Azeto[1,2-*a*]quinoxaline-1,3-diones, A New Class of Bridgehead Nitrogen β-Lactams

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Two synthetic procedures have been developed for the preparation of azeto[1,2-*a*]quinoxaline-1,3-diones, a novel class of fused heterocyclic β-lactams possessing a bridgehead nitrogen atom. Both processes are general and afford the title compounds in good yield. The infrared, proton magnetic resonance, and mass spectroscopic properties of the title compounds are discussed.

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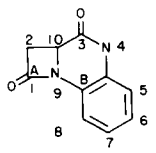
The widespread occurrence of the β-lactam ring in nature (1) has prompted us (2) and others (3) to synthesize a variety of compounds containing this ring system. A review of the literature shows that only a few different representative types of bridgehead nitrogen β-lactams have been made (4), some of the claimed syntheses being questionable (5).

The azeto[1,2-*a*]quinoxaline-1,3-dione nucleus (I) is a novel heterocycle not described in the literature. Because we were intrigued by the potential for antimicrobial activity of the bridgehead nitrogen β-lactam unit present in (I), we undertook its synthesis.



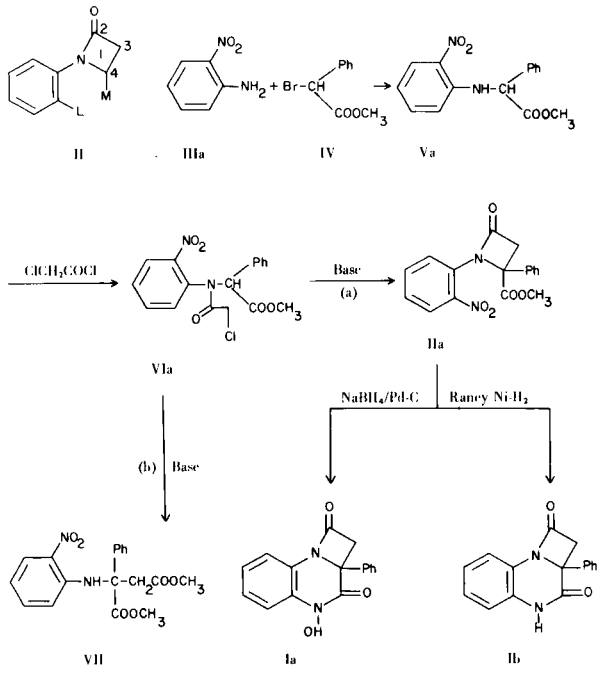
I

Any proposed route to fused heterocycles possessing a β-lactam ring must contend with the lability of that ring to the action of nucleophiles (6), Lewis and other acids (7), and to its thermal instability (8). We were encouraged by precedents in the synthesis of more complex heterocycles commencing from preformed β-lactams, under experimental conditions in which the β-lactam unit remained intact during the course of the reaction (9). We, therefore, speculated on two courses for the synthesis of (I). As a first process, we decided to cyclize the β-lactam ring before annelating the quinoxaline portion of the molecule; and as a second process, we decided to cyclize the quinoxaline ring as the initial step and then close the β-lactam ring as the terminal step of our synthesis.

The Ring A Before Ring B Synthesis.

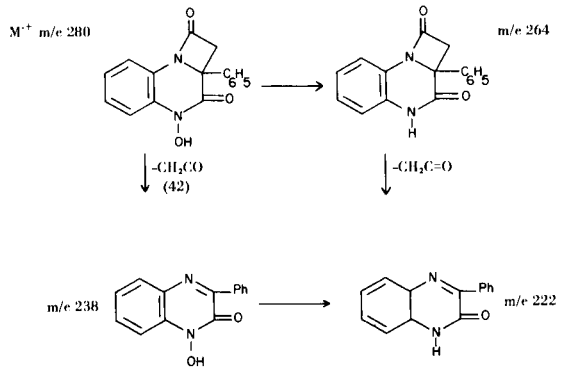
To prepare I *via* this approach, we needed a key intermediate II with an *N*-aryl group carrying an *o*-substituted function L and a second function M on C_4 of the β-lactam ring. Furthermore, L and M would have to be inert to each other under the conditions of the synthesis of the β-lactam ring A. They must interact chemically at a later stage, however, under conditions of our choosing which must be sufficiently mild to prevent β-lactam ring fission. The key intermediate *N*-(*o*-nitrophenyl)-2-oxo-4-phenyl-4-methoxycarbonylazetidine (IIa) was prepared in three steps from *o*-nitroaniline (III) and methyl-α-bromophenylacetate (IV) as outlined in Scheme 1. The choice of the cyclization catalyst for *N*-chloroacetyl-*N*-(*o*-nitrophenyl)-2-phenylglycine methyl ester (VIa) was important. Potassium hydroxide in anhydrous methanol gave *N*-(*o*-nitrophenyl)-2-phenylasparagine dimethyl ester (VII) arising from β-lactam ring formation followed by ring fission at the N_1-C_2 bond. With potassium hydroxide in anhydrous ethanol, there was no asparagine formation, and the key intermediate (IIa) was produced as a crystalline solid in a high state of purity. The intramolecular reductive acylation of IIa to 4-hydroxy-10-phenyl-9,10-dihydroazeto[1,2-*a*]-quinoxaline-1,3-dione (Ia), and to Ib, was smoothly achieved by sodium borohydride/palladium-on-carbon catalyst in aqueous methanol, and by Raney nickel in absolute ethanol, respectively. The overall reaction sequence is shown in Scheme 1. The hydroxamic acid Ia gave a deep-violet ferric chloride color reaction, possessed a β-lactam carbonyl stretching band at 1780 cm^{-1}, and showed bands at 1680 and 1645 cm^{-1} characteristic for hydroxamic carbonyl groups in the infrared spectrum. Furthermore, the 1745 cm^{-1} band present in the ester IIa

Scheme 1



was absent in Ia. The nmr spectrum of the hydroxamic acid Ia indicated that after reductive annelation the carbomethoxy group was lost (no signal at 3.83 ppm). Also absent in the nmr was a multiplet at 7.83 ppm characteristic for the proton *ortho* to the nitro group in the uncyclized intermediate β-lactam (IIa). The ring A methylene protons of Ia appeared as a quartet centered at 3.53 ppm (J = 15 Hz) (deuteriochloroform). Additional confirmation of our structural assignment was obtained by the identification of mass peaks corresponding to 280 ($M^{\cdot+}$, m/e), 264, 238, and 222 mass units in the molecular ionization spectrum of Ia. The mass spectral fragmentation data are summarized in Scheme 2.

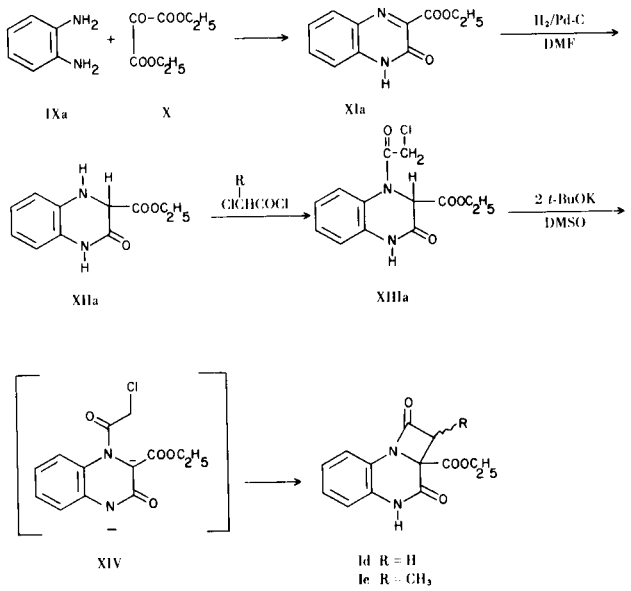
Scheme 2
Mass Spectral Fragmentation of Ia (10)



The Ring B Before Ring A Synthesis.

The structure of I suggests that it should be readily synthesized starting from a quinoxaline. In earlier work Sheehan (11) had established conditions needed for cyclizing chloroacetanilidomalonates to azetidin-2-ones. Keeping in mind the minimum number of parameters needed for the activation of the methine hydrogen atom which is eliminated in the cyclization to β-lactam (12), we realized that the intermediate, 3,4-dihydro-4-α-chloroacetyl-3-ethoxycarbonylquinoxalin-2(1*H*)one (XIIIa), should be easily annelated to the required azeto[1,2-*a*]-quinoxaline-1,3-dione (Id) with a base. Scheme 3 outlines the synthesis of the key intermediate XIIIa in three steps, starting from a *symmetrically substituted o*-phenylenediamine (IXa) and diethyl ketomalonate (X). The 3-ethoxycarbonylquinoxalin-2(1*H*)one (XIa) produced was reduced to 3,4-dihydro-3-ethoxycarbonylquinoxalin-2(1*H*)-one (XIIa) with hydrogen/palladium-on-carbon in dimethylformamide solution. Chloroacetylation with chloroacetyl chloride in anhydrous benzene gave XIIIa. The final ring closure to the β-lactam was accomplished using two equivalents of potassium *t*-butoxide in anhydrous dimethyl

Scheme 3

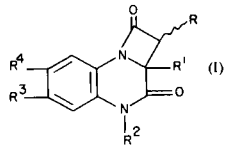


sulfoxide solution, but the yields were low. The dianion XIV is presumably first formed and undergoes exclusive intramolecular alkylation on carbon. The main advantage of this route was that it was possible to prepare 2-substituted azeto[1,2-*a*]quinoxaline-1,3-diones inaccessible by the previous process.

Limitations of the Ring B Before Ring A Synthesis.

The quinoxalines that are produced in this process have

Table I



No.	R	R^1	R^2	R^3	R^4	M.p., °C	Crystallization Solvent	IR C_2=O	IR cm^{-1} C_3=O	NMR Spectrum C_2 Proton(s)	J_{AB} cps
Ia	H	Ph	OH	H	H	152-154		1780	1645, 1680	3.60 (a)	15
Ib	H	Ph	H	H	H	192-193	Hexane/2-Propanol	1780	1690	3.78 (a)	15
Ic	H	Ph	H	Cl	H	238-239	Hexane/Chloroform	1790	1690	3.96 (b)	15
Id	H	COOEt	H	H	H	153-154	Hexane/2-Propanol	1785	1690	3.78 (b)	16
Ie	Me	COOEt	H	H	H	181-182	Hexane/2-Propanol	1785	1695	---	---
If	Me	COOEt	H	Cl	Cl	213-215	Benzene/Hexane	1770	1715	---	---

(a) Deuteriochloroform, tetramethylsilane as internal reference. (b) Deuteriodimethylsulfoxide (d_6), tetramethylsilane as internal reference. Chemical shifts in ppm.

to be made from symmetrically substituted *o*-phenylenediamines because the condensation with diethyl ketomalonate is not an unambiguous process.

The bridgehead nitrogen β-lactams that were synthesized, either monocyclic or bicyclic, possessed no antimicrobial activity, in a standard agar dilution test using several test organisms.

EXPERIMENTAL

Melting points are uncorrected and were determined on a Thomas Hoover capillary tube melting point apparatus. Proton magnetic resonance spectra were obtained on a Varian T-60 Spectrometer and infrared spectra were obtained on a Perkin-Elmer Model 267 Grating Infrared Spectrophotometer.

N-(*o*-Nitrophenyl)-2-phenylglycine Methyl Ester (Va).

A mixture of 27.6 g. (0.02 mole) of finely crushed *o*-nitroaniline and 22.9 g. (0.01 mole) of methyl α-bromophenylacetate was placed in a 250-ml. round-bottom flask, evacuated to 15 torr, and heated to an external temperature of 60-70° for seven days. After cooling, the mass was extracted with benzene and filtered to remove *o*-nitroaniline hydrobromide. The filtrate was washed with 2*N* hydrochloric acid (5 x 200 ml.), dried over magnesium sulfate, and evaporated *in vacuo*. The remaining yellow oil crystallized upon trituration with 2-propanol to give 16.3 g. (56%) of Va, m.p. 108-109°; ir (Nujol) $\bar{\nu}$ cm^{-1}: 3365 (N-H), 1733 (ester >C=O); nmr δ (deuteriochloroform): 8.2 (m, 9, aromatic), 7.3 (m, 6, aromatic), 6.6 (m, 2, aromatic), 5.2 (d, 1, -C-H), 3.8 (s, 3, $-OCH_3$).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 62.93; H, 4.93; N, 9.79. Found: C, 63.09; H, 5.20; N, 9.61.

N-(*o*-Nitrophenyl)-*N*-chloroacetyl-2-phenylglycine Methyl Ester (VIa).

A mixture of 7.56 g. (0.0264 mole) of Va and 10 ml. of freshly distilled chloroacetyl chloride was heated at 110° for four hours and 120° for one additional hour. The mixture was cooled and poured into 45 ml. of ice-cold methanol. Upon standing, a white precipitate was formed and removed by filtration. The white material was recrystallized from 2-propanol to give 8.82 g. (92%) of VIa as white crystals, m.p. 137-138°; ir (Nujol) $\bar{\nu}$ cm^{-1}: 1745 (ester >C=O), 1685 (amide >C=O); nmr δ (deuteriochloroform): 8.2-6.6 (m, 9, aromatic), 6.1 (s, 1, -CH), 3.9 (s, 2, $-CH_2-$), 3.7 (s, 3, OCH_3).

Anal. Calcd. for $C_{17}H_{15}ClN_2O_5$: C, 56.29; H, 4.17; N, 7.72. Found: C, 56.04; H, 3.99; N, 7.55.

1-(*o*-Nitrophenyl)-2-oxo-4-phenyl-4-methoxycarbonylazetidine (IIa).

To a warm solution of 3.62 g. (0.01 mole) of VIa in 50 ml. of anhydrous ethanol was added 0.63 g. (0.011 mole) of potassium hydroxide in 10 ml. of ethanol dropwise with stirring. The mixture was stirred for one-half hour, then neutralized with one drop of glacial acetic acid. The solution was evaporated *in vacuo*. The residue was taken up in benzene, washed with water, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was recrystallized from 2-propanol to give 2.7 g. (83%) of IIa, m.p. 99-100°; ir (Nujol) $\bar{\nu}$ cm^{-1}: 1775 (β-lactam carbonyl), 1740 (ester carbonyl); nmr δ (deuteriochloroform): 8.0-6.9 (m, 9, aromatic), 3.9 (d, 1.5, J = 15 cps), 3.8 (s, 3, $-OCH_3$), 3.4 (d, 1.5, J = 15 cps).

N-[4-Chloro-2-nitrophenyl]-2-phenylglycine Methyl Ester (Vb).

A mixture of 30.0 g. (0.174 mole) of finely divided 2-nitro-4-chloroaniline and 22.0 g. (0.09 mole) of methyl α-bromophenylacetate was placed in a 250-ml. round-bottom flask, evacuated to 18 torr and incubated for five days at an external temperature of 80°. The reaction mixture was cooled and extracted with methylene chloride and filtered to remove 2-nitro-4-chloroaniline hydrobromide. The filtrate was evaporated *in vacuo*. The remaining yellow solid was heated in a Kugelrohr at 135°/0.1 torr to remove the remaining 2-nitro-4-chloroaniline, and the residue was recrystallized from 2-propanol to give 8.2 g. (27%) of Vb, m.p. 99-100°;

nmr δ (deuteriochloroform): 9.1 (broad doublet, 1, N-H), 8.2 (d, 1, aromatic), 7.7-7.1 (m, 6, aromatic), 6.6 (d, 1, aromatic), 5.3 (d, 1, -C-H), 3.8 (s, 3, CH_3); ir (Nujol) $\bar{\nu}$ cm^{-1}: 3370 (N-H), 1748 (>C=O).

Anal. Calcd. for $C_{15}H_{13}ClN_2O_4$: C, 56.17; H, 4.09; N, 8.73. Found: C, 56.13; H, 3.85; N, 8.71.

N-Chloroacetyl-*N*-[4-chloro-2-nitrophenyl]-2-phenylglycine Methyl Ester (VIb).

A mixture of 7.7 g. (0.024 moles) of Vb and 10.0 ml. of α-chloroacetyl chloride was heated to 115° for six hours under nitrogen. The mixture was cooled and poured into 30 ml. of ice-cold methanol. After the excess acid chloride had been destroyed, the solution was evaporated *in vacuo*. The remaining oil was cooled in ice and crystallization induced by scratching, 30 ml. of 2-propanol was added, and the entire mixture refrigerated overnight. Filtration and washing with ice-cold 2-propanol gave 7.2 g. (75%) of VIb as white cubic crystals, m.p. 122-123°; nmr δ (deuteriochloroform): 8.3-6.8 (m, 8, aromatic), 6.2 (s, 1, -CH-), 3.95 (s, 2, $-CH_2-$), 3.8 (s, 3, $-CH_3$).

Anal. Calcd. for $C_{17}H_{14}Cl_2N_2O_5$: C, 51.40; H, 3.55; N, 7.05. Found: C, 51.21; H, 3.61; N, 6.94.

N-[2-Nitro-4-chlorophenyl]-2-oxo-4-phenyl-4-methoxycarbonylazetidine (IIb).

To a methanolic solution of 6.0 g. (0.015 mole) of VIb was added 0.95 g. (0.017 mole) of potassium hydroxide in methanol dropwise over a 15-minute period. The reaction was stirred at room temperature for 15 minutes and the *p*H adjusted to 6.5 by the dropwise addition of acetic acid. The solvents were removed *in vacuo*, and the remaining residue taken up in methylene chloride, washed with water, dried over magnesium sulfate, and evaporated *in vacuo* to give a yellow oil which deposited 3.8 g. (70%) of cubic crystals when dissolved in hot anhydrous ethanol and allowed to cool, m.p. 106-107°; ir (Nujol) $\bar{\nu}$ cm^{-1}: 1785 (β-lactam >C=O), 1755 (ester >C=O); nmr δ (deuteriochloroform): 7.9 (d, 1, aromatic), 7.5 (m, 6, aromatic), 7.1 (d, 1, aromatic), 4.1-3.3 (m, 5).

Anal. Calcd. for $C_{17}H_{13}ClN_2O_5$: C, 56.60; H, 3.53; N, 7.77. Found: C, 56.34; H, 3.83; N, 7.96.

1,3-Dioxo-4*H*-4-hydroxy-10-phenyl-9,10-dihydroazeto[1,2-*a*]-quinoxaline (Ia).

Palladized carbon (100 mg., 5% palladium-on-charcoal) was added to 5 ml. of water in a round-bottom three-necked flask equipped with a dropping funnel, nitrogen inlet, and thermometer. To the flask was then added 0.6 g. of sodium borohydride in 16.0 ml. of water under a steady stream of nitrogen gas. A solution of 1.63 g. of *N*-(*o*-nitrophenyl)-2-oxo-4-phenyl-4-methoxycarbonylazetidine (IIa) in 120 ml. of methanol was then introduced into the stirred reaction mixture over a period of five minutes, keeping the internal temperature at 25° by external cooling. After stirring an additional 15 minutes, glacial acetic acid was added dropwise to to *p*H 6.5. Filtration gave a colorless solution which was evaporated to dryness under reduced pressure. The oily residue was dissolved in methylene chloride which was once extracted with water, dried over magnesium sulfate, and filtered. Evaporation of the methylene chloride gave Ia as a white glassy solid in 1.4 g. (100%) crude yield. The crystalline analytical sample was prepared by plate chromatography (R_f = 0.5, 5% methanol/chloroform on silica gel) as a snow-white solid, m.p. 152-154° (hexane/benzene); ir (Nujol) $\bar{\nu}$ cm^{-1}: 1780 (β-lactam CO); 1680, 1645 (hydroxamic acid CO). Mass spectrum: M^{+} m/e = 280; nmr δ (deuteriochloroform): 3.53 (q, 2, J = 15 Hz, CH_2), 7.17 (m, 9, aromatic).

Anal. Calcd. for $C_{16}H_{12}N_2O_3$ (hemihydrate): C, 66.43; H, 4.53; N, 9.68. Found: C, 66.58; H, 4.37; N, 9.46 (hemihydrate). Karl Fischer estimation required water 3.11%. Found: 3.85.

1,3-Dioxo-4*H*-10-phenylazeto[1,2-*a*]quinoxaline (Ib).

A solution of 4.0 g. of *N*-(*o*-nitrophenyl)-2-oxo-4-phenyl-4-methoxycarbonylazetidine (IIa) in 300 ml. of ethanol and 50 ml. of methanol was hydrogenated for two hours over six level teaspoonfuls of Raney nickel W2 catalyst at 50 psi. Filtration and evaporation gave 2.7 g. (72%) of the title compound as an off-white solid. Recrystallization from hexane/2-propanol gave analytically pure Ib as white cubes, m.p. 192-193°; ir (Nujol) $\bar{\nu}$ cm^{-1}: 1780 (CO, β-lactam), 1690 (CO, 3-oxo); Mass spectrum: M^{+} m/e = 264; nmr δ (deuteriochloroform): 3.77 (q, J = 16 cps, CH_2) (2H); 7.0-7.7 (m, 9, aromatic), 10.43 (s, 1, N-H).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 73.01; H, 4.88; N, 10.30.

1,3-Dioxo-4*H*-6-chloro-9,10-dihydro-10-phenylazeto[1,2-*a*]quinoxaline (Ic).

A solution of 3.2 g. of *N*-(2-nitro-4-chlorophenyl)-2-oxo-4-phenyl-4-methoxycarbonylazetidine (IIb) in 250 ml. of anhydrous ethanol was hydrogenated at 50 psi in the presence of three level teaspoonfuls of Raney nickel W2 catalyst for 2.5 hours. The reaction mixture was filtered, and the filtrate was stripped to give an off-white solid. The solid was once recrystallized from 2-propanol/hexane to give Ic in white needles, m.p. 236° (2.0 g., 75%). An additional crystallization from chloroform/hexane afforded the analytical sample, m.p. 238-239°; ir (Nujol) $\bar{\nu}$ cm^{-1}: 1790 (CO, β-lactam); 1690 (CO, 3-oxo); nmr δ (deuteriodimethylsulfoxide/deuterium oxide) 3.83 (q, J = 16 cps, 2H) $-CH_2-$; 7-8 (m- 8H) aryl protons.

Anal. Calcd. for $C_{16}H_{11}ClN_2O_2$: C, 64.33; H, 3.71; N, 9.38. Found: C, 64.05; H, 3.91; N, 9.61.

2-Oxo-1*H*-3-ethoxycarbonylquinoxaline (XIa).

To 10.8 g. (0.1 mole) of *o*-phenylenediamine in 400 ml. of absolute ethanol was added 17.4 g. (0.10 mole) of diethyl ketomalonate. The mixture was refluxed for 13 hours and then cooled. The crystals that were deposited were removed by filtration and recrystallized from ethanol to give 18.0 g. (82.5%) of XIa as long prisms, m.p. 266°.

3,4-Dihydro-3-ethoxycarbonyl-2-oxo-1*H*-quinoxaline (XIIa).

A mixture of 13.0 g. (0.05 mole) of XIa, and 1.5 g. of 5% palladium on carbon in 100 ml. of anhydrous dimethylformamide was hydrogenated on a Parr hydrogenator until the theoretical amount of hydrogen had been taken up. The catalyst was removed by filtration and the filtrate poured into ice water. The white precipitate was removed by filtration, washed with water, and dried. The product was recrystallized from chloroform to give 10 g. (91%) of XIIa as white crystals, m.p. 144-145°; ir (Nujol) $\bar{\nu}$ cm^{-1}: 3260 (broad N-H), 1730 (ester >C=O), 1685 (amide >C=O); nmr δ (deuteriodimethylsulfoxide): 10.0 (broad singlet, 1, N-H), 6.9 (m, 4, aromatic), 5.4 (broad singlet, 1, N-H), 4.6 (d, 1, C-H), 4.2 (q, 2, $O-CH_2$), 1.1 (t, 3, CH_3).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.02; H, 5.28; N, 12.51.

4-Chloroacetyl-3,4-dihydro-3-ethoxycarbonyl-1*H*-2-oxoquinoxaline (XIIIa).

A mixture of 3.8 g. (0.0173 mole) of XIIa and 5.0 ml. of chloroacetyl chloride was heated to 120° for one hour. The

Diels-Alder Cycloadditions of *N*-Substituted-1,2-Dihydropyridines with 1,2,4-Triazoline-3,5-diones and Maleimides

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The reaction of *N*-substituted-1,2-dihydropyridines **1** with 1,2,4-triazoline-3,5-diones **2** and maleimides **9** proceeds stereospecifically to afford *endo* cycloaddition products. *N*-Acetyl-1,2-dihydropyridines react with **2** to afford a stereo isomeric mixture of **3** and **4** whereas those possessing a *N*-ethoxycarbonyl, methoxycarbonyl, methanesulfonyl or benzenesulfonyl substituent yield **3** exclusively: similar results are also obtained in reactions employing maleimides. Stereochemistry was assigned on the basis of nmr data and use was made of the anisotropic effects of the 7,8 unsaturation on the R_1 and R_2 substituents.

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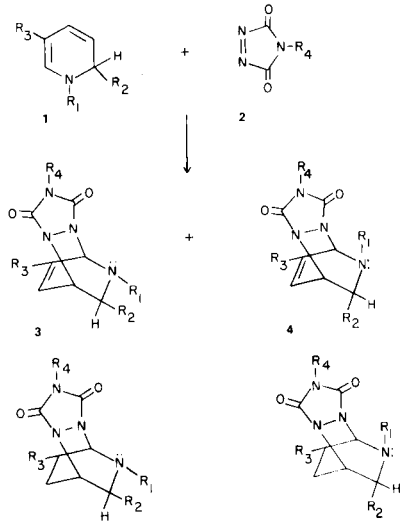
The ($\pi 2 + \pi 4$) cycloaddition of dienamines with alkenes (the Diels-Alder reaction) is an attractive method for the synthesis of pharmacologically interesting bicyclic compounds. Recent examples involve reaction of *N*-methyl-2-pyridone with maleic anhydride and *N*-phenylmaleimide (1). In an earlier study it was shown that reaction of *N*-lithio-1,2-dihydropyridines with acyl chlorides and esters afford *N*-substituted-1,2-dihydropyridines (2). We now describe the facile reaction of these dienamines with 1,2,4-triazoline-3,5-diones and maleimides (3).

The major drug classes used clinically as antiepileptic agents include the hydantoin, barbiturate, succinimide, oxazolidinedione and more recently the benzodiazepine ring structure. A common structural feature of these compounds is the -CONH- unit which may be the biologically active center or requirement for antiepileptic activity. It would be of interest, therefore, to develop new bicyclic ring structures possessing this pharmacophoric group (4).

Treatment of 4-phenyl-1,2,4-triazoline-3,5-dione **2a** with *N*-ethoxycarbonyl-2-phenyl-1,2-dihydropyridine **1a** at -65° results in a discharge of the red color and a quan-

2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-*endo*-dicarboxylic acid *N*-phenylimide **3a**. On the basis of mechanistic considerations for ($\pi 2 + \pi 4$) cycloadditions, **2a** should add to the less hindered face of **1a** to form the *endo* adduct **3a** with the phenyl group on the side of the molecule away



Anal. Calcd. for $C_{14}H_{12}Cl_2N_2O_4$: C, 49.00; H, 3.52; N, 8.15. Found: C, 49.26; H, 3.25; N, 8.18.

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