A and B, which were further purified by decolorization followed by crystallization.

Sapelin A was obtained as long colorless thick needles from methanol, mp 219–220° with initial sweating. It was identical in all respects with the authentic specimen[3].

Anal.—Calc. for $C_{30}H_{50}O_4$: C, 75.9; H, 10.6; mol. wt. 474. Found: C, 75.31; H, 10.10; *m/e* 474 (M^+).

Sapelin B was obtained as tiny colorless needles from ethyl acetate–petroleum ether, mp 174–176° with initial sweating. It was identical in all respects with the authentic specimen.

Anal.—Calc. for $C_{30}H_{50}O_4$: C, 75.9; H, 10.6; mol. wt. 474. Found: C, 75.32; H, 10.13; *m/e* 474 (M^+).

REFERENCES

(1) W. R. Chan, D. R. Taylor, and T. Yee, *J. Chem. Soc. C*, **1970**, 311.

(2) R. I. Geran, N. H. Greenberg, M. N. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep.*, 3(3), 9 (1972).

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[x] To whom inquiries should be directed.

Quinuclidine Chemistry: Autocondensation Reactions of 3-Quinuclidinone

R. A. SANDMANN [x] and W. C. McHUGH, Jr.

Abstract □ During the synthesis of 3-hydroxy-3-ethinylquinuclidine (I), two additional products were isolated and identified as (*E*)-3-[2-(3-oxoquinuclidine)]quinuclidylidene (III) and (*E*)-3-[2-(3-hydroxy-3-ethinylquinuclidine)]quinuclidylidene (V). The base-catalyzed autocondensation of 3-quinuclidinone resulted in the α,β-unsaturated ketone dimer (III) as a single isomer. The geometric configuration was deduced by examination of the NMR spectra of the methyl iodide salt. Compound V was thus the result of attack on the carbonyl carbon of III by the acetylide anion. The isolation and identification of these compounds clarified the reported differences in the physical properties of I and its analogs.

Keyphrases □ Quinuclidines, substituted—synthesized, structures, stereoisomers, and physical properties identified □ Autocondensation—3-quinuclidinone, products identified

It was necessary to synthesize significant quantities of 3-hydroxy-3-ethinylquinuclidine (I) as an intermediate in preparing a series of potential antidepressant agents. However, there was a disparity in the physical properties of I prepared by two different methods (1, 2). The synthetic method employed by Ernest (2) gave a compound melting at 192°, and that of Clemo and Hoggarth (1) gave a compound melting at 159°.

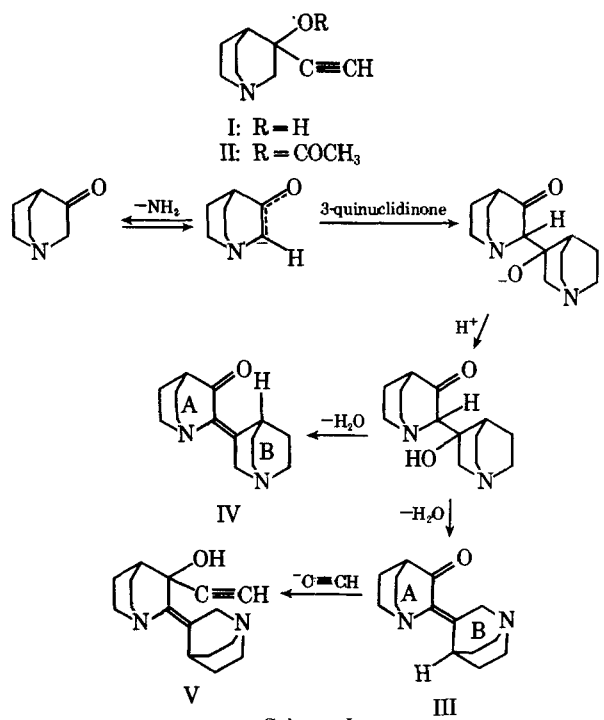
A clarification of these discrepancies by the synthesis of I and (*E*)-3-[2-(3-oxoquinuclidine)]quinuclidylidene (III) (mp 159°) is now reported.

DISCUSSION

The preparation of I involved dispersing acetylene gas through a tetrahydrofuran solution of 3-quinuclidinone and sodium amide. Three products were isolated, the major compound being I and having the same characteristics as demonstrated by Ernest (2). Mass spectra of the remaining two compounds indicated masses of 258 and 232. The difference in masses was 26, the molecular weight of acetylene. IR analysis of the 258 compound indicated a terminal acetylene (ν_{max} at 3240 and 2095 cm^{-1}). The IR spectrum for the 232 compound showed an α,β-unsaturated ketone (ν_{max} 1685 and 1615 cm^{-1}).

3-Quinuclidinone condenses with aldehydes under basic conditions (3–5); autocondensation under similar conditions and by the same aldol-type mechanism can now be demonstrated (Scheme I). A base such as sodium amide generates the enolate, which condenses by nucleophilic attack with another molecule of 3-quinuclidinone. The resultant dimer alkoxide is protonated, and dehydration of the ketol should result in a mixture of α,β-unsaturated ketone isomers, III and IV, its (*Z*)-isomer.

Conventional synthesis of III employed the use of potassium *tert*-butoxide in *tert*-butyl alcohol as the condensing agent for 3-quinuclidinone. The product (mol. wt. 232) proved to be identical with the one isolated from the acetylene–sodium amide reaction. Thus, the reaction between III and the acetylide ion gave (*E*)-3-[2-(3-hydroxy-3-ethinylquinuclidine)]quinuclidylidene (V, mol. wt. 258).



Scheme I

Basic conditions need not necessarily be employed in obtaining III. While attempting to make a dioxolone quinuclidine by reacting 3-quinuclidinone with glycolic acid and a catalytic amount of *p*-toluenesulfonic acid, a small amount of III was isolated.

Since only one isomer (III) was isolated, comparative spectral data between the (*E*)- and (*Z*)-configurations were not available to substantiate their geometry. However, inspection of molecular models of the two isomers indicated that the nitrogen in ring A (the ring containing the carbonyl) was sterically hindered by the bridgehead proton in ring B for the (*E*)-isomer. If this configuration was correct for the (*E*)-isomer, only the monomethyl iodide salt could be formed, since the formation of the dimethyl iodide salt would be impeded. NMR and elemental analysis confirmed that just one methyl iodide added, indicating the (*E*)-isomer.

Thermal and chemical techniques were employed to induce isomerization of the (*E*)-form. These attempts failed, as indicated by no significant changes in the NMR spectra. Again, models help to explain why the (*E*)-isomer would be favored over the (*Z*)-form. The model of the (*Z*)-isomer indicates very unfavorable steric interactions between the carbonyl oxygen in ring A and the bridgehead hydrogen on ring B. The space-filling models actually show that the valence orbitals of the bridgehead hydrogen and the oxygen overlap and that considerable twisting of the carbonyl is necessary to prevent this interaction. The rigidity of the quinuclidine cage maintains the bridgehead hydrogen in a fixed position. Thus, the carbonyl is forced out of its normal plane, increasing strain in the quinuclidine ring and causing a loss of conjugation with the exocyclic double bond. The (*Z*)-isomer is definitely the thermodynamically less stable configuration.

The rate of dimer formation is fairly rapid. Clemo and Hoggarth (1) used potassium metal in *tert*-amyl alcohol to generate the acetylide anion *in situ*. The result was the condensation product III, incorrectly identified as I. Ernest (2) generated the acetylide anion in liquid ammonia and then added 3-quinuclidinone, obtaining the expected product I. The formation of the (*E*)-isomer is stereoselective, and its formation should be considered in reactions using 3-quinuclidinone and base, especially in solvents that enhance aldol condensations.

The hydrochloride salt of 3-acetoxy-3-ethinylquinuclidine (II) was previously reported (6). Since the method of Clemo and Hoggarth (1) was used in obtaining I, the values are suspect. The results of Grob *et al.* (6) would not be corroborated, since they did not report the free base. Also, their melting points for the hydrochloride (234–240°) and the picrate (181–183°) were dissimilar to those found.

EXPERIMENTAL

3-Hydroxy-3-ethinylquinuclidine (I)—Sodium amide (10.5 g, 0.26 mole) was suspended in 90 ml of tetrahydrofuran, which had been dried over potassium hydroxide pellets and distilled. Dry acetylene gas was bubbled into the suspension; positive pressure was maintained using a mercury trap. 3-Quinuclidinone (32.3 g, 0.26 mole), which had been recrystallized from petroleum ether, was dissolved in 90 ml of dry tetrahydrofuran and dropped into the mixture over 4 hr. The reaction was allowed to continue for another 19 hr. After that time, most solvent was removed *in vacuo*. Ice and then ice water were added to the residue. The precipitate that resulted was filtered and dried, giving 25.47 g. It was recrystallized from ethanol–water, giving 13.52 g (34.76%), mp 191–193°; IR (KBr): 3225 (≡C—H) and 2090 (C≡C) cm^{-1}.

Anal.—Calc. for $C_9H_{13}NO$: C, 71.52; H, 8.60; N, 9.27. Found: C, 71.49; H, 8.86; N, 9.23.

The hydrochloride salt, recrystallized from 2-propanol, gave a melting point of 198–199°.

(*E*)-3-[2-(3-Oxoquinuclidine)]quinuclidylidene (III)—*Method A: Dihydrochloride*—The basic solution from which I was filtered was extracted with methylene chloride, decolorized with activated charcoal, and dried over magnesium sulfate. Hydrogen chloride gas was bubbled into the methylene chloride, and the solvent was removed *in vacuo*. The residue was recrystallized from water–methanol–2-propanol, yielding 2 g of white needle crystals, mp 275–276°. The IR spectrum indicated a hydrate, as was confirmed by Karl Fischer titration.

Anal.—Calc. for $C_{14}H_{22}Cl_2N_2O{\cdot}H_2O$: C, 52.05; H, 7.49; N, 8.67. Found: C, 51.99; H, 7.58; N, 8.37.

Method A: Free Base—The dihydrochloride was dissolved in water and made basic with 10% NaOH solution. This solution was extracted with methylene chloride and dried over magnesium sulfate. The solvent was removed *in vacuo*, and the residue was recrystallized from absolute ether (mp 159–160°).

Method B—3-Quinuclidinone (50 g, 0.4 mole) was dissolved in 200 ml of *tert*-butyl alcohol containing 23 g (0.205 mole) of potassium *tert*-butoxide. This mixture was stirred under a nitrogen atmosphere for 4 hr, giving a red-brown solution. After that time, the solvent was removed *in vacuo*. Water was added to the residue, this solution was extracted with hot benzene, and the benzene was dried over magnesium sulfate. The solvent was removed *in vacuo*, giving 42.7 g (92%) of a light-yellow powder, mp 148–157°, soften 138°. Recrystallization in absolute ether gave prism crystals having a green tint, mp 159–160°; IR (KBr): 1685 (C=O) and 1615 (conjugated C=C) cm^{-1}; NMR ($CDCl_3$): δ 1.90 [m, 8H, $(CH_2)_2C$], 2.5 (quintet, 1H, bridgehead hydrogen, ring A), 2.87 [t, 8H, $(CH_2)_2N$], 3.33 (quintet, 1H, bridgehead hydrogen, ring B), and 3.83 (s, 2H, $=CCH_2N$) ppm.

Anal.—Calc. for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.45; H, 8.96; N, 11.87.

The methyl iodide salt was recrystallized from methanol–acetone–absolute ether, mp 225–226°.

Anal.—Calc. for $C_{15}H_{23}IN_2O$: C, 48.14; H, 6.19; N, 7.48. Found: C, 47.20; H, 6.29; N, 7.48.

The picrate was recrystallized from ethanol, mp 207–208°.

(*E*)-3-[2-(3-Hydroxy-3-ethinylquinuclidine)]quinuclidylidene (V)—From the ethanol–water solution from which I was recrystallized, V was isolated by a number of selective recrystallizations using methanol until TLC indicated one component [silica gel developed with chloroform–methanol–ammonium hydroxide (85:15:1)]. The yield was 550 mg, mp 245–247°; IR (KBr): 3240 (≡CH) and 2090 (C≡C) cm^{-1}. Preparation of the hydrochloride salt of V was accomplished by preparing a solution in hot tetrahydrofuran and treating with hydrogen chloride gas. The solvent was removed *in vacuo*, and the solid was recrystallized from methanol–2-propanol, mp 259–260°.

Anal.—Calc. for $C_{16}H_{24}Cl_2N_2O$: C, 58.04; H, 7.25; N, 8.46. Found: C, 57.82; H, 7.35; N, 8.12.

3-Acetoxy-3-ethinylquinuclidine (II)—To 7.85 g (0.52 mole) of I was added 85 ml of acetic anhydride and 550 mg of zinc chloride. This mixture was refluxed for 2 hr. After that time, the excess acetic anhydride was distilled off under reduced pressure to a volume of approximately 15 ml. Ice was then added. The pH was adjusted to 12 with cold saturated potassium carbonate, and the solution was extracted with chloroform. The chloroform was dried over magnesium sulfate, and the solvent was removed *in vacuo*. An oil resulted and then crystallized upon scratching. Absolute ether–acetone was used for recrystallization. Large colorless prisms resulted, 4.61 g (46%), mp 89–91°; IR (KBr): 3250 (≡CH), 2100 (C≡C), and 1730 (C=O) cm^{-1}.

Anal.—Calc. for $C_{11}H_{15}NO_2$: C, 68.39; H, 7.77; N, 7.25. Found: C, 68.49; H, 7.99; N, 7.10.

The hydrochloride had a melting point of 217–219° dec., and the picrate had a melting point of 149°.

REFERENCES

(1) G. R. Clemo and E. Hoggarth, *J. Chem. Soc.*, **1941**, 476.

(2) J. Ernest, *Collect. Czech. Chem. Commun.*, **15**, 322 (1950).

(3) A. T. Nielsen, *J. Org. Chem.*, **31**, 1053 (1966).

(4) L. Stermbach and S. Kaiser, *J. Am. Chem. Soc.*, **74**, 2215 (1952).

(5) E. J. Warawa, N. J. Mueller, and R. Jules, *J. Med. Chem.*, **17**, 497 (1974).

(6) C. A. Grob, A. Kaiser, and E. Renk, *Helv. Chim. Acta*, **40**, 2170 (1957).

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[x] To whom inquiries should be directed.