The 1-Azoniabicyclo[3.1.0]hexane System in a β-Benzomorphan Synthesis*

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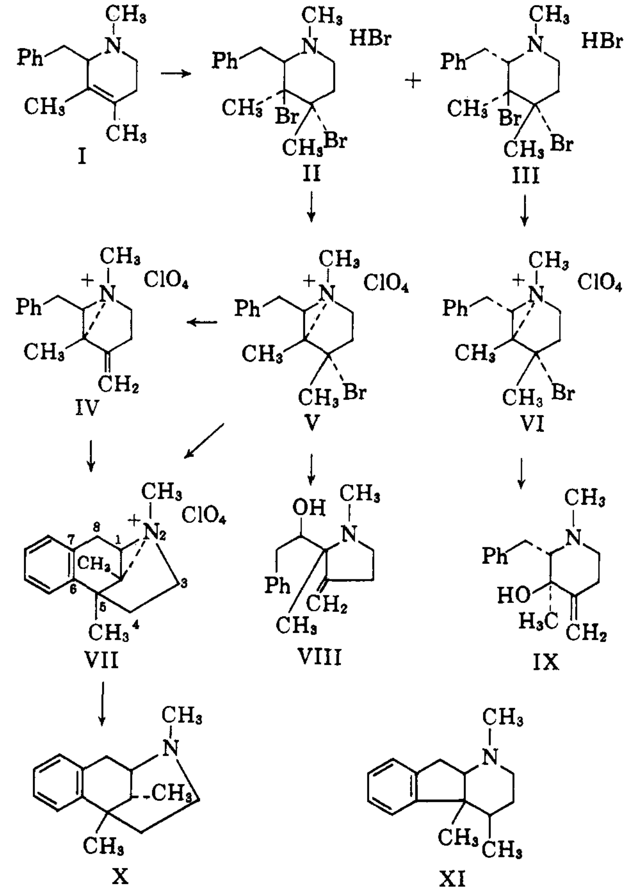
Until recently[1] the 1-azabicyclo[3.1.0]hexane ring system has not appeared in the literature as a discrete structure, but rather has been invoked as an intermediate in the transition between the pyrrolidine and piperidine ring systems.[2]

This note is concerned with the synthesis of the two isomers of 6-benzyl-4-bromo-1,4,5-trimethyl-1-azoniabicyclo[3.1.0]hexane perchlorate, V and VI, with the use of one of these salts in the synthesis of a β-benzomorphan, and with other pertinent reactions.

The dibromo derivative of 2-benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine was obtained as a crystalline mixture of two hydrobromide salts, II and III, which on decomposition with sodium bicarbonate solution and extraction into ether gave only one of the isomeric bases. The other was transformed during this process into a quaternary salt which was recovered from the aqueous alkaline solution as the crystalline perchlorate in 14% yield and is designated the α-perchlorate. A similar transformation of the major basic constituent took place in acetone solution with sodium perchlorate[3] to give the β-perchlorate in 49% yield. These perchlorates could be formulated as isomeric azabicyclo salts VI and V, respectively, epimeric at the benzyl substituent. Both structures are based on the assumption of a *trans* addition of bromine to the double bond with subsequent backside displacement of the bromine on position 3 by nitrogen. A model shows that in only one of these (V) is the benzene ring in position to bond with the 4-position of the piperidine ring to give a cyclobenzomorphan VII. This fused ring system can exist in only one configuration and could be expected to yield the β-benzomorphan X if hydrogenolysis with inversion could be effected at the 9-position. Experimentally this route was realized for the β-perchlorate, henceforth V, and subsequent opening of the aziridinium ring with lithium aluminum hydride gave the known β-benzomorphan.[4] By the action of silver perchlorate on V, the elements of hydrogen bromide were removed to give the methylene derivative IV which likewise was converted to the cyclobenzomorphan VII.

The α-perchlorate VI proved to be relatively stable under the aluminum chloride cyclization conditions and the major portion was recovered. A cyclization route to XI is a tempting speculation, but this product was not found, and indeed no example of a Friedel–Crafts alkylation utilizing a quaternary ammonium salt appears in books on this subject.[5]

SCHEME I



The inference that VI is epimeric with V at the benzyl position was confirmed as a result of attempted hydrogenolysis of the aziridinium rings. In effect, bromine was removed from both V and VI and the ring opened with reconstitution of the starting material I. Catalytic reduction of IV likewise regenerated I as did the action of the benzyl Grignard reagent on V. However, the reaction of lithium aluminum hydride with V took another, as yet unidentified, course.

Potassium acetate in acetone converted both V and VI into acetoxy bases, which, after conversion to alcohols and characterization by the elegant method of Chapman and King[6] were assigned structures VIII and IX. Attempts to cyclize IX to a benzomorphan were without success.

If the assumption of SN2 transition states for II and III is correct, the only difference between the two lies in the configuration of the benzyl substituent, and a model suggests that only in the case of the more easily formed isomer VI is there even a possibility of bulk interference. It can only be observed that if the methyl group on the incipient quaternary nitrogen and the benzyl group are *trans*, the necessary condition for ring closure of the more easily cyclized isomer III is met; the other isomer has a *cis* requirement. It is perhaps no more than fortuitous that the same consideration

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* To Professor Louis F. Fieser.

[1] A. L. Logothetis, Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964; C. Schöpf, German Patent 1,054,088 (1959); *Chem. Abstr.*, **55**, 8439*g* (1961).

[2] R. C. Fuson and C. L. Zirkle, *J. Am. Chem. Soc.*, **70**, 2760 (1948). For leading references to other work in this field see A. Ebnöther and E. Jucker, *Helv. Chim. Acta*, **47**, 745 (1964).

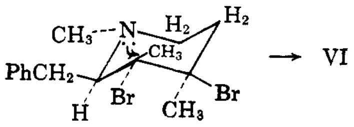
[3] S. Winstein, S. Smith, and D. Darwish, *J. Am. Chem. Soc.*, **81**, 5511 (1959).

[4] E. M. Fry, *J. Org. Chem.*, **28**, 1869 (1963); **29**, 1647 (1964).

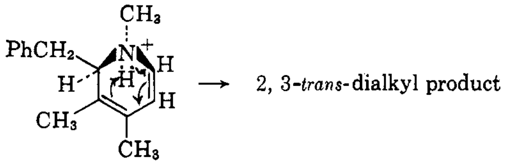
[5] C. A. Thomas, "Anhydrous Chloride in Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1941; G. A. Olah, "Friedel–Crafts and Related Reactions," Interscience Publishers, Inc., New York, N. Y., 1963, 1964.

[6] O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964).

can be applied to the results of the rearrangements of the presumed ammonium salts in the dihydro series.[4] The similarities are shown in the following diagram (see also Scheme I).



III



Experimental

Microanalyses are by the Analytical Services Unit of this laboratory, Dr. W. C. Alford, director. N.m.r. spectra, 60 Mc., are with tetramethylsilane as internal reference standard. Integrated benzene areas were used as standards and τ values are reported on center for all bands including fused multiplets. Melting points are uncorrected.

2-Benzyl-3,4-dibromo-1,3,4-trimethylpiperidine Hydrobromide (II and III Mixture).—To 2-benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine,[4] 9.9 g., first dissolved in 10 ml. of acetic acid and then converted to the hydrobromide with 9.6 ml. (1 equiv.) of 4.8 *N* hydrogen bromide in acetic acid, was added 7.4 g. (2 equiv.) of bromine in 10 ml. of acetic acid portionwise and with intermittent cooling. The product began to crystallize within a few minutes, and after it stood overnight the mixture was filtered and the salt was washed with acetic acid. It weighed 17.6 g., m.p. 143–145° (gas). After the solvent was removed under reduced pressure, more product was obtained for a total of 19.5 g. (93%).

Anal. Calcd. for $C_{15}H_{22}Br_3N$: C, 39.50; H, 4.86. Found: C, 39.57; H, 4.75.

The salt (47 g.) was decomposed in an aqueous solution of a small excess of sodium bicarbonate to give an oil which crystallized. After 2 hr. the crystals were shaken into and recovered from ether under reduced pressure, yielding 28 g. (72%), m.p. 54–61°. The base, **2-benzyl-3,4-dibromo-1,3,4-trimethylpiperidine**, was purified by washing with cold methanol, m.p. 60–63°.

Anal. Calcd. for $C_{15}H_{21}Br_2N$: C, 48.02; H, 5.64; Br, 42.6. Found: C, 48.08; H, 5.50; Br, 42.7.

6-Benzyl-4-bromo-1,4,5-trimethyl-1-azoniabicyclo[3.1.0]hexane Perchlorates (V and VI).—The α-isomer VI was precipitated from the above aqueous solution by means of perchloric acid, yielding 5.8 g. (14% over-all). Recrystallized from alcohol it melted at 176–179°.

Anal. Calcd. for $C_{15}H_{21}BrClNO_4$: C, 45.64; H, 5.36; N, 3.55. Found: C, 45.81; H, 5.47; N, 3.52.

The β-isomer V formed in a solution of 28 g. of the crystalline dibromo base and 14 g. of sodium perchlorate in 280 ml. of acetone at room temperature with the precipitation of sodium bromide. After 24 hr. all solvent was removed under reduced pressure, the solid mixture was washed with water to remove the inorganic salt, then with alcohol, and finally with ether, yielding 20.0 g. (49% over-all), m.p. 165–169°. Recrystallized from alcohol it melted at 169–173°.

Anal. Calcd. for $C_{15}H_{21}BrClNO_4$: C, 45.64; H, 5.36. Found: C, 45.46; H, 5.50.

The α- and β-perchlorates were readily distinguishable by means of infrared spectra run on Nujol mulls.

6-Benzyl-1,5-dimethyl-4-methylene-1-azoniabicyclo[3.1.0]hexane Perchlorate (IV).—A solution of silver perchlorate was made by dissolving 10 g. of silver carbonate in 10 ml. of 9.0 *N* perchloric acid. Nine-tenths of a milliliter of this solution with 2.0 g. of V dissolved in 20 ml. of acetone deposited silver bromide which was filtered after 70 min. The acetone was removed under reduced pressure and the crystalline residue was purified by dissolving in acetone, filtering through Celite, then adding ethyl acetate to the concentrated solution, yielding 0.75 g. (47%), m.p. 108–110°. Purified further it melted at 113–114°. This salt was not decomposed by a sodium bicarbonate solution; n.m.r. showed ($CDCl_3$ solvent) τ 8.23 singlet (*t*-CH_3) 3H, 4.5 broad (=CH_2) 2H.

Anal. Calcd. for $C_{15}H_{20}ClNO_4$: C, 57.41; H, 6.42. Found: C, 57.56; H, 6.14.

2,5,9-Trimethyl-2,9-cyclo-6,7-benzomorphan Perchlorate (VII). **A.**—IV (0.1 g.) was added to a suspension of 0.12 g. of aluminum chloride in 1.5 ml. of carbon disulfide. A yellow oil formed on trituration and after 20 min. the mixture was chilled and decomposed with water. After acidification with perchloric acid the solid product was recovered and dissolved in acetone, inorganic material was filtered, and the solvent was removed under reduced pressure. The product was washed with alcohol, yielding 0.070 g. (70%), m.p. 158–160°. It was purified by recrystallization from hot alcohol which caused some decomposition. The analytical sample melted at 160–162°. The salt was not decomposed by dilute sodium hydroxide.

Anal. Calcd. for $C_{15}H_{20}ClNO_4$: C, 57.41; H, 6.42. Found: C, 57.71; H, 6.64.

B.—To a suspension of 1.2 g. of aluminum chloride and 12 ml. of carbon disulfide chilled in ice was added 2.5 g. of V. Trituration resulted in the formation of a yellow oil and slow evolution of hydrogen bromide. After 1 hr. the mixture was warmed to room temperature and after 20 min. was decomposed and worked up as described above. The product weighed 1.38 g. (69%), m.p. 162–165°. The melting point was not depressed on admixture with the above sample and the infrared spectra were the same.

Aluminum Chloride on VI.—To a suspension of 0.063 g. of aluminum chloride in 1 ml. of carbon disulfide was added 0.1 g. of VI. A yellow adduct formed on triturating the mixture. After 80 min. at room temperature the mixture was chilled, water was added, and the organic material was taken into and recovered from chloroform. The crystalline material was washed with alcohol to give 0.059 g. of VI, m.p. 169–172°, identified by its infrared spectrum.

β-2,5,9-Trimethyl-6,7-benzomorphan (X).—Lithium aluminum hydride was added to an ethereal suspension of 0.10 g. of VII. The solid went into solution. After decomposition of the excess hydride with ethyl acetate, water was added with stirring until all inorganic material had collected in a magma. The ether solution contained 0.66 g. of oil which yielded a methiodide, 0.050 g. (44%), m.p. 237–239°, sinter 198°. By mixture melting point and infrared spectrum this proved to be the same compound as that previously reported.[4]

1-(1,2-Dimethyl-3-methylenepyrrolidin-2-yl)-2-phenylethyl Alcohol (VIII).—A solution of 2.0 g. of V in 50 ml. of acetone with 2.0 g. of potassium acetate was refluxed for 4 hr. Potassium bromide replaced potassium acetate in suspension. The acetone solution was decanted, the salt was washed with ether, and all solvent was removed to give 1.53 g. of oily acetoxy compound which was dissolved in ether and converted to alcohol with lithium aluminum hydride. The semicrystalline product was freed of oil with alcohol for a total of 0.55 g. (47%), m.p. 79–84°. Recrystallized from alcohol it melted at 86–88°; n.m.r. showed ($CDCl_3$ solvent) τ 8.87 singlet (*t*-CH_3) 3H, 5.0 broad (=CH_2) 2H; (DMSO solvent) 5.59 doublet, $J =$ 6.5 c.p.s., disappeared with D_2O (secondary OH).

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 77.66; H, 9.26.

1-(1,2,3-Trimethyl-3-pyrrolin-2-yl)-2-phenylethyl Alcohol.—The above alcohol solution containing other products was acidified with 9 *N* hydrobromic acid and a total of 0.28 g. (17%) of salt melting at 195–218° was isolated. Purified from 50% alcohol the **hydrobromide** melted at 220–222°; n.m.r. showed (base in $CDCl_3$) τ 8.89 singlet (*t*-CH_3) 3H, 8.35 doublet (CH=C—CH_3) 3H, 4.63 broad (=CH—) 1H; (DMSO solvent) 5.71 doublet, J = 5 c.p.s., vanished with D_2O (secondary OH).

Anal. Calcd. for $C_{15}H_{22}BrNO$: C, 57.69; H, 7.10. Found: C, 57.95; H, 6.99.

The same compound was obtained in 79% yield when 0.6 g. of VIII was heated for 20 min. at 130° in solution in 3 ml. of 9 *N* hydrobromic acid.

2-Benzyl-1,3-dimethyl-3-hydroxy-4-methylenepiperidine (IX).—A solution of 2 g. of VI in 50 ml. of acetone with 2.3 g. of potassium acetate was refluxed overnight. The precipitate of potassium bromide was separated and washed with ether. The red oil recovered from the acetone–ether dissolved for the most part in petroleum ether (b.p. 30°) to give 1.45 g. of acetoxy compound which was converted to the alcohol with lithium aluminum hydride in the usual manner. A crystalline **picrate** was obtained, 1.68 g. (72%), m.p. 175–178°. Purified from alcohol it melted at 177–179°.

Anal. Calcd. for $C_{21}H_{24}N_4O_8$: C, 54.78; H, 5.25. Found: C, 54.86; H, 5.03.

The base was recovered from a cold petroleum ether solution after decomposing the picrate with lithium hydroxide solution, m.p. 76–82°; n.m.r. showed ($CDCl_3$ solvent) τ 8.9 singlet (t-CH_3) 3H, 4.87 and 5.10 singlets (=CH_2) 2H; (DMSO solvent) 5.54 singlet vanished with D_2O (t-OH).

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.87; H, 9.15. Found: C, 77.72; H, 8.90.

2-Benzyl-3-hydroxy-1,3,4-trimethyl-1,2,3,6-tetrahydropyridine Hydrobromide.—The hydrobromide of IX was made and was found to melt at 167–169°, but was not further characterized. A solution of 0.40 g. of this salt in 2 ml. of 8.8 *N* hydrobromic acid was refluxed for 20 min. The solvent was removed under reduced pressure, and the crystalline product was recovered from acetone in 76% yield. Recrystallized by adding ethyl acetate to a solution in alcohol it melted at 209–211°; n.m.r. showed (base in $CDCl_3$) τ 8.9 singlet (t-CH_3) 3H, 9.12 doublet (CH=C—CH_3) 3H, 4.33 singlet (=CH) 1H; (DMSO) 5.72 singlet disappeared with D_2O (t-OH).

Anal. Calcd. for $C_{15}H_{22}BrNO$: C, 57.69; H, 7.10. Found: C, 57.97; H, 6.90.

2-Benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine was isolated as the picrate[7] in the stated yields following catalytic (palladium–barium sulfate) reductions in alcohol solutions of the following: IV (81%), V (82%), VI (77%). By the action of 1 ml. of 1 *N* benzyl Grignard reagent on 0.3 g. of V the picrate of I was isolated in a 58% yield. All identifications were made by mixture melting points and by infrared spectra.

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[7] E. M. Fry and E. L. May, *J. Org. Chem.*, **26**, 2592 (1961).

Formation of Desoxybenzoin in the Borohydride Reduction of the Reaction Mixture of Benzoin with Thionyl Chloride and Pyridine*

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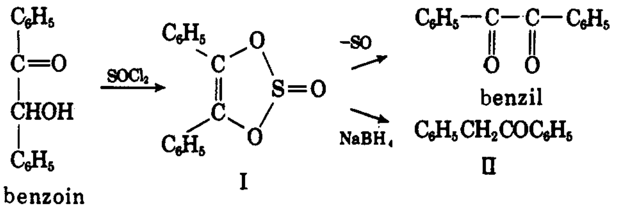
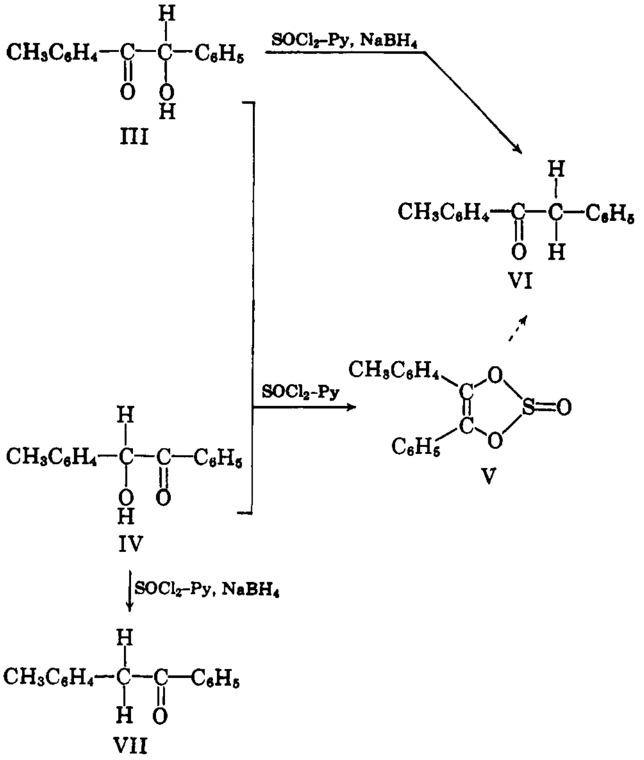
It was suggested in the previous reports[1a,b] that borohydride reduction of *cis*-stilbene-α,α'-diol sulfite (I) to desoxybenzoin (II) would account for the formation of II which had been encountered in the preparation of *trans*-stilbene[1a] and observed in the reaction of benzoin with thionyl chloride and pyridine in methylene chloride followed by treatment with sodium borohydride in 95% ethanol.[1b] This suggestion was derived only from the fact that borohydride reduction of desyl chloride gives only a mixture of 2-chloro-1,2-diphenylethanols rich in the *erythro* isomer,[1a] and thionyl chloride converts benzoin into benzil at room temperature *via* the enediol sulfite (I).[1a,b]



Borohydride reduction of I to II is understandable as an S_N1 reaction by analogy to borohydride reduction of an alkyl tosylate.[2] In the ring-substituted derivative of I derived from the asymmetric benzoin bearing an electron-releasing group in the *para* position on one phenyl ring, the electron-releasing group would facilitate the ionization of the C–O bond α to the unsubstituted phenyl ring, and, therefore, borohydride reduction would yield the 4-substituted desoxybenzoin. Thus, both 4-methylbenzoin[3] (III) and 4'-methylbenzoin[4] (IV) are postulated to yield 4-methyldesoxybenzoin[5] (VI) *via* *cis*-4-methylstilbene-α,α'-diol sulfite (V) in the reaction with thionyl chloride–pyridine followed by treatment with sodium borohydride. However, III and IV gave the corresponding desoxybenzoins, VI in 74.6% yield and 4'-methyldesoxybenzoin[5] (VII) in 71.7% yield, respectively. This fact eliminates the possibility of borohydride reduction of I to desoxybenzoin.



Although Goto and Kishi had reported debromination in borohydride reduction of α'-bromo ketones by the catalytic action of metal salts,[6] desyl chloride gave no appreciable amount of desoxybenzoin under the same conditions as in the formation of desoxybenzoin from benzoin.

There remains another possibility, the borohydride reduction of desyl chlorosulfite (VIII) to desoxybenzoin. The reaction mixture of benzoin with thionyl chloride–pyridine in methylene chloride at −20° shows two absorption bands at 1698 and 1214 cm.$^{-1}$ due to carbonyl group and S=O group, respectively. On borohydride reduction, the reaction mixture gave desoxybenzoin in 46.4% yield when the molar ratio of benzoin to thionyl chloride was 1, but the reaction mixture with the molar ratio 2 gave desoxybenzoin in 20.5% yield. When the reaction mixture in methylene chlo-

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* To Professor Louis F. Fieser.

[1] (a) L. F. Fieser and Y. Okumura, *J. Org. Chem.*, **27**, 2247 (1962); (b) Y. Okumura, *ibid.*, **28**, 1075 (1963).

[2] H. C. Brown and H. M. Bell, *ibid.*, **27**, 1928 (1962).

[3] A. Weissberger, *et al.*, *Ann.*, **478**, 112 (1930).

[4] R. T. Arnold and R. C. Fuson, *J. Am. Chem. Soc.*, **58**, 1295 (1936).

[5] M. Tiffeneau and J. Lévy, *Bull. soc. chim. France*, **49**, 1738 (1931).

[6] T. Goto and Y. Kishi, *Tetrahedron Letters*, No. **15**, 513 (1961).