The Synthesis of Two Novel Pyridazines; A New Ring System

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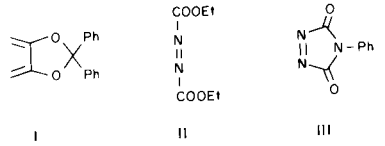
The Diels-Alder reaction of 4,5-dimethylene-2,2-diphenyldioxolane with diethyl azodicarboxylate and 4-phenyl-1,2,4-triazoline-3,5-dione was investigated. Reduction of the resultant adducts followed by hydrolysis provided hexahydro-4,5-dihydroxy-1,2-pyridazine dicarboxylic acid diethylester and 1,3,5,6,7,8-hexahydro-6,7-dihydroxy-2-phenyl-2*H*-*s*-triazolo[1,2-*a*]pyridazine-1,3-dione.

The pyridazine and condensed pyridazine ring systems have not been investigated as thoroughly as the analogous pyrazine and pyrimidine systems. A search of the literature does not show the preparation of saturated 4,5-dihydroxypyridazines or their 1,2-derivatives.

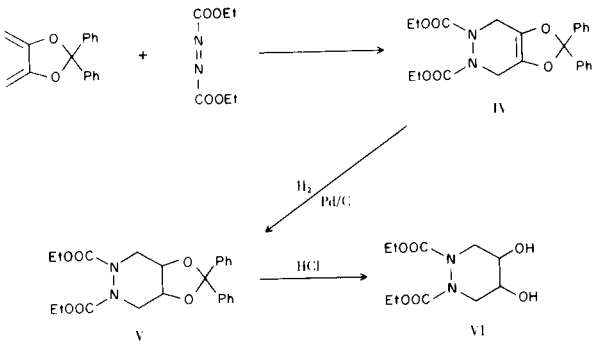
A useful synthetic method which directly affords these pyridazines is the Diels-Alder reaction of a conjugated diene with an appropriate azo dienophile.



I II III

Synthesis of the new pyridazine (Scheme I) begins with the reaction of 4,5-dimethylene-2,2-diphenyldioxolane (I) (I) with diethyl azodicarboxylate (II). The resulting adduct, isolated in 43% yield, was surprisingly stable as it withstood attempts at both acidic and basic hydrolysis. The reduction of (IV) over 5% palladium on carbon at atmospheric pressure proceeded smoothly and afforded (V) in quantitative yield. Subsequent acidic hydrolysis of the ketal furnished the dihydroxypyridazine (VI) in 77% yield.

SCHEME I

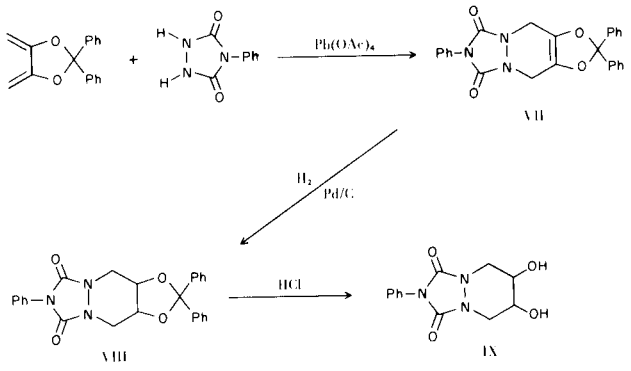


Cookson, Gilani, and Stevens (2) established 4-phenyl-1,2,4-triazoline-3,5-dione (III) as a highly reactive dienophile by its reactions with butadiene, cyclopentadiene, cycloheptatriene, and bicycloheptadiene. It was found that a new ring system could be developed through a Diels-Alder reaction of (III) with (I).

The most advantageous method for generating the dienophile is the *in situ* oxidation of 4-phenylurazole (3) at 0 to 5° using lead tetraacetate as the oxidizing agent (4).

Following this procedure, we attempted the synthesis of the new ring system (Scheme II). When (I) was reacted with (III), the reaction proceeded slowly and the adduct (VII) was isolated in only 6% yield. Varying the reaction conditions and times did not appreciably affect the yield.

SCHEME II



Reduction of (VII) was accomplished in quantitative yield by catalytic hydrogenation over 5% palladium on carbon at 3.5 atmospheres.

In both reductions of (IV) and (VII) it is assumed that the saturation of the olefinic linkage occurs in a *cis* fashion due to the orientation of the substrate with the surface of the catalyst. No stereochemical evidence of

cis or *trans* addition of hydrogen is evident in the nmr spectra.

Compound (VIII) was then hydrolyzed under acidic conditions. The product (IX) was not isolated from the reaction mixture but was identified by vapor phase chromatography followed by mass spectral analysis of the resulting fractions.

Further studies on the synthesis of (VI) and (IX), and analogous reactions of other reactive dienophiles with (I) are in progress.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457 spectrophotometers. All pure materials were run as nujol and halocarbon mulls. Nuclear magnetic resonance spectra were determined on a Varian T-60 spectrometer using tetramethylsilane as an internal reference. Mass spectra were determined on an LKB 9000 spectrometer.

Interpretation of nmr data: δ chemical shift ppm (multiplicity, number of protons). s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

4,5,6,7-Tetrahydro-2,2-diphenyl-2*H*-1,3-dioxolo[4,5-*c*]pyridazine-5,6-dicarboxylic Acid Diethylester (IV).

To a solution of 18 g. of 4,5-dimethylene-2,2-diphenyldioxolane (I) in 300 ml. of hexane was added 11 g. of diethyl azodicarboxylate. The resulting solution was stirred at 25° for 24 hours. The resulting solid was filtered and recrystallized from ethanol yielding 12.9 g. (43%) of 4,5,6,7-tetrahydro-2,2-diphenyl-2*H*-1,3-dioxolo[4,5-*c*]pyridazine-5,6-dicarboxylic acid diethylester (IV), m.p. 135 to 137°; ir (chloroform): 2860, 1760, 1715, 1235, 1195, 1150, 1115, 1045 cm^{-1}; nmr (deuteriochloroform): δ 7.4 (m, 10), 4.35 (q, 4, J_{gem} = 8 cps), 4.2 (q, 4), 1.25 (t,6) ppm.

Anal. Calcd. for $C_{23}H_{24}N_2O_6$: C, 65.0: H, 5.7; N, 6.6. Found: C, 64.9; H, 5.7; N, 6.4.

3a,4,5,6,7,7a-Hexahydro-2,2-diphenyl-2*H*-1,3-dioxolo[4,5-*c*]pyridazine-5,6-dicarboxylic Acid Diethylester (V).

A solution of 3 g. of IV in 100 ml. of absolute ethanol was catalytically hydrogenated over 5% palladium on carbon at one atmosphere and 25° for 18 hours. The catalyst was filtered from the reaction mixture and the solvent was removed under reduced pressure. The resulting oil was dissolved in methylene chloride and treated with decolorizing carbon. Evaporation of the solvent under reduced pressure yielded 2.95 g. (100%) of 3a,4,5,6,7,7a-hexahydro-2,2-diphenyl-2*H*-1,3-dioxolo[4,5-*c*]pyridazine-5,6-dicarboxylic acid diethylester (V); ir (chloroform): 2935, 1710, 1415, 1235, 1175, 1150, 1115, 1090 cm^{-1}; nmr (deuteriochloroform): δ 7.3 (m, 10), 4.4 (m, 4), 4.2 (q, 4), 3.2 (m, 2), 1.3 (t, 6) ppm.

Anal. Calcd. for $C_{23}H_{26}N_2O_6$: C, 64.7; H, 6.1; N, 6.6. Found: C, 64.4; H, 6.0; N, 6.6.

Hexahydro-4,5-dihydroxy-1,2-pyridazine Dicarboxylic Acid Diethylester (VI).

A solution of 2.4 g. of (V) in 35 ml. of dioxane, containing 1 ml. of 2*N* hydrochloric acid, was heated at 85° for 24 hours. The solvent was removed under reduced pressure and the resulting oil was chromatographed on a column of silica gel using a 2% solution of ethanol/chloroform to elute the product. Evaporation of the solvent afforded 1.2 g. (77%) of hexahydro-4,5-dihydroxy-1,2-pyridazine dicarboxylic acid diethylester (VI); ir (chloroform): 3550, 2940, 1710, 1415, 1270, 1235 cm^{-1}; nmr (deuteriochloroform): δ 4.2 (q, 4), 4.0 (m, 6), 3.2 (m, 2), 1.3 (t, 6) ppm.

Anal. Calcd. for $C_{10}H_{18}N_2O_6$: C, 45.8; H, 6.9; N, 10.7. Found: C, 46.0; H, 7.0; N, 10.4;

2,3,7,10-Tetrahydro-2,2,7-triphenyl-1,3-dioxolo[4,5-*d*]-*s*-triazolo-[1,2-*a*]pyridazine-6,8(6*H*,8*H*)dione (VII).

To a solution of 4.3 g. of I in 75 ml. of methylene chloride was added 3.0 g. of 4-phenylurazole. The resulting suspension was cooled to 0 to 5°, then a cold solution of 10 g. of lead tetraacetate in 75 ml. of methylene chloride was added dropwise. The reaction mixture was stirred at 0 to 5° for one hour at 25° for 17 hours. The inorganic material was filtered off and the solvent was removed under reduced pressure. Methanol was added to the resulting oil and the excess lead salts were removed by filtration. The filtrate was chromatographed on a column of silica gel and the product was eluted with chloroform. Evaporation of the solvent under reduced pressure yielded 230 mg. (6%) of 2,4,7,10-tetrahydro-2,2,7-triphenyl-1,3-dioxolo[4,5-*d*]-*s*-triazolo[1,2-*a*]pyridazine-6,8(6*H*,8*H*)dione (VII), m.p. 192° to 194°; ir (chloroform): 2870, 1790, 1720, 1425, 1260, 1140, 1080, 1045 cm^{-1}; nmr (deuteriochloroform): δ 7.4 (m, 15), 4.4 (s, 4) ppm.

Anal. Calcd. for $C_{25}H_{19}N_3O_4$: C, 70.6; H, 4.5; N, 9.9. Found: C, 70.3; H, 4.6; N, 9.6.

2,3a,4,7,10,10a-Hexahydro-2,2,7-triphenyl-1,3-dioxolo[4,5-*d*]-*s*-triazolo[1,2-*a*]pyridazine-6,8(6*H*,8*H*)dione (VIII).

A solution of 225 mg. of (VII) in 25 ml. of absolute ethanol was catalytically hydrogenated over 5% palladium on carbon at 3.5 atmospheres for 24 hours; 50 ml. of methylene chloride was added to dissolve any precipitate. Filtration of the catalyst and evaporation of the solvent under reduced pressure yielded 223 mg. (100%) of 2,3a,4,7,10,10a-hexahydro-2,2,7-triphenyl-1,3-dioxolo-[4,5-*d*]-*s*-triazolo[1,2-*a*]pyridazine-6,8(6*H*,8*H*)dione (VIII), m.p. 210 to 214°; ir (chloroform): 2930, 1770, 1710, 1420, 1250, 1140, 1130, 1100, 1070 cm^{-1}; nmr (deuteriochloroform): δ 7.3 (m, 15), 4.4 (d, 2), 4.0 (q, 4 J_{gem} = 8 cps) ppm.

Anal. Calcd. for $C_{25}H_{21}N_3O_4$: C, 70.2; H, 4.9; N, 9.9. Found: C, 69.8; H, 4.8; N, 9.9.

1,3,5,6,7,8-Hexahydro-6,7-dihydroxy-2-phenyl-2*H*-*s*-triazolo[1,2-*a*]-pyridazine-1,3-dione (IX).

A solution of 50 mg. of VIII in 3 ml. of dioxane, containing 0.2 ml. of 2*N* hydrochloric acid, was heated at 85° for 48 hours. The solvent was removed under reduced pressure and the resulting solid was gas chromatographed to yield 85% of 1,3,5,6,7,8-hexahydro-6,7-dihydroxy-2-phenyl-2*H*-*s*-triazolo[1,2-*a*]pyridazine-1,3-dione (IX); m/e 263.

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