A Note on the Stereospecific Formation of α-Aminoalcohols*

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In previous papers[1a] the present authors have reported on the synthesis of *dl*-muscarine and its stereoisomers. In connection with synthetic studies in this field,[1b] the synthesis of a compound described as Ia, which probably possesses an erythro configuration, was performed. The structure Ib was erroneously proposed for muscarine by Kögl[2] in 1931.

First, attempts were made to prepare bromoacetal (III) through bromoaldehyde (II), which was obtained by the bromination of the sodium salt of acetoacetaldehyde.[3] The latter salt was conveniently prepared by the alkaline hydrolysis of commercially-available 1, 1-dimethoxybutanone-3.[4] However, since the overall yield of the sequence of reactions was quite poor, another method for obtaining bromoacetal (III) from butanonal acetal directly by means of a suitable brominating agent was next attempted. For this purpose we examined pyridine perbromide, which is expected to keep the reaction medium nearly neutral, thus minimizing undesirable side reactions. Although the resultant products consisted of various substances, the products were separable through fractional distillation into the desired bromoacetal (16%), methylmethoxybromovinyl ketone ($\lambda_{max}^{EtOH}=237$) and bromoaldehyde (II). The formation of these products indicates that the reaction was accompanied by elimination and hydrolysis reactions, and suggested that the addition of methanol to the reaction system would be favorable for the formation of the desired product. In fact, by the addition of methanol, the yield was raised to 37%.

Dimethylaminoketoacetal (IV) was readily

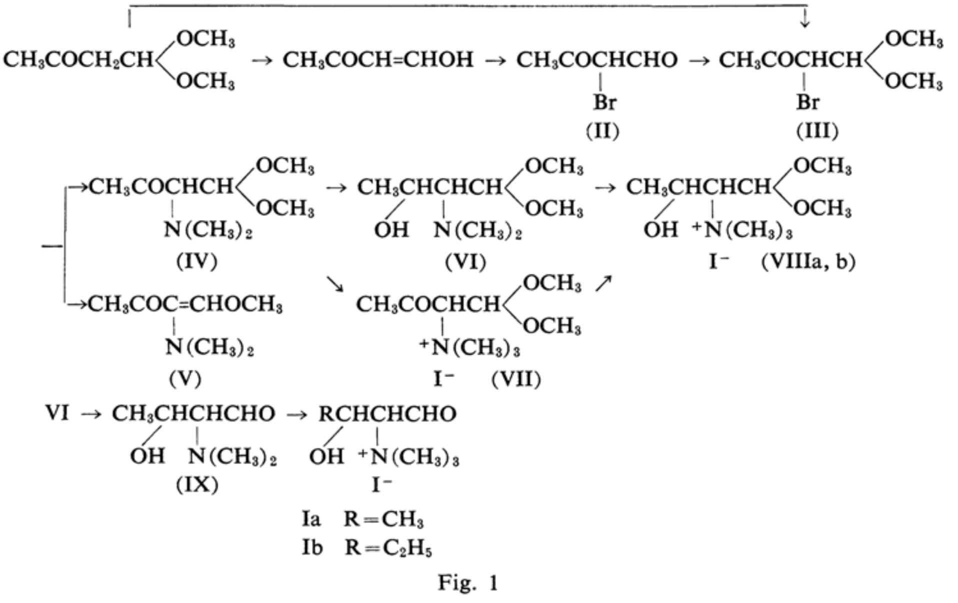

Fig. 1

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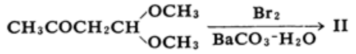
1) a) T. Matsumoto and H. Maekawa, *Angew. Chem.*, **70**, 507 (1958); T. Matsumoto and A. Ichihara, *Biochem. Z.*, **331**, 580 (1959); H. Maekawa, A. Ichihara and T. Matsumoto, This Bulletin, **38**, 1161 (1965). b) T. Matsumoto and A. Ichihara, This Bulletin, **33**, 1015 (1960); A. Ichihara, T. Yamanaka and T. Matsumoto, ibid., **38**, 1165 (1965).

2) F. Kögl, H. Duisberg and H. Erxleben, *Ann.*, **489**, 156 (1931).

3) The compound has been obtained by N. K. Kochetkov and E. E. Nifant'ev through the following sequence. *Doklady Akad. Nauk U. S. S. R.*, **121**, 462 (1958):



$$CH_3COCH_2CH(OCH_3)_2 \xrightarrow[BaCO_3\text{-}H_2O]{Br_2} II$$

4) In general, β-ketoaldehyde dimethylacetal affords β-hydroxyvinyl ketone by alkaline hydrolysis (H. Shirahama and T. Matsumoto, in preparation).

obtained by the treatment of bromoacetal (III) with dimethylamine in benzene. Besides the expected product (IV) (b. p. 34—36°C/0.2 mmHg), a small amount of a fraction (b. p. 67—72°C/4 mmHg) was obtained through distillation. Since the latter compound showed in the infrared spectrum strong bands at 1640, 1605 (α, β-unsaturated carbonyl system), 1050 cm^{-1} (ether), and a positive test to sodium tetraphenylboronate, indicating the presence of the dimethylamino group, the structure V was tentatively assigned. The structure of this compound will be studied in the near future.

The dimethylaminoketone (IV) was next converted to a dimethylaminoalcohol (VI) by means of sodium borohydride in methanol. In this reaction, the formation of a mixture of two diastereoisomers is to be expected. However, gas chromatography of the product indicated only one peak. Moreover, the methiodide (VIIIa) derived from VI showed a melting point of 123.5—125°C, which did not change after repeated recrystallizations.

Therefore, the reduction proceeded in a stereospecific manner, producing only one stereoisomer. A similar stereoselective reduction of aminoketone hydrochloride to erythro-aminoalcohol by sodium borohydride has been observed and explained as the attack on the least-hindered site with the participation of a lone pair of nitrogen atom, as is expressed by the following formula[5] (Fig. 2):

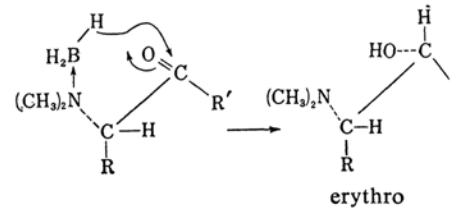
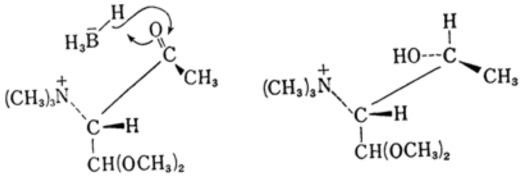


Fig. 2

Since a similar steric course can be assumed for the case of dimethylaminoketone (IV), the product VI most probably possesses the erythro configuration.

On the other hand, the reduction of trimethylammonium ketone (VII), derived from IV by means of methyl iodide under the same conditions gave a hydroxy compound (VIIIb), whose infrared spectra in the solid state and in solution and whose melting point (122—124°) were identical with those of trimethylammonium iodide (VIIIa) derived from the dimethylaminoalcohol (VI) obtained above. These results suggest that the product from VII is also an erythro isomer. The preferential formation of the erythro isomer may be accounted for by the mechanism involving an ion pair (Fig. 3):



(VIIIb)

Fig. 3

All attempts to hydrolyze the methiodide (VIIIa, b) of dimethyl aminoalcohol (VI) to the desired aldehyde (Ia) were unsuccessful. Even when it was refluxed for several hours, the formation of the aldehyde group could not be detected with tetrazolium chloride. This may be explained in terms of the presence of a charged quarternary nitrogen atom.[6] On the other hand, tertiary aminoalcohol (VI) was slowly but gradually hydrolyzed with 6 N hydrochloric acid to the aldehyde (IX).

Finally, the desired Ia was obtained by the treatment of IX with methyl iodide.

Although the methiodide Ia of 2-dimethylamino-3-hydroxybutanal was not obtained in a crystalline state, reineckate was crystallized and gave the correct analytical values.

Experimental

2-Bromo-3-keto-*n*-butyraldehyde (II).—*By Claisen Condensation.*—The sodium salt of 3-keto-*n*-butyraldehyde was prepared in the usual manner from 27 g. of sodium methoxide, 29 g. of acetone and 38 g. of ethyl formate in 300 ml. of absolute ether. After the completion of the reaction, the ether was removed and the residue was dried in a vacuum desiccator. To a suspended solution of 20 g. of the sodium salt in 150 ml. of carbon tetrachloride, 29.6 g. of bromine in 50 ml. of carbon tetrachloride was added slowly under ice cooling. The precipitate was then filtered off, and the filtrate was poured into an equal volume of petroleum ether. After the precipitate had been removed, the filtrate was concentrated in vacuo. The solidified residue was crystallized from carbon tetrachloride to afford 1.2 g. of II; m. p. 108—109°C (decomp.), λ_{max}^{EtOH} 228 mμ (ε 9570), (lit.[8] m. p. 109—110°C (decomp.)).

Found: C, 29.40; H, 3.15, mol. wt. (Rast) 161. Calcd. for $C_4H_5O_2Br$: C, 29.12; H, 3.05%, mol. wt. 164.

From 3-Keto-n-butyraldehyde Dimethylacetal. — A mixture of 1.6 g. of acetal, 0.48 g. of sodium hydroxide and 4 ml. of water was shaken for 10 hr. at room temperature. The solution was then evaporated

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[5] D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959); T. Matsumoto, T. Nishida and H. Shirahama, *J. Org. Chem.*, **27**, 79 (1962).

[6] R. B. Woodward, *Angew. Chem.*, **69**, 50 (1957).

in vacuo and dried in a vacuum desiccator. The sodium salt thus obtained (1.1 g.) was treated in the manner described above to give 0.2 g. of a crystalline bromide, m. p. 108—109°C (decomp.), which was identical with the II prepared by the Claisen condensation.

2-Bromo-3-keto-*n*-butyraldehyde Dimethylacetal (III).—*From 2-Bromo-3-keto-n-butyraldehyde (II).*—A mixture of 2.1 g. of bromoaldehyde (II) and 24 ml. of 6.6% methanolic hydrogen bromide was gently refluxed for 8 hr. on a water bath. The reaction mixture was then concentrated in vacuo and the residue extracted several times with petroleum ether. The combined petroleum solution was dried over magnesium sulfate and distilled to give 0.7 g. of III, b. p. 73—75°C (6 mmHg).

From 1,1-Dimethoxybutanone-3.—Pyridine perbromide was prepared by the procedure of McElvain and Morris.[7] A mixture of 21 g. of powdered dry pyridine perbromide, 10 g. of 1,1-dimethoxybutanone-3 and 1 ml. of absolute methanol was shaken for 10 min., and the orange-colored solution was allowed to stand for 2 hr. under ice-cooling. The reaction mixture was extracted with several portions of warm petroleum ether. The turbid petroleum solution was clarified with celite. After the solvent had been removed, the residue was distilled under reduced pressure to give 5.9 g. (yield 37%) of bromoacetal, b. p. 70—74°C (7 mmHg).

Found: C, 33.67; H, 5.22. Calcd. for $C_6H_{11}O_3Br$: C, 34.14; H, 5.25%.

2-Dimethylamino-3-keto-*n*-butyraldehyde Dimethylacetal (IV).—To a solution of dimethylamine (ca. 30%, 50 ml.) in benzene was added, drop by drop, 2 g. of bromoacetal (III) in 5 ml. of benzene; the mixture was then allowed to stand for 24 hr. at room temperature. The resulting precipitates of dimethylamine hydrobromide were filtered off, and the filtrate was concentrated in vacuo. The residue was extracted with several portions of benzene, and the combined extracts were dried over anhydrous potassium carbonate. After the solvent had been removed, the crude product was distilled, yielding 1.1 g. of the desired aminoketone, b. p. 34—36°C (0.2 mmHg) and a small amount of a fraction with a b. p. of 67—72°C (0.4 mmHg). The infrared spectrum of the former compound exhibited absorption bands at 2820, 2660, 1704, and 1073 cm^{-1}, while the latter compound did at 1640, 1605, and 1060 cm^{-1}, suggesting the presence of a COC=C system.

Tetraphenylboronate of IV.—A small amount of IV was dissolved in 1 ml. of water and slightly acidified with acetic acid. To this solution a 50% aqueous solution of sodium tetraphenylboronate was added to give white precipitate which, on being recrystallized from water-ethanol, gave pure tetraphenylboronate of IV, m. p. 123—124°C (decomp.).

Found: N, 2.83. Calcd. for $C_{32}H_{38}O_3NB$: N, 3.03%.

The Reduction of Dimethylaminoketone (IV).—A mixture of 0.6 g. of dimethylaminoketone in 4 ml. of methanol and a few drops of a 10% aqueous solution of sodium hydroxide was added to a solution of 0.6 g. of sodium borohydride in 6 ml. of methanol. The solution was then allowed to stand overnight at room temperature. After the solvent had been removed, the residue was repeatedly extracted with ethyl acetate, and the combined solutions were dried over anhydrous sodium carbonate and distilled to give 0.48 g. of hydroxyaminoacetal (VI), b. p. 68—71°C (4 mmHg). Vapor phase chromatography showed only one peak with the retention time of 15 min. on a PEG 1000 column at 152°C (carrier gas, H_2). The Reinecke salt of VI was recrystallized from ethanol; m. p. 135—136°C (decomp.).

Found: C, 28.99; H, 4.92; N, 19.56. Calcd. for $C_{12}H_{26}O_3N_7S_4Cr$: C, 29.02; H, 4.87; N, 19.74%.

The Methiodide (VII) of Dimethylaminoketone.—An excess of methyl iodide was added to a solution of 1 g. of dimethylaminoketone (IV) in 3 ml. of absolute methanol. The resulting mixture was then allowed to stand for 3 hr. at room temperature. After the solvent had been evaporated to dryness, the red-colored residue was solidified by rubbing it with a glass rod. The recrystallization of the crude product from absolute ethanol yielded 1.5 g. of plates, m. p. 152—153°C (decomp.).

Found: C, 34.30; H, 6.48; N, 4.09. Calcd. for $C_9H_{20}O_3NI$: C, 34.08; H, 6.36; N, 4.42%.

The Methiodide (VIIIa) of VI.—A small amount of hydroxydimethylaminoacetal (VI) was dissolved in methanol, and to this solution an excess of methyl iodide was added. The reaction mixture was then allowed to stand at room temperature for 3 hr. After the solvent had been removed, the residue was dried in a vacuum desiccator for several hours to give an amorphous solid, which, on being recrystallized from ethanol, afforded white crystals, m. p. 120—124°C. Further purification of this compound with chloroform - ethylacetate raised the m. p. to 123.5—125°C (decomp.).

Found: C, 33.70; H, 6.68; N, 4.65. Calcd. for $C_9H_{22}O_3NI$: C, 33.86; H, 6.95; N, 4.45%.

The Reduction of VII to VIIIb.—The compound VII (0.6 g.) in 6 ml. of methanol was added, drop by drop, to 9 ml. of methanol containing 500 mg. of sodium borohydride. The reaction mixture was then allowed to stand overnight at room temperature. After the solvent had been removed, the reduction product was extracted with several portions of warm chloroform. The recrystallization of the crude product with absolute ethanol gave hydroxytrimethylammonium iodide, m. p. 122—124°C, undepressed upon the admixture of VIIIa.

Found: C, 34.34; H, 7.40; N, 4.51. Calcd. for $C_9H_{22}O_3NI$: C, 33.86; H, 6.95; N, 4.45%.

The Hydrolysis of Hydroxydimethylaminoacetal (VI).—Hydroxydimethylaminoacetal (0.26 g.) was dissolved in 2 ml. of 6 N hydrochloric acid and allowed to hydrolyze at room temperature for 5 hr. After the reaction mixture had then been concentrated in a vacuum desiccator, the residue was dissolved in 1 ml. of methanol, and to this solution 31 mg. of sodium in 1 ml. of methanol was added. The separated layer was extracted with several portion of chloroform. The combined chloroform solutions were dried over anhydrous potassium carbonate and concentrated under reduced pressure

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[7] S. M. McElvain and Leo R. Morris, *J. Am. Chem. Soc.*, **73**, 206 (1951).

to leave IX as an oil. The reineckate of IX was purified by recrystallization from water-ethanol; m. p. 232—233°C (decomp.).

Found: C, 26.54; H, 4.57; N, 21.23. Calcd. for $C_{10}H_{20}O_2N_7S_4Cr$: C, 26.64; H, 4.43; N, 21.35%.

The Methiodide of IX.—To an ethanolic solution of the aldehyde (IX), excess methyl iodide was added and the mixture was allowed to stand overnight. The removal of the solvent left a red-colored residue which exhibited, in the infrared spectrum, bands for aldehyde at 2740 and 1717 cm^{-1}. The reineckate of Ia was obtained in a crystalline state and showed a m. p. of 221—222°C after recrystallization from water-ethanol.

Found: C, 28.04; H, 5.11. Calcd. for $C_{11}H_{22}O_2N_7S_4Cr$: C, 28.43; H, 4.77%.

Summary

The synthesis of the compound which was erroneously proposed for muscarin by Kögl in 1931 has been described.

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