimethylallyl)phenol (4b).** 3-Methyl-2-butenyl phenyl ether (**3**, 1.0 g), 1.0 g of anhydrous NaOAc, and 15 ml of Ac_2O was heated for 21 h under argon in a stainless steel bomb at 200 °C (bath temperature). The mixture was worked up exactly as described in the previous experiment. After evaporation of the ether, the crude residue was filtered through silica gel (15 g; CH_2Cl_2/petroleum ether 1/3) giving 0.976 g of a pale yellow oil. GLC analysis[14] showed *o*-(1,1-dimethylallyl)phenyl acetate (**4a**, 66.5%), phenyl acetate (19%), **3** (6.3%), and two unidentified compounds (total of 8.2%).

The crude mixture dissolved in 15 ml of dry ether was added dropwise to a suspension of 280 mg of $LiAlH_4$ in 50 ml of dry ether under argon. Once the addition was complete the mixture was refluxed for 15 min, cooled in an ice bath, and acidified to pH 1 with 3 N HCl. The organic layer was separated and the aqueous layer back-extracted with 35 ml of ether. The combined ether extracts were washed with two 50-ml portions of saturated NaCl solution, dried over Na_2SO_4, and ether evaporated. The residue was purified by column chromatography (35 g of silica gel; CH_2Cl_2/petroleum ether 1/6) to give 438 mg (44%) of *o*-(1,1-dimethylallyl)phenol (**4b**) as a colorless oil (homogeneous by TLC): ir (CH_2Cl_2) 3460, 1620, 1575, 1480, 1340, 1200, 925 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (s, 6, CH_3), 5.27 (dd, 1, J = 10, 1 Hz, $CH{=}CH_2$), 5.31 (dd, 1, J = 18, 1 Hz, $CH{=}CH_2$), 6.20 (dd, 1, J = 18, 10 Hz, $CH{=}CH_2$), 6.76–7.32 (m, 5, aromatic).

A phenylurethane of **4b** gave mp 105–105.5 °C after one recrystallization from hexane.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this work.

Registry No.—**4a**, 59671-72-6; **4b** phenylurethane, 59671-71-5; phenyl acetate, 122-79-2; 1-chloro-3-methyl-2-butene, 503-60-6; geranyl bromide, 5389-87-7; 1-naphthol, 90-15-3; 5-quinolinol, 578-67-6.

References and Notes

(1) For recent reviews, see A. Jefferson and F. Scheinmann, *Q. Rev., Chem. Soc.*, **22**, 391 (1968); S. J. Rhoads and N. R. Raulins, *Org. React.*, **22**, 1 (1975).
(2) J. Borgulya, H. J. Hansen, R. Barner, and H. Schmid, *Helv. Chim. Acta*, **46**, 2444 (1963).
(3) F. Scheinmann, R. Barner, and H. Schmid, *Helv. Chim. Acta*, **51**, 1603 (1968).
(4) For examples of abnormal rearrangement see ref 1.
(5) H. Nakata, H. Harada, and Y. Hirata, *Tetrahedron Lett.*, 2515 (1966); N. Sakabe, H. Harada, and Y. Hirata, *ibid.*, 2523 (1966).
(6) A. Jefferson and F. Scheinmann, *J. Chem. Soc. C*, 243 (1969).
(7) R. D. H. Murray and M. M. Balantyne, *Tetrahedron*, **26**, 4667 (1970).
(8) Approximately 1 M solution in butyric anhydride/DMA (3/5, v/v).
(9) Product ratios determined by NMR and GLC analysis.
(10) L. Claisen, F. Kremers, F. Roth, and E. Tietze, *J. Prakt. Chem.*, **105**, 65 (1922); L. Claisen and E. Tietze, *Ber.*, **58**, 275 (1925).
(11) E. A. Vdovtsova, *Zh. Org. Khim.*, **5**, 498 (1969). The author claims to detect **4b** by GLC after heating **3** in the presence of Na_2CO_3. However, the compound was not isolated and no spectral data or other means of structure proof were presented.
(12) Yield was not optimized.
(13) Prepared by method of P. R. Oritz de Montellano, Thesis, Harvard University, 1968, p 75, using Aldrich gold label geraniol.
(14) Auto programmer: initial temperature 150 °C; final temperature 225 °C; initial delay 1 min; program rate: 20 °C/min; final delay 1 min.

Pyridopyrimidines. 5. N-Oxidations and Rearrangements in the Pyrido[2,3-*d*]pyrimidine Series

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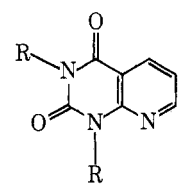
Received March 9, 1976

A number of pyrido[2,3-*d*]pyrimidine derivatives have been recently synthesized as potential antitumor,[1-3] carcinogenic,[4] or antibacterial[5] agents. Our interest in the antitumor properties of certain of these compounds has prompted a study of the synthesis and reactivity of the 8-*N*-oxides of 2,4-dioxopyrido[2,3-*d*]pyrimidine (**1**) and its 1,3-dimethyl derivative



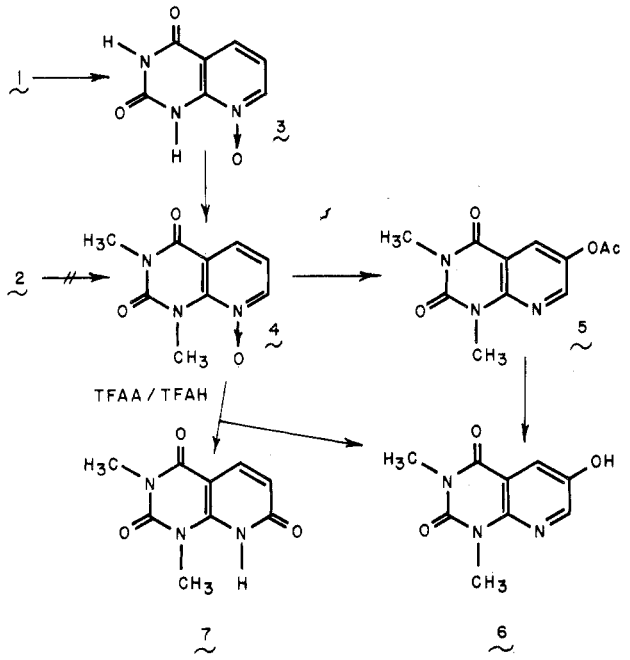
1, R = H
2, R = CH_3

2; these starting materials were prepared according to Robins and Hitchings[6] and McLean and Spring,[7] respectively.

The preparation of 2,4-dioxopyrido[2,3-*d*]pyrimidine 8-*N*-oxide (**3**) was carried out very simply in 80% yield by oxidation of **1** with *m*-chloroperbenzoic acid in glacial acetic acid (Scheme I). Because of the lactam structure of **1**, the only nitrogen atom available for N-oxidation should be N-8. Indeed, only one *N*-oxide was formed, which had similar physical properties to the same compound recently prepared[4] by an involved, much lower yield (42%) procedure. Additional support for the structural assignment was found in the uv spectrum; a very intense band (not previously reported[4]) at 237 nm, characteristic of *N*-oxide bonds in heteroaromatic systems,[8] was observed.

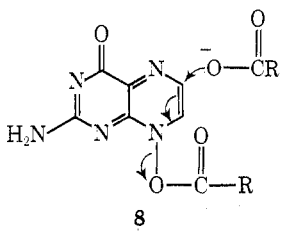
Oxidation of the 1,3-dimethyl derivative **2** could not be accomplished, presumably because of steric hindrance of the peri methyl group at N-1. Even trifluoroperacetic acid in refluxing trifluoroacetic acid failed to oxidize compound **2**. A study of the methylation of *N*-oxide **3** was therefore undertaken. The conditions usually used for the N-methylation of heteroaromatic lactam systems, e.g., dimethyl sulfate in aqueous base[7] or methyl iodide in an aprotic solvent in the presence of potassium carbonate,[9] failed to give a reasonable yield of the desired 1,3-dimethyl derivative. The use of diazomethane, which has the smallest steric requirements of all methylating agents, gave a good yield of a dimethylpyrido[2,3-

Scheme I



d]pyrimidine. Because diazomethane is known to give mixtures of *N*- and *O*-methyl derivatives in many cases,[10] it was necessary to establish that the reaction product was indeed **4**. Three lines of evidence firmly established the structure: the ^{1}H NMR spectrum in $(CD_3)_2SO$ revealed two sharp methyl singlets at δ 3.30 and 3.89, both of which are at higher field than would be the case for *O*-methyl signals; irradiation of **4** in aprotic media at 254 nm gave a product identical (TLC) with **2**; and, finally, the mass spectrum gave a relatively small molecular ion (M^+ 207) with the base peak at *m/e* 191 and all other peaks in the spectrum corresponding essentially identically to those of compound **2** as previously reported.[11]

N-Oxide rearrangements in heteroaromatic compounds are frequently induced by either photochemical or acid anhydride initiated processes, and usually involved formation of a C–O bond at the carbon α to the original *N*-oxide.[12] Two interesting exceptions to the latter generalization have been recently reported. The first of these was the observation by Taylor[13] that 2-amino-4-oxopteridine 8-*N*-oxide, although stable to prolonged refluxing in acetic anhydride–acetic acid mixtures, underwent a facile β-rearrangement in trifluoroacetic acid–trifluoroacetic anhydride (TFAH–TFAA) mixtures to give xanthopterin (2-amino-4,6-dioxopteridine) as the sole product. Taylor proposed that the reaction was facilitated by the rapid loss of a proton from N-1 to give an intermediate such as **8**, which was susceptible to direct attack at the β position



8

by trifluoroacetate as shown. He supported his argument with the observation that the 2,4-diamino derivative underwent the same reaction only under more vigorous conditions. The second recently reported exception was the $POCl_3$ induced rearrangement of 1-hydroxy-2,4-dioxopyrido[2,3-*d*]pyrimidine,[4] in which the newly formed leaving group was at N-1 and the product was 6-chloro-2,4-dioxopyrido[2,3-*d*]pyrimidine. These intriguing observations prompted us to study the rearrangements of *N*-oxides **3** and **4**.

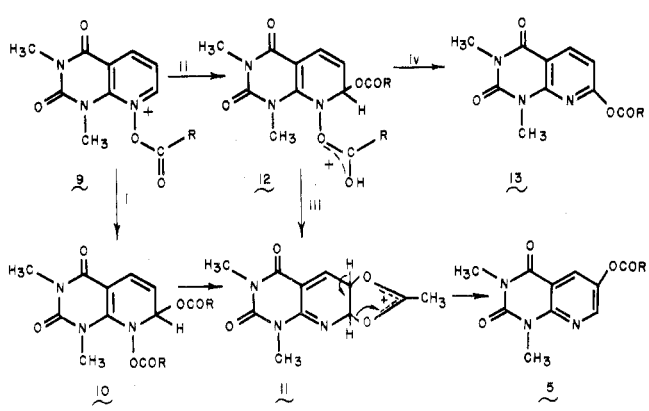
The reaction of **4** with a solution of acetic anhydride in acetic acid (1:1) at 90 °C gave only one product as judged by TLC. This new compound was readily characterized as the 6-acetoxy derivative **5** by elemental analysis and ^{1}H NMR spectroscopy. The signal at about δ 7.5 attributable to the proton at C-6 of **4** was missing and the remaining aromatic protons gave doublets having a coupling constant of 2.7 Hz, typcial of meta couplings of pyridine protons.[14] The acetyl methyl signal appeared as a sharp singlet at δ 2.40. Compound **5** underwent rapid deacylation with methanolic ammonia to give the 6-hydroxy derivative **6**. Similarly, treatment of **4** with neat trifluoroacetic anhydride at reflux followed by workup in aqueous base gave the 6-hydroxy derivative **6** as the *only* product in 97% isolated yield.

When the reaction was run at reflux in TFAH–TFAA a different rearrangement pattern emerged. As the reaction proceeded, two products were formed in nearly equal amounts; 46% isolated yields of each of the products were obtained. One was identical with the 6-hydroxy derivative **6**. The other was proved to be 1,3-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (**7**) by establishing its identity (TLC, ^{1}H NMR, uv, ir, mass spectrum) with the authentic material which had been prepared by an unequivocal procedure and reported elsewhere.[1]

Thus, it is clear that the rearrangement of **4** induced by acetic anhydride in acetic acid or TFAA gave only the product of β-rearrangement whereas the strongly acidic system TFAH–TFAA led to the formation of equal amounts of both α and β rearrangement products. Because the pyridopyrimidine ring system is isoelectronic with the pteridine system, one might expect a marked facilitation of the β-rearrangement in the case of **3** by analogy with the previously noted ability of the pyridine ring to electronically enhance the rate of such a reaction.[13] It was therefore quite surprising to find that **3** is *completely resistant* to rearrangement; even under such forcing conditions as refluxing TFAH–TFAA for 30 h only starting material was present.

A mechanistic scheme has been developed (Scheme II)

Scheme II



which is consistent with these observations and which could be invoked to account for the β-rearrangement of 2,4-diaminopteridine 8-*N*-oxide under forcing conditions as described by Taylor.[13] The *N*-acyloxypyridinium cation (**9**) is the initial product of the reaction of an acid anhydride with *N*-oxide **4**. The course of subsequent reactions depends in part upon the presence or absence of a strong acid. In the absence of strong acid, i.e., in acetic anhydride–acetic acid or neat trifluoroacetic anhydride, addition of acetate to the α position must occur in the usual way to give **10** (Scheme II, i); this relatively stable (toward elimination) molecule then suffers intramolecular

attack by the acetate or trifluoroacetate carbonyl[15] with concomitant elimination of the N-8 acyloxy group to give **11**. The latter can undergo facile ring opening incident to loss of the more acidic allylic proton to give **5**. An alternative explanation involves addition of an additional acetate or trifluoroacetate moiety to carbon 6 of intermediate **10**, leading to a 6,7-dihydro-6,7-diacetoxy derivative which could undergo aromatization to give **5**. The former explanation is preferred because of the absence of trifluoroacetate ion in the neat TFAA reaction mixture (intermediate **10** incorporates all the elements of one TFAA molecule). In the strongly acidic medium containing TFAH, the intermediate trifluoroacetate adduct **12** may be protonated (ii), thereby enhancing the leaving ability of the trifluoroacetoxy group and enabling the simple β-elimination (iv) to compete effectively with the allylic nucleophilic displacement (iii). Although other parameters may be important in determining the details of the reaction mechanism (i.e., nucleophilicity vs. leaving ability), it is felt that the general features of the proposed mechanism are substantially correct in accounting for the rearrangements observed in this study and the β-rearrangement unfacilitated by rapid ionization of the pyrimidine ring proton in the pteridine series.[13] The strikingly enhanced reactivity of **4** relative to the unmethylated derivative **3** must arise from relief of the steric strain imposed upon **4** by the peri interaction of the 1-methyl and 8-*N*-oxide groups.

Experimental Section

Melting points were obtained on a Thomas-Hoover instrument and are uncorrected. ^{1}H NMR data were obtained using a JEOL C6OH NMR spectrometer at ambient temperature using $(CD_3)_2SO$ with 2,2-dimethyl-2-silapentanesulfonic acid sodium salt (DSS) as internal reference or in trifluoroacetic acid with tetramethylsilane as internal reference. Uv spectra were recorded by means of a Cary 15 spectrophotometer. Thin layer chromatography was carried out on SilicAR 7GF coated glass plates using ethyl acetate–water–1-propanol (4:2:1, upper phase) as developing solvent. Microanalyses were carried out by Heterocyclic Chemical Co., Harrisonville, Mo. Diazomethane solutions were prepared according to Noller.[16] Photolyses were carried out in a Rayonet photoreactor using GE "germicidal" (254 nm peak output) lamps.

2,4-Dioxopyrido[2,3-*d*]pyrimidine 8-*N*-Oxide (3). Compound **1**[6] (5 g, 30.6 mmol) was suspended in 60 ml of glacial acetic acid, 85% *m*-chloroperbenzoic acid (16.2 g, 80 mmol) was added, and the mixture heated at 55–60 °C for 3 h. 1,2-Dimethoxyethane (DME, 20 ml) was added to the mixture, followed by 40 ml of ethyl ether, and the mixture refrigerated for several hours. The white solid was collected, washed with DME and then ethyl ether, and dried to a fine powder: 4.4 g (80%); mp 332 °C dec; ^{1}H NMR (TFAH) δ 9.03 (d, C-5 H), 7.90 (t, C-6 H), 9.18 (d, C-7 H); uv max ($\epsilon_{max} \times 10^{-3}$) [pH] 237 nm (33.8), 336 (5.38) [1]; 237 (23.8), 257 (21.4), 363 (5.48) [7]; 257 (26.2), 280 (11.5), 368 (7.14) [11].

Anal. Calcd for $C_7H_5N_3O_3$: C, 46.93; H, 2.82; N, 23.46. Found: C, 46.91; H, 2.95; N, 23.49.

1,3-Dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine 8-*N*-Oxide (4). Compound **3** (3.0 g, 16.7 mmol) was suspended in 1,4-dioxane, and ethereal diazomethane (approximately 2.8 g, 67 mmol of diazomethane) was added in 20-ml portions over a 2-h period. The mixture was stirred at room temperature until solution was complete, and 5 ml of 50% aqueous acetic acid was added to decompose the excess diazomethane. The clear solution was evaporated to dryness and the solid residue was recrystallized from 80 ml of ethanol (after treatment with carbon) to yield 2.8 g (81%) of the desired compound: mp 174–175 °C; mass spectrum (70 eV) *m/e* (rel intensity) 207 (8), 191 (100), 163 (20), 134 (52), 106 (22); ^{1}H NMR ($(CD_3)_2SO$) δ 8.30 (s, CH_3), 3.89 (s, CH_3), 8.02 (d of d, C-5 H), 7.48 (q, C-6 H), 8.63 (d of d, C-7 H); uv max ($\epsilon_{max} \times 10^{-3}$) [pH] 243 nm (27.0), 342 (3.42) [1]; 243 (27.8), 344 (3.53) [7]; 247 (14.5) [11].

Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.09; H, 4.40; N, 20.28.

1,3-Dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine (2). Compound **4** (100 mg) was irradiated in deoxygenated DME for 3 h under 254-nm uv light. Thin layer chromatography in the solvents $CHCl_3$–MeOH (19:1) and concentrated NH_4OH–MeOH–DME (1.5:1.5:17) indicated that a significant amount of deoxygenation to 2 (prepared according to McLean and Spring[7]) occurred. No other photoproducts were observed.

1,3-Dimethyl-6-hydroxy-2,4-dioxopyrido[2,3-*d*]pyrimidine (6) and 1,3-Dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (7). Compound **4** (900 mg, 4.35 mmol) was refluxed in 60 ml of 50% trifluoroacetic anhydride–trifluoroacetic acid (TFAA–TFAH) for 28 h. The clear solution was evaporated to a yellow oil, 15 ml of 2 N NaOH was added, and the mixture was heated on a steam bath for 5 min. The solution was cooled, adjusted to pH 5 with glacial acetic acid, and refrigerated. The solid weighing 850 mg was chromatographed on 30 g of deactivated silica gel. Elution with concentrated NH_4OH–MeOH–DME (1.5:1.5:22) afforded 415 mg (46%) of the 6-hydroxy compound **6**: mp 265 °C; ^{1}H NMR (TFAH) δ 3.76 (s, CH_3) 4.05 (s, CH_3), 8.67 (d, C-5 H), 9.06 (d, C-7 H), $J_{5,7}$ = 2.8 Hz; uv max ($\epsilon_{max} \times 10^{-3}$) [pH] 307 (13.1) [pH]; 273 (7.56), 308 (19.5), 321 (17.6) [7]; 273 (7.05), 308 (19.2), 321 (17.6) [11].

Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.81; H, 4.60; N, 20.55.

Concentrated NH_4OH–MeOH–DME (1:3:16) eluted the 7-oxo compound **7**. The combined fractions were evaporated, and the residue remaining was dissolved in 25 ml of H_2O, adjusted to pH 5 with acetic acid, and refrigerated. The white solid was collected and dried to a weight of 412 mg: mp 282 °C (45.8%); ^{1}H NMR (TFAH) δ 3.74 (s, CH_3), 4.00 (s, CH_3), 8.74 (d, C-5 H), 6.97 (d, C-6 H), $J_{5,6}$ = 9.5 Hz; uv ($\epsilon_{max} \times 10^{-3}$) [pH] 248 nm (8.95), 338 (6.00) [1]; 340 (4.98) [7]; 268 (11.2) [11].

Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.01; H, 4.45; N, 20.00.

6-Acetoxy-1,3-dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine (5). Compound **4** (300 mg, 1.45 mmol) was heated at 90 °C in acetic anhydride–glacial acetic acid (2:1) for 24 h. The excess solvents were evaporated and the residue was dissolved in 15 ml of methanol, treated with carbon, filtered, and refrigerated. The crystals that separated were collected and dried to give 129 mg, mp 198–199 °C. Concentration of the filtrate produced a second crop of crystals weighing 50 mg, giving a total of 179 mg (50%): ^{1}H NMR ($(CD_3)_2SO$) δ 2.40 (s, CH_3), 3.53 (s, CH_3), 3.77 (s, CH_3), 8.31 (d, C-5 H), 8.47 (d, C-7 H), $J_{5,7}$ = 2.7 Hz; uv max ($\epsilon_{max} \times 10^{-3}$) [pH] 317 nm (6.38) [1]; 317 (6.50) [7]; 269 (11.6), 322 (3.05) [11].

Anal. Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 52.89; H, 4.68; N, 16.75.

1,3-Dimethyl-6-hydroxy-2,4-dioxopyrido[2,3-*d*]pyrimidine (6). Method A. Compound **4** (700 mg, 3.4 mmol) was refluxed in 15 ml of TFAA (neat) for 1.5 h, and the excess solvents were evaporated. The white residue remaining was heated in 2 N NaOH for 5 min on a steam bath, neutralized with acetic acid, and refrigerated. The precipitate, 678 mg (97%), was collected and dried, mp 265 °C, and was chromatographically pure 6-hydroxy product **6**.

Method B. Compound **5** (50 mg) was dissolved in 10 ml of methanolic ammonia (saturated with NH_3 at 0 °C) and kept at room temperature for 0.5 h. Evaporation of the solvents afforded **6**, 40 mg (98%), mp 263–265 °C.

Acknowledgments. The authors are grateful to the National Cancer Institute, NIH, for support of this work by Research Grant CA 12823, and for support (D.G.B.) by Training Grant CA 05209. The assistance of Dr. James A. McCloskey in obtaining the mass spectra is also gratefully acknowledged.

Registry No.—**1**, 21038-66-4; **3**, 56783-86-9; **4**, 59588-16-8; **5**, 59588-17-9; **6**, 59588-20-4; **7**, 57821-20-2.

References and Notes

(1) Part 4: G. L. Anderson, J. L. Shim, and A. D. Broom, *J. Org. Chem.*, **41**, 1095 (1976).
(2) B. H. Rizkalla and A. D. Broom, *J. Org. Chem.*, **37**, 3980 (1972).
(3) B. H. Rizkalla, A. D. Broom, M. G. Stout, and R. K. Robins, *J. Org. Chem.*, **37**, 3975 (1972).
(4) T.-C. Lee and G. Salemnick, *J. Org. Chem.*, **40**, 3609 (1975).
(5) S. Nishigaki, K. Ogiwara, K. Senga, S. Furazawa, K. Aida, Y. Machida, and F. Yoneda, *Chem. Pharm. Bull.*, **18**, 1385 (1970).
(6) R. K. Robins and G. H. Hitchings, *J. Am. Chem. Soc.*, **77**, 2258 (1955).
(7) A. C. McLean and F. S. Spring, *J. Chem. Soc.*, 2582 (1949).
(8) G. B. Brown, *Prog. Nucleic Acid Res. Mol. Biol.*, **8**, 209 (1968).
(9) A. D. Broom, L. B. Townsend, J. W. Jones, and R. K. Robins, *Biochemistry*, **3**, 494 (1964).
(10) P. B. Farmer, A. B. Foster, M. Jarman, and M. J. Tisdale, *Biochem. J.*, **135**, 203 (1973).
(11) I. R. Gelling, W. J. Irwin, and D. G. Wibberley, *J. Chem. Soc.*, 513 (1969).

(12) A. R. Katritsky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides", Academic Press, New York, N.Y., 1971, p 153 ff.
(13) E. C. Taylor and P. A. Jacobi, *J. Am. Chem. Soc.*, **95**, 4455 (1973).
(14) S. Sternhell, *Q. Rev., Chem. Soc.*, **23**, 236 (1969).
(15) T. Cohen and G. L. Deets, *J. Org. Chem.*, **37**, 55 (1972).
(16) C. R. Noller and I. Bergsteinsson, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 164.

A New Pathway for Oxidation of Alcohols to Carbonyl Compounds[1]

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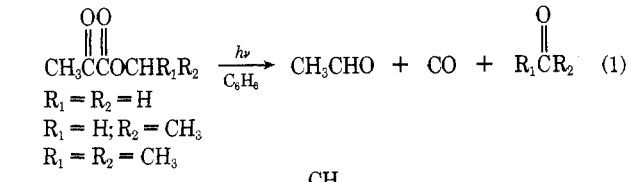
Received May 7, 1976

In the early 1960's several research groups studied the photochemistry of alkyl esters of pyruvic acid. Arising from these studies were the findings that in benzene pyruvates fragment photochemically as shown in eq 1[2,3] but they pho-

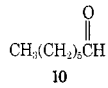
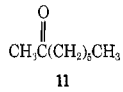
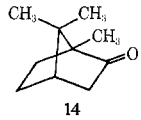
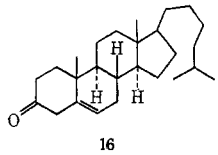
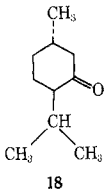
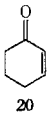


toreduce when hydrogen donating solvents are used[4] (eq 2). Any interest in utilizing pyruvate photoreaction as a synthetic tool was tempered by the knowledge that the available syntheses of these compounds employed unacceptably forcing conditions for use with sensitive materials.[5] A recent report[6] of a new, simple synthesis of the acid chloride of pyruvic acid raised the possibility that esters of this acid easily could be formed under mild conditions and that synthetically useful photochemical reactions involving these compounds now could be considered. Specifically, the synthesis of pyruvates followed by their reaction as shown in eq 1 could represent an effective sequence for oxidation of alcohols to carbonyl compounds. Assuming that this oxidation sequence could be of general value, a variety of pyruvates were synthesized and irradiated. The results from study of these reactions suggest that the pyruvate oxidation sequence could be useful in solving problems of synthesis in a variety of areas.

In the opening phase of this investigation, the pyruvate esters of seven alcohols [1-phenylethanol (1), benzyl alcohol (2), 1-heptanol (3), 2-octanol (4), cyclohexanol (5), cyclopentanol (6), and borneol (7)] were prepared and irradiated. Alcohol esterification was quantitative. Photochemical reaction of the resulting esters, although not usually quantitative, produced good to excellent yields of the carbonyl compounds 8–14 (Table I). Analysis of the information in Table I reveals the following features for the pyruvate oxidation sequence: (a) the oxidation sequence works well for simple compounds of various structures; (b) primary alcohols are oxidized to aldehydes without further reaction; and (c) essentially complete photochemical reaction of pyruvates can be accomplished without noticeable secondary reaction.

The effect of five solvents on the photochemical reaction of 1-phenylethyl pyruvate is summarized in Table II. The photochemical process is quite solvent dependent. Benzene is an excellent choice and carbon tetrachloride appears to be equally good. Pentane and ethyl ether are poor reaction solvents since irradiation in either of these two results in considerable solvent incorporation.[4]

Table I. Alcohol Oxidation Products and Yields

Alcohol	Oxidation product	Yield, %	Unreacted alcohol, %
1	 8	100	None
	 9	95	4
3	 10	77	6
4	 11	85	None
5	 12	100	None
6	 13	84	None
7	 14	85	1
15	 16	80	None
17	 18	88	None
19	 20	76	2

Since the pyruvate synthesis–photoreaction combination was effective for oxidation of alcohols which are relatively easily oxidized, it was decided to test this combination in several situations where the oxidation products are known to be capable of facile, further reaction or where other reactions could intervene. Conditions for oxidation of cholesterol (15), for example, easily lead to isomerization of the carbon–carbon double bond into conjugation with the newly formed carbonyl.[7,8] In order to determine whether the pyruvate oxidation pathway would also lead to this isomerization, the pyruvate ester of cholesterol was synthesized and irradiated. No isomerization was observed; a good yield (Table I) of the nonconjugated enone (16) was obtained.

Oxidation of alcohols to aldehydes and ketones can be complicated by epimerization at the center next to the carbonyl. Conversion of menthol (17) to menthone (18), for example, is accompanied by formation of isomenthone, unless precautions are taken.[9] To test the possibility of epimerization in the pyruvate oxidation sequence, methyl pyruvate was