Registry No.—1, 54125-41-6; 2 (R_1 = C_6H_5, R_2 = COC_6H_5), 68408-95-7; 4, 15677-03-9; 6, 68408-86-6; 7, 68408-87-7; 9, 68408-88-8; 10, 68408-89-9; 12, 68408-90-2; 15 (R_1 = Ph, R_2 = COOEt), 68408-76-4; 16 methiodide, 68408-91-3; 20, 68408-92-4; 21, 66606-23-3; 22, 68408-93-5; 22 MeI, 68408-94-6; CH_2=CR_1R_2 (R_1 = $COOC_2H_5$, R_2 = H), 140-88-5; CH_2=CR_1R_2 (R_1 = $COOCH_3$, R_2 = CH_3), 80-62-6; CH_2=CR_1R_2 (R_1 = CN, R_2 = H), 107-13-1; CH_2=CR_1R_2 (R_1 = C_6H_5, R_2 = H), 100-42-5; CH_2=CR_1R_2 (R_1 = C_6H_5, R_2 = CH_3), 98-83-9; CH_2=CR_1R_2 (R_1 = C_6H_5, R_2 = C_6H_5), 530-48-3; CH_2=CR_1R_2 (R_1 = α-naphthyl, R_2 = H), 826-74-4; CH_2=CR_1R_2 (R_1 = β-naphthyl, R_2 = H), 827-54-3; CH_2=CR_1R_2 (R_1 = C_6H_5, R_2 = $COOC_2H_5$), 22286-82-4; CH_2=CR_1R_2 (R_1 = C_6H_5, R_2 = $COCH_3$), 32123-84-5; CH_2=CR_1R_2 (R_1 = C_6H_5, R_2 = COC_2H_5), 66551-91-5; CH_2=CR_1R_2 (R_1 = C_6H_5, R_2 = COC_6H_5), 4452-11-3; 3,4-dihydro-2-methylene-1(2*H*)-naphthalenone, 13203-73-1; dimethylamine hydrochloride, 506-592; formaldehyde, 50-00-0; 1-phenyl-2-butanone, 1007-32-5; dimethylformamide dimethyl acetal, 4637-24-5; α-benzoyl-β-(dimethylamino)styrene, 17059-74-4; deoxybenzoin, 451-40-1; 3-(dimethylamino)-2-phenylpropiophenone methiodide, 31035-04-8; methyl 2,5-dimethylisoxazolidine-5-carboxylate methiodide, 68408-96-8; 3-(dimethylamino)-2-phenylpropiophenone, 22563-99-1.

Supplementary Material Available: Full NMR and analytical data for all isoxazolidines, γ-(dimethylamino)carbinols, and their acetate esters (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) The following reviews provide a wealth of information concerning nitrones and cycloaddition thereof to unsaturated systems: J. Hamer and A. Macaluso, *Chem. Rev.*, **64**, 473 (1964); D. St. Clair Black, R. F. Crozier, and V. Davis, *Synthesis*, 205 (1975). (b) R. Huisgen et al., *Tetrahedron Lett.*, 9 (1960). (c) *ibid.*, 2548 (1968). (d) *ibid.*, 2559 (1968). (e) *ibid.*, 2568 (1968).
(2) C. W. Brown, K. Marsden, M. A. Thorold Rogers, C. M. B. Tyler, and R. W. Wright, *Proc. Chem. Soc., London*, 254 (1960); C. W. Brown and M. A. Thorold Rogers, British Patent 850 418, Oct 5, 1960.
(3) G. Zinner and W. Kliegel, *Chem. Ber.*, **99**, 2886 (1966).
(4) The NMR spectra reported throughout this study were determined using a Varian A-60 or T-60 spectrometer with deuteriochloroform or dimethyl sulfoxide as solvent and are recorded as parts per million downfield from tetramethylsilane.
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(6) This ring cleavage is probably limited to 6-carbalkoxytetrahydro-1,3-oxazines since the 6,6-diphenyl analogue was inert to hydrazine under the same conditions.
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N-Acylcarbamates as Intermediates in Synthetic Approaches to a Bicyclic Trimethylene-Bridged 2,4-Oxazolidinedione and Hydantoin[1]

Wayne J. Brouillette,[2] Edward E. Smissman,[3] and Gary L. Grunewald*

Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045

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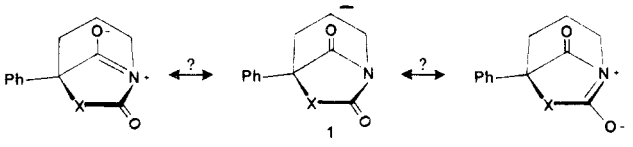
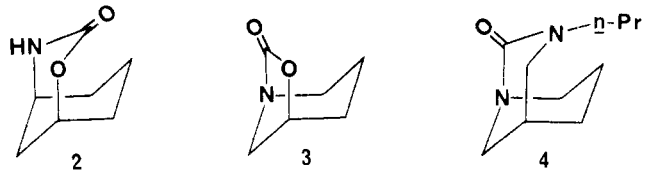
The syntheses of the bicyclic 2,4-oxazolidinedione **1a** and the bicyclic hydantoin **1b** were attempted from several new *N*-acylcarbamates patterned after known precursors to monocyclic 2,4-oxazolidinediones. Heating 3-chloro-1-(ethoxycarbonyl)-3-phenyl-2-piperidinone (**13**) resulted in ester pyrolysis, and the reaction of 3-hydroxy-3-phenyl-2-piperidinone (**22**) with $ClCO_2Et$ and K_2CO_3 yielded 1-(ethoxycarbonyl)-3-hydroxy-3-phenyl-2-piperidinone (**24**). The monocyclic analogue **31** rapidly cyclized at room temperature to yield 5-ethyl-3-methyl-5-phenyl-2,4-oxazolidinedione (**32**), potentially representing a new, mild, neutral method for the synthesis of 2,4-oxazolidinediones. However, heating **24** resulted in decomposition or polymer formation, and the reaction of **24** with NaH resulted in an intramolecular ethoxycarbonyl migration to give 3-(ethoxycarbonyloxy)-3-phenyl-2-piperidinone (**35**). An analogous approach to the bicyclic hydantoin **1b** utilized 3-amino-1-(ethoxycarbonyl)-3-phenyl-2-piperidinone (**26**), but was also unsuccessful.

Bicyclic imides of the type shown in structure **1** were proposed by Smissman[3] as potential stereoselective anticonvulsant agents. As part of a continuing study, we were interested in synthesizing the bicyclic 2,4-oxazolidinedione **1a** (5-phenyl-7,8-dioxo-6-oxa-1-azabicyclo[3.2.1]octane) and the bicyclic hydantoin **1b** (5-phenyl-7,8-dioxo-1,6-diazabicyclo[3.2.1]octane).



	X	
1a	O	2,4-oxazolidinedione
1b	NH	hydantoin
1c	CONH	barbiturate

The stability of the compounds suggested by structure **1** is questionable. One likely destabilizing influence is that the resonance forms for the imide moiety may not be allowed because they would involve double-bond formation to the bridgehead nitrogen, and double bonds to the bridgehead are prohibited in carbocyclic systems by Bredt's rule.[4] However, it has been demonstrated that some bicyclic, carbocyclic ring systems with double bonds to the bridgehead are stable if the ring size is large enough. For example, $\Delta^{1,8}$-bicyclo[4.2.1]-nonene has been reported,[5] but the carbocyclic system analogous to **1a** and **1b**, $\Delta^{1,7}$-bicyclo[3.2.1]octene, could only be isolated as a Diels–Alder adduct with diphenylisobenzofuran.[6] Studies on bicyclic amides with nitrogen at the bridgehead suggest a similar size limit. Hall[7] reported the synthesis of the bicyclic carbamate **2**, but the attempted preparation of the bridgehead nitrogen analogue **3** was unsuccessful. Hall[8] was also able to obtain the bicyclic imide **4**, but its stability was in part attributed to resonance involving the N-3 nitrogen.



2 **3** **4**

Smissman[9] reported an attempt to form the bicyclic hydantoin **1b** from **5** via an intramolecular N-alkylation. The observed product was the bicyclic hydantoin **6**, resulting from intramolecular alkylation on the amide rather than the imide nitrogen. Smissman also reported[10] a similar result when he tried to form the bicyclic barbiturate **1c** via an analogous approach utilizing **7**. In this case the observed product was **8**, resulting from O- rather than N-alkylation. Surprisingly, the

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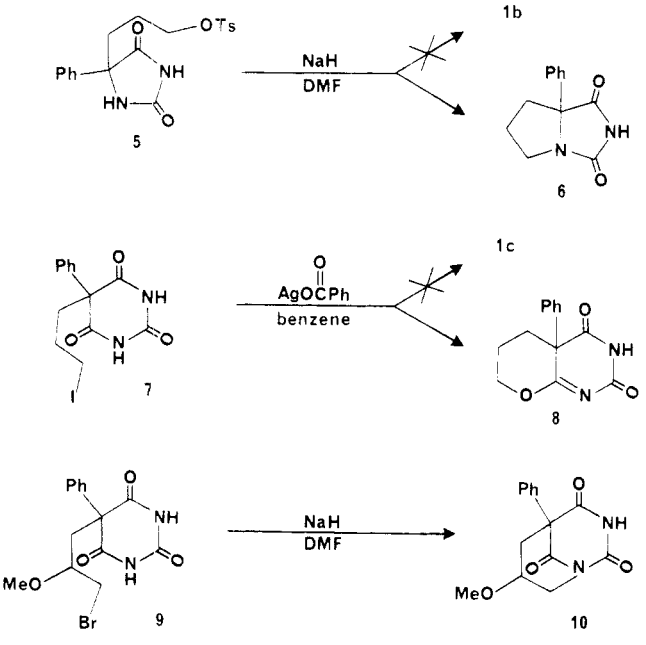
bicyclic barbiturate **10** was reported[11] to result from the reaction of **9** with NaH, but it was unclear why a similar approach would not yield **1c.**

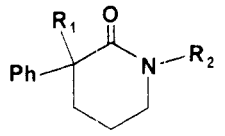
The alternate sites for intramolecular alkylation are inherent weaknesses of the above approach. We hoped to avoid this in our synthetic design for **1a** and **1b** by formation of the dione ring as the final step. The necessary intermediates are new *N*-acylcarbamates. Those used in the approaches to **1a** were patterned after known synthetic methods for the formation of 2,4-oxazolidinediones and will be discussed first.

It has been reported[12] that *N*-α-chloroacylcarbamates yield



2,4-oxazolidinediones upon heating at 180 °C. Although **1a** may be thermally unstable, the relative ease of this procedure and the high yields obtained suggested the treatment of **13** under similar conditions as a reasonable first approach to **1a.** A potential advantage of this method is that basic conditions are not required; it was anticipated that **1a** would be sensitive to base.

Carbamate **13** was prepared from 3-phenyl-2-piperidinone (**11**), which was available from another study in these laboratories.[13] Lactam **11** was acylated with $ClCO_2Et$ in toluene at reflux to give carbamate **12,** which was cleanly chlorinated

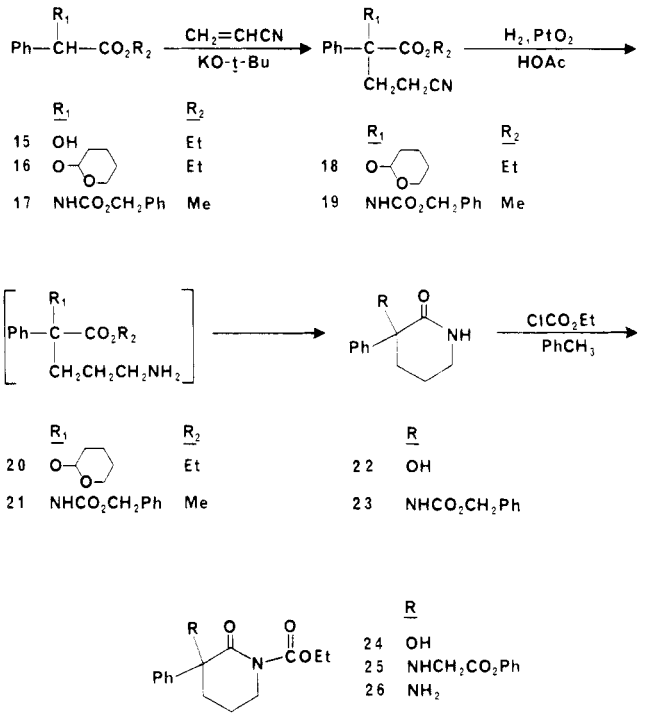


	R_1	R_2
11	H	H
12	H	CO_2Et
13	Cl	CO_2Et
14	Cl	H

with SO_2Cl_2 in $CHCl_3$ to provide **13** in high yield. Heating **13** at temperatures lower than 180 °C resulted in recovered starting material, while heating at 180 °C for 4 h did not yield **1a** but gave a product for which the IR spectrum contained one major carbonyl absorption at 1670 cm^{-1}. This is consistent with the formation of 3-chloro-3-phenyl-2-piperidinone (**14**) via decarboxylative elimination of the ethoxycarbonyl group, and, as will be discussed later, such pyrolytic loss of the ethoxycarbonyl group was also observed for analogues of **13.**

A second general procedure for the synthesis of 2,4-oxazolidinediones in high yield involves treating appropriately substituted α-hydroxyamides with NaOMe and $EtOCO_2Et$[14] or K_2CO_3 and $ClCO_2Et$.[15] The α-hydroxylactam necessary for this approach to **1a** is 3-hydroxy-3-phenyl-2-piperidinone (**22**), which was prepared from ethyl mandelate (**15**)[16] as

Scheme I



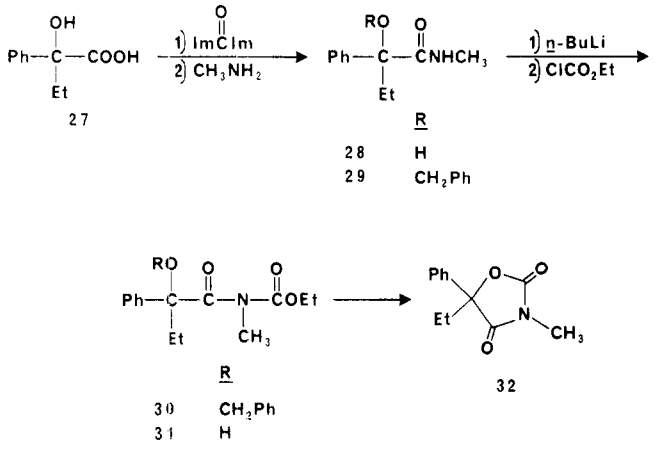
shown in Scheme I. In this procedure the hydroxyl group of **15** was protected by reaction with dihydropyran and $POCl_3$ according to a modification of the procedure of Ayres[17] to provide the tetrahydropyranyl ether **16.** As we have previously reported,[18] **16** could be cyanoethylated with CH_2=CHCN and KO-*t*-Bu to give **18.** Nitrile **18** was hydrogenated over PtO_2 in HOAc to yield the amine **20,** which was not isolated but was heated at reflux in aqueous HOAc and neutralized to provide the α-hydroxylactam **22.**

The treatment of lactam **22** with $EtOCO_2Et$ and NaOMe according to literature conditions[14] for the preparation of monocyclic 2,4-oxazolidinediones with KO-*t*-Bu in *t*-BuOH or with NaH in DMF resulted in recovered starting material. The reaction of **22** with $ClCO_2Et$ and K_2CO_3 also failed to give **1a,** but yielded the *N*-acylcarbamate **24.** Such *N*-α-hydroxyacylcarbamates (e.g., **31**) are likely intermediates in the conversion of α-hydroxyamides to 2,4-oxazolidinediones with $EtOCO_2Et$ or $ClCO_2Et$. Carbamate **24** therefore represented a promising synthetic precursor to **1a.** We subsequently found that **24** could be prepared in higher yield by reacting **22** with $ClCO_2Et$ in toluene at reflux.[18]

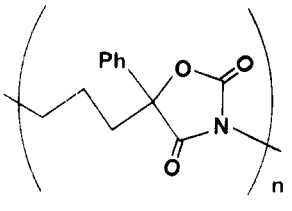
The ring closure of **24** to **1a** could potentially be effected by several methods, including thermal and base-promoted reactions. In order to determine appropriate conditions for cyclization in this system, the acyclic analogue of **24,** carbamate **31,** was prepared from 2-hydroxy-2-phenylbutyric acid (**27**)[19] as shown in Scheme II. Compound **27** was reacted with carbonyl diimidazole followed by 40% $MeNH_2$ in H_2O to give α-hydroxyamide **28.** Although lactams **11** and **22** could be conveniently N-acylated with $ClCO_2Et$ in toluene at reflux, treatment of **28** under these conditions produced unreacted starting material. The alcohol in **28** was therefore protected by reaction with $PhCH_2Br$ and NaH to give **29,** which was treated with *n*-BuLi followed by $ClCO_2Et$ to provide **30.** The benzyl ether **30** was cleaved at room temperature with 1 atm of H_2 over Pd–C in EtOH to provide **31,** but **31** could not be isolated because it rapidly cyclized to yield the 2,4-oxazolidinedione **32.** Such a result suggests that this procedure may be useful as a new, extremely mild synthesis of 2,4-oxazolidinediones.

The *N*-acylcarbamate **24** was then subjected to thermal cyclization conditions. However, heating **24** in various solvents

Scheme II

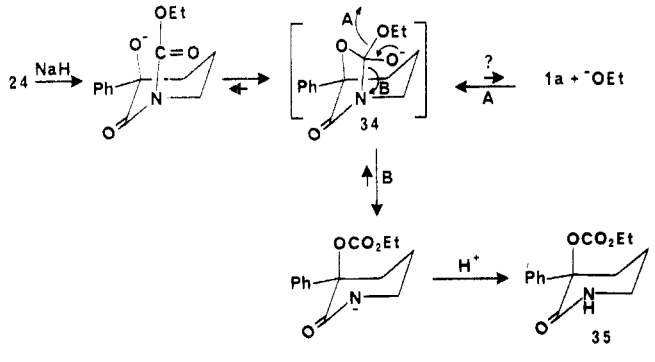


at temperatures between 180 and 222 °C resulted either in no reaction or ester pyrolysis to provide **22.** Carbamate **24** was then heated at 220 °C for 3 h under a vacuum of 0.05 mm to yield the ester pyrolysis product **22.** A second product was isolated as a tan powder, mp 200–237 °C dec. The spectra, an osmometric molecular weight determination, and a gel filtration study (see Experimental Section) for this powder were all consistent with a polymer of repeating 2,4-oxazolidinedione units with the general structure **33.** The ^1H NMR analysis of the lowest molecular weight sample of polymer **33** also contained resonances typical for an ethyl ester, yet these resonances were barely visible in the higher molecular weight samples. This is consistent with the termination of polymer **33** in an ethyl ester.



33

A base-catalyzed ring closure of **24** was next considered. The reaction of **24** with *n*-BuLi at −78 °C in Et_2O did not yield **1a,** but gave a multicomponent mixture for which the IR spectrum contained no characteristic 2,4-oxazolidinedione absorptions. Treatment with NaH in benzene and Me_2SO at reflux, as we have previously reported,[18] resulted in an intramolecular ethoxycarbonyl migration to provide **35,** and the proposed mechanism is given here. The fact that intermediate **34** did not collapse via pathway A to yield any detectable



amount of **1a** suggests that **1a** may be unstable under these conditions.

Although the conversion of **24** to **1a** was unsuccessful, it was postulated that a similar approach involving the *N*-α-aminoacylcarbamate **26** (Scheme I) might be successful for preparing the bicylic hydantoin **1b.** The conversion of **26** to **1b** would involve the attack of an amine on an ester, and the activation energy for attack by the amine should be lower than for the alcohol in **24.** Furthermore, **1b** contains a nonbridgehead NH group which could be utilized in stabilizing the molecule via lactam–lactim tautomerism and resonance.

The synthesis of amine **26** from amino ester **17**[20] was patterned after that for **24** as shown in Scheme I, except the protecting group in **25** was removed by hydrogenolysis over Pd–C to give **26.**

The cyclization of **26** to **1b** was next attempted. Heating **26** under a vacuum of 0.05 mm at 180 °C for 3 h yielded a white powder, mp 170–230 °C dec. The IR spectrum contained carbonyl absorptions at 1780 and 1720 cm^{-1}, consistent with a hydantoin moiety. An osmometric molecular weight determination in $CHCl_3$ gave a value of 547, suggesting polymer. Because of similar results with **33,** and since it was clear that **1b** was not obtained, this product was not further pursued.

The inability to obtain **1a** and **1b** by the above approaches may be attributed either to prohibitively high activation energies or to the instability of the bicyclic products under the conditions employed. The former appears to be in operation for those approaches to **1a** and **1b** which involved thermal cyclization of the *N*-acylcarbamates **13, 24,** and **26,** although the model reactions were very facile. The activation energy must indeed be very high in these cases as exemplified by the observation that no reaction occurred at temperatures less than 180 °C, yet forcing the reaction at higher temperatures resulted in a relatively unfavorable pyrolytic loss of the ethoxycarbonyl group or polymerization. In contrast, the base-catalyzed rearrangement of **24** was postulated to involve the intermediate **34,** which was theoretically capable of breaking down to yield **1a** but provided only the carbonate **35.** This suggests that **1a** may be unstable under these conditions. Although the application of Bredt's rule to heterocycles is unclear, a likely contributing factor for the instability of **1a** is an inability to undergo resonance stabilization, since the resonance forms would involve double-bond formation to the bridgehead nitrogen.

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-33 spectrophotometer. The ^1H NMR spectra were obtained on Varian Associates T60 and EM 360 spectrophotometers with 1% Me_4Si as an internal standard. Electron impact mass spectra were recorded using a Varian CH-5 spectrometer. Elemental analyses were performed on a Hewlett-Packard 185B CHN Analyser at the University of Kansas. R_f values were determined using Brinkmann precoated silica gel plates (silica gel 60 F-254, 5 × 10 cm, 0.25-mm layer). The osmometric molecular weight determinations were conducted in $CHCl_3$ by Galbraith Laboratories in Knoxville, Tenn.

1-(Ethoxycarbonyl)-3-phenyl-2-piperidinone (12). A solution of 5.0 g (0.029 mol) of 3-phenyl-2-piperidinone (**11**)[13] and 3.5 g (0.032 mol) of $ClCO_2Et$ in 600 mL of toluene was heated at reflux for 9 h, concentrated in vacuo to a volume of 20 mL, diluted with 40 mL of Et_2O, cooled, and filtered to yield 1.2 g of starting material **11.** The filtrate was concentrated, and the oily residue was chromatographed on a 3.5 × 80 cm silica gel column using 10% Et_2O in $CHCl_3$ as eluent. The fractions containing material with R_f 0.56 were concentrated to yield 2.7 g (51%) of **12** as a colorless oil: IR (liquid film) 1775 (C=O) and 1715 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2 (s, 5 H, aromatic), 4.3 (q, 2 H, J = 7 Hz, ester CH_2), 3.8 (m, 3 H, CH_2N and PhCH), 2.0 (m, 4 H, $PhCCH_2CH_2$), 1.3 (t, 3 H, J = 7 Hz, ester CH_3). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.10; H, 6.95; N, 5.48.

3-Chloro-1-(ethoxycarbonyl)-3-phenyl-2-piperidinone (13). A solution of 0.80 g (0.0060 mol) of freshly distilled SO_2Cl_2 in 1 mL of $CHCl_3$ was added dropwise to a solution of 1.4 g (0.0056 mol) of carbamate **12** in 1 mL of $CHCl_3$, and the mixture was stirred under N_2 for 4 h. The $CHCl_3$ was removed in vacuo, and the residue was

dissolved in 2 mL of Et_2O and cooled to give 1.3 g (82%) of **13** as white crystals: mp 51–52 °C (Et_2O–hexane); IR ($CHCl_3$) 1780 (C=O) and 1725 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 7.4 (m, 5 H, aromatic), 4.3 (q, 2 H, J = 7 Hz, ester CH_2), 3.8 (m, 2 H, CH_2N), 2.8–1.6 (m, 4 H, $PhCCH_2CH_2$), 1.4 (t, 3 H, J = 7 Hz, ester CH_3); MS (70 eV) m/e 281 (M^+). Anal. Calcd for $C_{14}H_{16}NO_3Cl$: C, 59.68; H, 5.73; N, 4.97. Found: C, 59.39; H, 5.86; N, 4.67.

Ethyl 2-Phenyl-2-(2-tetrahydropyranyloxy)butyrate (16). To a stirred mixture of 50 g (0.28 mol) of ethyl mandelate (**15**)[16] and 26 g (0.31 mol) of dihydropyran was added 0.5 mL of $POCl_3$, and the solution was stirred at room temperature for 5 h. The reaction mixture was distilled from four KOH pellets to yield 54 g (74%) of **16** as a colorless oil, bp 110 °C (0.2 mm) [lit.[17] bp 114 °C (0.2 mm)].

Methyl 2-(Benzyloxycarbonylamino)-4-cyano-2-phenylbutyrate (19). To a solution of 65 g (0.22 mol) of the protected amino ester **17**[20] in 430 mL of t-BuOH was added 9.0 g (0.08 mol) of KO-t-Bu with stirring. After the mixture had become homogeneous, a solution of 53 g (1.0 mol) of CH_2=CHCN in 200 mL of t-BuOH was added over 45 min and stirring was continued for 9 h. The reaction mixture was poured into 500 mL of 1% HCl and extracted with 3 × 300 mL of Et_2O, the extracts were dried ($MgSO_4$), and the Et_2O was removed in vacuo to yield 71 g (93%) of **19** as an orange oil. An analytical sample was obtained by chromatographing 0.35 g of the oil on a preparative silica gel plate (20 × 20 × 0.2 cm), using 6.7% Et_2O in $CHCl_3$ as eluent. The band at R_f 0.5 was isolated to give 0.23 g of **19** as a colorless oil: IR (liquid film) 3400 (NH), 2260 (CN), and 1730 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3 (d, 10 H, aromatic), 6.4 (brs. 1 H, NH), 5.1 (s, 2 H, $PhCH_2$), 3.7 (s, 3 H, CH_3), 3.0 (m, 2 H, CH_2N), 2.3 (m, 2 H, $PhCCH_2$). Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.13; H, 5.66; N, 7.63.

3-Hydroxy-3-phenyl-2-piperidinone (22). To a solution of 6.0 g (0.019 mol) of the nitrile **18**[18] in 50 mL of glacial acetic acid was added 0.5 g of PtO_2. The mixture was hydrogenated on a Parr shaker at 50 psi for 3 h and filtered, the filtrate was diluted with an equal volume of water, and the aqueous solution was heated at reflux for 90 min. The cooled solution was made basic with 30% NaOH and extracted with 3 × 175 mL of $CHCl_3$, the extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. The oily residue was triturated with Et_2O, cooled, and filtered to yield 1.7 g (47%) of **22**, mp 194–196 °C (acetone) (lit.[17] mp 192–194 °C).

3-(Benzyloxycarbonylamino)-3-phenyl-2-piperidinone (23). The procedure was the same as that for the preparation of **22**, except that 23 g (0.065 mol) of nitrile **19** and 0.7 g of PtO_2 in 220 mL of glacial acetic acid were used and the refluxing period was omitted. This yielded 6.6 g (31%) of **23** as a white solid: mp 154–155 °C (MeOH–H_2O); IR (KBr) 3220 (NH), 1730 (C=O), and 1665 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4 (m, 10 H, aromatic), 6.5 (br s, 1 H, $NHCO_2$), 6.0 (brs, 1 H, CONH), 5.1 (s, 2 H, $PhCH_2$), 3.3 (m, 2 H, CH_2N), 2.7 (m, 2 H, CH_2–C–N), 1.8 (m, 2 H, $PhCCH_2$). Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.15; H, 6.14; N, 8.54.

3-(Benzyloxycarbonylamino)-1-(ethoxycarbonyl)-3-phenyl-2-piperidinone (25). A solution of 4.0 g (0.012 mol) of the lactam **23** and 1.4 g (0.013 mol) of $ClCO_2Et$ in 300 mL of toluene was heated at reflux for 48 h, and the solvent was removed in vacuo. The residual oil was dissolved in 15 mL of Et_2O and cooled to yield 3.6 g (74%) of **25** as a white solid: mp 100–101 °C (Et_2O); IR (KBr) 3350 (NH) and 1740–1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4 (m, 10 H, aromatic), 6.0 (br s, 1 H, NH), 5.1 (s, 2 H, $PhCH_2$), 4.4 (q, 2 H, J = 7 Hz, ester CH_2), 3.6 (m, 2 H, CH_2N), 2.8 (m, 2 H, CH_2–C–N), 1.8 (m, 2 H, $PhCCH_2$), 1.4 (t, 3 H, J = 7 Hz, ester CH_3). Anal. Calcd $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.78; H, 6.13; N, 6.91.

3-Amino-1-(ethoxycarbonyl)-3-phenyl-2-piperidinone (26). A solution of 3.6 g (0.0091 mol) of carbamate **25** in 150 mL of MeOH was added to 0.4 g of 5% Pd–C, and H_2 gas was bubbled through the mixture with stirring for 3 h. The mixture was filtered, the filtrate was concentrated in vacuo, and the solid residue was recrystallized from Et_2O–Skelly B to yield 1.8 g (76%) of **26** as a white solid: mp 70–71 °C; IR ($CHCl_3$) 3400 (NH), 1770 (C=O), and 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4 (m, 5 H, aromatic), 4.4 (q, 2 H, J = 7 Hz, ester CH_2), 3.7 (m, 2 H, CH_2N), 2.8–1.7 (m, 6 H, $PhCCH_2CH_2$ and NH_2), 1.4 (t, 3 H, J = 7 Hz, ester CH_3); MS (70 eV) m/e 262 (M^+). Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.50; H, 7.15; N, 10.37.

***N*-Methyl-2-hydroxy-2-phenylbutyramide (28).** To a solution of 7.5 g (0.042 mol) of the hydroxy acid **27**[19] in 200 mL of Et_2O was added 6.8 g (0.042 mol) of carbonyl diimidazole. The solution was stirred under Ar for 2 h, 3.8 mL (1.5 g of $MeNH_2$, 0.048 mol) of 40% aqueous $MeNH_2$ was added, and stirring was continued overnight. The mixture was extracted with 30 mL of 5% HCl followed by 50 mL of water, the organic layer was dried ($MgSO_4$), and the solution was concentrated in vacuo to a volume of 30 mL. To this was added 20 mL of hexane, and the solution was cooled to yield 5.7 g of **28** as a white solid. The combined aqueous layers were extracted with 2 × 50 mL of EtOAc, dried ($MgSO_4$), and concentrated to give an additional 1.3 g of **28**. The total yield of **28** was 7.0 g (86%): mp 117–118 °C (Et_2O–hexane); IR (KBr) 3380 (OH, NH) and 1660 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.7–7.1 (m, 5 H, aromatic), 6.5 (br s, 1 H, NH), 3.2 (br s, 1 H, OH). 2.8 (d, 3 H, NCH_3), 2.5–1.7 (m, 2 H, CH_2), 1.0 (t, 3 H, CH_3). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.39; H, 7.84; N, 7.16.

***N*-Methyl-2-(benzyloxy)-2-phenylbutyramide (29).** To a solution of 3.5 g (0.018 mol) of the amide **28** in 60 mL of anhydrous benzene and 3 mL of anhydrous Me_2SO was added 0.91 g (0.52 g of NaH, 0.022 mol) of 57% NaH in mineral oil. The mixture was heated at reflux under Ar for 1 h and cooled, and a solution of 3.8 g (0.022 mol) of $PhCH_2Br$ in 30 mL of benzene was added dropwise. This solution was heated at reflux for 3 h, stirred overnight at room temperature, and extracted, respectively, with 100 mL of water, 50 mL of 2% aqueous NH_3, and 50 mL of saturated aqueous NaCl. The organic layer was dried ($MgSO_4$) and concentrated to give 5.5 g of a yellow oil. The oil was chromatographed on a 250 g silica gel column using 10% Et_2O in $CHCl_3$ as eluent, and the fractions with R_f 0.59 were concentrated to yield 2.7 g (53%) of **29** as white crystals: mp 95–96 °C (Et_2O–hexane); IR (KBr) 3380 (NH) and 1660 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3 (m, 10 H, aromatic), 6.9 (br s, 1 H, NH), 4.4–4.0 (m, 2 H, $PhCH_2$), 2.8 (d, 3 H, NCH_3), 2.7–1.9 (m, 2 H, CH_2), 1.0 (t, 3 H, CH_3). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.94. Found: C, 76.23; H, 7.43; N, 4.80.

***N*-(Ethoxycarbonyl)-*N*-methyl-2-(benzyloxy)-2-phenylbutyramide (30).** A solution of 0.20 g (0.00071 mol) of amide **29** in 10 mL of Et_2O was cooled to −78 °C, and 0.29 mL (0.00072 mol) of 2.5 M n-BuLi was added. The solution was stirred under Ar for 5 min, 0.079 g (0.00072 mol) of $ClCO_2Et$ was added, and stirring was continued for 2 h. The mixture was allowed to warm to room temperature, stirred overnight, and filtered, and the filtrate was concentrated in vacuo. The residual oil was chromatographed on a preparative silica gel plate (20 × 20 × 0.2 cm) using 10% Et_2O in $CHCl_3$ as eluent. The band with R_f 0.67 was extracted with Et_2O and concentrated to yield 0.15 g (60%) of **30** as a plate yellow oil: IR (liquid film) 1745 (C=O) and 1675 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3 (m, 10 H, aromatic), 4.4 (q, 2 H, J = 7 Hz, ester CH_2), 3.9 (m, 2 H, $PhCH_2$), 3.0 (s, 3 H, NCH_3), 2.3 (m, 2 H, ethyl CH_2), 1.4–0.4 (m, 6 H, ester CH_3 and ethyl CH_3). Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.60; H, 7.16; N, 3.72.

5-Ethyl-3-methyl-5-phenyl-2,4-oxazolidinedione (32). To a suspension of 0.10 g of 5% Pd–C (50% wet with water) in 20 mL of absolute EtOH was added 1.0 g (0.0028 mol) of carbamate **30**. The mixture was hydrogenated at 1 atm for 5 h and filtered, and the filtrate was concentrated in vacuo to yield 0.60 g (97%) of **32** as a clear oil: bp 90 °C (0.2 mm); IR (liquid film) 1820 (C=O) and 1740 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3 (m, 5 H, aromatic), 3.0 (s, 3 H, NCH_3), 2.2 (q, 2 H, CH_2), 0.9 (t, 3 H, CH_3); MS (70 eV) m/e 219 (M^+). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 66.04; H, 5.89; N, 6.22.

Preparation of Polymer 33. In one end of an L-shaped 1.3 × 42 cm Pyrex tube was placed 3.0 g (0.011 mol) of **24**, and the tube was sealed under a vacuum of 0.050 mm. The end containing **24** was heated at 225 °C for 4 h while the other end was immersed in a dry ice–acetone bath. The tube was cooled and opened. The end in the cold bath contained a small amount of liquid which was shown by NMR to be C_2H_5OH. The residue from the other end was triturated with boiling methanol, cooled, and filtered to yield 0.25 g of **33** as a tan powder: mp 200–237 °C dec; UV max ($CHCl_3$) 237 nm (A = 0.72, C = 0.083 g/L); osmometric molecular weight determinations for different runs gave values ranging from 730 to 2205; gel filtration in $CHCl_3$ (using Waters ALC/GPC 244 with three μ-Styragel columns of 10^3, 500, and 100 Å in series) indicated no monomeric species; ^1H NMR ($CDCl_3$) δ 7.4 (m, 5 H, aromatic), 3.5 (m, 2 H, CH_2N), 2.4–1.0 (m, 4 H, CH_2CH_2–C–N); IR (KBr) 1820 (C=O) and 1740 (C=O) cm^{-1}; MS (70 eV) m/e 173. Anal. Calcd for $C_{12}H_{11}NO_3$ (**1a**): C, 66.35; H, 5.10; N, 6.45. Found: C, 66.47; H, 5.37; N, 6.47.

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Registry No.—**1a**, 68475-08-1; **1b**, 68475-09-2; **11**, 51551-56-5; **12**, 68475-10-5; **13**, 68475-11-6; **15**, 774-40-3; **16**, 65379-05-7; **17**, 68475-12-7; **18**, 65379-04-6; **19**, 68475-13-8; **22**, 65379-06-8; **23**, 68475-14-9; **24**, 65379-07-9; **25**, 68475-15-0; **26**, 68475-16-1; **27**, 35468-69-0; **28**,

68475-17-2; **29**, 68475-18-3; **30**, 68475-19-4; **32**, 68475-20-7; **33**, 68475-33-2; ethyl chloroformate, 541-41-3; dihydropyran, 25512-65-6; acrylonitrile, 107-13-1; benzyl bromide, 100-39-0.

References and Notes

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Transannular Cyclization Reactions of Pentacyclo[6.2.1.$0^{2,7}$.$0^{4,10}$.$0^{5,9}$]undecane-3,6-diones. Formation of Aza- and Oxa-Birdcage Compounds

Prithipal Singh

Contribution No. 72 from Syva Research Institute, Palo Alto, California 94304

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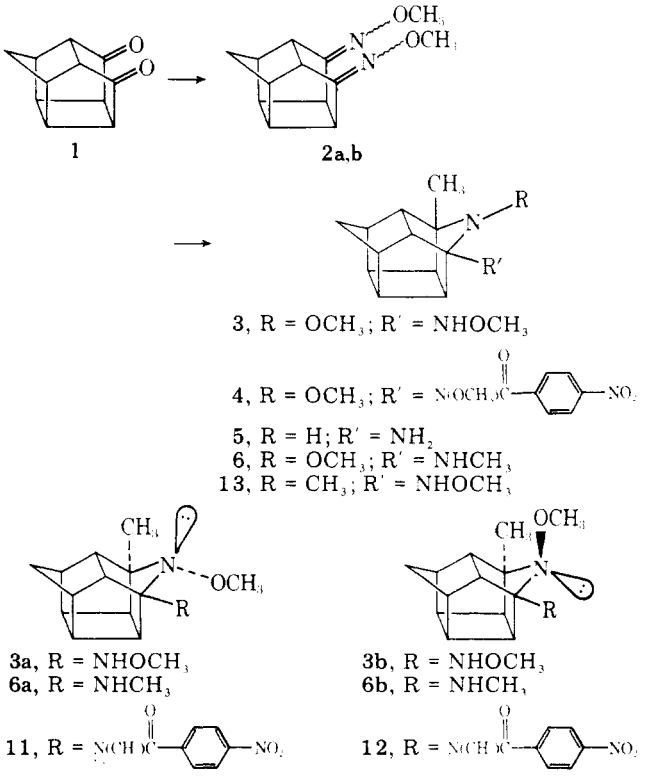
Methoxyamine reacts with cage diketone **1** to afford in excellent yield a mixture of two stereoisomeric di-*O*-methyloximes **2a** and **2b**, methylation of which gives quantitatively dimethoxy aza-birdcage amine **3**. Further reaction with lithium dimethylcuprate results in displacement of one of the methoxy groups in **3** with a methyl group to give yet another aza-bird compound **6**, and its reduction with sodium in liquid ammonia affords cage diamine **5**. NMR data of **3** and **6** suggest that both exist as isomeric pairs differing by stereoisomerism at their apical nitrogen atoms, and the hypothesis is supported by isolation of a pair of stereoisomeric *p*-nitrobenzoates **11** and **12**, prepared by reacting **6** with *p*-nitrobenzoyl chloride. Whereas the diketone **1** reacts with hydroxylamine and *tert*-butylamine to give bis(hydroxylamine) **14** and a mono-*tert*-butylimine **15**, the tetrachloro cage diketone **16** exhibits only the transannular reactions with nucleophiles. Thus, the oxa-birdcage compounds **17–19** are obtained in near quantitative yields by treating **16** with water, ethanol, and hydroxylamine, respectively.

Transannular cyclizations of appropriately functionalized molecules often provide a convenient method for preparation of heterocage compounds which are otherwise difficult to obtain.[1,3] Such transannular cyclization reactions of pentacyclo[6.2.1.$0^{2,7}$.$0^{4,10}$.$0^{5,9}$]undecane-3,6-dione (**1**) have been reported by different laboratories.[2,3] We have now extended these studies further with a hope of transforming the cage diketone **1** and its tetrachloro derivative **16** into heterobirdcage compounds and would like to report our findings below.

Treatment of diketone **3** with methoxyamine hydrochloride in pyridine afforded quantitatively a mixture of stereoisomeric di-*O*-methyloximes **2a** and **2b** in an ca. 1:1 ratio, which could be separated on silica TLC plates. Both of the oximes analyzed for $C_{13}H_{16}N_2O_2$, showed characteristic C=N stretching vibration in their IR spectra, and exhibited the expected methoxy singlets and nonequivalent apical protons as AB quartets in their NMR spectra. No attempt was, however, made to assign individual stereochemistry to these compounds believed to differ at the C=N bonds.[4] When the mixture of di-*O*-methyloximes was treated with methyllithium, aza-birdcage compound **3** was obtained as a colorless, volatile liquid in quantitative yield. Its structure is in agreement with its combustion analysis, spectral data, and mode of formation. The presence of a secondary amino group in the molecule was substantiated by its transformation to mono-*p*-nitrobenzoate **4** and to a short-lived nitroxide radical (three-line ESR spectrum, A_N 21.5 G)[5] upon oxidation. The NMR spectrum of **3** showed, in addition to other expected signals, its methyl group as a pair of singlets at δ 1.27 and 1.33 in a relative ratio



of ca. 1:4. This observation, as well as the appearance of a pair of singlets for one methyl group in its *p*-nitrobenzoate **4** and

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