The Mannich Reaction. 6-Alkoxytetrahydro-5,5-dimethyl-1,3-oxazines

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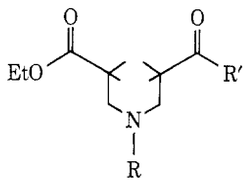
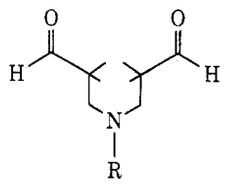
The syntheses of 6-ethoxytetrahydro-3,5,5-trimethyl-2*H*-1,3-oxazine (**6a**) and 6-*tert*-butoxytetrahydrooxazine **6b**, using a modification of the Mannich condensation which involves reaction of 2 equiv of formaldehyde with 1 equiv of methylamine hydrochloride and isobutyraldehyde in the appropriate alcohol solvents, are reported. The importance of this new class of molecules as reaction intermediates is demonstrated by using **6a** to synthesize both ester aldehyde **2b** and dialdehyde **3b** by simple one-step routes. When poorly ionizing solvents or hindered amine salts were used in these reactions, the 2nd equiv of formaldehyde was found not to participate in the reaction and acetals **5a**, **5b**, and **12**, respectively, became the major products. Dialdehyde **3b** could also be obtained in low yield using a double Mannich-type condensation under conditions where all other products were kept in equilibrium.

Recently we reported[1] on the anticancer properties of the hindered *N*-*tert*-butyl-3,3′-imino diester **1**. Our continuing interest in this area has led us to undertake the syntheses of the corresponding hindered ester aldehydes **2a** and **2b**, and dialdehydes **3a** and **3b**.



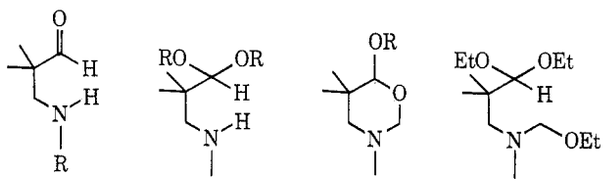
1, R′ = OEt; R = *t*-Bu
2a, R′ = H; R = *t*-Bu
b, R′ = H; R = CH_3



3a, R = *t*-Bu
b, R = CH_3

Our initial attempts to synthesize the less hindered *N*-methyl dialdehyde **3b** by a modification of the Mannich reaction which used 2 equiv of isobutyraldehyde and formaldehyde and 1 equiv of methylamine hydrochloride with ethanol as the solvent did not give dialdehyde **3b**, or its tetraethyl acetal, in appreciable yield, but rather gave a mixture of products, **4a**, **5a**, **6a**, and **7**, as shown in Chart I, the major product being 6-ethoxytetrahydro-3,5,5-trimethyl-2*H*-1,3-oxazine (**6a**).

CHART I



4a, R = CH_3 **5a**, R = Et **6a**, R = Et **7**
b, R = benzyl **b**, R = *n*-Bu **b**, R = *n*-Bu
c, R = *t*-Bu **c**, R = *t*-Bu

We have now shown that tetrahydrooxazine **6a** can serve as a precursor for the syntheses of both **2b** and **3b**. Because of the apparent use of this new class of molecules as synthetic intermediates[2] and because of the observed physiological properties of **6a**,[3] we have investigated the scope of this type of double Mannich condensation by studying the reactions of isobutyraldehyde with several amine hydrochlorides and formaldehyde in different alcohol solvents and would like to report our results in this area.

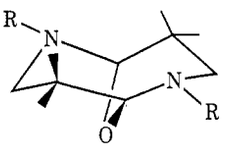
(1) P. Y. Johnson and I. Jacobs, *Chem. Commun.*, 925 (1972).

(2) For examples of the use of dihydro-1,3-oxazines as reaction intermediates, see A. I. Meyers and E. M. Smith, *J. Org. Chem.*, **37**, 4289 (1972), and references cited therein.

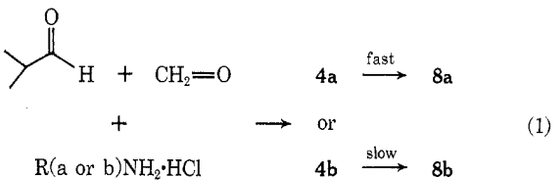
(3) This molecule was shown to cause an average 50% increase in the survival times of mice infected with P388 lymphocytic leukemia at doses ranging from 44 to 200 mg/kg of animal. Testing was kindly performed by CCNSC, National Cancer Institute (NIH).

Results

The original reactions of isobutyraldehyde with formaldehyde and primary amine hydrochlorides were reported in 1932 by Mannich and Wieder.[4] When they used the hydrochloride salts of small amines, such as methylamine, they found that a novel dimer, **8a**, of the desired secondary β-amino aldehyde, **4a**, was formed in 40% yield. They also noted some formation of amino aldehyde **4a**; however, it was observed to self-condense upon standing at 25°. Later workers[5] noticed that self-condensation of an initially formed β-amino aldehyde, **4b**, occurred less readily when salts of bulkier amines such as benzylamine were employed (eq 1).



8a, R = CH_3
b, R = benzyl



(1)

These results suggested that reaction of the initially formed secondary β-amino aldehyde with a second reactive aldehyde, such as formaldehyde, would be expected to take place unless the nitrogen atom of the amino aldehyde was sterically hindered. This being the case, a double Mannich-type condensation appeared to represent a feasible route leading to the synthesis of **3b**. In fact, when the water formed from the initial condensation of the amine salt and formaldehyde was not removed from the reaction mixture, dialdehyde **3b** could be obtained in 16% yield after acid hydrolysis of the reaction mixture and work-up. The only other major product observed in this reaction was aldehyde **4a** which resulted from the hydrolysis

(4) C. Mannich and H. Wieder, *Ber.*, **65**, 385 (1932).

(5) M. W. Williams, *J. Org. Chem.*, **33**, 3946 (1968).

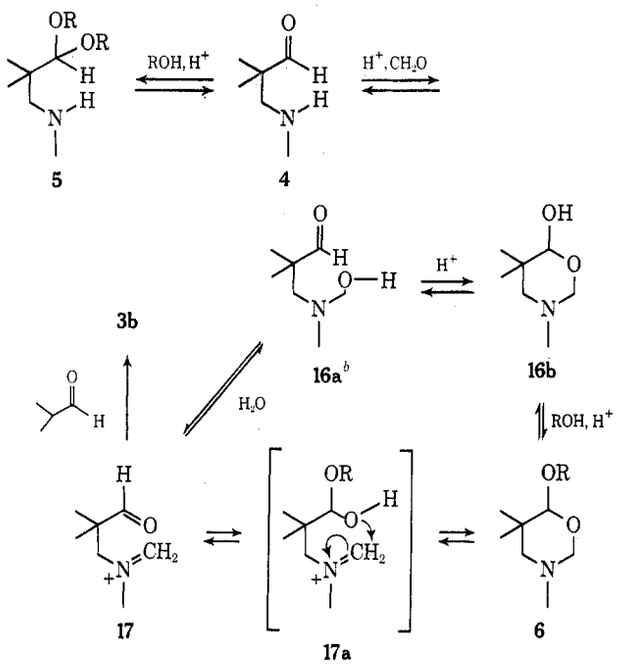
TABLE I
SUMMARY OF GENERAL EXPERIMENTAL PROCEDURE

Runs	RXN solvent for 1-hr reflux (ml)	Bz added after 3-hr reflux, ml	H_2O, ml, removed by azeotrope	(% product yield isolated)
A[a]	EtOH (200)	200	100	**6a** (84[b])
B[a]	*t*-BuOH (200)	200	100	**6c** (25 isolated from mixture)
C[c]	EtOH (100)	100	100	**6a** (25); **8a** (36)
D[c]	EtOH (150), Bz (150)	0	70	**5a** (60)
E[a]	*n*-BuOH (200)	200	100	**5b** (30)
F[d]	EtOH (100)	100	50	**12** (56); **4c** (32)

[a] 0.25-mol scale but 0.50 mol of formaldehyde. [b] Reference 11. [c] 0.25-mol scale for all reagents. [d] *tert*-butylamine salt (0.1 mol; see Experimental Section) was used in this reaction.

of the other potential products. The reaction was run in this manner after early experiments indicated that the yield of **3b** could probably be increased if all other potential products, in particular **6a**, were allowed to remain in equilibrium under hydrolytic conditions so that the only obvious irreversible step in the reaction would be formation of **3b** (Scheme I). This

SCHEME I[a]



[a] Aldehyde species can exist in their hemiacetal or acetal forms; amines can exist as their HCl salts. [b] Structures similar to **16a**, **16b**, and **17** have been postulated to be important in the reactions of β-amino ketones with pyridoxal phosphate in aqueous solvents: M. Skyvova and L. Machelan, *Collect. Czech. Chem. Commun.*, **35**, 2345 (1970).

approach was found to require a 60-hr reaction time to allow for the slow formation of **3b**. After 60 hr other side reactions became important causing a decrease in the already low yield of **3b**.

When the water formed during the reaction was removed from the mixture by azeotrope (Az) in hopes of increasing the concentration of immonium **17** (the procedure employed in our initial studies), the main products were those shown in Chart I. While the product distribution for these reactions was found to be extremely dependent on reaction conditions, the major product, **6a**, could be obtained in as high as 80% yield following the general procedure given in the Experimental Section (see Table I, run A). When less ethanol was used as the solvent in this reaction, there was an over-all decrease in the amount of recovered amine-containing products, but the isolated yield of dimer **8a** was found to increase (Table I, run C). This was probably due to the increased concentration of aldehyde **4a** under these conditions. When larger volumes of ethanol were employed, the amount of acetal **5a** isolated increased as would be expected since ethanol is a reactant in this reaction. When the solvating power of the solvent was decreased by the use of benzene (Bz) as a cosolvent, the amount of acetal **5a** also increased, probably because of a decrease in the concentration of free amine **4a** compared to amine hydrochloride in this poorly ionizing solvent mixture. This would cause a retarding effect on the reaction of **4a** with the 2nd equiv of formaldehyde relative to acetal formation. Using this knowledge we were able to synthesize acetal **5a** in 60% yield (Table I, run D).

Tetrahydrooxazine **6a** was identified by its spectra. Its ir spectra showed no OH, NH, or carbonyl absorptions. The nmr spectrum (100 Mc) showed singlets at δ 0.84 and 0.95 attributable to the nonequivalent methyl groups at C-5. The methylene protons at C-2 and C-4 both gave rise to AB patterns centered at δ 3.72 (J = 8 Hz) and 2.11 (J = 11 Hz), respectively. The methine proton at C-6 appears as a sharp singlet at δ 3.94 showing that it is not coupled to any other protons. Interestingly, while the methyl protons of the ethoxy group give rise to a clean triplet at δ 1.12 (J = 7 Hz), the methylene protons (CH_3CH_2O) appear as two multiplets centered at δ 3.49. Spectra obtained at 60° were identical with those obtained at 25°; however, decoupled spectra obtained by irradiation at δ 1.1 (CH_3-CH_2O) showed that the multiplets were converted into clean pairs of doublets (J = 10 Hz) centered at δ 3.26 and 3.62, respectively, indicating that the ethoxy methylene protons are nonequivalent owing to the chiral center at C-6 and not to hindered rotation about the C-6–O or O–Et bonds.

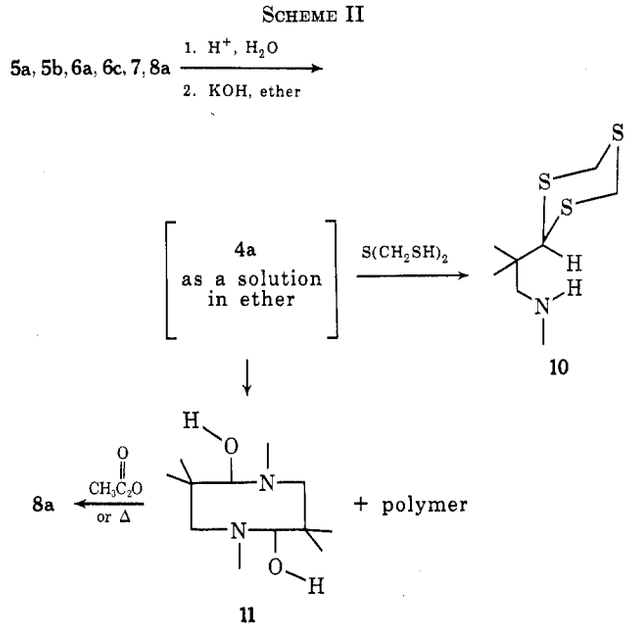
Attempts to make 6-*n*-butoxytetrahydrooxazine **6b** following the general procedure, but using *n*-butyl alcohol as the solvent (Table I, run E), gave instead di-*n*-butyl acetal **5b** as the only major product observed in the crude reaction mixture. Distillation of the crude material gave pure **5b** in 30% yield. The lack of formation of the desired tetrahydrooxazine **6b** is again believed to be due to the low concentration of free secondary amine capable of reacting with the second formaldehyde molecule in this solvent. On the other hand, similar reactions in *tert*-butyl alcohol gave several products from which 6-*tert*-butoxytetrahydrooxazine **6c** could be isolated in 25% yield by careful vacuum distillation of the crude material (Table I, run B). The

other major amine containing product was identified as aldehyde **4a**.

Compounds **5a**, **5b**, **6a**, **6c**, **7**, and **8a** could all be hydrolized in aqueous acid to give, after neutralization and work-up, amino aldehyde **4a** which was stable in solution at 0°.

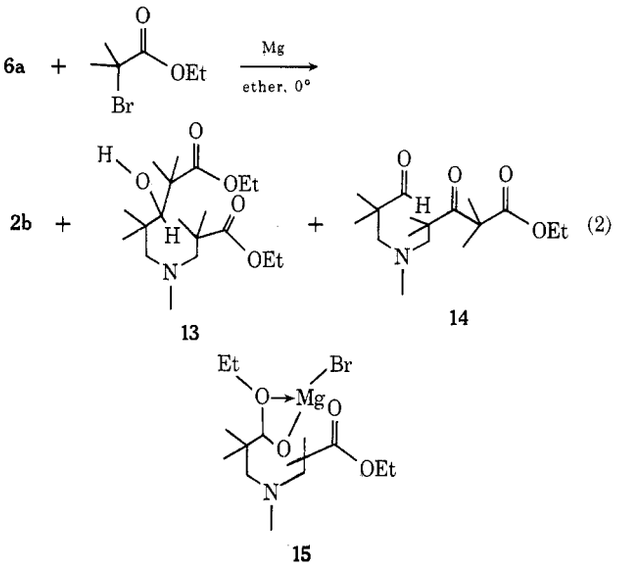
Amino aldehyde **4a** was characterized as its benzenesulfonamide, **9**, and trithiane, **10**, derivatives. While the trithiane was obtained as a white solid (mp 52–54°) using the literature procedure[6] given for the synthesis of these molecules and displayed clean spectra (see Experimental Section) when fresh, it became gummy after standing several days at 25°. When the solvent was allowed to evaporate from an ether solution of aldehyde **4a** over several days, an "oily" solid remained which was shown by nmr not to be dimer **8a**. However, reaction of this solid with acetic anhydride or vacuum distillation of it resulted in low yields of bicyclo ether **8a**. The initial solid has been assigned the amino hemiacetal structure **11**[7] (and related linear polymers of it). These reactions are summarized in Scheme II.

SCHEME II

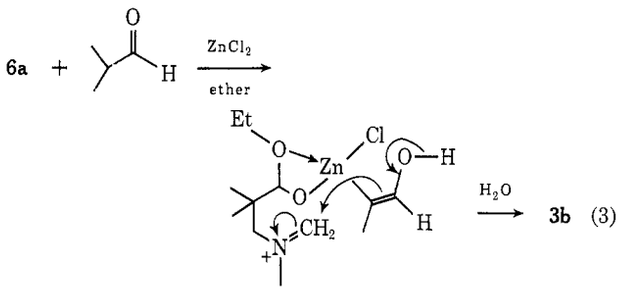


Reaction of the more hindered *tert*-butylamine hydrochloride with isobutyraldehyde and formaldehyde in ethanol gave no tetrahydrooxazine derivatives, but rather gave the diethyl acetal of aldehyde **4c** (**12**) in 56% yield and aldehyde **4c** itself in 32% yield. No products resulting from reaction of the 2nd equiv of formaldehyde were observed in this reaction. Acetal **12** was readily hydrolyzed in aqueous acid to give the stable *tert*-butylamino aldehyde **4c**, in high yield.

Tetrahydrooxazine **6a** was found to be a valuable reaction intermediate. The desired ester aldehyde **2b** could be obtained pure in 40% yield from the reaction of **6a** with a slight excess of the Grignard reagent made from ethyl α-bromoisobutyrate and magnesium at 0° in ether.[8] Two minor amine products, identified as **13** (9%) and **14** (1%), were also isolated from this reaction. Since aldehyde ester **2b** was obtained in high yield relative to **13** in this reaction, it is concluded that the magnesium halide complex of the hemiacetal, **15**, must be formed initially in this reaction preventing, for the most part, free aldehyde formation during the reaction, and that the free aldehyde group results from aqueous work-up of complex **15** (eq 2).



Dialdehyde **3b** could also be synthesized in good yield from **6a**. Treatment of **6a** and isobutyraldehyde in ether with zinc chloride for 3 hr gave, after work-up and purification, **3b** in 49% yield. The mechanism of this reaction is believed to involve attack of the enol of isobutyraldehyde on the zinc halide hemiacetal complex of immonium ion **17a** (eq 3).[9] A small amount



of the bicyclic ether dimer **8a** was also isolated from this reaction. We are currently undertaking other studies of this new class of reaction intermediates at this time.

Experimental Section

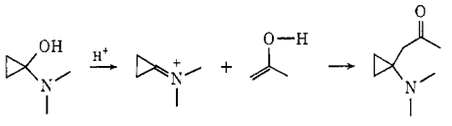
Melting points were taken on a calibrated Mel-Temp apparatus. Ir spectra were taken on a Perkin-Elmer 337 spectrometer; nmr spectra were recorded on Jelco MH-100 and Varian A-60 spectrometers using TMS as an internal standard; and mass spectra were obtained on a Hitachi RMU6D mass spectrometer. Vpc analyses were performed using program temperature con-

(6) See P. Y. Johnson, *Chem. Commun.*, 1083 (1971), for typical procedure.

(7) This type of dimer has been suggested before for secondary amino aldehydes. See E. J. Browne, *Aust. J. Chem.*, **24**, 2389 (1971).

(8) For an example of a similar type of reaction involving an oxazolidine system, see P. Johnson and M. Davis, *Tetrahedron Lett.*, 293 (1973).

(9) This reaction is believed to be analogous to a Mannich-type reaction reported by Deboer, *et al.* [*Tetrahedron Lett.*, 1677 (1972)], which involves addition of acetone to an amino hemiacetal in the presence of acid.



trol on a Hewlett-Packard 5750 gas chromatograph equipped with 8 ft × 0.25 in. 10% Carbowax on Chromosorb P and 8 ft × 0.25 in. 10% SE-30 on Chromosorb P stainless steel columns. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

General Mannich Reaction Procedure.—The general procedure described here for the synthesis of **6a** was used with variations as noted in Table I for the syntheses of **5a**, **5b**, **6c**, **8a**, and **12**.

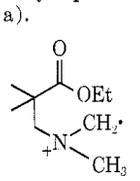
To a dry 1000-ml three-neck flask, under N_2, was added 200 ml of ethanol, 15 drops of concentrated HCl, 16.87 g (0.25 mol) of methylamine hydrochloride, and 15 g (0.5 mol) of formaldehyde (trioxane). The stirred reaction mixture was heated at reflux for 1 hr at which time 18 g (0.25 mol) of isobutyraldehyde was added dropwise to the mixture which was then refluxed an additional 3 hr. After the mixture was allowed to cool, 200 ml of benzene was added to the reaction mixture. A Dean-Stark trap was attached to the reaction flask and 100 ml of solvent was slowly removed as an azeotrope.

After removal of the specified amount of solvent, the reaction mixture was cooled to 0° and 100 ml of ice water was added. The cold acidic layer was separated, after the mixture was shaken well, and washed several times with ether. The acidic aqueous layer was made basic (keep cold) with solid Na_2CO_3 or KOH[10] and the amine products were extracted from the basic layer with four 150-ml portions of cold ether which were dried with $MgSO_4$, filtered, and evaporated. Careful distillation of the crude residue using a 20-cm column gave 36.5 g (84% yield) of **6a**:[11] bp 42–45° (1.5 mm), 28–29° (0.2 mm); ir and nmr (see text); mass spectrum (70 eV) *m/e* (rel intensity) 173 (7, M^+), 128 (10), 102 (15), 100 (54), 99 (20), 72 (30), 59 (25), 58 (60), 45 (100).

Anal.[12] Calcd for $C_9H_{19}NO_2$: C, 62.30; H, 11.02; N, 8.07. Found: C, 61.19; H, 10.78; N, 7.84.

Synthesis of *N*-Methyl-3-imino-2,2-dimethylpropanal Diethyl Acetal (5a).—This reaction was run using the general procedure given above (Table I, run D) affording **5a**: bp 25–26° (0.15 mm), 80–85° (25 mm); ir (CCl_4) 3345 cm^{-1}, no C=O stretch; nmr (CCl_4) δ 0.88 (s, 6), 1.18 (t, 6), 1.42 [s, 1, not present in D_2O (NH)], 2.37 (s, 3), 2.41 (s, 2), 3.65 (m, 4, OCH_2CH_3), 4.21 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 189 (1, M^+), 128 (1), 114 (1), 103 (19), 101 (4), 100 (75), 98 (7), 75 (15), 72 (30), 60 (50), 57 (10), 47 (20), 44 (100).

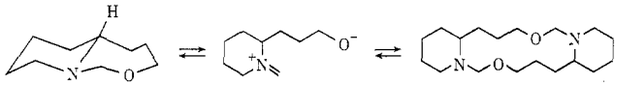
***N*-Ethoxymethyl-*N*-methyl-3-imino-2,2-dimethylpropanal Diethyl Acetal (7).**—Acetal **7** [bp 50–54° (0.1 mm)] was isolated as a minor product from several of these reactions and was identified by its spectra (Table I, runs A, C, and D): ir (CCl_4) no OH, C=O; nmr shows a series of multiplets which are not unambiguously assigned but which are compatible with the proposed structure; mass spectrum shows *m/e* 172 as the highest molecular weight ion (a) (all other major peaks can be accounted for by further breakdown of ion a).



a

(10) Tertiary amines (**6a**, **6c**, **8a**, **2b**, and **3b**) could be extracted from an aqueous Na_2CO_3 solution with ether; however, secondary amines (**4a**, **5a**, and **5b**) could only be extracted from an aqueous hydroxide solution. This observation allowed for a simplified purification of products in many cases; *e.g.*, acetal **5a** could be separated from **6a** by first neutralizing the acidic mixture with Na_2CO_3, washing with ether, and then adding KOH to the aqueous layer and reextracting it with ether, giving **5a** free of **6a** after evaporation of the solvent. **6a** could be recovered from the first ether wash if desired.

(11) This represents the highest yield obtained for **6a**. Average yields were closer to 50–60%. Lower yields were obtained when the mixture was overconcentrated during the azeotrope step or when higher distillation temperatures were used [bp 65–75° (20 mm)]. This is not surprising in light of the report by D. A. Whiting, R. Cahill, and T. H. Crabb [*Chem. Commun.*, 1307 (1972)] of the dimerization of an oxazepine from the liquid state.



(12) We found it difficult to obtain proper analyses for several of these labile molecules; however, hydrolysis and spectra data support structure assignments and purity of fresh samples.

Synthesis of 2,4,4,6,8,8-Hexamethyl-2,6-diaza-9-oxabicyclo[3.2.1]nonane (8a).—This reaction was run using the general procedure given above (Table I, run C) affording **8a**: mp (EtOH) 64.5–65.5° (lit.[4] mp 68°); ir (CCl_4) no OH, C=O stretch; nmr (CCl_4) δ 0.73 (s, 6), 1.21 (s, 6), 2.27 (d, 2, J = 15 Hz), 2.71 (s, 6), 3.27 (d, 2, J = 15 Hz), 3.77 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) 212 (5, M^+), 197 (1), 169 (10), 156 (1), 155 (3), 154 (2), 141 (4), 127 (1), 115 (2), 113 (3), 99 (5), 98 (100).

Anal. Calcd for $C_{12}H_{24}N_2O$: C, 67.94; H, 11.31; N, 13.20. Found: C, 68.00; H, 11.31; N, 13.06.

Synthesis of 6-*tert*-Butoxytetrahydro-3,5,5-trimethyl-2*H*-1,3-oxazine (6c).—This reaction was run using the general procedure given above (Table I, run B) affording **6c**: bp 49–51° (0.5 mm); ir (CCl_4) no OH, C=O stretch; nmr (CCl_4) δ 0.89 (s, 3), 0.99 (s, 3), 1.22 (s, 9), 2.04 (d, 1, J = 10 Hz), 2.09 (s, 3), 2.38 (d, 1, J = 10 Hz), 3.71 (d, 1, J = 7 Hz), 4.10 (d, 1, J = 7 Hz), 4.32 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 201 (7, M^+), 144 (8), 128 (41), 99 (26), 72 (100), 59 (10), 58 (27), 57 (28), 56 (14), 44 (82).

Synthesis of *N*-Methyl-3-imino-2,2-dimethylpropanal Di-*n*-butyl Acetal (5b).—This reaction was run using the general procedure given above (Table I, run E) affording **5b**: bp 64–66° (0.1 mm); ir (CCl_4) 3345 cm^{-1}, no C=O stretch; nmr (CCl_4) δ 0.86 (s, 6), 0.93 (t, 6), 1.1–1.7 (m, 8), 2.36 (s) and 2.38 (s, 5 total), 3.2–3.9 (m, 4), 4.13 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 245 (M^+, none), 160 (4), 128 (48), 98 (87), 72 (85), 60 (19), 57 (62), 56 (43), 44 (100), 43 (43), 42 (49), 41 (55).

Hydrolysis of 5a, 5b, 6a, 6c, 7, and 8a.—Amines **5a**, **5b**, **6a**, **6c**, **7**, and **8a** were stirred either separately or as a mixture in H_2O–H_2SO_4 (pH 1) for 24 hr. The acid mixture was extracted several times with ether and then cooled in ice. Fresh ether (the amount depends on the desired concentration of aldehyde **4a**) was added to the cooled acid layer and KOH pellets were added slowly with stirring until the aqueous layer was basic. The ether layer was separated and dried over $MgSO_4$. Aldehyde **4a** was further used in solution where it was stable at 0°: nmr (CCl_4) δ 1.10 (s, 6), 2.44 (s, 3), 2.69 (s, 6), 9.45 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 115 (1, M^+), 98 (40), 72 (14), 44 (100), 43 (25), 42 (40), 41 (20).

Synthesis of *N*-Methyl-3-imino-2,2-dimethylpropanal Benzenesulfonamide (9).—A concentrated ether solution of **4a** generated from a known amount of **5a** was shaken with 1.2 equiv of benzenesulfonyl chloride in concentrated NaOH according to the standard procedure[13] giving a good yield (based on **5a**) of **9** which was recrystallized from hexane: mp 54–55°; ir (CCl_4) 2800, 2710, 1735 cm^{-1}; nmr (CCl_4) δ 1.14 (s, 6), 2.68 (s, 3), 3.16 (s, 2), 7.70 (m, 5), 9.79 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 255 (none, M^+), 218 (8), 184 (100), 172 (19), 141 (84), 125 (20), 77 (95), with a large metastable peak at 108.0 (141^2/184).

Anal. Calcd for $C_{12}H_{17}NO_3S$: C, 56.49; H, 6.66; N, 5.48. Found: C, 56.20; H, 6.48; N, 5.23.

Synthesis of 2-(2-*N*-Methylamino-1,1-dimethylethyl)-1,3,5-trithiane (10).—Trithiane **10** was synthesized according to the literature procedure for amino aldehydes[6] from an ether solution of amino aldehyde **4a**. Recrystallization of **10** from hexane gave a good yield of a white solid: mp 52–54° dec; nmr ($CDCl_3$) δ 1.09 [s, 6, $>C(CH_3)_2$], 1.22 (br s, 1, NH), 2.46 (s, 3, CH_3N), 2.58 (s, 2, CCH_2N), 4.05 (d, 2, J = 13 Hz, SCH_aHS), 4.48 (s, 1, SCHS), 4.51 (d, 2, J = 13 Hz, $SCHH_eS$). This material turned to a gum after several days.

Direct Synthesis of *N*-Methyl-3,3′-imino-2,2,2′,2′-tetramethyldipropanal (3b) *via* a Double Mannich-Type Reaction.—To a flask was added 16.87 g (0.25 mol) of methylamine hydrochloride, 7.5 g (0.25 mol) of formaldehyde (trioxane), 0.5 ml of H_2SO_4, and 200 ml of ethanol. After this mixture refluxed for 1 hr, 18 g (0.25 mol) of isobutyraldehyde was added to the flask dropwise. Then, after 1-hr intervals, formaldehyde (7.5 g) and isobutyraldehyde (18 g) were added to the mixture which was then allowed to stir at reflux under N_2 for 60 hr. (This reaction time was determined by monitoring hydrolized aliquots.) Aqueous HCl [200 ml (5%)] was added to the reaction mixture which was stirred for an additional 3 hr and cooled to 50°. The ethanol was removed from the mixture under vacuum (20 mm) at 50°. The aqueous amine salts were washed with ether and neutralized with KOH. The basic layer was extracted thoroughly with

(13) R. Shriner, R. Fuson, and D. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1969, p 119.

ether and the ether was washed three times with saturated $NaHSO_3$.

Treatment of the bisulfite layer with KOH followed by extraction with ether gave, after drying the ether with K_2CO_3 and evaporation of solvents, 16 g of crude amino aldehyde containing products. Distillation gave 8 g of aldehyde **4a** and 6 g (16.2%) of dialdehyde **3b**: bp 62–64° (0.01 mm); ir (CCl_4) 2960, 2860, 2770, 2690, 1720 cm^{-1}; nmr (CCl_4) δ 1.03 (s, 12), 2.12 (s, 3), 2.62 (s, 4), 9.65 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) 197 (1, M^+), 128 (54), 98 (17), 72 (10), 58 (100). Dialdehyde **3b** was characterized as its disemicarbazone derivative, mp (MeOH) 148–149°.

Anal. Calcd for $C_{13}H_{27}N_7O_2$: C, 49.82; H, 8.68; N, 31.29. Found: C, 49.72; H, 8.50; N, 31.08.

Synthesis of Aldehyde 3b *via* Tetrahydrooxazine 6a.—To a dry Morton flask equipped with an overhead stirrer was added 250 ml of dry ether, 10 g (0.062 mol) of anhydrous zinc chloride, and 10 g (0.14 mol) of isobutyraldehyde. While the mixture was stirred at 25° under nitrogen, 10 g (0.058 mol) of **6a** in 50 ml of ether was added dropwise to it over 1 hr. After the mixture was allowed to stir for an additional hour, 50 ml of THF was added and stirring was continued for 1 hr at which time 50 ml of concentrated HCl in 150 ml of water was added to the reaction mixture. The acidic mixture was stirred for 1 hr at 25° and the acidic aqueous layer was separated from the ether. The ether layer was back-washed with fresh aqueous acid and the combined acid layers were washed several times with ether. The acid layer was neutralized with Na_2CO_3 and the basic layer was extracted six times with ether which was dried with $CaCl_2$, filtered, and evaporated to give 10.5 g of a crude oil from which 4 g of a white solid crystallized out after 12 hr. After vacuum filtration of the solid, the resulting oil was distilled to give 5.9 g (49%) of pure dialdehyde **3b**, bp 82–85° (0.5 mm).

The white solid was recrystallized from hexane to give 2.4 g of material which was shown to be **8a**, mp 63–65°.

If necessary, the crude dialdehyde could be further purified by standard bisulfite procedures before distillation.

Synthesis of Ethyl *N*-Methyl-3-imino-2,2-dimethylpropanal-3′-imino-2′,2′-dimethylpropionate (2b).—To a dry Morton flask containing 250 ml of dried ether and 3.0 g (0.125 g-atom) of Mg under N_2 at −10° was added dropwise, over 0.5 hr, 22.0 g (0.11 mol) of ethyl α-bromoisobutyrate. After disappearance of most of the Mg, tetrahydrooxazine **6a** [17.3 g (0.1 mol)] was added dropwise to the mixture over 0.5 hr. The reaction was stirred for 3 hr at 0° and allowed to warm to 25° over 1.5 hr at which time it was quenched with aqueous NH_4Cl. The mixture was made acidic with HCl and the aqueous acid layer was separated and washed with ether. The ether layer was shown to contain ethyl isobutyrate, starting bromo ester, and some ethyl isobutyrisobutyrate. The acid layer was cooled, made basic with K_2CO_3, and extracted with ether which was dried and evaporated to give 15 g of crude amine products. Distillation gave 9.7 g (40%) of pure ester aldehyde **2b** and 4.5 g of higher boiling material which was shown by vpc to contain two products (see below). **2b** had the following properties: bp 82–83° (0.125 mm); ir (CCl_4) 2965, 2785, 2695, 1735, 1395, 1375, 1275, 1195, 1150, 1122, 1049 cm^{-1}; nmr (CCl_4) δ 1.04 (s, 6), 1.14 (s, 6), 1.26 (t, 3), 2.13 (s, 3), 2.60 (s, 2), 2.62 (s, 2), 4.10 (q, 2), 9.85 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 243 (1, M^+) 242 (1), 228 (1), 214 (1), 198 (3), 172 (28), 128 (100), 98 (7), 58 (75), 44 (42). Ester aldehyde **2b** was characterized as its 2,4-DNP derivative, mp (EtOH) 75–76°.

Anal. Calcd for $C_{19}H_{29}N_5O_6$: C, 53.89; H, 6.90; N, 16.54. Found: C, 53.84; H, 6.79; N, 16.48.

The higher boiling materials were partitioned between ether and saturated bisulfite. The ether layer was dried over K_2CO_3, filtered, and evaporated and the resulting oil was distilled to give 3.2 g (9%) of a material which was identified as alcohol **13** [bp 122–125° (0.15 mm)] from its spectra: ir ($CHCl_3$) 3210, 2970, 1730, 1475, 1390, 1368, 1260, 1145, 861 cm^{-1}; nmr (CCl_4) δ 0.68 (s, 3), 0.98 (s, 3), 1.10 (s, 3), 1.18 (s, 6 + 3 = 9), 1.22 (t, 3), 1.24 (t, 3), 2.21 (s, 3), 2.30 (AB pattern, 2), 2.62 (br s, 2), 3.74 (s, 1), 4.02 (2 q, 4), 5.6 (br s, 1, OH).

The bisulfite layer gave, after destruction of the bisulfite adduct with KOH, extraction with ether, and distillation, 0.3 g of aldehyde diadduct **14**: bp 118° (0.15 mm); ir ($CHCl_3$) 2980, 2790, 2695, 1745, 1730, 1698, 1470, 1385, 1365, 1250, 1145, 1030 cm^{-1}; nmr (CCl_4) δ 1.01 (s, 6), 1.13 (s, 6), 1.30 (t, 3), 1.32 (s, 6), 2.10 (s, 3), 2.56 (s, 2), 2.62 (s, 2), 4.14 (q, 2), 9.45 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 313 (trace, M^+), 268 (4), 242 (10), 128 (100).

Attempted Synthesis of Tetrahydrooxazine 6c.—Reaction of 7.21 g (0.1 mol) of isobutyraldehyde, 6.0 g (0.2 mol of $CH_2{=}O$) of trioxane, and 10.95 g (0.1 mol) of *tert*-butylamine hydrochloride in 100 ml of ethanol according to the general procedure given for the synthesis of **6a** (Table I, run F) gave, after work-up, two amine-containing products. *N-tert*-Butyl-3-imino-2,2-dimethylpropanaol (**4c**) was obtained in 32% yield: bp 118–120° (30 mm); ir (CCl_4) 3310, 3170, 2960, 2700, 1390, 1360, 1238, 1218, 1110, 888 cm^{-1}; nmr (CCl_4) δ 1.01 (s, 6), 1.03 (s, 9), 2.60 (s, 2), 9.72 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 157 (trace, M^+), 156 (1), 142 (19), 129 (9), 113 (7), 86 (29), 72 (32), 70 (77), 58 (32), 57 (64), 56 (10), 55 (19), 43 (30), 41 (100). The acetal of **4c**, *N-tert*-butyl-3-imino-2,2-dimethylpropanal diethyl acetal (**12**) was obtained in 56% yield: bp 130–135° (30 mm); ir (CCl_4) no C=O stretch; nmr (CCl_4) δ 0.82 (s, 6), 1.04 (s, 9), 1.19 (t, 6), 2.88 (s, 2), 3.3–4.0 (m, 4, OCH_2CH_3), 4.19 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 231 (none, M^+), 169 (5), 155 (9), 154 (12), 126 (7), 112 (4), 100 (15), 85 (12), 72 (31), 71 (10), 70 (66), 57 (100), 46 (36), 45 (87), 44 (42), 43 (60), 41 (100).

Acetal **12** was readily hydrolyzed in aqueous HCl to aldehyde **4c**, which was a stable liquid characterizable as its 2,4-DNP hydrogen sulfate salt derivative, mp (EtOH) 205–205.5°.

Anal. Calcd for $C_{15}H_{23}N_5O_8S$: C, 41.56; H, 5.76; N, 16.10. Found: C, 41.48; H, 5.91; N, 16.02.

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Registry No.—**2b**, 41348-48-5; **2b** 2,4-DNPH, 41348-49-6; **3b**, 41348-50-9; **3b** disemicarbazone. 41348-51-0; **4a**, 41348-52-1; **4c**, 41348-53-2; **4c** 2,4-DNPH hydrogen sulfate salt, 41348-54-3; **5a**, 41348-55-4; **5b**, 41348-56-5; **6a**, 41348-57-6; **6c**, 41348-58-7; **7**, 41348-59-8; **8a**, 17288-11-8; **9**, 41348-61-2; **10**, 41348-62-3; **12**, 41348-63-4; **13**, 41348-64-5; **14**, 41348-65-6; methylamine hydrochloride, 593-51-1; formaldehyde, 50-00-0; isobutyraldehyde, 78-84-2; *tert*-butylamine hydrochloride, 10017-37-5; butylamine hydrochloride, 3858-78-4; ethyl α-bromoisobutyrate, 600-00-0.