A Novel Ring Expansion of a Diazacyclopentadienone Dioxide[1]

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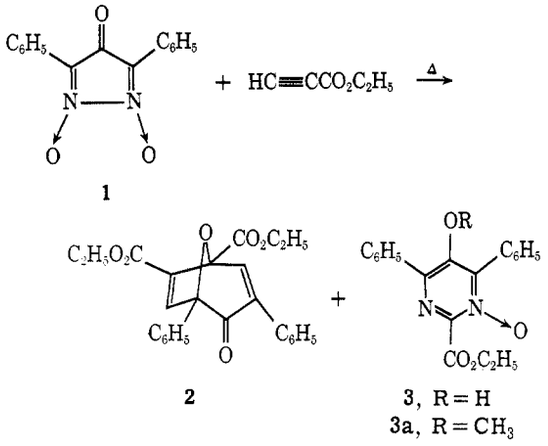
During a study of the cycloaddition reactions of diazacyclopentadienone oxides with acetylenic dipolarophiles,[3] an unusual ring expansion was observed when 2,5-diphenyl-3,4-diazacyclopentadienone 3,4-dioxide (**1**) was heated with ethyl propiolate in benzene. Although the expected[3] oxabicyclooctadienone derivative **2** was present in small amounts,[4] the major product (20%) was a nitrogen-containing compound, **3**.



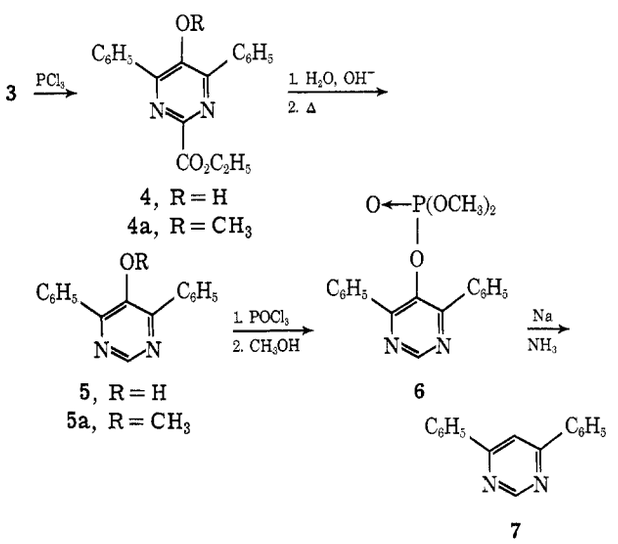
1

2

3, R = H
3a, R = CH_3

The structure of **3** is based upon its elementary analysis, spectral properties, its acidic character, and its degradation to 4,6-diphenylpyrimidine (Chart I). Treatment of **3** with phosphorus trichloride produced the corresponding pyrimidine **4**. A comparison of the aromatic proton regions of the nmr spectra of the methyl ethers of **3a** and **4a** was the original clue that a pyrimidine rather than a pyridazine ring was present, since the two phenyl groups, magnetically nonequivalent in **3a**, became equivalent in **4a**.[5] Alkaline hydrolysis of **4** followed by heating produced the hydroxypyrimidine **5**. The structure of **5** is supported

CHART I



by the appearance in its nmr spectrum of a sharp one-proton singlet at δ 9.09, typical of the shift of the 2 proton in pyrimidines.[6] In addition, the isomer of **4** with the hydroxyl and ethoxycarbonyl groups interchanged was synthesized independently by bromine oxidation of the condensation product of benzaldehyde, urea, and ethyl benzoylacetate. This compound proved to be different from **4**. The hydroxyl group of **4** was removed by the method of Pelletier and Locke,[7] which involves the dissolving metal reduction of the dimethyl phosphate ester **6**. The resulting 4,6-diphenylpyrimidine **7**, mp 99.5–101° (lit.[8] mp 102–103°), was identical with an authentic sample prepared by the condensation of dibenzoylmethane with formamide.[8]

This ring enlargement appears to be related to that observed in the reaction of isatogens with acetylenic esters.[9] In those reactions also, one of the acetylenic carbon atoms is lost through an obscure deacylation process. However, the present case differs in that insertion is into an N–N bond rather than into the C–N bond of the original nitrone function. Another ring expansion of the diazacyclopentadienone oxides was observed during oxidation, but in that case C–C bond insertion occurred.[10]

Experimental Section

2,5-Diphenyl-3,4-diazacyclopentadienone 3,4-Dioxide and Ethyl Propiolate.—A mixture of 20.0 g (0.075 mol) of dioxide 1[11] and 15.0 g (0.15 mol) of ethyl propiolate in 150 ml of benzene was heated under reflux for 24 hr. Upon cooling, a yellow solid separated. Recrystallization of this solid from CH_2Cl_2–hexane gave 5.25 g (20%) of **2-ethoxycarbonyl-5-hydroxy-4,6-diphenylpyrimidine 1-oxide (3)**: mp 218–219°; ir (KBr) 1745, 1550 cm^{-1}.

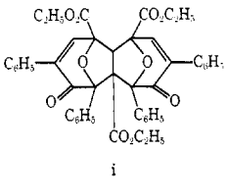
Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.84; H, 4.80; N, 8.30. Found: C, 67.46; H, 5.09; N, 8.43.

(1) This research was carried out under grant number CA-10742 from the National Cancer Institute, National Institutes of Health.

(2) (a) NSF Undergraduate Research Participant, Summer 1970; (b) National Defense Education Act Fellow, 1966–1969.

(3) J. P. Freeman and M. J. Hoare, *J. Org. Chem.*, **36**, 19 (1971).

(4) There is still some uncertainty in structure **2** as to whether the olefinic ester function is α or β with respect to the bridgehead ester group. In addition to **2**, traces of a $C_{45}H_{38}O_{10}$ compound were isolated. Although the structure of this compound has not been completely elucidated, it is believed to be of the type i, resulting from capture of the intermediate zwitterion[3] by product **2** instead of by ethyl propiolate.



i

(5) The spectra of the methyl ethers were used because the low solubility of the parent hydroxy compounds resulted in poor spectra.

(6) G. S. Reddy, R. T. Hobgood, Jr., and J. H. Goldstein, *J. Amer. Chem. Soc.*, **84**, 336 (1962); S. Gronowitz, B. Norrman, H. Gestbloom, B. Mathiasson, and R. A. Hoffman, *Ark. Kemi*, **22**, 65 (1964).

(7) S. W. Pelletier and D. M. Locke, *J. Org. Chem.*, **23**, 131 (1958).

(8) H. Bredereck, R. Gompper, and G. Morlock, *Chem. Ber.*, **90**, 942 (1957).

(9) W. E. Noland and R. F. Modler, *J. Amer. Chem. Soc.*, **86**, 2086 (1964).

(10) J. P. Freeman, D. L. Surbey, and J. E. Kassner, *Tetrahedron Lett.*, 3797 (1970).

(11) J. P. Freeman, D. L. Surbey, and J. J. Gannon, *J. Org. Chem.*, **34**, 184 (1969).

Methyl ether 3a was prepared in the standard way by reaction of **3** with diazomethane in tetrahydrofuran: mp 170–171° (CH_2Cl_2–hexane); nmr ($CDCl_3$) δ 8.09 (m, $W_{1/2}$ = 11 Hz,[12] 2 H), 7.74 (m, 2 H), 7.50 (m, 6 H), 4.52 (q, J = 7 Hz, 2 H), 3.31 (s, 3 H), and 1.43 (t, J = 7 Hz, 3 H).

Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.41; H, 5.10; N, 8.01.

The benzene mother liquor (above) was concentrated and the residue was taken up in 200 ml of boiling ethanol. After standing overnight the solution deposited 4.5 g (23%) of unreacted **1**. The solution was concentrated to 75 ml and chilled overnight to yield 4.9 g of a tan powder that was recrystallized from C_2H_5OH, then from benzene–Skellysolve B to yield pale yellow needles of **2**: mp 124–126°; nmr ($CDCl_3$) δ 7.90 (s, 1), 7.2–7.6 (m, 11), 4.1–4.5 (overlapping m, 4), 1.2–1.4 (overlapping m, 6); mass spectrum *m/e* (rel intensity) 418 (12), 373 (22), 344 (10), 317 (10), 215 (10), 106 (11), 105 (100), 77 (22).

Anal. Calcd for $C_{25}H_{22}O_6$: C, 71.76; H, 5.30. Found: C, 71.33; H, 5.48.

The ethanol mother liquor was evaporated to dryness. The residue was dissolved in 1:1 benzene–Skellysolve B and placed on a silica gel column. Elution with the same solvent mixture yielded an additional 0.18 g of **2**, total yield 5.08 g (13%).

Elution with benzene yielded a yellow oil which deposited 0.66 g of yellow crystals from ethanol: mp 189–191°; nmr ($CDCl_3$) δ 6.9–8.1 (m, 20), 5.13 (s, 1), 4.99 (s, 1), 3.75–4.40 (overlapping m, 7), 1.18 (t, J = 7 Hz, 3), 1.00 (*t*, J = 7 Hz, 3), 0.89 (t, J = 7 Hz, 3); mass spectrum *m/e* (rel intensity) 738 (8), 321 (41), 320 (16), 319 (9), 291 (24), 105 (100), 77 (11).

Anal. Calcd for $C_{45}H_{38}O_{10}$: C, 73.15; H, 5.20. Found: C, 73.03; H, 5.40.

2-Ethoxycarbonyl-5-hydroxy-4,6-diphenylpyrimidine (4).—A mixture of 1.5 g (4.46 mmol) of **3** and 2 ml (10 mmol) of phosphorus trichloride in 20 ml of $CHCl_3$ was allowed to stand at room temperature overnight. Evaporation of the solvent and recrystallization of the residue from ethanol produced 1 g (76%) of white crystals of **4**, mp 227–228°. Traces of this compound were also found in the eluent from the silica gel column separation of the product from the ethyl propiolate reaction.

Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.23; H, 5.03; N, 8.80. Found: C, 70.05; H, 5.21; N, 8.60.

The acetate ester of 4 had mp 113–115° (C_2H_5OH).

Anal. Calcd for $C_{21}H_{18}N_2O_4$: C, 69.20; H, 5.01; N, 7.73. Found: C, 69.33; H, 5.12; N, 7.50.

Methyl ether 4a had mp 117–119° (C_2H_5OH); nmr ($CDCl_3$) δ 8.17 (m, $W_{1/2}$ = 11 Hz,[12] 4 H), 7.50 (m, 6 H), 4.51 (q, J = 7 Hz, 2 H), 3.38 (s, 3 H), and 1.45 (t, J = 7 Hz, 3 H); mass spectrum *m/e* (rel intensity) 334 (32), 213 (14), 262 (100), 261 (29), 129 (10), 89 (16), 77 (12).

Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.73; H, 5.55; N, 8.29.

5-Hydroxy-4,6-diphenylpyrimidine (5).—A suspension of 1.0 g (3.2 mmol) of **4** in 25 ml of 20% aqueous KOH was heated on a steam bath for 1 hr. The solution was cooled and acidified to congo red and the solid that separated was collected. It was dried and heated without solvent at 200° for 30 min. Recrystallization of the residue from CH_2Cl_2–hexane gave a pale yellow solid: mp 181–182°; ir (KBr) 3 μ (broad), 1570, 1550, 1520 cm^{-1}; mass spectrum *m/e* (rel intensity) 248 (82), 247 (100).

Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.39; H, 4.87; N, 11.28. Found: C, 77.09; H, 5.08; H, 11.50.

Methyl ether 5a had mp 69–70° from petroleum ether (bp 30–60°); nmr ($CDCl_3$) δ 9.09 (s, 1 H), 8.12 (m, $W_{1/2}$ = 11 Hz, 4 H), 7.50 (m, 6 H), and 3.35 (s, 3 H); mass spectrum *m/e* (rel intensity) 263 (13), 262 (73), 261 (100), 89 (28).

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 78.35; H, 5.45; N, 10.79.

Dimethyl 4,6-Diphenyl-5-pyrimidyl Phosphate (6).—A mixture of 0.3 g (1.2 mmol) of 4,6-diphenyl-5-hydroxypyrimidine (**5**) and 5 ml of $POCl_3$ were heated under reflux for 1 hr. After evaporation of excess $POCl_3$ the residue was dissolved in 5 ml of CH_3OH and this solution was diluted with water. The white solid that separated was recrystallized from CH_3OH–H_2O, mp 123–125°.

Anal. Calcd for $C_{18}H_{17}N_2O_4P$: C, 60.67; H, 4.82; N, 7.86. Found: C, 60.87; H, 4.86; N, 7.87.

4,6-Diphenylpyrimidine (7).—Small pieces of sodium (45 mg) were added to a refluxing solution of 356 mg of phosphate **6** in liquid NH_3–tetrahydrofuran. After the usual work-up, 132 mg (57%) of **7**, mp 99.5–101° (*n*-C_6H_{14}), was obtained. It was identical with an authentic sample[8] (mixture melting point, ir spectra).

Ethyl 2-Hydroxy-4,6-diphenyl-1,6-dihydropyrimidine-5-carboxylate.—A mixture of 10.6 g (0.1 mol) of benzaldehyde and 12.0 g (0.2 mol) of urea in 100 ml of C_2H_5OH was treated with 8 ml of concentrated HCl and warmed on a steam bath for 15 min. Ethyl benzoylacetate, 19.2 g (0.1 mol), was added and the solution was heated under reflux overnight. The solvent was evaporated and the residual oil was crystallized from ethanol–hexane to yield 17.0 g (53%) of pale yellow crystals. Upon recrystallization from ethanol, two forms were observed, mp 158–159° and mp 172–173°. The low-melting modification partially resolidified on heating above its melting point and finally melted at 172–173°: nmr ($CDCl_3$) δ 7.90 (br s, 1), 7.17–7.50 (m, 10), 6.68 (br s, 1), 5.40 (br d, J = 3 Hz, 1 H), 3.81 (q, J = 7 Hz, 2 H), 0.80 (t, J = 7 Hz, 3 H).

Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.56; H, 5.45; N, 8.57.

Ethyl 2-Hydroxy-4,6-diphenylpyrimidine-5-carboxylate.—A solution of 3.22 g (0.01 mol) of the dihydro compound and 1.8 g (0.011 mol) of Br_2 in 30 ml of acetic acid was heated under reflux overnight. The solvent was evaporated *in vacuo* to yield a mixture of the pyrimidine and its dibromo intermediate. The dehydrobromination was completed by dissolving the mixture in ethanol and stirring overnight in the presence of excess solid K_2CO_3 at room temperature. The mixture was filtered, and the filtrate was evaporated to yield 2.68 g (84%) of white solid. A sample was recrystallized from ethanol–water and sublimed at 180° (0.5 mm): mp 215–216°; nmr ($CDCl_3$) δ 7.25–7.80 (m, 10 H), 3.90 (q, J = 7 Hz, 2 H), 0.83 (t, J = 7 Hz, 3 H)

Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.75. Found: C, 71.04; H, 5.12; N, 8.83.

Registry No.—**1**, 34982-07-5; **2**, 34906-18-8; **3**, 34906-19-9; **3a**, 34906-20-2; **4**, 34906-21-3; **4** acetate ester, 34906-22-4; **4a**, 34906-23-5; **5**, 34906-24-6; **5a**, 34906-25-7; **6**, 34906-26-8; **7**, 3977-48-8; ethyl 2-hydroxy-4,6-diphenyl-1,6-dihydropyrimidine-5-carboxylate, 34906-28-0; ethyl 2-hydroxy-4,6-diphenylpyrimidine-5-carboxylate, 34906-29-1.

(12) Band width at half height.

New Synthetic Methods from Dithianes. A Convenient Oxidation of Aldehydes to Acids and Esters

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The considerable literature on the chemistry of 2-lithio-1,3-dithianes which has been accumulating recently[1] attests to their great utility in organic synthesis. This contrasts with the present utility of metalated orthothioformates which suffer from being simultaneously less reactive and somewhat unstable.[2] Furthermore, neither their hydrolysis[2] nor alcoholysis[3] has produced outstanding yields. We wish to report a combination of reactions which leads from 2-substituted 1,3-dithianes to carboxylic acids and esters in good overall yields *via* 2-substituted 2-methylthio-1,3-dithianes.

Treatment of 2-lithio 2-substituted 1,3-dithianes

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(3) R. M. Carlson and P. M. Helquist, *Tetrahedron Lett.*, 173 (1969).