Cycloaddition Reaction with Methylnitrone

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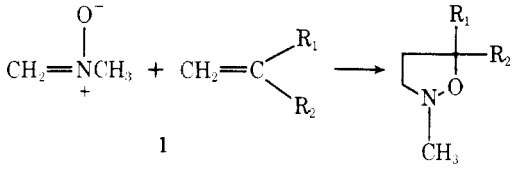
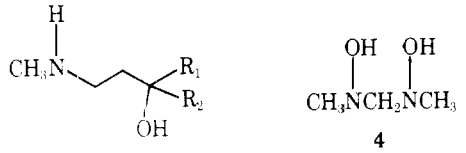
Cycloaddition of in situ prepared methylnitrone proceeds in good yields with active dipolarophiles. The resultant isoxazolidines were converted to various transformation products. A convenient synthesis of α-acylstyrenes is described.

Although many nitrones have been studied in the cycloaddition reaction with a wide variety of olefins,[1a] only one instance has been recorded of the use of methylnitrone (**1**). In 1960, Brown and co-workers[2] reported the reaction of 2,3-dimethyl-1,3-butadiene with *N*-methylhydroxylamine and paraformaldehyde to give a 1:1 adduct corresponding in structure to cycloaddition of methylnitrone to the olefin. Similarly, *N*-ethylhydroxylamine, paraformaldehyde, and cyclohexene were found to yield an isoxazolidine. Relatively vigorous conditions were applied in these reactions (100 °C/18 h), probably in part to ensure depolymerization of paraformaldehyde. On the other hand, with the more reactive dipolarophile styrene, Huisgen et al.[1b] found butyraldehyde and *N*-phenylhydroxylamine to react at somewhat lower temperature (65 °C).

The in situ reaction of formaldehyde, *N*-methylhydroxylamine, and dipolarophiles therefore appeared to provide a route to 2-methyl-5-substituted isoxazolidines **2**, suitable as



1 **2**



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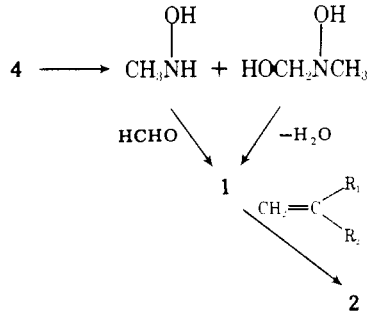
4

intermediates in the synthesis of γ-amino alcohols **3** and their derivatives with possible pharmacological activity. This paper records certain of our observations on the reaction of various terminal olefins with aqueous formaldehyde and *N*-methylhydroxylamine and some of the transformation products derived from the resultant isoxazolidines.

In our consideration of means to implement the reaction, it was anticipated that nitrone **1** would show a high order of reactivity toward cycloaddition, especially with acrylates, and substitution of aqueous formaldehyde for paraformaldehyde was expected to circumvent the necessity of depolymerization. However, the presence of water in the system raised the question of rate of cycloaddition vs. hydrolysis of the nitrone intermediate. In addition, the possibility of formation of the aminal **4**,[3] a product of reaction of *N*-methylhydroxylamine with formaldehyde, was considered.

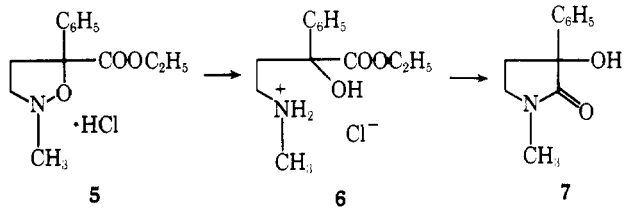
Both of these questions appeared to be resolved when slow addition of *N*-methylhydroxylamine hydrochloride to a mixture of aqueous formaldehyde, sodium acetate, and methyl methacrylate gave methyl 2,5-dimethylisoxazolidine-5-carboxylate in 53% yield. The 60-MHz NMR spectrum[4] showed sharp three-proton singlets at δ 1.5, 2.74, and 3.76 and broad two-proton multiplets at δ 1.6–2.6 and 2.8–3.55. The latter resonances, corresponding to C-4 and C-3 protons, respectively, were also observed by Huisgen et al.[1c] with 2-methyl-3,5-diphenylisoxazolidine and 2,3,5-triphenylisoxazolidine, wherein the ring substitutions permitted better resolution than was found with the C-3 unsubstituted compounds studied here.

The fact that cycloaddition occurs readily under the conditions outlined does not necessarily exclude involvement of the aminal. Substitution of the aminal **4** for *N*-methylhydroxylamine in the reaction with methyl methacrylate and aqueous formaldehyde gave an adduct identical with that described. It would appear that in aqueous medium aminal **4** is hydrolytically unstable and by loss of water from (hydroxymethyl)methylhydroxylamine or reaction of methylhydroxylamine with formaldehyde gives rise to **1**. Also, a series of equilibria may be operative, ultimately displaced by cycloaddition.



In Table I are listed the isoxazolidines obtained by the technique described above. In these examples, methylnitrone behaves in typical fashion[1] with conjugated terminal olefins.

Hydrogenolysis of Isoxazolidines. Catalytic hydrogenation, in the presence of 5% palladium–charcoal, of the 5-carbalkoxy- and 5-alkyl- or -arylisoxazolidine hydrochlorides studied was fairly rapid and ceased with absorption of 1 mol equiv of hydrogen. Of these, only the hydrochloride **5** gave a crystalline product (**6**); the rest yielded oily hydrochlorides. In the case of 5-cyano-2-methylisoxazolidine, the reduction product is, in fact, a cyanohydrin which proved to be unstable even as the hydrochloride. Treatment of the secondary amine hydrochloride **6** with aqueous alkali resulted in rapid cyclization to the lactam **7**.



5 **6** **7**

With 5-acylisoxazolidines, hydrogenation led to substituted pyrrolidines. Only in the case of the ketone **8** was this studied in any detail, the reduction with 1 mol equiv of hydrogen

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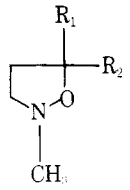
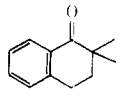
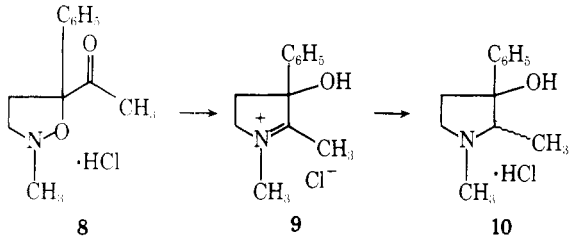
Table I. *N*-Methylisoxazolidines[a]



R_1	R_2	registry no.	mp of salt, °C	crystallization solvent	yield, %
$COOC_2H_5$	H	68408-62-8	82–83[b]	MeOH/Et_2O	85
$COOCH_3$	CH_3	68408-63-9	71/26 mm[c,d]		53
CN	H	68408-64-0	138 dec[e]	MeOH/Et_2O	63
C_6H_5	H	68408-66-2	102–103[b]	MeOH/EtOAc	74
C_6H_5	CH_3	68408-67-3	120–120.5[e]	MeOH/EtOAc	45
C_6H_5	C_6H_5	68408-68-4	198–199 dec[e]	MeOH/EtOAc	9.4
α-naphthyl	H	68408-69-5	165 dec[e]	MeOH/EtOAc	49
β-naphthyl	H	68408-70-8	168 dec[e]	MeOH/EtOAc	45
C_6H_5	$COOC_2H_5$	68408-71-9	106–107[e]	EtOAc/Et_2O	90
C_6H_5	$COCH_3$	68408-72-0	148–150 dec[e]	MeOH/Et_2O	79
C_6H_5	COC_2H_5	68408-73-1	156 dec[d,f]	MeOH/EtOAc	85[c]
C_6H_5	COC_6H_5	68408-74-2	155 dec[e,g]	MeOH/Et_2O	86
		68408-75-3	145[e]	MeOH/Et_2O	63

[a] All compounds showed elemental analyses and NMR spectra consistent with structure. [b] Maleate salt. [c] Free base. [d] No crystalline salt could be obtained. [e] HCl salt. [f] Methiodide. [g] Also crystallizes as free base, mp 77–79 °C.

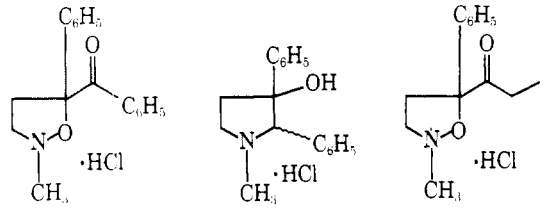
giving the salt **9**. Total hydrogenation of the ketone **8** yielded pyrrolidine **10**.



8 **9** **10**

The carbinol **10** was obtained as a pure diastereomer, possibly with a methyl–phenyl cis relationship in view of the method of formation. This substance, or its diastereomer, has been reported by Cavalla and Davoll,[5] who arrived at the same substitutions by another route.

The phenyl ketone **11**, analogous to **8**, gave the pyrrolidine **12** on reduction. However, the hydrogenation of the ethyl ketone **13** proceeded at a slower rate than either ketones **8** or

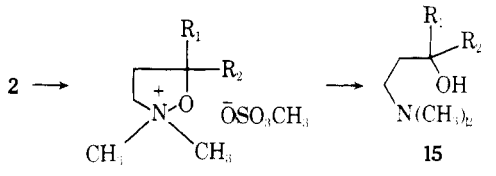


11 **12** **13**

11 and gave a mixture of products which was not studied further.

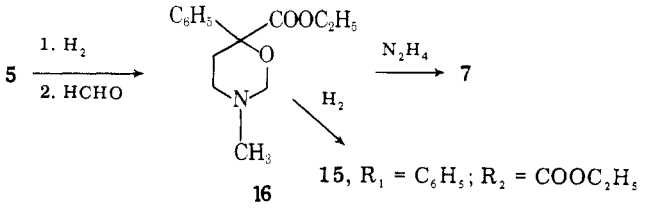
If the isoxazolidines were converted to methosulfates **14**, hydrogenolysis proceeded smoothly to the γ-(dimethylamino)carbinols **15**. The quaternary iodides were inert to hydrogenation in the presence of palladium–charcoal. Table II lists the carbinolamines thus prepared, together with their acetylation products.

In addition to the above transformations, the reduction products of the alkyl-, aryl-, or carbalkoxyisoxazolidines



14 **15**

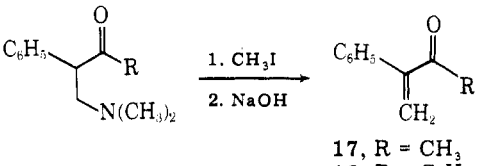
provide a means of attaining 6-substituted tetrahydro-1,3-oxazines by reaction of the γ-(methylamino)carbinols with formaldehyde, as shown by the conversion **5** → **16**. An interesting sidelight is the behavior of the oxazine **16** with refluxing



16

hydrazine hydrate, giving rise to the lactam **7**,[6] and catalytic hydrogenation, which affords the tertiary aminocarbinol **15**.

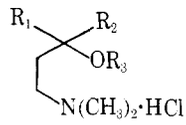
Preparation of α-Acylstyrenes. The α-acylstyrenes required for the synthesis of 5-acylisoxazolidines were prepared by base degradation of the appropriate Mannich base quaternary salts. The ketones **17** and **18** were obtained by the

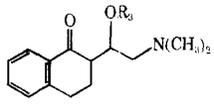


17, R = CH_3
18, R = C_6H_5
19, R = C_2H_5

method of Wilson and Kyi.[7] On the other hand, the synthesis of **19** by this route failed when Mannich condensation with 1-phenyl-2-butanone occurred at C-3, giving the base **20**.

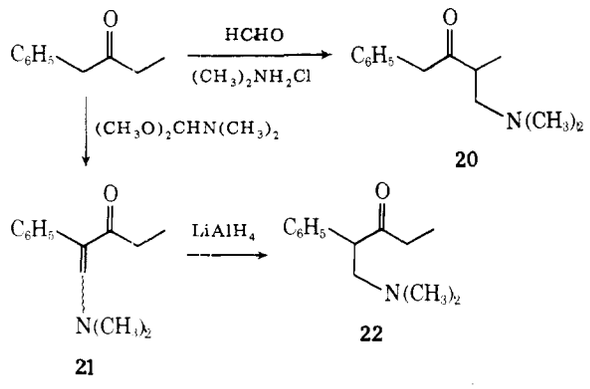
Table II[a]



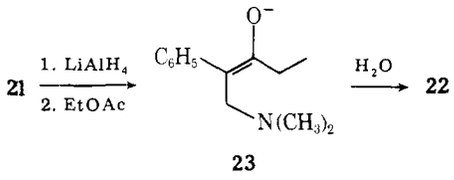
R_1	R_2	R_3	registry no.	mp, °C	crystallization solvent	yield, %
C_6H_5	CH_3	H	68424-03-3	164	MeOH/EtOAc	78
C_6H_5	$COOC_2H_5$	H	68408-76-4	162 dec	MeOH/EtOAc	57
C_6H_5	$COCH_3$	H	68408-77-5	178–180	MeOH/EtOAc	69
C_6H_5	COC_2H_5	H	68408-78-6	143	MeOH/EtOAc	79
C_6H_5	COC_6H_5	H	68408-79-7	205–206	MeOH/Et_2O	83
C_6H_5	CH_3	$COCH_3$	68408-80-0	173–174	MeOH/Et_2O	66
C_6H_5	$COOC_2H_5$	$COCH_3$	68408-81-1	151 dec	MeOH/EtOAc	77
C_6H_5	$COCH_3$	$COCH_3$	68408-82-2	182	MeOH/Et_2O	73
C_6H_5	COC_2H_5	$COCH_3$	68408-83-3	197–198	MeOH/Et_2O	92
C_6H_5	COC_6H_5	$COCH_3$	68408-84-4	210	MeOH/EtOAc	21
		$COCH_3$	68408-85-5	196	MeOH/Et_2O	18

[a] All compounds showed elemental analyses and NMR spectra consistent with structure.

However, dimethylformamide dimethyl acetal reacts exclusively at C-1, giving the enamino ketone **21**, which is reduced cleanly by lithium aluminum hydride to the desired product **22**.



This reduction is in close analogy to that of 1-(dimethylamino)-4-methyl-1-penten-3-one reported by Martin et al.[8] Although these authors did not stress the point, it is essential that the excess reductant be decomposed under nonprotic conditions. The use of ethyl acetate in their work, and also here, ensures nonprotonation of the reduced enolate **23**. Unless this order of reaction is followed during the isolation, any ketone formed is reduced by the $LiAlH_4$ still present and results in a mixture of the ketone **22** and the corresponding carbinol. Application of this overall synthesis to deoxybenzoin gave the Mannich base in 90% yield.



The direct formation of *N*-methylisoxazolidines serves to broaden the scope of the nitrone cycloaddition reaction and indicates that, at least with reactive dipolarophiles, an aqueous medium is compatible with the system. In addition, the various reduction techniques applied to suitably substituted isoxazolidines can lead to 1,2,3-substituted pyrrolidines.

Experimental Section

2-Methyl-5-substituted Isoxazolidines. A mixture of the dipolarophile (0.33 mol), sodium acetate trihydrate (0.3 mol), 37% aqueous formaldehyde (0.4 mol), and ~200 mL of ethanol or dioxane was stirred vigorously at room temperature during the dropwise addition over ~3 h of a solution of 0.3 mol of *N*-methylhydroxylamine hydrochloride in 5 mL of water and 70 mL of ethanol or dioxane. Stirring was continued for 3 h, or the mixture was allowed to stand overnight. The sodium chloride was removed by filtration. The filtrate was concentrated somewhat under reduced pressure and diluted with an equal volume of water. Neutralization with sodium bicarbonate, extraction with ethyl acetate, drying, and concentration under reduced pressure gave the isoxazolidine usually as a colorless liquid. For convenience, the products were normally converted to the hydrochloride salts; Table I lists the cycloaddition products obtained in this fashion.

***N,N'*-Dimethyl-*N,N'*-dihydroxyaminal (4) as a Source of Methylnitrone.** A solution of 1.33 g (0.0125 mol) of the aminal **4**,[3] 5.5 g (0.055 mol) of methyl methacrylate, and 8.1 g (0.1 mol) of 37% aqueous formaldehyde in 50 mL of dioxane and 10 mL of water was stirred at room temperature for 17 h. The basic product (1.6 g) isolated as above was allowed to stand in ether solution with excess methyl iodide for 2 h. The isolated methiodide (2.31 g, mp 150 °C dec) was identical in all respects with the methiodide of the product of the above procedure.

Hydrogenolysis of Isoxazolidine Salts. Of the reductions attempted, only the isoxazolidine hydrochloride **5** gave a crystalline product; the others of Table I produced oily hydrochlorides. The hydrogenation of **5** is typical.

A mixture of 5.43 g (0.02 mol) of the isoxazolidine hydrochloride **5**, 50 mL of ethanol, and 0.5 g of 5% palladium–charcoal catalyst was shaken in a Parr apparatus. When absorption of hydrogen ceased (~2 h), the mixture was filtered and the filtrate was evaporated to a colorless glass which crystallized readily from methanol–ethyl acetate (5.14 g, 94%; mp 137–139 °C, raised to 138–139 °C by recrystallization): NMR (Me_2SO) δ 1.2 (t, J = 7 Hz, 3), 2.49 (s, 4), 2.7–3.15 (m, 4), 4.17 (q, J = 7 Hz, 2), 7.4 (m, 5), 11.5 (broad, 1).

Anal. Calcd for $C_{13}H_{20}ClNO_3$: C, 57.04; H, 7.36; N, 5.12; Cl, 12.95. Found: C, 57.16; H, 7.10; N, 5.06; Cl, 13.07.

γ-Dimethylamino Tertiary Carbinols (15). The isoxazolidine base was treated in ethyl acetate solution with a slight excess of dimethyl sulfate and allowed to stand at room temperature for 24 h. The volatile materials were removed under reduced pressure, and the resulting crude methosulfate was hydrogenated in ethanol solution in the presence of 5% palladium–charcoal catalyst. Filtration of the mixture and conversion to the hydrochloride salt gave the carbinol hydrochloride (Table II).

Acetylation of γ-Dimethylamino Tertiary Carbinols. A mixture of 0.02 mol of the carbinol hydrochloride, 50 mL of pyridine, and 30 mL of acetic anhydride was heated on a steam bath for 20 h. The almost black residue from evaporation of the reaction mixture was taken

up in water, neutralized with bicarbonate, and extracted with ether. Occasionally, filtration was required to break emulsions that formed. The dark red ether extract was washed exhaustively with water and shaken with charcoal. Filtration gave an almost colorless solution which was dried (sodium sulfate) and treated with gaseous hydrogen chloride (Table II).

4-(Dimethylamino)-3-methyl-1-phenyl-2-butanone Hydrochloride (20). A mixture of 14.8 g (0.1 mol) of 1-phenyl-2-butanone, 13.05 g (0.16 mol) of dimethylamine hydrochloride, 4.8 g (0.16 mol) of paraformaldehyde, 1 mL of concentrated hydrochloric acid, and 60 mL of ethanol was heated under reflux for 16 h. The cooled mixture was diluted with 1 N HCl, extracted with ethyl acetate, and made alkaline with aqueous ammonia, and the precipitated oil was taken up in ether. Washing, drying, and treatment with anhydrous hydrogen chloride gave 4.34 g of white crystalline product. The recrystallized material melted at 108–109 °C: NMR (Me_2SO) δ 1.25 (d, J = 6 Hz, 3), 2.75 (s, 6), 2.9–3.8 (m, 3), 4.1 (s, 2), 7.4 (s, 5), 11.0 (broad, 1).

Anal. Calcd for $C_{13}H_{20}ClNO$: C, 64.59; H, 8.34; N, 5.79. Found: C, 64.47; H, 8.16; N, 5.83.

α-Propionyl-β-(dimethylamino)styrene (21). A mixture of 16.1 g (0.135 mol) of dimethylformamide dimethyl acetal and 20 g (0.135 mol) of 1-phenyl-2-butanone, protected by a drying tube, was heated under gentle reflux overnight. Removal of the volatile components under reduced pressure on a hot water bath gave an amber liquid, 94% pure by GLC. A colorless to light yellow product resulted upon distillation: 63% yield; bp 161 °C (15 mm); NMR ($CDCl_3$) δ 0.95 (t, J = 7 Hz, 3), 2.2 (q, J = 7 Hz, 2), 2.65 (s, 6), 7.25 (m, 5), 7.62 (s, 1).

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6 89; O, 7.87. Found: C, 76.53; H, 8.34; N, 6.63; O, 7.94.

α-Benzoyl-β-(dimethylamino)styrene. Molar proportions of deoxybenzoin and dimethylformamide dimethyl acetal stirred overnight at room temperature gave the product in 88% yield as a light yellow crystalline solid; mp 124–127 °C from methylene chloride–Skellysolve B. Further recrystallization raised the melting point to 127–129 °C: NMR ($CDCl_3$) δ 2.6 (s, 6), 7.2–7.6 (m, 11).

Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.45; H, 6.80; N, 5.77.

1-(Dimethylamino)-2-phenylpentan-3-one Hydrochloride (22). A solution of 10.15 g (0.05 mol) of the enamino ketone **21** in 40 mL of dry ether was added drop by drop to an ice-cooled stirred suspension of 5.68 g (0.15 mol) of lithium aluminum hydride in 100 mL of dry ether. Stirring was continued for 3 h at room temperature. With ice cooling, 50 mL of ethyl acetate was added slowly, followed by water and 20% aqueous sodium hydroxide. The residue was removed by filtration. The filtrate was washed well with water, dried (sodium sulfate), and concentrated to ~150 mL. Treatment with gaseous hydrogen chloride gave 6.51 g (54%) of white solid, crystallized from methanol–ether, mp 117–120 °C. An analytical sample melted at 119–120 °C: NMR ($CDCl_3$) δ 0.97 (t, J = 7.5 Hz, 3), 2.56 (2 doublets, J = 7.5 Hz, 2), 2.8 (2 doublets, J = 5.5 Hz, 6), 3.25 (2 triplets, J = 5 Hz, 1), 4.03 (m, 1), 4.3 (2 doublets, J = 7 Hz, 1), 7.35 (s, 5), 12.3 (m, 1).

Anal. Calcd for $C_{13}H_{20}ClNO$: C, 64.59; H, 8.34; N, 5.79; Cl, 14.66. Found: C, 64.38; H, 8.55; N, 5.51; Cl, 14.69.

Methiodide. The free base from 6.09 g of the above Mannich salt **22** was allowed to stand in ethyl acetate overnight with 3.1 mL of methyl iodide. Dilution with ether and cooling gave 7.8 g (90%) of colorless crystalline solid: mp 169–170 °C, unchanged upon recrystallization from acetonitrile–ether; NMR (Me_2SO) δ 0.9 (t, J = 7.5 Hz, 3), 2.6 (m, 2), 3.15 (s, 9), 3.5–3.9 (2 doublets, J = 13 Hz, 1), 4.15–4.45 (2 doublets, J = 13 Hz, 1), 4.85 (2 doublets, J = 5.5 Hz, 1), 7.42 (s, 5).

Anal. Calcd for $C_{14}H_{22}INO$: C, 48.43; H, 6.39; N, 4.03; I, 36.55. Found: C, 48.21; H, 6.24; N, 4.08; I, 36.33.

3-(Dimethylamino)-2-phenylpropiophenone Methiodide. To a suspension of 5.68 g of $LiAlH_4$ in 150 mL of dry ether, cooled in ice, was added with stirring over ~5 min 12.57 g (0.05 mol) of solid β-(dimethylamino)-α-benzoylstyrene. After overnight stirring, the Mannich base was isolated as above: NMR ($CDCl_3$) δ 2.1 (s, 6), 2.5 (2 doublets, J = 12 Hz, 1), 2.35 (2 doublets, J = 12 Hz, 1), 4.8 (2 doublets, J = 9 Hz, 1), 7.0–8.1 (m, 10).

The crude base with excess methyl iodide gave 10.88 g of white crystalline solid: mp 181 °C from methanol–ether; NMR (Me_2SO) δ 3.21 (s, 9), 3.87 (2 doublets, J = 7 Hz, 1), 4.5 (2 doublets, J = 7 Hz, 1), 5.7 (2 doublets, J = 5 Hz, 1), 7.2–8.4 (m, 10).

Anal. Calcd for $C_{18}H_{22}INO$: C, 54.69; H, 5.61; N, 3.54; I, 32.10. Found: C, 54.47; H, 5.59; N, 3.25; I, 32.07.

2-Methyl-5-acyl-5-phenylisoxazolidines. To a well-stirred mixture of 16 g (0 4 mol) of sodium hydroxide dissolved in 200 mL of water and 100 mL of ether at room temperature was added in small portions 0.11 mol of the appropriate Mannich base methiodide. When two homogeneous layers had formed, the ether layer was separated, filtered if necessary, washed well with water, and evaporated under reduced pressure at room temperature to an almost colorless liquid. Conversion to the isoxazolidine hydrochloride as described gave the respective products listed in Table I.

1,2-Dimethyl-3-hydroxy-3-phenyl-Δ¹-pyrrolinium Chloride (9). A mixture of 0.97 g of ketone **8**, 0.1 g of 5% palladium–charcoal catalyst, and 20 mL of ethanol was stirred in a hydrogen atmosphere until 95% of 1 mol equiv of hydrogen had been absorbed (~20 min). The filtered mixture was evaporated to a crystalline residue which was recrystallized from methanol–ether, giving 0.77 g of white solid, mp 193–197 °C dec. An analytical sample melted at 208–210 °C dec: NMR ($CDCl_3$) δ 2.3 (s, 3), 2.6–3.0 (m, 2), 3.79 (s, 3), 4.4–4.9 (m, 2), 7.0–7.9 (m, 5).

Anal. Calcd for $C_{12}H_{16}ClNO$: C, 63.85; H, 7.15; N, 6.21; Cl, 15.71. Found: C, 63.57; H, 7.36; N, 6.31; Cl, 16.07.

1,2-Dimethyl-3-hydroxy-3-phenylpyrrolidine Hydrochloride (10). When 0.73 g of ketone **8** was hydrogenated until absorption ceased, 0.49 g of the pyrrolidine hydrochloride **10** was obtained, mp 199–200 °C from methanol–ethyl acetate. Recrystallization raised the melting point to 200–202 °C: NMR (Me_2SO) δ 1.1 (d, J = 7 Hz, 3), 2.7–2.9 (m, 1), 2.95 (s, 3), 3.1–4.0 (m, 4), 6.14 (s, 1), 7.2–7.9 (m, 5), 10.5 (broad, 1).

Anal. Calcd for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.97; N, 6.15; Cl, 15.57. Found: C, 63.32; H, 7.95; N, 6.36; Cl, 15.37.

1-Methyl-2,3-diphenyl-3-hydroxypyrrolidine Hydrochloride (12). A mixture of 9.2 g of isoxazolidine hydrochloride **11**, 1.0 g of 5% palladium–charcoal catalyst, and 150 mL of ethanol was shaken in a Parr apparatus until absorption of hydrogen ceased. The catalyst was removed by filtration, and the filtrate was made alkaline with potassium carbonate. The base was extracted into ethyl acetate, washed with water, dried with sodium sulfate, and precipitated as the hydrochloride: 8.2 g (93%) of white solid; mp 218–220 °C dec, unchanged by recrystallization; NMR (Me_2SO) δ 2.8 (d, J = 6.5 Hz, 2), 3.58 (s, 1), 3.7 (s, 3), 4.75 (m, 2), 7.0–7.7 (m, 11), 8.4 (s, 1).

Anal. Calcd for $C_{17}H_{20}ClNO$: C, 70.46; H, 6.96; N, 4.83; Cl, 12.23. Found: C, 70.24; H, 6.73; N, 4.87; Cl, 12.26.

1-Methyl-3-hydroxy-3-phenyl-2-pyrrolidone (7). A solution of 5 g of ethyl 2-hydroxy-4-(methylamino)-2-phenylbutyrate hydrochloride in 50 mL of ethanol was treated with 30 mL of 1 N aqueous sodium hydroxide and allowed to stand for 1 h. Dilution with water and extraction with ethyl acetate gave the lactam: 2.3 g; mp 101–102 °C from ethyl acetate–Skellysolve B, unchanged by further recrystallization; NMR ($CDCl_3$) δ 2.4 (t, J = 6.5 Hz, 2), 2.92 (s, 3), 3.33 (t, J = 5.5 Hz, 2), 4.05 (m, 1), 7.33 (m, 5).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.06; H, 6.80; N, 7.34. Found: C, 69.17; H, 6.52; N, 7.32.

6-Carbethoxy-3-methyl-6-phenyltetrahydro-1,3-oxazine Hydrochloride (16). A solution of 2.0 g of the amine hydrochloride **6** in 10 mL of 37% aqueous formaldehyde was heated on a steam bath for 5 h. The cooled mixture was neutralized with bicarbonate and extracted with ethyl acetate. The washed extract was dried (sodium sulfate), concentrated somewhat, and treated with gaseous hydrogen chloride. Recrystallization of the hydrochloride from acetonitrile–ether gave 1.84 g of oxazine **16**: mp 181–183 °C dec, unchanged by further recrystallization; NMR ($CDCl_3$) δ 1.23 (t, J = 7.5 Hz, 3), 2.88 (m, 5), 3.5 (m, 2), 4.25 (q, J = 7.5 Hz, 2), 4.9 (m, 2), 7.42 (m, 5).

Anal. Calcd for $C_{14}H_{20}ClNO_3$: C, 58.84; H, 7.05; N, 4.90; Cl, 12.41. Found: C, 58.67; H, 6.92; N, 4.93; Cl, 12.18.

Reaction with Hydrazine Hydrate. A solution of 1.42 g (5 mmol) of hydrochloride **16**, 10 mL of 95% ethanol, and 10 mL of 85% hydrazine hydrate was heated under reflux for 5 h. Removal of the volatile materials in vacuo gave a colorless oil which crystallized readily from methylene chloride–Skellysolve B (97%); mp 100–101 °C, undepressed on admixture with **7**.

Hydrogenolysis. A mixture of 1.42 g (5 mmol) of hydrochloride **16**, 20 mL of ethanol, and 0.2 g of 5% palladium–charcoal catalyst was shaken in a hydrogen atmosphere until absorption ceased. Filtration and evaporation of the filtrate gave a crystalline residue which was recrystallized from methanol–ether to give 1.06 g (76%) of ethyl 4-(dimethylamino)-2-hydroxy-2-phenylbutyrate hydrochloride, mp 162 °C dec. The NMR spectrum was identical with that observed with the product of hydrogenolysis of the isoxazolidine methosulfate described above.

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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

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(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).
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N-Acylcarbamates as Intermediates in Synthetic Approaches to a Bicyclic Trimethylene-Bridged 2,4-Oxazolidinedione and Hydantoin[1]

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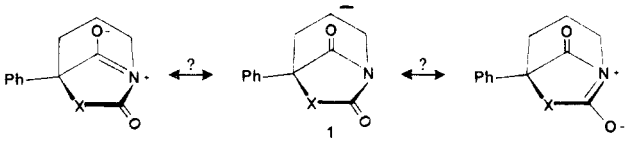
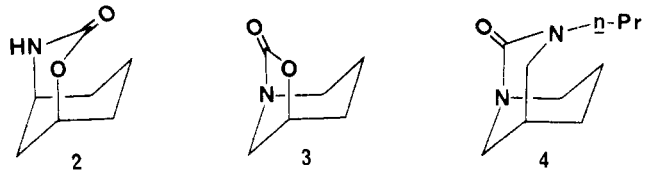
The syntheses of the bicyclic 2,4-oxazolidinedione **1a** and the bicyclic hydantoin **1b** were attempted from several new *N*-acylcarbamates patterned after known precursors to monocyclic 2,4-oxazolidinediones. Heating 3-chloro-1-(ethoxycarbonyl)-3-phenyl-2-piperidinone (**13**) resulted in ester pyrolysis, 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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