yields 20–30% of product A as a white glass: ^{1}H NMR ($CDCl_3$) δ 0.9–2.0 (m, 14), 2.2–3.2 (m, 32), 6.7 (d, 2), 7.3 (d, 2), 7.8 (m, 4); UV (EtOH, H_2SO_4) 285 nm (ϵ 8.7 × 10^3), 328 (1.4 × 10^3); (EtOH, NaOH) 246 nm (ϵ 3.0 × 10^4), 313 (8.3 × 10^3); MS m/e calcd for $C_{41}H_{54}N_4O_2$ 634.424 67, found 634.427 15.

Elution with acetic acid yields, upon evaporation, 15% of product B. The ^{1}H NMR spectra of products A and B show quantitative differences in the δ 2.3–3.2 region. UV (EtOH, H_2SO_4) 285 nm (ϵ 1.0 × 10^4), 328 (1.8 × 10^3); (EtOH, NaOH) 247 nm (ϵ 3.3 × 10^4), 311–318 (7.6 × 10^3); MS m/e calcd for $C_{41}H_{54}N_4O_2$ 634.424 67, found 634.422 44.

Acknowledgment. Financial support from the National Science Foundation, Grant No. CHE 75-07771, is gratefully acknowledged.

Registry No. **3**, 67277-61-6; **4**, 71718-58-6; **5**, 54307-68-5; **5** oxime, 71749-88-7; **6**, 54307-69-6; **6** amine salt, 71749-87-6; **10**, 71718-59-7; **11**, 71718-60-0; **12**, 71718-61-1; **13** isomer 1, 71718-62-2; **13** isomer 2, 71718-63-3; **14**, 71718-64-4; **15**, 71718-65-5; 1,6-bis[1′-dimethylamino-3′-carbethoxy-4′-methyl-7′-naphthyl]hexane, 71718-66-6; 1,6-bis[1′-dimethylamino-3′-hydroxymethyl-4′-methyl-7′-naphthyl]hexane, 71718-67-7; 1,6-bis[1′-dimethylamino-3′-carboxy-4′-methyl-7′-naphthyl]hexane, 71718-68-8; 1,6-diphenylhexane, 1087-49-6; 2,2-bis(acetoxymethyl)propionyl chloride, 17872-59-2; *N,N′*-dimethyl-1,5-diaminopentane, 56992-95-1; 1,2-ethanedithiol, 26914-40-9.

Synthetic Routes to 1,5-Diazacyclooctanes via 2,6-Diketo-1,5-diazabicyclo[3.3.1]octanes

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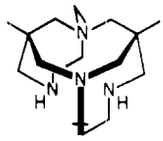
Reactions of 3-pyrazolidinones with primary β-chloropropionyl chlorides provide a satisfactory synthetic route to 2,6-diketo-1,5-diazabicyclo[3.3.0]octanes (**4**). The corresponding secondary halides cannot be induced to undergo cyclization. The Stetter procedure, reaction of acrylic acid derivatives with hydrazine at 200 °C, provides an acceptable route to derivatives that bear 4- or 8-alkyl substituents. Reactions of **4** with sodamide in ammonia generate sodium enolates that undergo C-alkylation and C-acylation reactions in high yield. Two new procedures are described for reduction of **4** to 1,5-diazacyclooctanes, treatment with diborane in refluxing THF and sodium–ammonia treatment, followed by reduction by lithium aluminum hydride (LAH). Reductions of **4** with sodium–ammonia or by sodium naphthalenide in dimethoxyethane generate 2,6-diketo-1,5-diazacyclooctanes in excellent yield. Convenient preparations of 3,6-dibromohexanoic acid and 2-acetyl-3-chloro-2-methylpropionic acid are described.

A wide variety of cyclic or polycyclic ethers, amines, and thioethers have recently been described as having unusual coordination and ion-binding properties.[1] We have been attracted to a series of cage structures, exemplified by **1**, **2**, and **3**, which have highly flexible medium-sized rings



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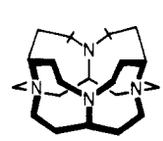
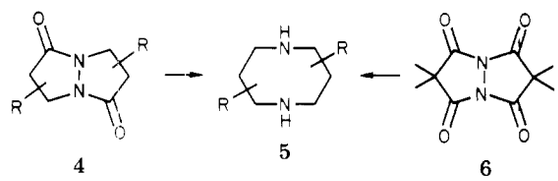


3

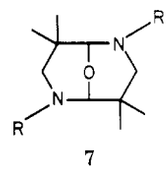
as structural subunits and which can undergo cooperative conformational changes, as illustrated by **1** and **3**. Elsewhere,[2] we describe a convenient route to 3,3,7,7-tetrasubstituted 1,5-diazacyclooctanes of the type required for the synthesis of **1**.[3] This route involves diborane reduction of the readily available tetrones **6**. General and reliable



4 5 6

synthetic routes to the 1,5-diazacyclooctane building block are essential prerequisites for the synthesis of cage species like **1**, **2**, or **3**. Here we report observations concerning the utility of an alternative route to **5** via the bicyclic diones **4**.

A variety of syntheses of 1,5-diazacyclooctanes have been described. Direct synthesis of the eight-membered ring has been reported by β-tosylamino epoxide dimerization,[4] by ring expansion,[5] and by a novel pericyclic reaction of azines.[6] Reductive cleavage of the anhydro dimers (**7**) of



7

Mannich products of secondary amines, formaldehyde, and α-branched aldehydes appears to be a method that is generally applicable to the synthesis of 3,3,7,7-tetrasubstituted 1,5-diazacyclooctanes.[7] Stetter and co-workers[8] have reported the reaction of hydrazine with acrylic acids or esters to form diones **4** which these workers reduce in two steps, LAH followed by hydrogenolysis of the N–N bond, to 1,5-diazacyclooctanes **5**. Diones **4** have also been

(1) J. Christensen, D. Eatough, and R. Izah, *Chem. Rev.*, **74**, 351 (1974); C. J. Pedersen and H. K. Frensdorff, *Angew. Chem., Int. Ed. Engl.*, **11**, 16 (1972); H. E. Simmons and C. H. Park, *J. Am. Chem. Soc.*, **90**, 2428, 2431 (1968); B. Dietrich, J. M. Lehn, and J. P. Sauvage, *Tetrahedron Lett.*, 2885, 2889 (1969).

(2) D. S. Kemp, R. V. Punzar, and J. C. Chabala, *Tetrahedron Lett.*, **547** (1978). X-ray analysis (Dr. J. P. Springer) has shown that the substance reported as **1** is in fact its trans isomer.

(3) D. S. Kemp, J. C. Chabala, and S. A. Marson, *Tetrahedron Lett.*, **543** (1978).

(4) V. R. Gaertner, *Tetrahedron*, **23**, 2123 (1967); W. N. Paudler and A. G. Zeiter, *J. Org. Chem.*, **32**, 2425 (1967).

(5) M. Rothe and R. Timler, *Chem. Ber.*, **95**, 783 (1962); H. K. Hall, *J. Chem. Soc.*, **80**, 6404 (1958).

(6) T. Wagner-Jauregg, L. Zirngibl, A. Demolis, H. Gunther, and S. Tam, *Helv. Chim. Acta*, **52**, 1672 (1969).

(7) C. Mannich and H. Wieder, *Chem. Ber.*, **65**, 385 (1932); M. W. Williams, *J. Org. Chem.*, **33**, 3946 (1968).

(8) H. Stetter and H. Spangerberger, *Chem. Ber.*, **91**, 1982 (1958); H. Stetter and K. Findeisen, *ibid.*, **98**, 3228 (1965).

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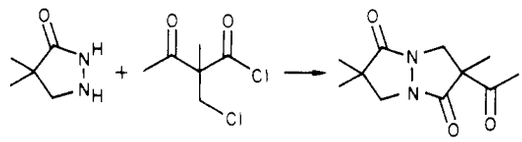
synthesized by Bellasio and co-workers[9] by cyclization of 1,2-diacylhydrazides of α-substituted β-halopropionic acids.

We were attracted to the latter two routes because they seemed to offer considerable versatility in choice of starting materials, they allow synthesis of either 2,6- or 3,7-substituted 1,5-diazacyclooctanes, and they involve an intermediary diacyl hydrazide (**4**) that could permit application of enolate alkylation reactions as a further means of elaborating the carbon framework.

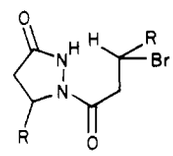
2,6-Diketo-1,5-diazabicyclo[3.3.0]octanes (4) from Pyrazolidin-3-ones and β-Halopropionyl Halides. In accord with the findings of Bellasio et al.,[9] we have observed that α-mono- or disubstituted β-halopropionyl halides react smoothly with pyrazolidin-3-ones to form *N*-acylpyrazolidinones that readily cyclize to species **4** in the presence of tertiary amines. These cyclizations proceed satisfactorily even if other reactive functional groups are present. Thus, the novel acid chloride **8**, formed in 44% yield by reaction of α-methyl-α-(hydroxymethyl)acetoacetic acid with triphenylphosphine dichloride, reacts with 4,4-dimethylpyrazolidin-3-one[9] to give the tetrasubstituted trione **9** in 69% yield.



8 **9**

Standard carbonyl chemistry can be conducted on the ketone **9**. Bromination (Br_2 in CH_2Cl_2, $AlCl_3$) gives the α-bromo ketone (62%, mp 108–110 °C)[10] which can be reduced with sodium borohydride to an epimeric mixture of bromohydrins (62%, mp 106 and 122 °C).[10]

The cited cases of successful syntheses of **4** by β-haloamide cyclizations have all involved primary alkyl halides. We have consistently failed in all attempts to induce halides of structure **10** to undergo cyclization. Thus,

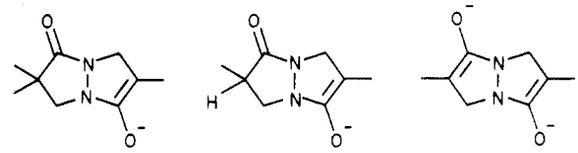


10

treatment of **10** (R = CH_3 or $(CH_2)_3Br$) with bases or by heating in polar solvents (conditions ranging from refluxing DMF to lithium 2,2,6,6-tetramethylpiperidide in THF at −50 °C) has resulted either in recovery of **10** or in tar formation. We conclude that the route from β-halopropionic acid derivatives is very suitable for the synthesis of 3- and 7-substituted diones **4** but cannot be used to generate diones **4** with 4- and 8-substituents.

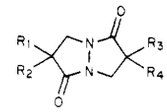
Alkylation and Acylation of Enolates from 2,6-Diketo-1,5-diazabicyclo[3.3.0]octanes. In contrast to other tetrasubstituted hydrazine derivatives, 1,2-diacylhydrazides are feeble reducing agents with little tendency to undergo N–N bond cleavage under most reaction conditions. Generation and C-alkylation of enolates derived from diones **4** that bear 3-hydrogens proceed uneventfully, as the following examples illustrate.

Reaction of 3,3,7-trimethyl-2,6-diketo-1,5-diazabicyclo[3.3.0]octane with sodamide in ammonia, followed by evaporation of solvent, generates the crude enolate **11** as a grey solid. Similarly, from 3,7-dimethyl-2,6-diketo-1,5-diazabicyclo[3.3.0]octane one can generate either the monoenolate **12** or, with 2 equiv of base, the dienolate **13**.



11 **12** **13**

Table I. Alkylation Reactions of 11, 12, and 13

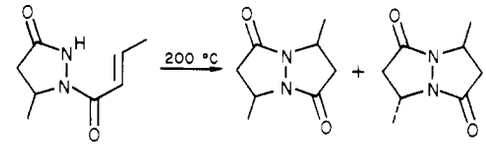


alkyl halide	solvent	product	yield, %	mp, °C
A. Enolate **11**: $R_1 = R_2 = R_3 = Me$				
MeI	DMF	R_4 = Me	80	150–152[a,b]
$BzlOCH_2Cl$	DMF	$R_4 = BzlOCH_2$	37	74–75[b]
AcCl	Et_2O	$R_4 = COCH_3$	70	91–92[c]
B. Enolate **12**: $R_1 = R_3 = Me$; R_2 = H				
$MeOCH_2Cl$	DMF	$R_4 = CH_2OCH_3$	65	63–65[b,d]
				104–106[b,e]
$BzlOCH_2Cl$	DMF	$R_4 = CH_2OBzl$	27	86–88[b,d]
				120–122[b,e]
C. Enolate **13**: $R_1 = R_3 = Me$				
MeI	DMF	$R_2 = R_4$ = Me	72	151–152[a,b]
n-BuCl	DMF	$R_2 = R_4$ = *n*-Bu	44	35–37[b,d]
				40–40[b,e]

[a] Reference 9 reports mp 158–160 °C. [b] Satisfactory elemental analysis was observed. [c] See Experimental Section. [d] For cis isomer. [e] For trans isomer.

As **2,6-Diketo-1,5-diazabicyclo[3.3.0]octanes** in Table I, **11** reacts in DMF with alkyl halides to give *C*-alkyl diones **4**. Reaction of **12** as a suspension in ether with acetyl chloride generates the *C*-acyl derivatives **9**, and this is the most convenient preparative route to this species. Using **13** or **14**, one can achieve sequential or one-pot dialkylation in the 3- and 7-positions. Roughly equal amounts of cis and trans isomers were isolated from the alkylation reactions of **13**.

4,8-Disubstituted 2,6-Diketo-1,5-diazabicyclo-[3.3.0]octanes (4) from Hydrazine and Acrylic Esters. In accord with the observations of Stetter and Findeisen,[8] we find that heating **14** at 200 °C for 2 h results in an 80% conversion to **15**, which we have obtained as a 1:1 mixture of cis and trans isomers. This reaction is strikingly temperature dependent; reaction at 165 °C for 24 h resulted largely in recovery of starting materials. Since heating of **15a** and **15b** to 200 °C for 22 h results in no interconversion, the reaction cannot be reversible. Heating *N,N'*-dicrotonylhydrazide to 200 °C resulted in rapid decomposition, without detectable formation of **15**.



14 **15a** **15b**

In an attempt to achieve synthesis of enantiomerically pure **15a**, **15** ($[\alpha]^{-72}_D$) was prepared from resolved pyrazolidinone and heated to 200 °C. The mixture of **15a** and **15b** that was formed had a very low rotation, assignable

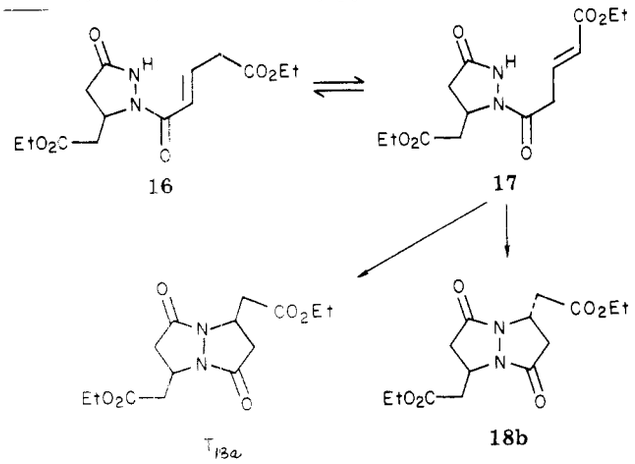
(9) E. Bellasio and G. Gallo, *Farmaco, Ed. Sci.*, **25**, 295 (1970); *Chem. Abstr.*, **72**, 132598 (1970); E. Bellasio, G. Pagani, A. Ripamonti, and E. Testa, *Farmaco, Ed. Sci.*, **20**, 428 (1965); *Chem. Abstr.*, **63**, 9945 (1965).

(10) Satisfactory elemental analysis has been obtained on this substance.

to the lower melting isomer. On this basis, we tentatively assign this species the cis configuration. Although the mechanism of racemization remains uncertain, it is clear that chiral integrity is not maintained under the harsh conditions required to effect this cyclization.

Attempts to induce ring formation from **14** by reaction with electrophilic reagents (I_2, Tfa, Hg^{2+}, Br_2 on imino ether), bases (Et_3N, NaH), or electrophiles with the *vic*-dibromide ($AgBF_4$) consistently failed.

Diethyl glutaconate is an acrylic ester derivative that may provide a mechanistic alternative for the formation of a bicyclic system. The acylpyrazolidinone **16** which is



forced to undergo an endocyclic ring closure in order to form **18** is expected to be in equilibrium with **17**, for which exocyclic closure is possible.[11] Heating **16**, **17**, or their HCl adducts to 200 °C does in fact generate **18**, although in low yield. Practically speaking, **18** is best prepared by heating diethyl glutaconate with hydrazine to 200 °C (0.2 mm), followed by repeated distillation of the distillate. A combined yield of 15–25% of a mixture of cis and trans isomers is obtained. Acidic hydrolysis of the lower melting isomer and resolution by means of the strychnine salt establishes this species to be the cis isomer. Despite the low yield, this one-step synthesis of **18a** provides convenient access to a chirally pure species that may allow synthesis of **3**.

Reductions of 2,6-Diketo-1,5-diazobicyclo-[3.3.0]octanes to 1,5-Diazacyclooctanes. We found two procedures, diborane reduction and a two-step reductive cleavage of the N–N bond, followed by LAH reduction, to be more convenient than the procedure of Stetter et al.[8] for carrying out the above transformation. For example, if **15** is treated with excess diborane in THF at 0 °C and then brought to reflux (24 h), acidic workup, followed by basification, results in the recovery of 65% of 2,6-dimethyl-1,5-diazacyclooctane.[12]

Alternatively, reduction of **4** with sodium in liquid ammonia or with sodium naphthalenide in dimethoxyethane results in clean, nearly quantitative conversion to the cyclic diamide **19**. Unlike the isomeric 2,4-diketo-1,5-diazacyclooctanes, which appear to be highly labile if substituted in the 3- and 7-positions,[13] the amides **19** are obtained as

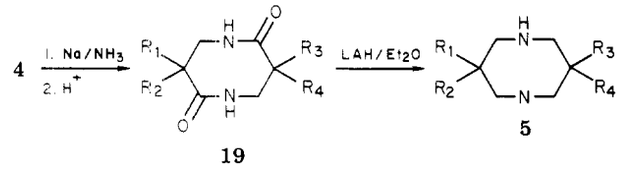


Table II. Reduction of 4 to 5

substrate	reagent[a]	yield, %	mp, °C
A. 4 ⟶ 19: $R_1 = R_2 = R_3$ = Me			
R_4 = Me	Na/NH_3	95	350-354[a]
R_4 = THE	Na/Naphth	86	348-352[a]
R_4 = CH_2OBzl	Na/NH_3	94	265-267[a,b]
R_4 = H	Na/NH_3	77	273-276[a]
R_4 = $COCH_3$	Na/Naphth	39	273-276[c]
B. 4 ⟶ 19: $R_1 = R_3$ = Me			
R_2 = H; R_4 = $MeOCH_2$	Na/NH_3	89	216-220[a]
C. 19 ⟶ 5			
$R_1 = R_2 = R_3 = R_4$ = Me	LAH/Et_2O	75	68-69[d]
$R_1 = R_2 = R_3$ = Me; R_4 = CH_2OH	LAH/Et_2O	50	124-127[a]

[a] Satisfactory elemental analysis has been obtained. [b] Product is the 3,3,7-trimethyl-7-(hydroxymethyl)diamide **19**. [c] Product is the 3,3,7-trimethyldiamide **19**; cleavage of the β-dicarbonyl system occurs under the conditions of reduction. [d] Reference 9.

stable crystalline solids of very high melting point. Reduction of amides **19** with lithium aluminum hydride proceeds uneventfully in the cases studied, yielding 1,5-diazacyclooctanes. Examples are given in Table II.

Experimental Section

3,7-Dimethyl-2,5-diketo-1,5-diazabicyclo[3.3.0]octane. Illustrative General Procedure. Solutions of 106 g (1.06 mol) of 3-methyl-2-pyrazolidinone[14] and 100 g (0.53 mol) of 3-bromo-2-methylpropionyl chloride[15] each in 100 mL of CH_2Cl_2 were added simultaneously with vigorous stirring to 100 mL of CH_2Cl_2 at 0 °C. Ten minutes after the addition is complete, 500 mL of water is added, the two-phase mixture is filtered, and the organic phase is diluted with 1 L of petroleum ether, chilled to precipitate more intermediate, and then filtered. The combined wet solids are dissolved in 500 mL of CH_2Cl_2 and treated with 65 g (0.64 mol) of triethylamine, added rapidly in portions. The solution is separated from water, dried ($MgSO_4$), and concentrated to a residue on the rotary evaporator. Warm ethyl acetate (40–45 °C, 500 mL) is added, and the solution is filtered, condensed to 100 mL, refiltered while hot, and allowed to deposit product: yield 7.5 g, 87%; mp 93–95 °C. Dissolution in a minimum volume of hot ethyl acetate, followed by slow cooling in a water bath, yields nearly pure crystals of the higher melting isomer, mp 108–109 °C, as rhombohedrons. Concentration and seeding yield the other isomer as flat plates, mp 97–98 °C. The ^1H NMR spectra were similar: higher melting isomer ($CHCl_3$) δ 4.2 (dd, 13, J = 1 Hz, 2 $H^{\alpha}C$–N), 3.2 (dd, 13, J = 8 Hz, 2 $H^{\beta}C$–N), 2.8 (m, 2 HCCH$_3$), 1.2 (d, J = 7 Hz, 6 CH_3C)

Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.12; H, 7.19; N, 16.65. Found (mp 109 °C): C, 57.01; H, 7.23; N, 16.84. Found (mp 98 °C): C, 57.13; H, 6.99; N, 16.80.

2-Acetyl-3-chloro-2-methylpropionyl Chloride. By means of the potassium carbonate catalyzed procedure described by Burkhard[16] the analogous condensation of the ethyl ester, *tert*-butyl α-methylacetoacetate was allowed to react with aqueous formalin to generate *tert*-butyl α-(hydroxymethyl)-α-methylacetoacetate: 84%, bp 72–74 °C (1 mm).

Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.40; H, 8.83.

Into a stirred, chilled solution of 38.0 g (0.19 mol) of this ester in 70 mL of CH_2Cl_2 is passed dry HCl. After 2 h at 0 °C, this solution is added to 125 g (0.38 mol) of triphenylphosphine di-

(11) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976).
(12) For an earlier report of N–N bond cleavage during diborane reduction of an *N,N'*-diacylhydrazine, see: H. Feuer and F. Brown, Jr., *J. Org. Chem.*, **35**, 1468 (1970).
(13) F. Vellaccio, R. Punzar, and D. Kemp, *Tetrahedron Lett.*, 547 (1977).
(14) T. Lieser and K. Kemmner, *Chem. Ber.*, **84**, 4 (1951).
(15) Prepared by the addition of HBr to methacrylic acid, followed by treatment with thionyl chloride (4-h reflux, yield 93%, bp 65 °C at 13 mm[10]).
(16) J. Burkhard, *Bull. Soc. Chim. Fr.*, **5**, 1665 (1938).
(17) L. Horner, H. Oediger, and H. Hoffman, *Justus Liebigs Ann. Chem.*, **626**, 26 (1959).

chloride,[16] prepared by addition of a titrated solution of chlorine in CCl_4 to a chilled solution of phosphine. The solution is stirred at 0 °C for 3 h, the solvents are removed, and the residue is triturated and stirred with 500 mL of dry hexane. After 3 days, the filtrate was evaporated and the residue distilled: yield 15.2 g, 44%; bp 53–57 °C (1 mm); ^1H NMR (neat) δ 4.0 (q, 2, CH_2Cl), 2.4 (s, 3 CH_3CO), 1.6 (s, 3 CH_3C).

Anal. Calcd for $C_6H_8O_2Cl_2$: C, 39.37; H, 4.41; Cl, 38.74. Found: C, 39.58; H, 4.39; Cl, 38.47.

Sodium 3,3,7-Trimethyl-2,6-diketo-1,5-diazabicyclo[3.3.1]octane Enolate. General Procedure for Enolate Formation. To 100 mL of liquid ammonia containing 3.9 g (0.1 mol) of sodamide is added 18.2 g (0.1 mol) of bicyclooctane in small portions with stirring. The ammonia is allowed to evaporate, and the flask containing the enolate salt is evacuated at 0.01 mm for 24 h. Before use, the dry enolate salt is powdered with a glass rod.

3-Acetyl-3,7,7-trimethyl-2,6-diketo-1,5-diazabicyclo[3.3.0]octane. The enolate prepared as described above from 5 g (0.027 mol) of bicyclic hydrazide is suspended in 100 mL of ether and treated with 2.4 g (0.03 mol) of acetyl chloride. After 8 h of being stirred the suspension is filtered and the filtrate concentrated to an oily solid, which is dissolved in a minimum volume of dry ether and chilled: crude yield 4.3 g, 70%; mp 65–80 °C, 91–92 °C the pure sample; ^1H NMR (D_2O) δ 3.83 and 3.76 (AB q, J = 12 Hz, 2, CH–N), 3.68 and 3.49 (AB q, J = 12 Hz, 2, CH–N), 2.4 (s, 3, CH_3CO), 1.6 (s, 3, CH_3C), 1.3 (s, 3, CH_3C) 1.2 (s, 3, CH_3C).

Anal. Calcd for $C_{11}H_{16}N_2O_3$: C, 58.92; H, 7.15; N, 12.49. Found: C, 58.54; H, 7.12; N, 12.36.

Resolved 5-Methyl-3-pyrazolidin-2-one. The title compound[13] (15.6 g, 0.15 mol) is dissolved in 500 mL of boiling EtOH, and 22.5 g of (+)-tartaric acid is added in portions. The solution is then quickly cooled in an ice bath for 20 min, and the resulting crystals are collected and recrystallized from 800 mL of EtOH to give 18.2 g of product, mp 165–174 °C, as large prisms. Further recrystallization gives 4.7 g: mp 174–175 °C, $[\alpha]^{25}_D$ +18.9 (c 2.5, H_2O).

Anal. Calcd for $C_8H_{14}N_2O_7$: C, 38.39; H, 5.63; N, 11.19. Found: C, 38.45; H, 5.69; N, 11.27.

Solution of 20 g of the tartrate salt in 300 mL of cold, concentrated NH_4OH, followed by evaporation, solution in 300 mL of EtOH, filtration, evaporation, solution in 50 mL of $CHCl_3$, and evaporation gave 10.6 g of crude oil that was distilled, bp 160–162 °C (18 mm), to give 4.6 g of resolved amine, $[\alpha]^{22}_D$ +13.4 (c 1.9, EtOH).

3,6-Dibromohexanoic Acid. The literature procedure,[18] in our hands, was unsatisfactory. The following modification gave excellent results. Tetrahydrofuran-2-acetic acid (11 g, 0.084 mol) is dissolved in 150 mL of 48% HBr, and the solution is saturated with HBr gas and then heated on a steam bath for 5 h with periodic resaturation with HBr. The cooled solution was extracted with ether, which was dried and evaporated to yield an oil that was distilled (Kugelrohr, 170 °C, 0.1 mm): yield 18.7 g, 81%; ^1H NMR (CCl_4) δ 4.3 (m, 1, CHBr), 3.4 (t, 2, CH_2Br), 3.0 (d, J = 7 Hz, 2, CH_2CO_2), 2.0 (m, 4, CH_2CH_2).

2,6-Bis(carbethoxymethylene)-4,8-diketo-1,5-diazabicyclo[3.3.0]octane. Freshly distilled diethyl glutaconate (558 g, 3 mol) in 300 mL of EtOH is stirred in an ice bath as 48 g of 95+% hydrazine (1.5 mol) is added. After the exothermic addition is complete (25 min), the mixture was stirred at 25 °C for 15 min and then transferred to a distillation apparatus where it was heated in an oil bath at 185 °C for 1 h. Aspirator vacuum is then cautiously applied, and the bath temperature is raised to 215 °C. When the head temperature reaches 155 °C, the pot is cooled to 100 °C, the receiver is replaced, and a vacuum of 0.2 mm is applied, with an increase of bath temperature to 205 °C. The pot residue, a viscous red oil, is distributed while hot between four 500-mL round-bottomed flasks. Each flask is then connected to a wide-bore takeoff tube and receiver, clamped in a horizontal position, and heated at 0.01 mm in a modified Kugelrohr apparatus, formed by wrapping a 1 L beaker with nichrome ribbon and asbestos. Between oven temperatures of 180 and 210 °C, a forerun of 5-carbethoxymethylene-3-pyrazolidinone, mp 62–65 °C, is collected. Between 210 and 240 °C, a fraction containing the desired product is collected, the distillation being halted when a red-black oil begins to distill. The 210–240 °C fractions are pooled and redistilled at least three times in this apparatus, until charring of the pot residue is no longer noted. The resulting viscous yellow oil is mixed with an equal volume of ether, seeded, and chilled. From crystallization of this fraction and from the fractions obtained by redistillation of pot residues and other liquors, a total of 80 g of a mixture of the two isomers can be obtained. Crystallization from ether yields the less soluble trans isomer, mp 96–98 °C, and the more soluble cis isomer, mp 65 °C: MS m/e 312.131 66 (calcd for $C_{14}H_{20}N_2O_6$, m/e 312.1321). Both substances are readily soluble in water and are easily lost to an aqueous phase by extraction.

Anal. Calcd for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.97. Found (mp 96–98 °C): C, 53.90; H, 6.62; N, 9.04. Found (mp 65 °C): C, 54.05; H, 6.53; N, 9.07.

2,6-Dimethyl-1,5-diazacyclooctane. General Procedure for Diborane Reduction of 2,6-Diketo-1,5-diazabicyclo[3.3.0]-octanes. To 15 g of 2,6-dimethyl-4,8-diketo-1,5-diazabicyclo-[3.3.0]octane, cooled to 0 °C and maintained under N_2, is added 450 mL of 1 M diborane in THF. The chalky white suspension is stirred for 30 min on ice, warmed to 25 °C, and brought to reflux. After 24 h the mixture is cooled, cautiously treated with 100 mL of 5% HCl, and concentrated to dryness. The residue is taken up in 500 mL of 5% HCl and refluxed for 2 h. The cooled solution is extracted with ether and then brought to pH 13.5 with KOH (cooling). Extraction (CH_2Cl_2), drying, and concentration yield an oil that is distilled (8.6 g, 68%). Distillation at 24 mm gave the product: bp 47 °C; ^1H NMR ($CDCl_3$) δ 3.0 (m, 6, CH–N), 2.0 (s, 2, NH), 1.9 (m, 4, CH_2C), 1.2 (d, J = 6 Hz, 6, CH_3C).

3,3,7-Trimethyl-2,6-diketo-1,5-diazacyclooctane. General Procedure for the Reduction of 2,6-Diketo-1,5-diazabicyclo[3.3.0]octanes by Sodium in Ammonia. Dry ammonia (250 mL) is condensed in a three-necked flask equipped with Dewar condenser, and 10.0 g (0.055 mol) of 3,3,7-trimethyl-2,6-diketo-1,5-diazabicyclo[3.3.0]octane is dissolved by stirring and refluxing. Sodium metal is added to the solution (about 3 g) until a permanent blue color develops. A slight excess of ammonium chloride is added, and the solvent is evaporated. The product is extracted into hot ethanol, and the solution is filtered and evaporated. Recrystallization of the product from water yields 8.8 g (87%): mp 274–276 °C; ^1H NMR (CF_3CO_2H) δ 8.8 (br s, 2, NH), 2.6–4.1 (m 5, CH), 1.1 (s and d, 9, CH_3).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67, H, 8.75; N, 15.20. Found: C, 58.25; H, 8.90: N, 15.11.

3-(Hydroxymethyl)-3,7,7-trimethyl-1,5-diazacyclooctane. General Procedure for the LAH of 2,6-Diketo-1,5-diazacyclooctanes. A slurry of 8.7 g (0.041 mol) of 3-(hydroxymethyl)-3,7,7-trimethyl-2,6-diketo-1,5-diazacyclooctane in 100 mL of dry THF is treated with 8.5 g of lithium aluminum hydride, added rapidly, avoiding violent gas evolution. The solution is refluxed for 12 h, cooled, and poured into 2 L of ether saturated with water. The resulting suspension is filtered and concentrated to an oil by evacuation to 0.01 mm for 3 h. Addition of 20 mL of ether, seeding, and chilling at −10 °C for 3 days yields 3.8 g (50%) of solid: mp 124–127 °C; MS m/e 186. Alternatively, the diamine can be isolated as a dipicrate, mp 223–225 °C.

Anal. Calcd for $C_{10}H_{22}N_2$ (amine): C, 64.47; H, 11.90; N, 15.04. Found: C, 64.33; H, 11.78; N, 15.16.

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(18) M. Julia and M. Maumy, *Bull. Soc. Chim. Fr.*, 7, 2427 (1969).