

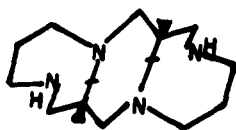
SYNTHESIS OF 1,5-DIAZACYCLOOCTANES FROM
2,4,6,8-TETRAKETO-1,5-DIAZABICYCLO[3,3,0]OCTANES

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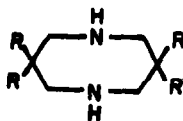
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A number of cage structures that appear to us to be attractive synthetic objectives contain substituted 1,5-diazacyclooctanes as structural elements. In the accompanying communication we report a synthesis of **1**, a tricyclic tetramine in which conformational changes can occur cooperatively among the three eight membered rings. We here summarize observations concerning our most convenient synthetic route to 3,3,7,7-tetrasubstituted 1,5-diazacyclooctanes.



1



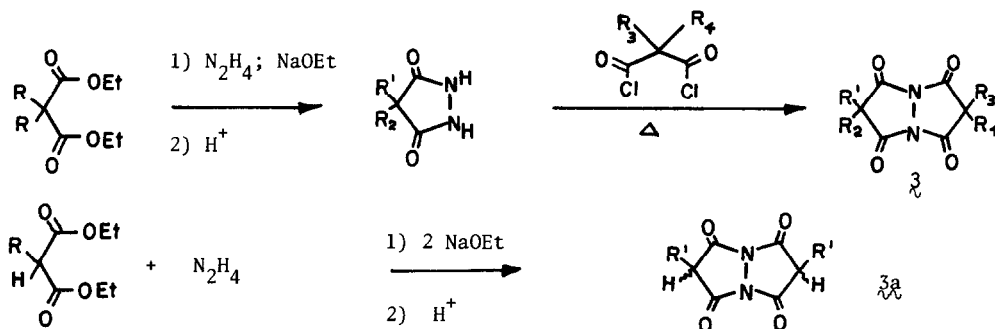
2

A number of direct syntheses of this ring system have been reported.¹ Alternatives to these include reduction of the anhydrodimers of Mannich products,² and reduction of 1,5-diazabicyclo[3,3,0]octane derivatives, formed by the condensation of hydrazine with a variety of three-carbon species.³ In this paper, we report an application of this approach using 3,7-alkylated 2,4,6,8-tetraketo-1,5-diazabicyclo[3,3,0]octanes, **3**. Under appropriate conditions reductions of derivatives **3** yield **2**.



The tetrones, **3**, have been reported to be conveniently available either, 1), in two steps, by formation of a pyrazoline-3,5-dione, followed by reaction with a malonyl dichloride,⁴ or, 2),

in one step, by reaction of two equivalents of an alkylmalonate ester with hydrazine in the presence of excess base.⁵

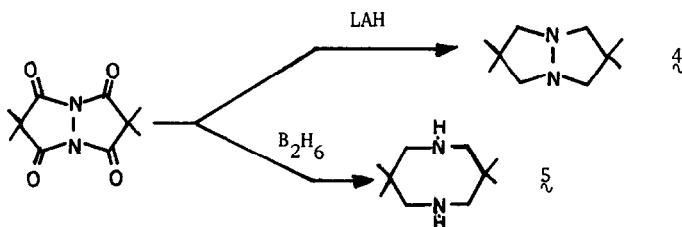


The latter reaction is clearly driven by ionization of the product. In fact, species $\tilde{3}a$, $R_1 = R_4 = H$, are exceedingly strong acids. Direct titration of $\tilde{3}$, $R_1 = R_3 = Et$, $R_2 = R_4 = H$ resulted in consumption of two equivalents of base. The second pK_a lies in the range of 6-7. The first pK_a was estimated from UV measurements in sulfuric acid-water mixtures to lie in the range of -1 to -2.⁶ This remarkable acidity must have its origin in a combination of favorable resonance and inductive factors and must clearly be considered in designing reaction conditions for acidic tetrone, $\tilde{3}$, or their conjugate bases. One consequence of this acidity is the difficulty of obtaining the species $\tilde{3}$, $R_1 = R_3 = Me$, $R_2 = R_4 = H$, by the sodium ethoxide-catalyzed condensation of hydrazine with diethyl methylmalonate.⁷

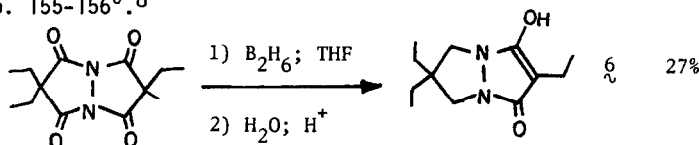
A striking consequence of this acidity is the reactivity of tetrone $\tilde{3}$, $R_1 = H$ as nucleophiles at very low pH values. For example, addition of formalin to a pH 0-1, ethanol-water solution of $\tilde{3}$, $R_1 = R_2 = R_3 = Me$, $R_4 = H$, results in an immediate precipitation of the hydroxymethyl derivative, 83%, m.p. 250-256°,⁸ and analogously, $\tilde{3}$, $R_1 = R_3 = Et$, $R_2 = R_4 = H$, provides 60% of a bis-hydroxymethyl derivative as a mixture of cis-trans isomers, m.p. 218-221°. Although Mannich reaction of $\tilde{3}$, $R_1 = R_3 = Et$, $R_2 = R_4 = H$, with dibenzylamine in water could only be induced to proceed in 37% yield, reaction in DMF between the tetrone dianion (generated with NaH) and N,N-dibenzyl chloromethylamine⁹ yielded 83% of bis Mannich product as a 1:2 ratio of isomers, m.p. 146-147°⁸ and 150-151°. Attempted reduction of the more abundant isomer with diborane in THF led to quantitative formation of methyl dibenzylamine, illustrating the ready reversibility of Mannich condensations with this special β -dicarbonyl system. Attempts at condensations with alkyl isocyanates or with cyanogen bromide failed to give products of reaction at carbon.

Clean C-alkylation is observed if tetrone mono or dianions are treated in DMF with alkyl halides. Thus $\tilde{3}$, $R_1 = R_2 = R_3 = Me$, $R_4 = H$ gave 94% of the tetramethyl tetrone with NaH, followed by MeI, and $\tilde{3}$, $R_1 = R_2 = R_3 = Et$, with NaH, then Et-I, gave 79% of the tetraethyl tetrone, also obtained in 71% yield from the alkylation of the dianion of $\tilde{3}$, $R_1 = R_3 = Et$, $R_2 = R_4 = H$. Even with the reactive halide, benzyl chloromethyl ether, the anion of $\tilde{3}$, $R_1 = R_3 = Me$, $R_2 = \phi CH_2OCH_2$, $R_4 = H$, reacted at carbon to give 48% of a cis-trans mixture of products.

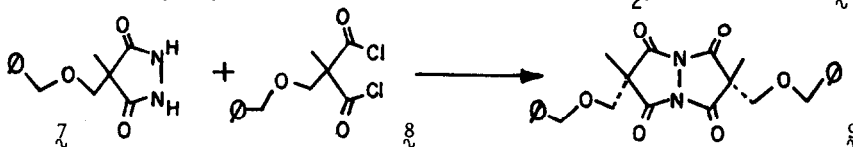
Reduction of the tetramethyltetrone, $\tilde{3}$ with LAH in ether or sodium bis(2-methoxyethyloxy) aluminum hydride in benzene gave results that were highly condition-dependent. With large excesses of reducing agent 50-65% yields of the bicyclic hydrazine, $\tilde{4}$, were observed.



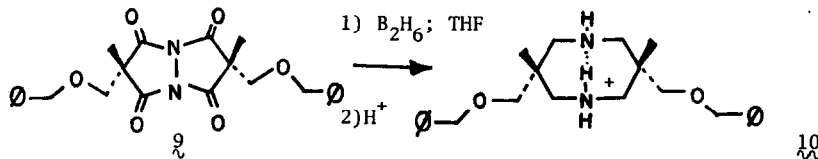
Reductive cleavage by diborane of the N-N bond of cyclic diacylhydrazides has been reported by Feuer and Brown.¹⁰ Reduction of the tetrasubstituted tetrones **3** with excess diborane in refluxing THF results in 30-70% conversion to the corresponding 1,5-diazacycloalkane, **5**. Thus the tetraethyl tetrone yielded 50% 3,3,7,7-tetraethyl-1,5-diazacyclooctane as the hydrochloride, m.p. 203-208° crude, 291-220° pure⁸; **3**, $R_1 = R_2 = R_3 = Me$, $R_4 = CH_2OH$ gave 64% of the corresponding diazacyclooctane, b.p. 92-96° (0.1 mm), m.p. 124-127°.⁸ The resonance stabilization available to salts or enol complexes of trisubstituted tetrones must be invoked to explain the reduction of **3**, $R_1 = R_2 = R_3 = Et$, $R_4 = H$ with diborane. A complex mixture resulted from which **6** was isolated in 27% yield, m.p. 155-156°.⁸



Because mono and dialkylmalonic acid derivatives are so readily available, the above routes allow synthesis of a wide variety of 3,3,7,7-substituted 1,5-diazacyclooctanes. From diethyl methyl benzyloxymethylmalonate,⁸ **7**, (77% from diethylmalonate and $KOBu^t$ in DMSO, followed by $Bzl-O-CH_2-Cl$) are prepared 4-benzyloxymethyl-4-methylpyrazolidine-3,5-dione, m.p. 184-185°⁸ (76% from the diester, $NaOEt$, and hydrazine in EtOH) and methyl benzyloxymethylmalonyl dichloride, **8**, (82% from the ester by saponification and reaction with $SOCl_2$). Reaction of **7** and **8** in dry



nitrobenzene at 105° for 1 hr., followed by cooling, evacuation on the aspirator to remove HCl , warming and seeding yields 26% of the cis isomer of **9**, m.p. 178-181°.⁸ Concentration yields isomer mixtures from which the trans isomer, m.p. 138-140°,⁸ can be obtained. Isomer identification rests on dipole moments: the 180° isomer has a moment of 2.8D; the 140° isomer has a moment of 0.0D.¹⁰



Treatment of the cis isomer of **9** with ca. six molar equivalents of diborane in THF, in several portions, followed by reflux for 20 hr., chilling, cautious addition of excess $2N$ HCl ,

solvent removal, 1 hr. reflux, basification, and extraction with CH_2Cl_2 gives **10** as the mono-hydrochloride, m.p. 156-158°. ⁸

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6. The aqueous UV spectra of the tetraethyltetrone, **3**, 232 nm (4.08) sh 262 nm the triethyltetrone anion, 247 (4.27), 292 nm (4.15), the 3,3-diethyltetrone anion, 244 (4.21), 274 (4.24), and the 3,3-diethyltetrone enol methyl ether⁴ 227 (4.06), 274 (4.19) were used as models. All tetrones exist as keto forms in THF, as does the 3,3-diethyl in water-sulfuric acid. This species is partly dissociated in water at sulfuric acid concentrations less than 30%. The 3,7-diethyl and the triethyltetrones are principally enolic in water. They appear to be half protonated in 30% sulfuric acid.
7. A crystalline sodium salt results from this condensation that retains sodium even when a solution is passed through a sulfonic acid resin. Precipitation of the silver salt, followed by acidification with HBr gave a solid, m.p. 267-272° after sublimation.⁸ A more convenient preparation of **3**, $\text{R}_1 = \text{R}_3 = \text{Me}$, $\text{R}_2 = \text{R}_4 = \text{H}$, results if lithium ethoxide is used as the base in the condensation. The resulting tetrone lithium salt can be converted to the tetrone by passage through a Dowex 50W-X sulfonate resin.
8. Satisfactory elemental analysis has been obtained.
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