Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.76; H, 11.24; N, 7.94.

Pyrolysis of Methohydrides.—After a mixture of 258 mg of the methiodide **21** and 378 mg of freshly washed silver oxide in 7 ml of water had been stirred for 1 hr, the mixture was filtered and the filtrate was concentrated under reduced pressure. A portion of the crude methohydride **23** in methanol solution was pyrolyzed directly on a gas chromatography column[32] at 144° and the remaining crude, partially crystalline methohydride was pyrolyzed in a short-path still at 160° and 80 mm pressure. In both cases, as well as in experiments where a solution of the methohydroxide in dimethylformamide was heated, the crude pyrolysate contained[32] four components. The material from the 160° pyrolysis contained, in order of increasing retention time, unidentified component A (*ca.* 13%), the methoxy amine **26** (*ca.* 14%), unidentified component B (*ca.* 9%), and the amino alcohol **5** (*ca.* 59%).

Similarly, the crude, partially crystalline methohydroxide **24** from 300 mg of the methiodide **22**, 393 mg of silver oxide, and 6 ml of water was pyrolyzed in a short-path still at 110–130° and 70 mm pressure. The crude distillate contained,[32] in order of increasing retention time, unidentified component A (*ca.* 9%), the methoxyamine **29** (*ca.* 17%), unidentified component B (*ca.* 8%), and the amino alcohol **8** (*ca.* 67%). Attempts to minimize intermolecular reaction by pyrolysis of methanol solutions of the crude methohydroxide **24** on a gas chromatography column at temperatures in the range 140–205° yielded comparable mixtures of products which contained the methoxyamine **29**.

The Stereochemistry of the N-Alkylation of Azabicyclic Systems with Methyl Bromoacetate[1a]

HERBERT O. HOUSE AND BEN A. TEFERTILLER[1b]

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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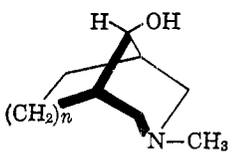
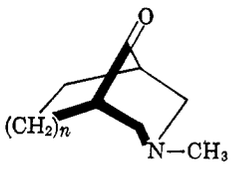
The stereochemistry of the N-alkylation of the amino alcohols **1a** and **3a** and the amino ketone **2a** has been studied. The alkylated product from the amino alcohol **1a** contained the hydroxy ester **6** (*ca.* 25%) and the lactone **12** (*ca.* 75%). Approximately equal amounts of the keto esters **8** and **9** were obtained from the amino ketone **2a**; the keto ester **9** was readily converted to the aldol condensation product **15**. Alkylation of the amino alcohol **3a** afforded the hydroxy ester **10** as the only quaternary ammonium salt isolated. Appropriate interconversions proved the stereochemistry of the various alkylated products.

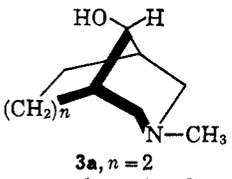
In the preceding paper[2] the reactions of the bicyclic amines **1–3** with trideuteriomethyl *p*-toluenesulfonate were found to be partially stereoselective, yielding a



1a, $n=2$
b, $n=1$ or 3



2a, $n=2$
b, $n=1$ or 3



3a, $n=2$
b, $n=1$ or 3

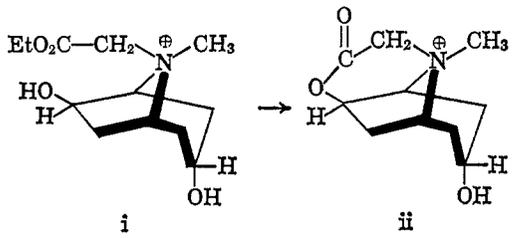
mixture of diastereoisomeric quaternary ammonium salts in which the major isomer comprised 60–90% of the mixture.[3] Within each ring system (*i.e.*, for each value of n in amines **1–3**) the preferred direction of alkylation was the same for the ketone **2** and the corresponding alcohols **1** and **3**.[3] Consideration of the positions of the N-methyl signals in the nmr spectra of these salts further suggested[2] that the preferred direction of N-alkylation was the same for the three homologous series (*i.e.*, n = 1, 2, or 3 in amines **1–3**) studied. However, these studies failed to prove which stereochemistry (*e.g.*, **4** or **5** from **2a**) was correct for the preferred isomer. To answer this stereochemical question, we have studied the N-alkylation of the amines **1a**, **2a**, and **3a** with methyl bromoacetate to form the quaternary salts **6–11**; appropriate ring closure reactions with certain of these derivatives were expected to provide rigorous chemical evidence upon which to base stereochemical assignments.[4]

(1) (a) This research has been supported by a research grant from the National Institutes of Health (Grant No. GM-08761). (b) National Institutes of Health Predoctoral Fellow, 1963–1965.

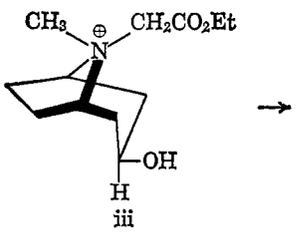
(2) H. O. House and C. G. Pitt, *J. Org. Chem.*, **31**, 1062 (1966).

(3) Experimental difficulties[2] prevented us from learning the degree of stereoselectivity in the N-alkylation of the azabicyclodecanol **3**, n = 3, and from interrelating the alkylation products of the alcohol **3**, n = 3, and the ketone **2**, n = 3.

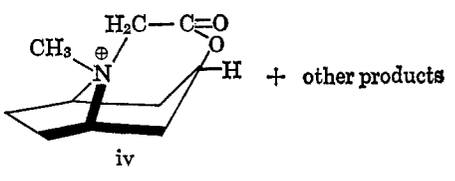
(4) This general approach was used by Fodor and co-workers to assign stereochemistry to the N-alkylated products derived from various tropane derivatives: (a) G. Fodor in "The Alkaloids," Vol. 6, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1960, pp 145–177. (b) The compounds included in this study differ from the previously studied tropane derivatives [*cf.* G. Fodor, K. Koczka, and J. Lestyan, *J. Chem. Soc.*, 1411 (1956)] in ease of lactone formation. For example, although the hydroxy tropane derivative i spontaneously formed the lactone ii, the pseudotropine salt iii (analogous to the salt **7**, which lactonizes spontaneously) formed the lactone iv only when heated to 200°.



i ii

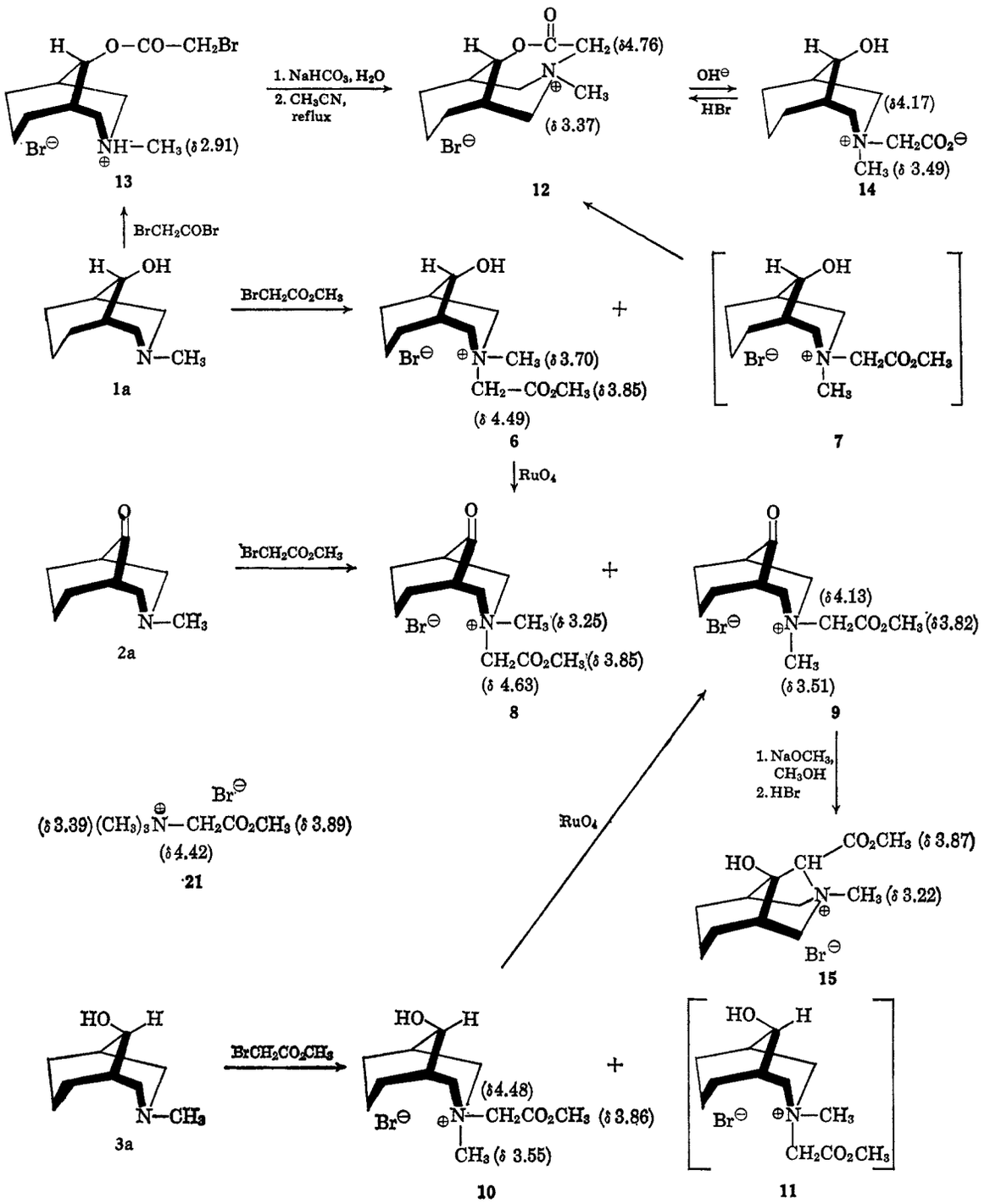


iii



iv + other products

SCHEME I

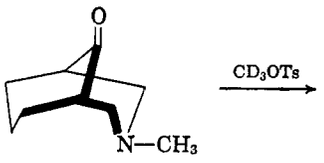


Reaction of the β-hydroxyamine **1a** with methyl bromoacetate yielded a mixture of the hydroxyammonium salt **6**[5] (*ca.* 25% of the mixture) and the lactone **12** (*ca.* 75% of the mixture). The same lactone **12** was obtained by neutralization of the amino ester hydrobromide **13**.[6] This lactone **12**, which could be reversibly converted to the betaine **14**, is presumably formed from rapid lactonization of the initially formed hydroxy ester **7**. Repeated attempts to prepare the hydroxy ester **7** from the betaine yielded the lactone. The minor N-alkylation product, the hydroxy ester **6**, was recovered unchanged after being subjected to the reaction conditions used in the initial alkylation reaction. The salts **6** and **12** may, therefore, be assigned the stereochemistry indicated (Scheme I).

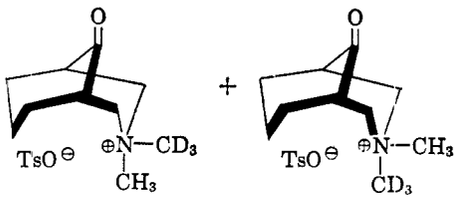
Alkylation of the ketoamine **2a** yielded a mixture of quaternary ammonium salts **8** (*ca.* 50% of the mixture, **9** (*ca.* 20% of the mixture), and **15** (derived from **9**, *ca.* 30% of the mixture). The salts **8** and **15** were separated from the mixture by fractional crystallization. The stereochemistry of isomer **8** was established by producing it from oxidation of the alcohol **6** with

(5) Throughout this paper, the conformational assignments given the quaternary ammonium salts are arbitrary.

(6) This general procedure has been used previously by G. Fodor, F. Uriesch, F. Dutka, and T. Szell, *Collection Czech. Chem. Commun.*, **29**, 274 (1964).



2a

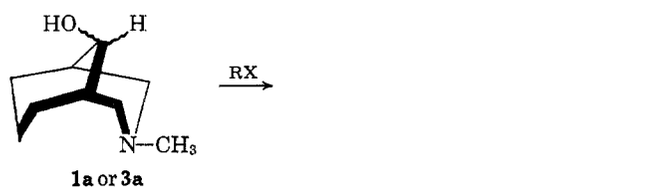


4 5

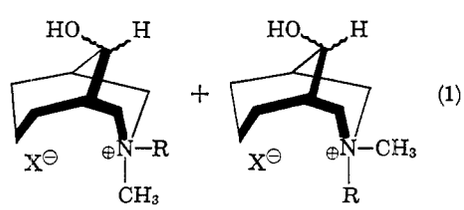
ruthenium tetroxide.[7] An unexpected transformation of the alkylation product **9**, conversion to the aldol condensation product **15** in the presence of bases, provided additional evidence for the stereochemistry of the two ketones **8** and **9**. This base-catalyzed aldol condensation occurred with such ease that it was necessary to recrystallize the keto ester **9** from solvents containing a few drops of hydrobromic acid if condensation was to be avoided.

Alkylation of the α-hydroxyamine **3a** yielded a crude quaternary ammonium salt which was apparently a mixture of stereoisomers **10** and **11**. As had been noted[2] for other quaternary ammonium salts derived from **3a**, the nmr signals for the N-alkyl groups would not be expected to differ in the two isomers **10** and **11**. Consequently, we had no direct method for determining the proportions of the two isomers **10** and **11** which were present in the crude alkylation product. Upon recrystallization a sample of the isomer **10** was the only pure material which could be isolated, suggesting that stereoisomer **10** is the major product formed in the alkylation reaction. Oxidation of this salt **10** with ruthenium tetroxide[7] yielded the pure ketone **9**, allowing us to define the stereochemistry of the salt **10**.

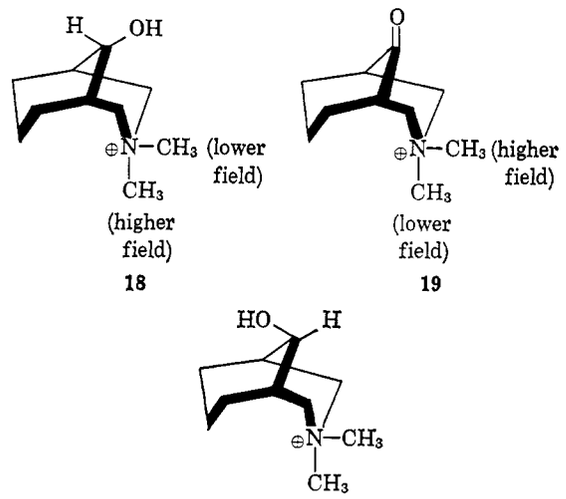
From these reactions with methyl bromoacetate, we conclude that the favored stereochemical path for alkylation of the amino alcohols **1a** and **3a** with methyl bromoacetate is that indicated in eq 1 to form salt **16** (R = $CH_2CO_2CH_3$). Assuming that the same pathway is preferred for reaction with other alkylating agents (such as methyl *p*-toluenesulfonate), we have made the stereochemical assignments given in the preceding paper.[2] The validity of this assumption is strengthened by the consistent empirical correlation which can be made between the stereochemistry of N-alkyl groups in the quaternary salts and the position of their nmr signals (see data in Scheme I). This correlation is summarized in structures **18–20**.



1a or 3a



16 (major product) 17 (minor product) (1)



18 19 20

Experimental Section[8]

Starting Materials.—The amino ketone **2a**[9a] was reduced with sodium borohydride to yield the amino alcohols **3a**, mp 95–96° (lit.[9b] mp 95.5–96°), and **1a**, mp 93.5–94° (lit.[9b] mp 94–94.1°). An ether solution of commercial methyl bromoacetate was washed with aqueous sodium bicarbonate and then dried, concentrated, and distilled to separate the pure ester, bp 55–58° (11 mm). Ruthenium tetroxide was prepared as previously described.[7] In a typical preparation, a solution of 111.0 mg (0.534 mmole) of ruthenium trichloride in 5 ml of 0.5 *M* aqueous hydrochloric acid was heated to boiling and then 1.5 ml (1.5 mmoles) of 1 *M* aqueous sodium bromate was added dropwise. The mixture of ruthenium tetroxide, bromine, and water which distilled from the boiling reaction mixture over a 15-min period was collected in a cold (0°) trap and then extracted with 20 ml of carbon tetrachloride. After the carbon tetrachloride extract had been washed successively with aqueous sodium bicarbonate and water (to remove any bromine which remained), the oxidizing solution was ready for use. In the preparation described, excess ethanol was added to the solution. After the resulting black precipitate of ruthenium dioxide had been collected and dried, it weighed 49.7 mg, corresponding to 0.371 mmole (69% yield) of ruthenium tetroxide. To obtain a model for nmr studies, a solution of 0.50 g (3.3 mmoles) of methyl bromoacetate and 2 ml of trimethylamine in 10 ml of acetone was stirred at room temperature for 5 min. The precipitate which separated was collected and recrystallized from ethanol to separate the salt **21** as white plates, mp 183–184° dec (lit.[10] mp 182–183°). This

(7) Repeated efforts to oxidize the alcohol **6** to the ketone **8** by the catalytic oxidation process we had employed previously[2] were unsuccessful and caused us to examine the use of ruthenium tetroxide. This oxidation procedure proved to be especially convenient for the oxidation of the water-soluble alcohol to the water-soluble ketone and is clearly preferable to catalytic oxidation for the compounds reported here. For discussions of the use of this reagent to oxidize secondary alcohols to ketones, see L. M. Berkowitz and P. N. Rylander, *J. Am. Chem. Soc.*, **80**, 6682 (1958); H. Nakata, *Tetrahedron*, **19**, 1959 (1963).

(8) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated, magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer Model 237 infrared recording spectrophotometer fitted with a grating. The nmr spectra were determined at 60 Mc with a Varian Model A-60 nmr spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

(9) (a) H. O. House, P. P. Wickham, and H. C. Müller, *J. Am. Chem. Soc.*, **84**, 3139 (1962); (b) H. O. House, H. C. Müller, C. G. Pitt, and P. P. Wickham, *J. Org. Chem.*, **28**, 2407 (1963).

(10) W. V. Cohen and A. H. Corwin, *J. Am. Chem. Soc.*, **75**, 5880 (1953).

product has infrared absorption[11] at 1755 cm^{-1} (ester C=O) with nmr singlets[12] at δ 4.42 (2 H, N-CH_2-CO), 3.89 (3 H, CO_2CH_3), and 3.39 [9 H, $(CH_3)_3\overset{\oplus}{N}$-].

The Amino Ester Hydrobromide 13.—A solution of 206.4 mg (1.33 mmoles) of the β-hydroxyamine **1a** and 300 mg (1.49 mmoles) of bromoacetyl bromide in 6 ml of chloroform was stirred at room temperature for 65 hr and then concentrated under reduced pressure. After the residue had been triturated with ether, the residual solid was recrystallized from ethanol to separate 360 mg (76%) of the ester **13** as white needles, mp 244–245.5° dec. Additional recrystallizations raised the melting point to 248–250° dec. This salt has infrared absorption[11,13] at 1745 cm^{-1} (ester C=O) with complex absorption in the region 2600–2800 cm^{-1} ($\geq \overset{\oplus}{N}$-H) but no absorption in the 3-μ region attributable to a hydroxyl function. The product has nmr peaks[12] at δ 4.97 (1 H, triplet with J = 3.5 cps, >CH-O-), 4.13 (2 H, singlet, -CO-CH_2Br), *ca.* 3.5 (4 H, broad, -CH_2-N), and 2.91 (3 H, singlet, CH_3N) as well as broad absorption in the regions δ 2.2–2.5 (2 H, bridgehead C-H) and 1.4–2.2 (6 H, aliphatic C-H).

Anal. Calcd for $C_{11}H_{19}Br_2NO_2$: C, 36.97; H, 5.32; N, 3.92. Found: C, 37.07; H, 5.50; N, 3.77.

The amino ester hydrobromide **13** (704 mg, 1.97 mmoles) was mixed with 20 ml of water and 20 ml of ether, and then aqueous sodium bicarbonate was added until the pH of the mixture was approximately 8. The aqueous phase was saturated with sodium chloride and the ether layer was separated and combined with the ether extract of the aqueous phase. The combined ether solutions were dried and concentrated to leave 360 mg (66%) of the crude amino ester as an amorphous solid. This crude amino ester sample had infrared absorption[14] at 1735 cm^{-1} (ester C=O) with nmr peaks[15] at δ 4.79 (1 H, triplet with J = 3 cps, >CH-O), 3.86 (2 H, singlet, -CO-CH_2Br), and 2.20 (3 H, singlet, CH_3-N) as well as complex absorption in the region δ 1.3–2.9. A solution of 300 mg (1.085 mmoles) of this crude amino ester in 75 ml of acetonitrile was refluxed for 24 hr and then concentrated under reduced pressure. The residual solid was triturated successively with ether and chloroform and then recrystallized from ethanol to separate 150 mg (50%) of the lactone **12**, mp 304–305.5° dec. This product was identified with a subsequently described sample of the lactone **12** by a mixture melting point determination and by comparison of infrared spectra.

Preparation of the Betaine 14.—To a solution of 146 mg (0.528 mmole) of the lactone **12** in 3.0 ml of water was added 250 mg (1.08 mmoles) of silver oxide. The resulting mixture was stirred at 25° for 4 hr and then filtered. After the filtrate had been concentrated under reduced pressure, the residual solid was recrystallized from ethanol to afford 100 mg (89%) of the betaine **14** as white plates, mp 242–243.5° dec. The sample has broad infrared absorption[13] centered at 3200 cm^{-1} (associated O-H) with peaks[11,13] at 1630 and 1390 cm^{-1} (-$COO^{\ominus}$). The nmr spectrum[12] of the sample has peaks at δ 4.17 (2 H, singlet, N-CH_2-$CO_2^{\ominus}$), 3.49 (3 H, singlet, CH_3-$\overset{\oplus}{N}<$), and 2.34 (2 H, broad with half-band width 14 cps, bridgehead C-H) as well as complex absorption in the regions δ 1.4–2.2 (6 H, aliphatic C-H) and 3.3–4.2 (5 H). The latter absorption appears to consist of an AB pattern with J = 14 cps and estimated δ values of 3.50 and 3.95 (4 H, further splitting is apparent but is not well resolved, -CH_2-N) and a partially superimposed multiplet centered at approximately δ 4.0 (1 H, >CH-O).

Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.97; H, 8.92; N, 6.57. Found: C, 61.67; H, 8.97; N, 6.41.

A solution of 52.8 mg (0.192 mmole) of the betaine **14** in 5 ml of water was treated with 3 drops of 48% aqueous hydrobromic acid. The resulting solution was stirred at 25° for 4 hr and then concentrated under reduced pressure to leave 63.4 mg of the crude lactone **12**, mp 284–289° dec. Recrystallization from ethanol afforded 8.9 mg of the lactone **12**, mp 304–306°, which was identified with the subsequently described sample by comparison of infrared and nmr absorptions.

Reaction of the β-Hydroxyamine 1a with Methyl Bromoacetate.—A solution of 1.390 g (8.97 mmoles) of the β-hydroxyamine **1a** and 2.0 g (13 mmoles) of methyl bromoacetate in 15 ml of acetonitrile was stirred at 25° for 5 days during which time a precipitate separated slowly. The reaction mixture was concentrated under reduced pressure and then triturated with ether. The residual, ether-insoluble solid contained[16] the ester **6** (eluted more rapidly) and the lactone **12** (eluted less rapidly). The crude, unchanged amine **1a**, recovered from the ethereal solution, amounted to 1.285 g. Extraction of the mixture of salts **6** and **12** with chloroform left the less soluble lactone **12** which was recrystallized from ethanol to separate the pure lactone as white plates, mp 310–310.5° dec, yield 213.9 mg (8.8%). The material has infrared absorption[11,13] at 1735 cm^{-1} (δ-lactone C=O) with no absorption in the 3-μ region attributable to a hydroxyl function. The nmr spectrum[12] of the sample has peaks at δ 4.76 (2 H, center of partially resolved multiplet, N-CH_2-CO-), 4.61 (1 H, triplet with J = 3.5 cps, >CH-O), 3.37 (3 H, singlet, N-CH_3), and 1.73 (6 H, center of broad peak, aliphatic C-H) with complex patterns in the regions δ 3.4–4.5 (4 H, CH_2-N) and 2.9–3.4 (2 H, bridgehead C-H).

Anal. Calcd for $C_{11}H_{18}BrNO_2$: C, 47.83; H, 6.52; Br, 28.99; N, 5.07. Found: C, 47.71; H, 6.60; Br, 28.90; N, 5.00.

The aforementioned chloroform extract (containing **6**) was diluted with ether to precipitate the hydroxy ester. After repeated recrystallizations from ether and chloroform and then from ethanol, the pure[16] hydroxy ester **6** was obtained as white prisms, mp 180–181.5° dec, yield 56 mg (2.0%). An additional recrystallization from an ethanol–ether mixture containing 1 drop of 48% aqueous hydrobromic acid raised the decomposition point to 182–183°. The material has infrared absorption[11,13] at 3275 (broad, associated O-H) and 1755 cm^{-1} (ester C=O) with nmr absorption[12] at δ 4.49 (2 H, center of partially resolved multiplet, N-CH_2-CO-), 3.85 (3 H, singlet, O-CH_3), 3.70 (3 H, singlet, N-CH_3), 2.48 (2 H, center of broad absorption, bridgehead C-H), and 1.67 (6 H, center of broad absorption, aliphatic C-H). In addition, there is complex absorption in the region δ 3.2–4.7 (5 H, >CH-O and CH_2-N).

Anal. Calcd for $C_{12}H_{22}BrNO_3$: C, 46.75; H, 7.14; Br, 25.97; N, 4.55. Found: C, 46.96; H, 6.90; Br, 25.85; N, 4.58.

Because the N-alkylation of the amine **1a** proceeded very slowly at room temperature in acetonitrile or acetone solution, in subsequent experiments the amino alcohol **1a** was mixed with excess methyl bromoacetate and either allowed to stand at room temperature or heated to 70°. The ether-insoluble product recovered after diluting these reaction mixtures with ether contained[16] the hydroxy ester **6**, the lactone **12**, and an additional product believed to be the hydrobromide salt of the starting amine **1a** (eluted more rapidly than the lactone **12** but less rapidly than the ester **6**). The amount of this by-product, which corresponds in R_f value[16] and in position of its N-methyl nmr signal (at δ 2.88)[12] to hydrogen halide salts of **1a**, was greater in reaction mixtures which had been heated. However, the ratio of the lactone **12** to the ester **6** (as estimated from the N-methyl peak heights at δ 3.37 and 3.70) was approximately 3:1 from both reactions.

In a preparative run, a solution of 302 mg (1.95 mmoles) of the hydroxy amine **1a** in 400 mg (2.62 mmoles) of methyl bromoacetate was heated to 70° for 4 hr. After the resulting mixture had been triturated with ether, the ether-insoluble residue (405 mg of a mixture[16] of the hydroxy ester **6**, the lactone **12**, and a component believed to be the hydrobromide salt of **1a**) was chromatographed on silicic acid. The hydroxy ester **6**, eluted with chloroform and 2% methanol in chloroform, was taken up in chloroform and stirred with solid sodium carbonate to remove some hydrobromide which was present. Dilution of the chloroform with ether precipitated the ester, which was collected and recrystallized from an ethanol–ether mixture to separate 60 mg (13%) of the hydroxy ester **6**, mp 182–183° dec. A solution of 5 mg of the ester **6** in 5 ml of acetone was refluxed overnight and then concentrated and mixed with ether. The recovered ether-insoluble material contained[16] the hydroxy ester **6**, but none of the lactone **12** was detected, indicating that rapid interconversion of the ester **6** and its isomer **7** (the precursor of lactone **12**) does not occur at the temperatures used in the alkylation experiments.

Oxidation of the Hydroxy Ester 6.—A cold (0–5°) solution of 38 mg (0.123 mmole) of the hydroxy ester **6** in 20 ml of water was

(11) Determined as a suspension in a potassium bromide pellet.
(12) Determined as a solution in deuterium oxide.
(13) Determined as a Nujol mull.
(14) Determined as a solution in chloroform.
(15) Determined as a solution in deuteriochloroform.

(16) This analysis was obtained on a thin layer chromatographic plate coated with silicic acid and eluted with a mixture of methanol–chloroform–concentrated hydrochloric acid (6:6:0.5 v/v).

shaken vigorously for *ca.* 2 min with 20 ml of a solution of ruthenium tetroxide (from 27 mg or 0.13 mmole of ruthenium trichloride) in carbon tetrachloride. The aqueous phase was separated, washed with carbon tetrachloride, filtered to remove the precipitated ruthenium dioxide, and then concentrated under reduced pressure. Recrystallization from ethanol afforded 24 mg (63%) of the **keto ester 8** as white plates, mp 189–191°, identified with the subsequently described sample by a mixture melting point determination and comparison of infrared and nmr spectra.

Reactions of the α-Hydroxyamine 3a with Methyl Bromoacetate.—A solution of 1.3441 g (8.69 mmoles) of the amine **3a** in 1.5 g (9.7 mmoles) of methyl bromoacetate was heated to 70° for 4 hr. The reaction mixture, which partially solidified after 1 hr of heating, was triturated with ether, and the ether-insoluble residue was recrystallized from ethanol. The hydroxy ester **10** (probably contaminated with small amounts of the stereoisomer **11**) separated as 1.2604 g (47.3%) of white plates, mp 173–179° dec. Our efforts to isolate a second pure ammonium salt from the mother liquors of the original reaction mixture were not successful; it seems probable that this crude material was a mixture of ammonium salts **10** and **11** accompanied by at least one other component. The recrystallized salt, mp 173–179° dec, has infrared absorption[11,18] at 3310 (associated OH) and 1755 cm^{-1} (ester C=O) with three nmr[12] singlets at δ 4.48 (2 H, $N-CH_2-CO-$), 3.86 (3 H, $-CO_2CH_3$), and 3.55 (3 H, $N-CH_3$) superimposed on complex absorption in the region δ 3.4–4.6 (5 H, $-CH_2-N$ and >CH–O). Additional complex absorption is present in the regions δ 2.0–2.5 (2 H, bridgehead C–H) and 1.3–2.0 (6 H, aliphatic C–H).

Anal. Calcd for $C_{12}H_{22}BrNO_3$: C, 46.75; H, 7.14; N, 4.55. Found: C, 46.85; H, 7.27; N, 4.31.

From reactions of the amino alcohol **3a** with methyl bromoacetate in acetone solution (either at reflux or at room temperature) the products isolated were the crude salt **10**, mp 160–175°, and a component which separated from an ether–ethyl acetate-methanol mixture as white plates, mp 235–238° dec. This material, believed to be the hydrobromide of the starting amino alcohol **3a**, has infrared absorption[13] at 3340 cm^{-1} (broad, associated OH) but lacks absorption in the 6-μ region attributable to a carbonyl function. The material has nmr absorption corresponding to that previously reported[9b] for the hydrochloride salt of **3a**.

Oxidation of the Hydroxy Ester 10.—A cold (0–5°) solution of 93 mg (0.302 mmole) of the hydroxy ester **10** in 20 ml of water was shaken for 1 min with 20 ml of a solution of ruthenium tetroxide (from 63 mg or 0.302 mmole of ruthenium trichloride) in carbon tetrachloride. The aqueous layer was washed with carbon tetrachloride, filtered, and concentrated under reduced pressure to leave the crude, solid keto ester **9**. Recrystallization from ethanol containing several drops of 48% aqueous hydrobromic acid[17] afforded 59 mg (63%) of the **keto ester 9** as white plates, mp 215–218° dec. The material has infrared absorption[13,18] at 1760 (ester C=O), 1710, and 1725 cm^{-1} (C=O, doublet presumably caused by Fermi resonance[19]) but no absorption in the 3-μ region attributable to a hydroxyl function. The nmr spectrum[12] has singlets at δ 4.13 (2 H, $N-CH_2-CO-$), 3.82 (3 H, $-CO_2CH_3$), and 3.51 (3 H, $N-CH_3$) superimposed on broad absorption in the region δ 3.8–4.5 (4 H, CH_2-N) with additional broad absorption in the regions δ 2.7–3.3 (2 H, bridgehead C–H) and 1.6–2.5 (6 H, aliphatic C–H).

Anal. Calcd for $C_{12}H_{20}BrNO_3$: C, 47.06; H, 6.54; Br, 26.14; N, 4.58. Found: C, 47.03; H, 6.64; Br, 25.80; N, 4.59.

When the above oxidation was run with a reaction time of 10 min rather than 1 min, the product isolated after recrystallization from ethanol was the crude aldol product **15**, mp 205–215°, yield 60%, identified with the subsequently described sample by comparison of infrared spectra. A solution of 35 mg (0.011 mmole) of the keto ester **9** in 5 ml of methanol containing several milligrams of sodium methoxide was stirred for 1 hr at 25° and then acidified by passing hydrogen bromide gas into the solution. The resulting mixture was concentrated under reduced pressure, and the residual solid was recrystallized from ethanol to separate 31 mg (88%) of the **aldol product 15** as white plates, mp 212–217° dec. An additional recrystallization sharpened the decomposition point to 215–217°. The product has infrared absorption[11,18] at 3175 (broad, associated O–H) and 1740 cm^{-1} (ester C=O) with nmr[12] singlets at δ 3.87 (3 H, $-CO_2CH_3$) and 3.22 (3 H, $N-CH_3$) superimposed on complex absorption in the region δ 3.2–4.4 (5 H, CH_2-N and $N-CH-CO-$); additional broad absorption is present in the regions δ 2.1–2.7 (2 H, bridgehead C–H) and 1.3–2.0 (6 H, aliphatic C–H). The nmr spectrum of a solution of this product **15** in dimethyl sulfoxide[20] exhibited a peak at δ 6.46 (1 H, O–H) which disappeared when deuterium oxide was added to the solution.

Anal. Calcd for $C_{12}H_{20}BrNO_3$: C, 47.06; H, 6.54; Br, 26.14; N, 4.58. Found: C, 47.30; H, 6.64; Br, 25.98; N, 4.45.

Reaction of the Amino Ketone 2a with Methyl Bromoacetate.—A solution of 2.737 g (17.8 mmoles) of the amino ketone **2a** and 3.0 g (19.6 mmoles) of methyl bromoacetate in 30 ml of acetone was stirred for 4 days at 25° and then diluted with ether. The crude salt, collected on a filter and washed with ether, amounted to 2.5 g. From the relative heights of the nmr O-methyl peaks (δ 3.82 for **9**, δ 3.85 for **8**, and δ 3.87 for **15**) and N-methyl peaks (δ *ca.* 3.24 for **8** and **15** and δ 3.51 for **9**), the composition of the product was estimated to be 20% of **9**, 30% of **15**, and 50% of **8**. The same composition was estimated for the crude mixture of salts obtained from reaction of the amino ketone **2a** with methyl bromoacetate in refluxing acetone. The product mixture from reaction at 25° was recrystallized from ethanol to separate 1.0074 g (19%) of the pure **keto ester 8** as white plates, mp 191–192° dec. This material has infrared absorption[11,18] at 1745 and 1725 (sh) cm^{-1} (C=O of ester and ketone) but lacks absorption in the 3-μ region attributable to a hydroxyl function. The sample has nmr[12] singlets at δ 4.63 (2 H, $N-CH_2-CO-$), 3.85 (3 H, $O-CH_3$), and 3.25 (3 H, $N-CH_3$) as well as complex absorption in the regions δ 4.1–4.4 (4 H, CH_2-N), 2.8–3.3 (2 H, bridgehead C–H), and 1.6–2.3 (6 H, aliphatic C–H).

Anal. Calcd for $C_{12}H_{20}BrNO_3$: C, 47.06; H, 6.54; Br, 26.14; N, 4.58. Found: C, 46.98; H, 6.53; Br, 25.96; N, 4.44.

The mother liquors from the crystallization of the keto ester **8** were concentrated to leave a crystalline solid, mp 170–185° dec. In order to simplify isolation of products from this mixture (**8**, **9**, and **15**), the ketone **9** was isomerized to the aldol product **15**. A solution of 0.7216 g of this solid in 50 ml of methanol containing several milligrams of sodium methoxide was allowed to stand at 25° for 2 hr, and 2 drops of 48% aqueous hydrobromic acid was added. The resulting solution was concentrated and diluted with ether. The precipitate which separated was collected and fractionally recrystallized from ethanol to separate 406.4 mg of a fraction, mp 185–191° dec, and 213.5 mg (4% yield based on the starting ketone **2a**) of the crude aldol product **15**, mp 208–213° dec. An additional recrystallization of this latter fraction afforded 196.4 mg (3.6%) of the **aldol product 15**, mp 213–217° dec, which was identified with the previously described sample by comparison of nmr and infrared spectra.

(17) When the precaution of keeping the recrystallizing solvent slightly acidic was not taken, repeated recrystallization of the keto ester **9** slowly converted it to the aldol condensation product **15**.

(18) Determined as a mull in perfluorokerosene.

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(20) (a) O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964); (b) see also J. M. Bruce and P. Knowles, *J. Chem. Soc.*, 5900 (1964).