

Synthesis of the 13,14-Diazasteroid Ring System

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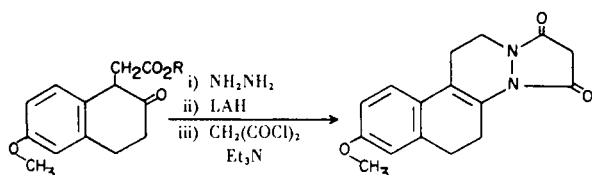
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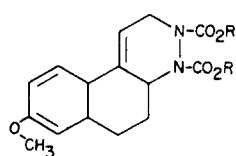
1-Vinyl-6-methoxy-3,4-dihydronaphthalene (I) reacted with azo dienophiles to form cycloadducts II, III, IV, and V. The reaction of adduct II with bromine resulted in the aromatization of the B ring to form the cycloadduct VIII.

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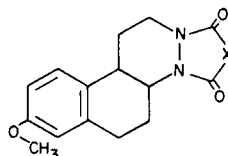
The pyrazolo[1,2-*a*]cinnoline-1,3-dione system has been reported to have pharmacological properties (antiinflammatory, analgesic, and antipyretic) (1,2). A steroid analogue of this system was prepared by Huisman (3), which also represents the only known 13,14-diazasteroid.



This note describes a simple, one step synthesis of the 13,14-diazasteroid skeleton by treatment of the diene, 1-vinyl-6-methoxy-3,4-dihydronaphthalene (I) (4) with various azo dienophiles. Reaction of this diene with ethyl azodicarboxylate, methyl azodicarboxylate, 4,4-diethylpyrazoline-3,5-dione, and 4-phenyl-1,2,4-triazolene-3,5-dione, gave the adducts II, III, IV, and V, respectively (Table I). The position of the double bond in the 9,11

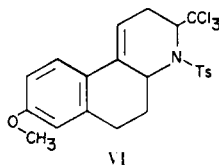


II R = Et
III R = Me



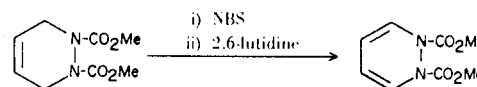
IV X = C(Et)₂
V X = N-C₆H₅

position was confirmed by nmr and uv measurements. The nmr of II-V shows a multiplet signal for the vinyl proton in the region of δ 6.0. Further, the λ max of II-V are similar to those of steroids having the same methoxystyrene nucleus. For example, VI has a λ max at 262.5 ($\epsilon = 19,600$) (5).



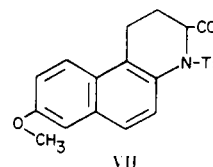
In an attempt to prepare a crystalline derivative of adduct II by reacting the 9,11 double bond with bromine, a white solid was formed. The mass spectrum indicated a molecular weight of 358, two mass units less than II. The position of the new double bond was not immediately apparent.

Altman (6) observed that dimethyl-1,2-dihydropyridazine-1,2-dicarboxylate can be formed from dimethyl-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate in an 81% yield *via* allylic bromination followed by debromination.



The product shows four vinyl hydrogens as an AA'XX' multiplet centered at δ 5.71 and δ 6.73. The product of reaction of II and bromine, however, does not show any protons in this region. The nmr spectrum shows five protons in the aromatic region as a multiplet from δ 7.05 to δ 7.90.

Zunnefeld (5) observed that V reacts with bromine to give a small yield of VII whose structure was confirmed



by double resonance nmr. This product exhibits a complex ultraviolet absorption similar to that of the product obtained from bromination of II (Table II).

This confirms VIII as the correct structure. The formation of the unexpected product VIII may occur by addition to the 9,11 double bond or substitution at the benzylic position followed by elimination of HBr and double bond migration.

Table I

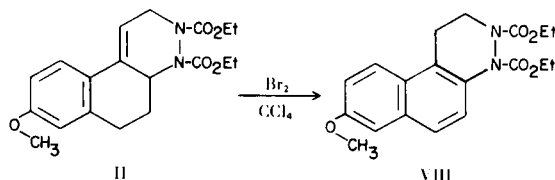
	ir (C=O) cm ⁻¹	Uv λ max nm (a) (ε)	Nmr, δ, ppm
II	1720 (b)	264 (15,500)	1.20 (t, 3, CH ₃ , J = 7 Hz), 1.22 (t, 3, CH ₃ , J = 7 Hz) 1.60-3.05 (m, 4, CH ₂), 3.69 (s, 3, OCH ₃), 4.04 (m, 4, CH ₂), 4.30-4.60 (m, 3, CH ₂ and CH), 5.83 (m, 1, vinylic H), 6.34-6.67 (m, 2, ArH <i>ortho</i>) and 7.14 (m, 1, ArH <i>meta</i>).
III (c)	1720 (d)	262 (17,500)	1.70-3.10 (m, 4, CH ₂), 3.58 and 3.53 (s, 9, -OCH ₃ and CH ₃), 4.20-4.60 (m, 3, CH ₂ and CH), 5.78 (m, 1, vinylic H), 6.20-6.60 (m, 2, ArH <i>ortho</i>) and 6.95 (m, 1, ArH <i>meta</i>).
IV (c)	1740 (d) 1690	261 (21,600)	0.90 (t, 3, CH ₃ , J = 7 Hz), 1.84 (q, 4, CH ₂), 2.85- 3.25 (m, 4, CH ₂), 3.81 (s, 3, OCH ₃), 4.15-4.75 (m, 3, CH ₂ and CH), 6.03 (m, 1, vinylic H), 6.55-7.00 (m, 1, ArH <i>ortho</i>) and 9.45 (m, 1, ArH <i>meta</i>).
V (c)	1770 (d) 1705	260 (18,600)	1.70-3.50 (m, 4, CH ₂), 3.81 (s, 3, OCH ₃), 4.00- 4.70 (m, 3, CH ₂ and CH), 6.10 (m, 1, vinylic H), 6.60-7.80 (m, 8, ArH).
VIII (c)	1710 (d)	240 (57,600)	1.22 (t, 3, CH ₃ , J = 7 Hz), 1.29 (t, 3, CH ₃ , J = 7 Hz) 2.95-2.65 (m, 3, CH ₂ and CH), 3.86 (s, 3, -OCH ₃), 4.10 (m, 1, CH), 4.30 (q, 4, CH ₂ , J = 7 Hz), 7.05- 7.90 (m, 5, ArH).

(a) 95% Ethanol. (b) Film spectrum. (c) Analysis better than ± 0.3%. (d) Nujol mull.

Table II

The Ultraviolet Spectrum of VII and VIII

Compound λ max nm (ε) (Ethanol)	I + Br ₂ λ max nm (ε) (95% Ethanol)
229 (47,600)	-----
241.5 (50,000)	240 (57,000)
270 (9,000)	267 (7,300)
280 (7,950)	278 (8,000)
291.5 (6,100)	288 (3,500)
322.5 (2,150)	327 (1,600)
347.5 (1,850)	341 (1,800)



EXPERIMENTAL

All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were taken with a Perkin-Elmer 137, Beckman IR-8, or IR-20 spectrometer. All spectra were calibrated with the 1602 cm⁻¹ peak of polystyrene.

The nuclear magnetic resonance spectra were obtained with a Varian Model A-60 using deuteriochloroform as solvent. Tetramethylsilane was used as a reference standard. The ultraviolet spectra were obtained on a Cary 14 spectrometer. The mass spectra were obtained on a AEI MS-902 spectrometer at 70 eV. Microanalysis were performed by A. Bernhardt Microanalytisches Laboratorium, Ubach, West Germany.

Ethyl azodicarboxylate was prepared by the method of Rabjohn (7). Methyl azodicarboxylate was prepared by the method of Kauer (8).

4-Phenyl-1,2,4-triazolone-3,5-dione was prepared *in situ* by the method of Gillis and Hagarty (9).

4,4-Diethylpyrazoline-3,5-dione was prepared *in situ* by the method of Gillis and Izydore (10).

1-Vinyl-6-methoxy-3,4-dihydronaphthalene was prepared by the method of Nazarov (4).

Adduct II.

To a solution of 5.52 g. (0.029 mole) of I in 100 ml. of methylene chloride at 0° was added 5.22 g. (0.030 mole) of ethyl azodicarboxylate. The solution was stirred for one hour at 0°. Alumina was added to the stirred mixture at room temperature, until the solution ceased to foam upon addition. This procedure resulted in the removal of excess ethyl azodicarboxylate. Solvent was removed *in vacuo* to leave an orange oil. The oil was chromatographed on Fisher alumina and eluted from the column with a solution of 2% ethanol in benzene.

The reaction resulted in the formation of 6.47 g. (62% yield) of II as a light yellow glass in which traces of solvent remained.

Adduct III.

To a solution of 11.40 g. (0.061 mole) of I in 150 ml. of

methylene chloride at 0° was added 7.05 g. (0.048 mole) of methyl azodicarboxylate. The solution was stirred for 2 hours at 0°. The solvent was removed *in vacuo*. The crude yellow oil was purified by dry column chromatography on Fisher alumina, deactivated with 6% water, using low boiling petroleum ether. The resulting oil solidified on standing and was recrystallized from methanol. The reaction resulted in 7.21 g. (60% yield) of III, m.p. 130.5-132.0°.

Anal. Calcd. for C₁₇H₂₀N₂O₅: C, 61.44; H, 6.03; N, 8.43. Found: C, 61.25; H, 6.12; N, 8.41.

Adduct IV.

Into a 250 ml. three-necked flask was placed a solution of 100 ml. of methylene chloride, 5.14 g. (0.028 mole) of I, and 2.08 g. (0.013 mole) of 4,4-diethylpyrazolidine-3,5-dione. The solution was cooled to 0° and 5.18 g. (0.013 mole) of lead tetraacetate in 100 ml. of methylene chloride was added dropwise over a period of 45 minutes. The solution was stirred for three hours at 0° and then filtered. The filtrate was washed with 50 ml. of water and two 50 ml. portions of 10% sodium bicarbonate. The organic layer was separated and dried over magnesium sulfate. The solvent was removed *in vacuo* to give a yellow solid. The crude product was recrystallized from ethanol-water to give pale yellow plates. The reaction yields 1.10 g. (25%) of IV, m.p. 144-145°.

Anal. Calcd. for C₂₁H₁₉N₃O₃: C, 69.80; H, 5.26; N, 11.63. Found: C, 69.98; H, 5.08; N, 11.65.

Adduct V.

Into a 250 ml. three-necked flask was placed 4.21 g. (0.022 mole) of I, 3.00 g. (0.017 mole) of phenylurazole, and 100 ml. of methylene chloride. The solution was cooled to 0° and 8.23 g. (0.01 mole) of lead tetraacetate in 100 ml. of methylene chloride was added. The mixture was stirred for 3 hours at 0°. The solution was allowed to warm to room temperature and stirred overnight. The mixture was then filtered and the filtrate was washed successively with a 100 ml. portion of water, 10% sodium bicarbonate, and water, and dried over magnesium sulfate. The solvent was removed *in vacuo* to give a red-brown oil. The oil was

crystallized from chloroform to yield 2.21 g. (35%) of V, m.p. 176-177°.

Anal. Calcd.: C, 69.80; H, 5.26; N, 11.63. Found: C, 70.02. H, 5.35; N, 11.45.

Reaction of II with Bromine.

To a solution of 7.02 g. (0.020 mole) of II in 75 ml. of carbon tetrachloride at 0° was added 3.13 g. (0.039 mole) of bromine in 50 ml. of carbon tetrachloride. The solution was stirred for one hour at 0°. The solvent was removed *in vacuo* and the black residue was dissolved in ethyl ether. The solution was washed with two 50 ml. portions of 10% sodium bicarbonate, dried over magnesium sulfate, filtered, and the diethyl ether was removed *in vacuo*. The white solid was recrystallized from methanol and sublimed (150°/0.1 mm). This resulted in 600 mg. (9% yield) of VIII, m.p. 152-154°.

Anal. Calcd. for C₁₉H₂₂N₂O₅: C, 63.69; H, 6.15; N, 7.82. Found: C, 63.50; H, 6.30; N, 7.76.

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