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242. Issei Iwai and Tetsuo Hiraoka : Studies on Acetylenic Compounds. XXXV.*1 The Cyclization Reaction of some Propargylammonium Derivatives. (1).

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In the previous paper, the chemical character and the reactions of propargylammonium derivatives have been discussed.[1] However, it was shown that there exists some differences in the chemical behaviors of phenylpropargylammonium halide and propargylammonium compounds which possesses an ethynyl hydrogen ($H\text{-}C\equiv C\text{-}CH_2\text{-}\overset{\oplus}{N}R_1R_2R_3$). One of the differences is that C-N bond of propargylammonium halide derivatives is easily cleaved. Thus, as already reported,[1] the treatment of benzyldimethyl-(2-propynyl)ammonium iodide with aqueous sodium hydroxide solution gave N,N-dimethylbenzylamine.

This kind of cleavage was observed in other cases also.[2] On the other hand, it was also found that a triple bond of propargylammonium halide derivatives is more reactive to an anionoid reagent as compared with the ordinary isolated triple bond. This suggests that the inductive effect of ammonium group is transmitted through the one methylene group to the triple bond. This effect is recognized in its infrared spectrum. A normal stretching vibration of ethynylhydrogen is reported to appear in 3300 cm^{-1} region,[3] whereas ethynyl hydrogen absorption band of propargylammonium halide is observed at 3120~3210 cm^{-1} as shown in Fig. 1. This electrophilic character of the triple bond of propargylammonium group would result in cyclization reaction without the cleavage of the propargyl group during an intramolecular addition reaction thereby neutralizing the positively charged nitrogen atom. This paper deals with intramolecular cyclization reaction of some propargylammonium derivatives.

Refluxing of dimethyl(2-propynyl)(3-phenyl-2-propynyl)ammonium bromide (II) with sodium ethoxide in alcohol, afforded a crystalline substance, m.p. 126~128°. In ultraviolet spectrum this compound showed 222, 275.5, 266.5, 276.5, and 286.5 mμ absorption bands which were characteristic for the naphthalene nucleus. Infrared spectrum absorptions in 690~850 cm^{-1} region showed it to be the 2,3-dialkyl substituted naphthalene derivatives. Thus it was inferred that a cyclization and transannular reaction occurred to give a naphthalene derivative. Considering the reaction mechanism this substance would be one of III, VI, and VII. The compound (VII) is presumed to be resulted from VIII by intramolecular Stevens' rearrangement. The substance obtained from II was converted into methylammonium iodide, m.p. 274~275°, by usual procedure. When this ammonium iodide was treated with sodium mercury in water (Emde degradation), no neutral substance (*i.e.* 2,3-dimethylnaphthalene) was obtained and this fact excluded

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*1 Part XXXIV : This Bulletin, **11**, 1556 (1963).

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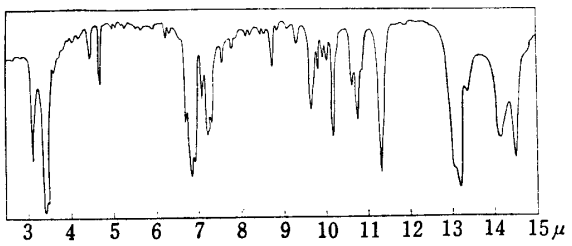
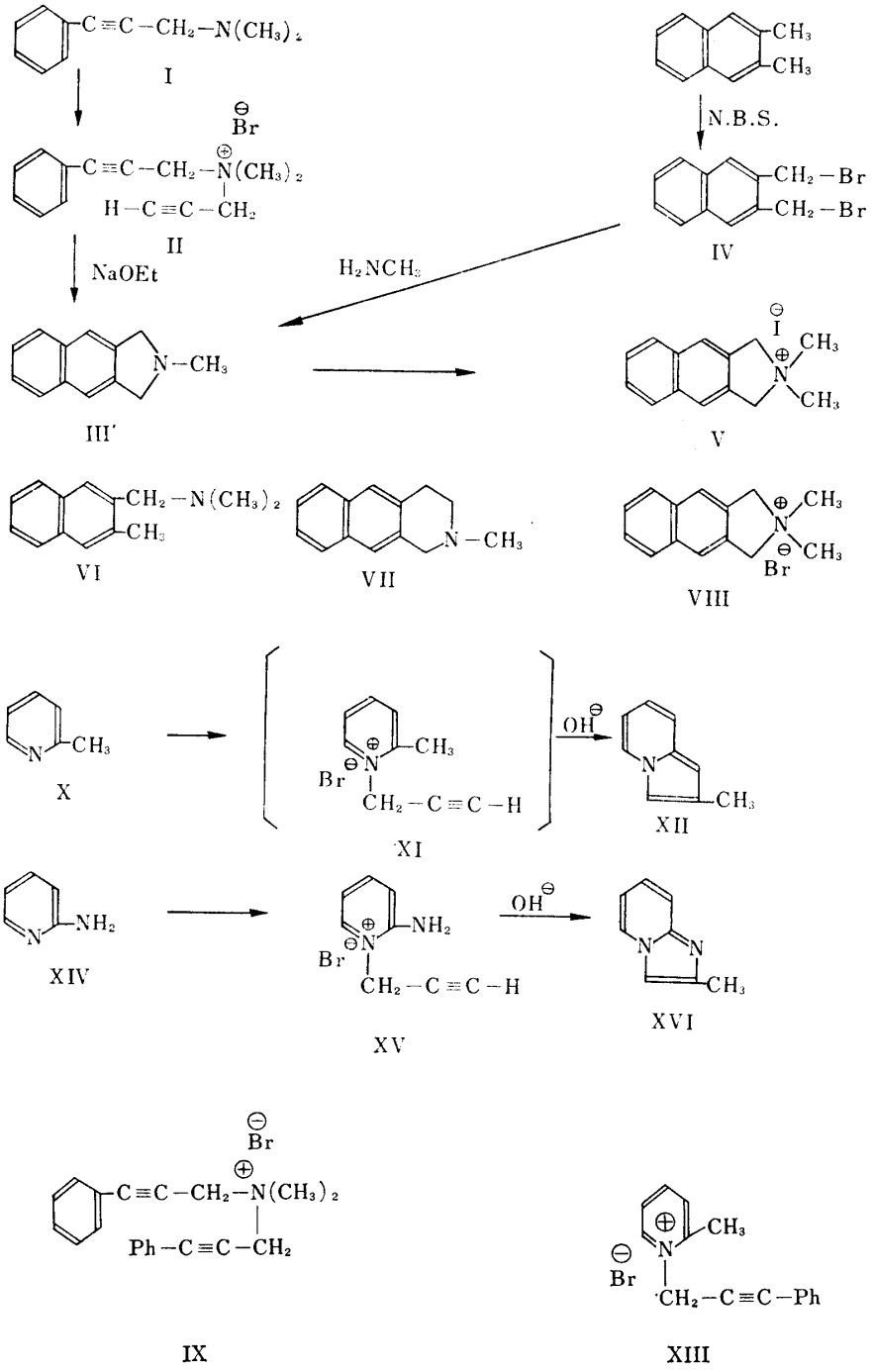
1) I. Iwai, T. Hiraoka : This Bulletin, **10**, 81 (1962), *Ibid.*, **11** 1556 (1963).

2) Unpublished data from our laboratory.

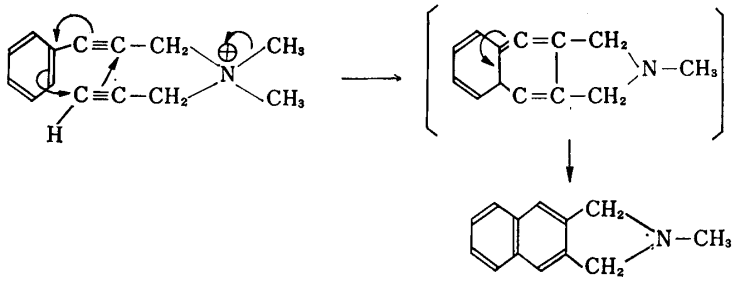
3) cf. L. J. Bellamy : "The Infrared Spectra of Complex Molecules," 58 (1958), Methuen & Co., Ltd., London.



F.g. 1. Infrared Spectrum of Dimethyl(2-propynyl) (3-Phenyl-2-propynyl)ammonium Bromide (Nujol)

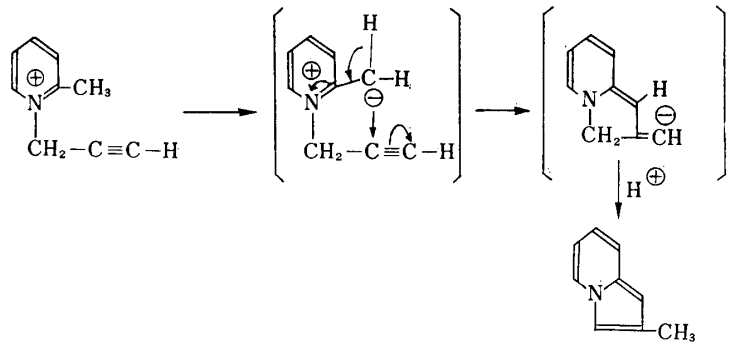


the possibility of the structure (VI). Then it was planned to synthesize the compound (III) starting from 2,3-dimethylnaphthalene. Bromination of 2,3-dimethylnaphthalene with N.B.S. according to the known method[4] gave corresponding 2,3-bis(bromomethyl)-naphthalene (IV). Treatment of IV with monomethylamine in large amount of alcohol in order to affect the intramolecular cyclization reaction, gave the expected 2-methyl-benz[*f*]isoindoline (III). By infrared and ultraviolet spectra, and mixed melting point determination this substance was identified with that obtained from II. Thus it was established that II gave III on treatment with NaOEt. The reaction mechanism for the formation of III from the acetylenic ammonium bromide (II) would be considered as follows :



Contrary to our expectation dimethylbis(3-phenyl-2-propynyl)ammonium bromide (IX) did not afford any naphthalene derivative, but gave Stevens' type rearrangement product.[1] The fact that IX did not cyclize to naphthalene derivative involves certain steric factors. In the compound (IX) the carbon atom adjacent to phenyl group can not approach to the other benzene ring, which hinders the cyclization reaction.

Then the reaction of a triple bond in the propargyl ammonium halide with active methylene group in the same molecule was attempted. 2-Picoline (X) was reacted with 2-propynyl bromide to give unstable 1-propargylpicolinium bromide (XI) which was submitted to the next reaction without isolation. To aqueous solution of XI was added solid sodium bicarbonate and the reaction mixture was submitted to steam distillation to give 2-methylindolizine (XII), m.p. 58°, which showed no depression of melting point on admixture with the authentic sample prepared from 2-picoline and monochloroacetone.[5] The mechanism of the formation of XII would be as follows :



2-Methyl-1-(3-phenyl-2-propynyl)pyridinium bromide (XIII) prepared from 2-picoline and 1-phenyl-3-bromo-1-propyne did not afford a characteristic substance.

4) G. Wittig, H. Ludwig : Ann., **589**, 55 (1954).
5) D.O. Holland, J.H.C. Nayler : J. Chem. Soc., **1955**, 1657.

Analogously, 2-amino-1-(2-propynyl)pyridinium bromide (XV), prepared from 2-aminopyridine (XIV) and propargyl bromide gave 2-methylimidazo[1,2-*a*]pyridine (XVI),[6] m.p. 39~41°, on treatment with aqueous sodium hydroxide solution.

From these result, it is clear that the reaction of the triple bond of propargylammonium salt with the anionoid substituent in the same molecule, is highly specific to the structure. Even slight change in a structure affects this reaction and as a result no definite substance was obtained.

Experimental*[3]

N,N-Dimethyl-3-phenyl-2-propynylamine (I)[7]——Dimethylamine hydrochloride (41 g. : 0.5*M*) was dissolved in H_2O(5 ml.), MeOH (230 ml.) and AcOH (5 ml.). To this solution was added aqueous HCHO solution (37%) (85 ml.). After 15 min. stirring phenyl-acetylene (51 g.: 0.5*M*) and CuCl (1.3 g.) were added, and the reaction mixture was heated on a water bath (60°) under continuous mechanical stirring for 43 hr. The cooled solution was poured into cold 10% HCl solution and extracted with Et_2O. The aqueous layer was made alkaline with 10% NaOH solution and again extracted with Et_2O. The combined extracts were dried over anhyd. Na_2SO_4 and evaporated. Distillation of the residue gave N,N-dimethyl-3-phenyl-2-propynylamine (I), b.p_8 105~106° (63 g.). *Anal.* Calcd. for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80. Found : C, 82.23; H, 8.06; N, 8.62.

Dimethyl(2-propynyl)(3-phenyl-2-propynyl)ammonium Bromide (II)——To N,N-dimethyl-3-phenyl-2-propynylamine (I) (1.6 g.) in benzene (2 ml.) was added propargyl bromide (1.2 g.) under ice-water cooling. After addition the reaction mixture was left overnight at room temperature. The crystalline substance was collected by filtration and washed with benzene. Recrystallization from 99% EtOH gave leaflets of m.p. 171~172° (2.2 g.). *Anal.* Calcd. for $C_{14}H_{16}NBr$: C, 60.44; H, 5.80; N, 5.04. Found: C, 60.16; H, 5.70; N, 4.93.

2-Methylbenz[*f*]isoindoline (III)——Na (20 g.) was dissolved in abs. EtOH (350 ml.) and to this solution was added dimethyl(2-propynyl)(3-phenyl-2-propynyl)ammonium bromide (II) (6.4 g.) in hot abs. EtOH (50 ml.). The reaction mixture was heated under reflux for 4.5 hr. The cooled solution was poured into H_2O (3.5 L.) and extracted with Et_2O. The conbined extracts were dried over anhyd. Na_2SO_4 and evaporated to give a semi-crystalline substance (3.72 g.). The crystalline substance was separated from the liquid substance by filtration and it was recrystallized from hexane to give 2-methylbenz[*f*]-isoindoline (III), m.p. 118~122° (600 mg.). Further recrystallization from the same solvent afforded a sample, m.p. 126~128°. From the mother liquor another crystalline substance was obtained which on recrystallization from EtOH gave needles, m.p. 238~239° (10 mg.). However this substance was not investigated further. The liquid substance obtained above and all the mother liquor of recrystallization were combined and the solvent was evaporated under reduced pressure. The residue was submitted to distillation and a fraction ofb. $p_{0.05}$ 90~150° (bath temperature) was collected which solidified on standing (3 g.). Recrystallization from hexane afforded further III, m.p. 120~123.5° (210 mg.). Picrolonate showed m.p. 225~226° after recrystallization from EtOH. *Anal.* Calcd. for $C_{23}H_{21}N_5O_5$: C, 61.74; H, 4.73; N, 15.65. Found : C, 61.57; H, 4.72; N, 15.52. UV λ_{max}^{EtOH} mμ (log ε) : 222 (5.00), 257.5 (3.64), 266.5 (3.71), 276.5 (3.74), 286.5 (3.58).

2,2-Dimethylbenz[*f*]isoindolinium Iodide (V)——To 2-methylbenz[*f*]isoindoline (III) (47 mg.) in abs. EtOH (2 drops) was added MeI (3 drops) to give a crystalline substance. Recrystallization from EtOH (95%) gave 2,2-dimethylbenz[*f*]isoindolinium iodide (V), m.p. 274~275°, with previous softening (reported m.p. : 285~286[4]). *Anal.* Calcd. for $C_{14}H_{16}NI$: C, 51.71; H, 4.96; N, 4.31. Found : C, 51.72; H, 4.86; N, 3.93.

2-Methylbenz[*f*]isoindoline (III) from 2,3-Bis(bromomethyl)naphthalene (IV)——To methylamine (3 g.) in 99% EtOH (100 ml.) was added 2,3-bis(bromomethyl)naphthalene (IV) (12.9 g.) in 99% EtOH (800 ml.) at room temperature during 48 hr. After addition the reaction mixture was allowed to stand at room temperature for 60 hr. Then, EtOH was evaporated under reduced pressure. To the residue was added 10% NaOH solution and extracted with Et_2O. The combined Et_2O extracts were again extracted with aq. 10% HCl. The combined HCl solution was made alkaline with 10% NaOH solution and extracted with Et_2O. The Et_2O extracts were dried over anhyd. Na_2SO_4 and evaporated to give a crystalline substance (3.5 g.). Recrystallization from hexane gave flaskes of 2-methylbenz[*f*]isoindoline (III), m.p. 123~125°, with previous softening (1 g.). Further recrystallization from aqueous EtOH gave a sample

*[8] All melting points are uncorrected.

6) A.E. Tschitschibabin : Ber., **59**, 2048 (1926); N. Campbell, E.B. McCall : J. Chem.Soc., **1951**, 2411.

7) C. Mannich, F. Chang : Ber., **66**, 418 (1933). The method described above is an improved one.

of m.p. 126~128° with previous softening. One more recrystallization from the same solvent did not alter this melting point. This substance (III) is relatively unstable to heating and therefore recrystallization should be done carefully. This substance showed no depression of melting point on admixture with the sample obtained from II, *Anal.* Calcd. for $C_{13}H_{13}N$: C, 85.20; H, 7.15; N, 7.64. Found : C, 84.76; H, 7.16; N, 7.58.

2-Methylindolizine (XII)——To 2-picoline (X) (9.3 g.) in benzene (18 ml.) was added propargyl bromide (11.9 g.) in benzene (4 ml.) under ice-water cooling. After addition the reaction mixture was stirred under ice water cooling for 6 hr. and then the temperature of the solution was gradually rised to room temperature. The reaction mixture was left at room temperature for 2 days. Then H_2O was added and extracted with Et_2O in order to remove the starting material. To the aqueous layer was added $NaHCO_3$ (16 g.) and the solution was heated on a steam bath for 20 min. The brown-black colored solution was submitted to steam distillation. From the distillate 2-methylindolizine (XII) was obtained as leaflets, m.p. 57~58° (1 g.), on admixture with the freshly prepared authentic sample[5] no depression of melting point was observed, and IR spectra of these two substances were superimposable.

2-Methyl-1-(3-phenyl-2-propynyl)pyridinium Bromide (XIII)——To 1-phenyl-3-bromo-1-propyne (3 g.) in abs. EtOH (5 ml.) was added 2-picoline (1.4 g.) under ice-water cooling. After addition, the reaction mixture was stirred at room temperature for 4 hr., then left for 2 days. The crystalline substance was collected by filtration and it showed m.p. 180~181.5° (3 g.). Recrystallization from abs. EtOH gave a sample, m.p. 181~182°. Once more recrystallization from the same solvent gave prisms, m.p. 183~184°. *Anal.* Calcd. for $C_{15}H_{14}NBr$: C, 62.51; H, 4.90; N, 4.86. Found : C, 62.46; H, 4.76; N, 4.85.

2-Amino-1-(2-propynyl)pyridinium Bromide (XV)——To 2-aminopyridine (9.4 g.) in EtOH (20 ml.) was added propargyl bromide (11.9 g.) under ice-water cooling. After addition the reaction mixture was left at room temperature for a night. Then, the solution was heated on a water bath (65°) for 4 hr. EtOH was evaporated under reduced pressure to give solid substance (21.2 g.). Recrystallization from abs. EtOH gave 2-amino-1-(2-propynyl)pyridinium bromide (XV) as needles of m.p. 154~155° (15 g.), *Anal.* Calcd. for $C_8H_9N_2Br$: C, 45.09; H, 4.26; N. 13.15. Found: C, 44.74; H, 4.37; N, 13.08.

2-Methylimidazo[1,2-*a*]pyridine (XVI)——To 2-amino-1-(2-propynyl)pyridinium bromide (XV) (20g.) in H_2O (150 ml.) was added 10% NaOH solution until any drop of NaOH solution caused no turbidity. The solution was extracted with Et_2O, and the combined extracts were dried over anhyd. Na_2SO_4 and evaporated. Distillation of the residue gave 2-methylimidazo[1,2-*a*]pyridine (XVI)[6] of $b.p_8$ 117~118° (8.3 g.), which solidified on standing. It melted at 39~41° and it was very hygroscopic. Picrate of XVI showed m.p. 196~198° after recrystallization from EtOH, on admixture with the authentic sample no depression of melting point was observed. *Anal.* Calcd· for $C_{14}H_{11}N_5O_7$: C, 46.54; H, 3.07; N, 19.39. Found: C, 46.66; H, 3.20; N, 19.49.

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Summary

The intramolecular cyclization reaction of propargylammonium halide derivatives was carried out and it was found that dimethyl(2-propynyl)(3-phenyl-2-propynyl)-ammonium bromide (II) gave 2-methylbenz[*f*]isoindoline (III) on treatment with sodium ethoxide in alcohol and 2-methyl-1-(2-propynyl)pyridinium bromide gave 2-methylindolizine (XII) on heating in sodium bicarbonate solution. Analogously, 2-amino-1-(2-propynyl)pyridinium bromide (XV) afforded 2-methylimidazo[1,2-*a*]pyridine (XVI).

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