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# SYNTHETIC APPROACHES TO AZETO[1,2-a ]QUINOXALIN-1,3-DIONES
## MEMBERS OF A NOVEL HETEROCYCLIC SYSTEM

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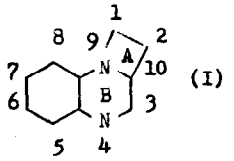
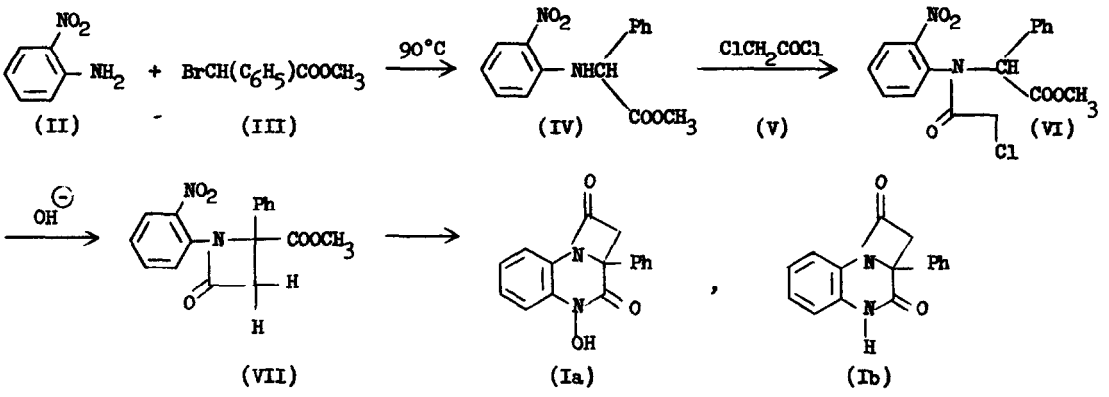
Owing to the potential medicinal importance of azetidin-2-ones that have the lactam nitrogen atom at a ring junction,[1] the interest of various groups has been directed towards synthesizing the so-called bridgehead nitrogen β-lactams. However, because of the lability of the lactam CO-N bond in such molecules, only a few different nuclear types have been made[2-5] and some of the claimed syntheses are questionable.[2,3] The current investigation of the hitherto unreported azeto[1,2-a]quinoxaline ring (I) was undertaken with the aim of elaborating the chemistry of new types of fused azetidin-2-ones.




The synthesis of azeto[1,2-a]quinoxalin-1,3-diones may be approached from two directions. A classical approach would be to first make the pyrazine ring B and annelate the sensitive azetidin-2-one ring A in the final step, while a nonclassical synthesis would involve the initial formation of the unstable azetidin-2-one ring A before annelation of the pyrazine ring B. In practice both general procedures have been realized. Scheme 1 shows the ring A before ring B synthesis. Condensation of o-nitroaniline with methyl α-bromophenylacetate at 90° C gave the o-nitrophenylglycine ester (IV) which was chloroacetylated at 130°C to the amide (VI). Annelation of (VI) with base gave N-(o-nitrophenyl)-4-phenyl-4-methoxycarbonylazetidin-2-one (VII) in 75% yield. [Ir (Nujol): $\bar{\nu}_{cm}^{-1}$ = 1770, CO β-lactam; 1745, CO ester; nmr ($CDCl_3$) = 3.83, $CH_3$ ester; 3.70 $-CH_2-$ ring methylene (q), $J_{AB}$ = 15 Hz.] The key intermediate could be annelated

to the desired azeto[1,2-a]quinoxalin-1,3-diones, (Ia) and (Ib), by the use of different reducing agents. The hydroxamic acid (Ia) was formed as the major product using sodium borohydride in aqueous methanol (violet color with ferric chloride).

Scheme 1




The assigned structure of (Ia) was based upon spectrographic and microanalytical data [Ir (Nujol): $\bar{\nu}_{cm^{-1}}$ = 1780, CO β-lactam; 1645, 1680, CO, hydroxamic acid; nmr ($CDCl_3$): δ = 3.6 (q, 2H, $J_{AB}$ = 15 Hz; absence of $OCH_3$ signal (no ester group); ms: $M^+$ m/e = 280; M - 16 = 264; Anal. calcd. for $C_{16}H_{12}N_2O_3$ (280.28) % C = 68.57; H = 4.32; N = 10.00; Found: % C = 66.58; H = 4.37; N = 9.46 (hemihydrate)]. The corresponding lactam (Ib) was produced in high yield and in a high state of purity by the reductive intramolecular acylation of (VII) with Raney Nickel W2 in absolute ethanol. The synthesis of (Ia) and (Ib) is quite general and unambiguously positions the quinoxaline ring substituents. However, this route suffers from one major disadvantage in that it cannot be used to prepare azetoquinoxalones with carbon or halogen substituents on $C_2$. To achieve the functionalization of $C_2$, alternative syntheses were considered.

The ring B before ring A approach outlined in Scheme 2 uses readily available symmetrically substituted o-phenylenediamines and diethylketomalonate to give 3-carbethoxyquinoxalin-2-ones (X). Reduction of (X) with Pd/C $H_2$ in DMF gave the 3,4-dihydroquinoxalone (XI) which underwent smooth chloroacetylation to give (XIII). Annelation with two equivalents of t-BuOK in anhydrous DMSO[6] gave the desired azeto[1,2-a]quinoxalin-1,3-dione system (I). The synthesis of (Ib) by

this method using ethyl phenylglyoxylate was unsuccessful at the annelation step. Retrograde amidification followed by *in situ* oxidation to 3-phenyl-2(1H)-quinoxalone was the only detectable reaction.

Scheme 2

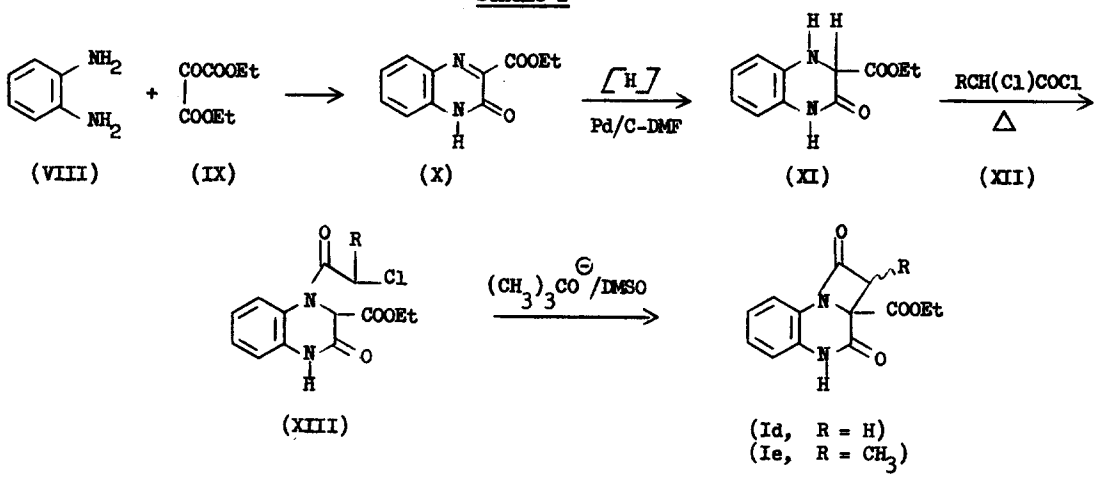
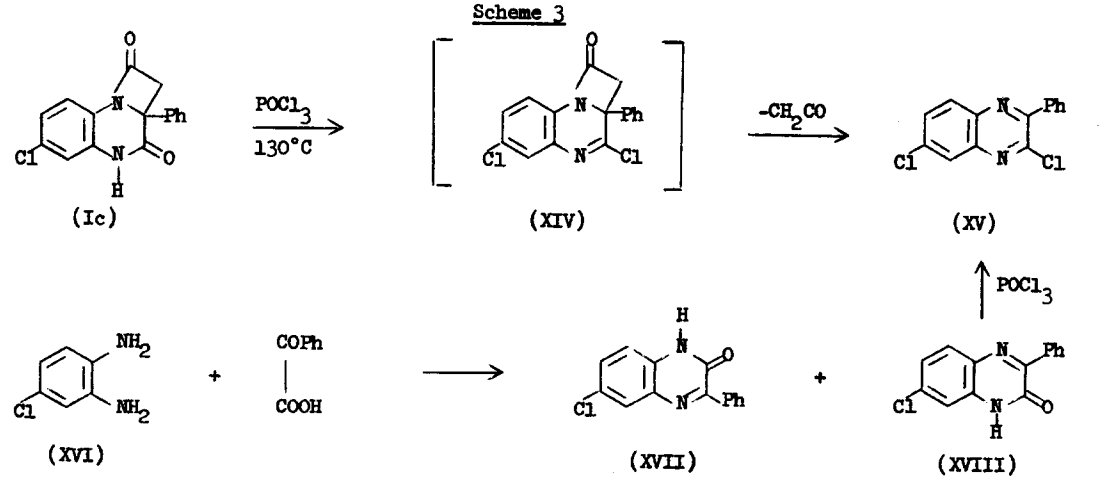
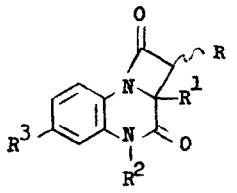



Table 1 lists some typical bridgehead nitrogen azetidin-2-ones that have been prepared using the syntheses outlined above. A third possible synthesis, viz cycloaddition of ketenes across the $C_3$-$C_4$ double bond in (X), was unsuccessful. Attempts to convert 6-chloro-2,2a-dihydro-2a-phenyl-1H-azeto[1,2-a]quinoxalin-1,3-dione (Ic) to the 3-chloro compound (XIV) resulted only in the isolation of 3-phenyl-2,7-dichloroquinoxaline which was identical to a sample made by an alternate process shown in Scheme 3.

Scheme 3





(I)

| No. | R | $R^1$ | $R^2$ | $R^3$ | m.p. °C | Crystallization Solvent | IR $C_1$=O | IR $C_3$=O ($cm^{-1}$) | nmr Spectrum $C_2$ Proton(s) | $J_{AB}$ Hz. |
|---|---|---|---|---|---|---|---|---|---|---|
| Ia | H | Ph | OH | H | 152-154 | (7) | 1780 | 1645, 1680 | 3.60* | 15 |
| Ib | H | Ph | H | H | 192-193 | Hexane/2-Propanol | 1780 | 1690 | 3.78* | 15 |
| Ic | H | Ph | H | Cl | 238-239 | Hexane/Chloroform | 1790 | 1690 | 3.96** | 15 |
| Id | H | COOEt | H | H | 153-154 | Hexane/2-Propanol | 1785 | 1690 | 3.78* | 16 |
| Ie | Me | COOEt | H | H | 181-182 | Hexane/2-Propanol | 1785 | 1695 | - | - |

* $CDCl_3$, TMS as internal reference.

**DMSO ($d_6$), TMS as internal reference. Chemical shifts in ppm.

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7) Ia was purified by preparative thin-layer chromatography on E. Merck silica gel 20 x 20 cm plates (60F - 254, 2 mm layer) using 5% MeOH/$CHCl_3$ as developing solvent; $R_f$ = 0.33.