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# 187. Tetsuo Miyadera, Eiji Ohki, and Issei Iwai : The Studies on Quinolizinium Salts. II.*1 Ring Opening Reactions of Quinolizinium Bromide by Grignard Reagents.

(*Research Laboratories, Sankyo Co., Ltd.*2)

The present investigation was undertaken to examine the reactivity of quinolizinium ion (I) toward various nucleophilic reagents. The chemistry of this ion has been little studied in spite of preparations of numerous derivatives. Richards, *et al.*[1] first investigated the chemical behavior of the ion and concluded that the ion resisted nucleophilic reactions giving no characterizable products.

Although the ion is the analog of quaternary quinolinium and isoquinolinium ions, a great difference may exist among them in nucleophilic reactions. A closer similarity to the quaternary pyridinium ion would be expected since quinolizinium ion constitutes two pyridinium structures fused at C–N bond. Richard's[1] and Hansen's[2] groups showed that the methyl derivatives of I substituted at the positions corresponding to 2- or 4-methyl quaternary pyridinium salts showed a similar reactivity toward reagents such as *p*-dimethylaminobenzaldehyde. This suggests that there should be some similarity in reactivity between the nucleus of I and the quaternary pyridinium ion toward nucleophilic reagents.

Since quinolizinium ion and naphthalene are isoelectronic,[3,4] the resonance structures of the ion are depicted as follows.

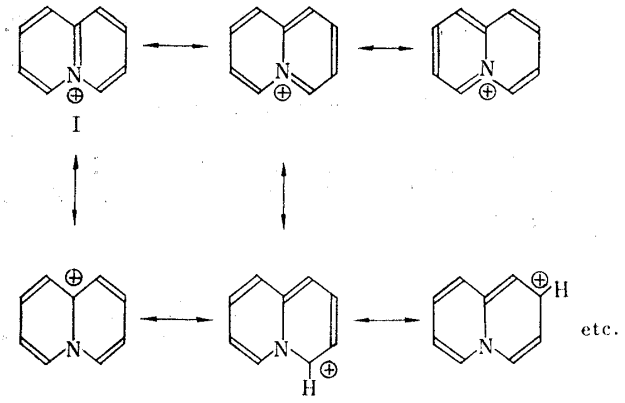


Chart 1.

Consequently, either of these three carbonium ions might undergo a reaction with anionoid reagents yielding one or a mixture of the three corresponding quinolizine derivatives.

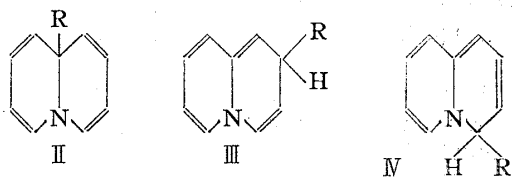


Chart 2.

Unexpectedly, none of these types of derivatives were obtained in nucleophilic reactions so far examined.

A suspension of quinolizinium bromide (V) in ether was treated with methylmagnesium iodide with no substantial reaction. Refluxing the mixture for a long period gave only a small amount of a very unstable oil (VI) which gradually deposited a brown precipitate on standing. The oil was purified as the picrate whose analytical values corresponded to $C_{16}H_{14}O_7N_4$. The spectral evidence of the free base showed the presence of an unsaturated system conjugated with pyridine ring. Namely, the infrared spectrum of VI

*1 Part I. T. Miyadera, I. Iwai : This Bulletin, **12**, 1338 (1964).

*2 1-888 Nishi-shinagawa, Shinagawa-ku, Tokyo (宮寺哲男, 大木英二, 岩井一成).

1) A. Richards, T. S. Stevens : J. Chem. Soc., **1958**, 3067.
2) H. V. Hansen, E. D. Amstutz : J. Org. Chem., **28**, 393 (1963).
3) T. E. Peacock : J. Chem. Soc., **1959**, 3645.
4) H. H. Jaffé, M. Orchin : "Theory and Applications of Ultraviolet Spectroscopy," 374 (1962), John Wiley & Sons, Inc., New York.

showed absorption bands at 1614 and 1615 $cm^{-1}$ (conjugated diene), 3020, 1590, 1560, and 743 $cm^{-1}$ (pyridyl ring), and 2940 and 1450 $cm^{-1}$ ($CH_3$), but no terminal methylene bands. The ultraviolet spectrum exhibited absorption maxima at 265 and 293.5 mμ. The oil was reduced using 5% Pd-C, absorbing 2 moles of hydrogen, to give a stable oil (Ⅶ) with a characteristic monosubstituted pyridine ultraviolet absorption.[5] From the above results the reduction product was assumed to be α-amylpyridine and this was confirmed by synthesis from 2-picolyllithium and butyl bromide. The geometry of the diene was not investigated because of the instability and poor yield, but would be mainly 1-*cis*-isomer of 1-(2-pyridyl)-1,3-pentadiene (Ⅵ) according to the reaction products described below.

In a tetrahydrofuran suspension quinolizinium bromide reacted exothermically with phenylmagnesium bromide at room temperature to give two reaction products (Ⅷ, Ⅸ). On catalytic hydrogenation both of them gave a same tetrahydro derivative (X) with infrared and ultraviolet spectra showing the presence of pyridyl and phenyl groups.

From the fact we assumed that two reaction products (Ⅷ, Ⅸ) were geometric isomers of 1-(2-pyridyl)-4-phenyl-1,3-butadiene. The one obtained in 67% yield was a colorless crystalline substance (Ⅷ), $C_{15}H_{13}N$, m.p. 91~92°, which showed infrared absorption bands at 1625 and 1615 $cm^{-1}$ (conjugated diene), 1000, 992, 965 $cm^{-1}$ (*trans* -CH=CH-) and the splitting bands due to monosubstituted aromatic ring near 700 $cm^{-1}$ suggesting the presence of *cis* olefin.[6] The ultraviolet spectra exhibited absorption maxima at 330 (31,300), 240 (15,200) and 247 mμ (ε 13,400) latter two of which are very similar to those characteristic of ***cis-trans***-1,4-diphenyl-1,4-butadiene.[7] The spectral data indicated that Ⅷ has one *cis* and one ***trans*** double bond. The other compound (Ⅸ) obtained in a small quantity was a colorless crystalline substance, $C_{15}H_{13}N$, m.p. 121~122°, with the ultraviolet spectrum showing absorption maxima at 332 (53,000) and 231 mμ (ε 9,000). The infrared spectrum of Ⅸ exhibited absorption bands at 1624 and 1610 $cm^{-1}$ (conjugated diene), 1000,

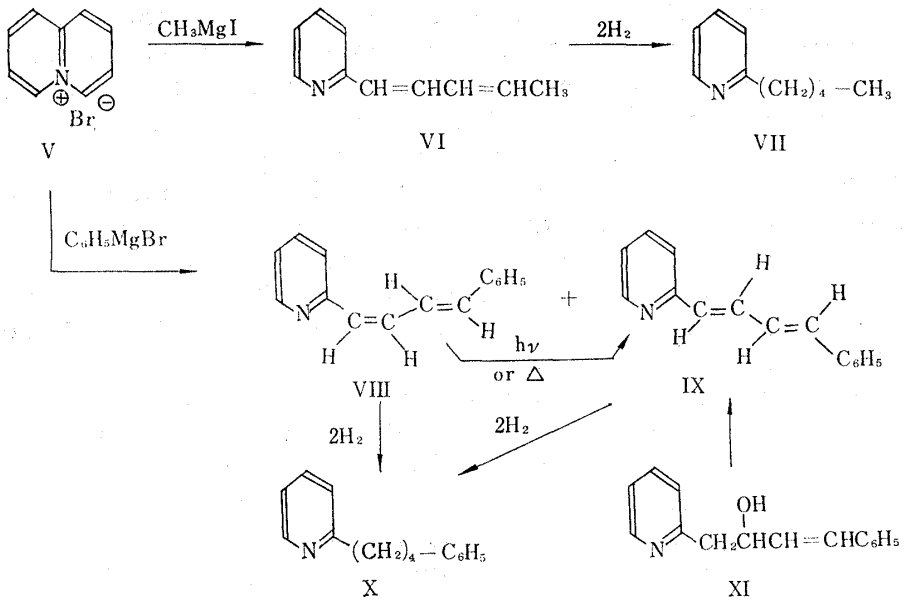



Chart 3.

5) N. Ikekawa, M. Maruyama, Y. Sato : This Bulletin, 2, 209 (1954).
6) K. Lunde, L. Zechmeister : Acta Chem. Scand., 8, 1421 (1954). In the infrared spectral study of some stereoisomeric α,ω-diphenylpolyenes K. Lund, *et al.* have stated that the absorption bands due to monosubstituted aromatic ring near 700 $cm^{-1}$ is influenced by the existence of a terminal *cis* double bond, causing a more or less extensive splitting of the band.
7) J. H. Dinckard, B. Wille, L. Zechmeister : J. Am. Chem. Soc., 70, 1938 (1948).

993 $cm^{-1}$ (*trans* -CH=CH-), but no splitting band in the out-of-plane region of the aromatic ring.[6]

The lower melting substance (Ⅷ) isomerized into Ⅸ in boiling *p*-cymene in the dark. Therefore, Ⅸ is thermodynamically more stable than Ⅷ suggesting that Ⅸ is a geometric isomer, the *trans-trans* diene. The structure of Ⅸ was determined by the *trans-trans* diene[8,9] synthesis from condensation of picolyllithium and cinnamaldehyde to give the alcohol (Ⅺ),[9] followed by dehydration of Ⅺ with boiling acetic anhydride.

The thermodynamically unstable isomer is probably 1-*cis*-3-*trans*-1-(2-pyridyl)-4-phenyl-1,3-butadiene on the basis of the arguments presented above and the reaction mechanism which will be discussed later. However, we could not exclude the possibility of the conversion of the *cis-trans* into a *trans-cis* diene. The correctness of the above configurational assignment was indirectly indicated further by the synthesis of *trans-cis* isomer as shown in Chart 4.

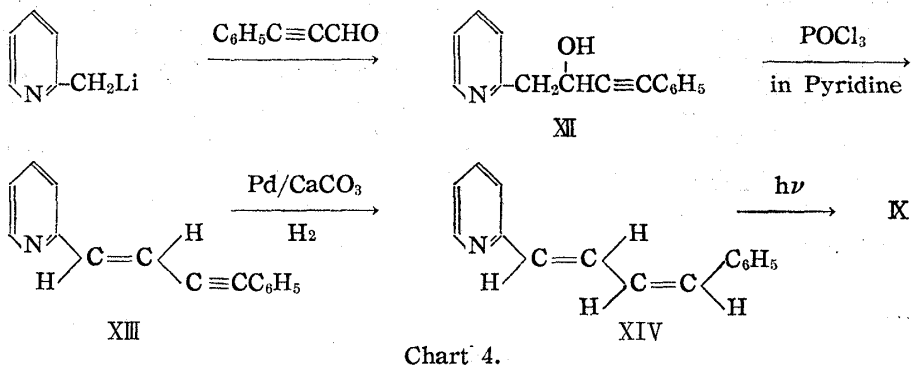



Chart 4.

Picolyllithium was reacted with phenylpropargylaldehyde giving an alcohol (Ⅻ) whose purification was unsuccessful because of the partial decomposition on distillation *in high vacuo*. Without further purification the crude alcohol was treated with phosphorus oxychloride in pyridine to yield the ene-yne compound (XIII) with infrared spectrum showing the presence of an acetylenic linkage and *trans* olefin. The *trans* ene-yne compound (XIII) was hydrogenated using Pd-$CaCO_3$ to give the *trans-cis* diene (XIV) as an oil. Physical data of XIV and the picrate showed that XIV was apparently different isomer from Ⅷ. The oil was photochemically very labile in the absence of solvent[7] and isomerized readily into the crystalline *trans-trans* isomer only on standing at room temperature under ordinary light. The *cis-trans* isomer was more stable photochemically than the *trans-cis* isomer, but when a benzene solution of Ⅷ was irradiated with a ultraviolet lamp, the *trans-trans* isomer was formed with about a half of the unchanged starting material, while no change was detected in the dark.

The preceding observations indicate that the *trans-trans* isomer formed in very low yield was probably a photo-isomerized product of the *cis-trans* diene during the Grignard reaction and subsequent work-up. However, we could not determine precisely whether the formation of the *trans-trans* diene resulted from the reaction itself or was photochemically induced from previously formed *cis-trans* diene.

From the above mentioned diene formation the triene syntheses were undertaken, together with an examination of the reactivity of the quinolizinium ion toward ethynyl and vinylmagnesium bromides.

The reaction of Ⅴ with phenylethynylmagnesium bromide did not proceed to any extent at room temperature, but occurred smoothly on refluxing to yield the expected

8) E. Späth, G. Kubiczek, E. Dubensky : Ber., **74**, 873 (1941).
9) B. M. Mikhailov, G. S. Ter-Sarkisyan : Izvest. Akad. Nauk S. S. S. R., Otdel. Khim. Nauk, **1956**, 1448.

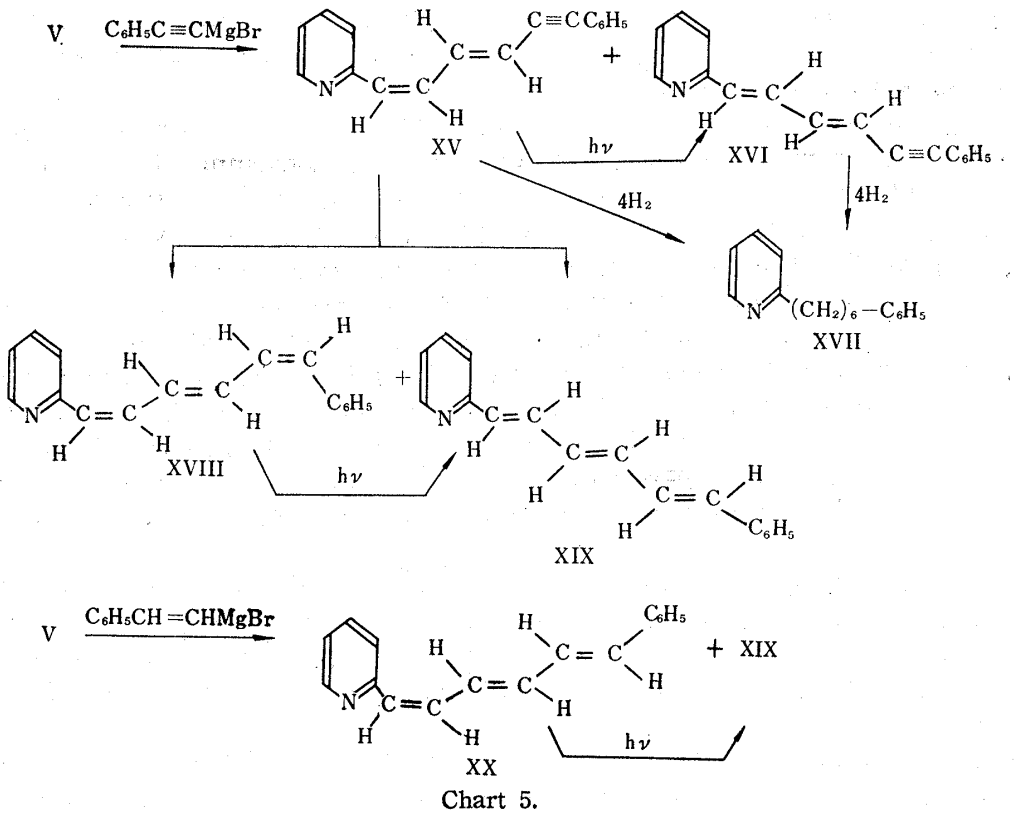



Chart 5.

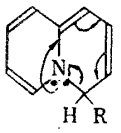
products, XV, m.p. 63~64°, and XVI, m.p. 91~92° in excellent yield. Both fitted the formula $C_{17}H_{13}N$ and gave a same octahydro derivative (XVII) on catalytic hydrogenation. The lower melting isomer was partly converted to the higher one by ultraviolet irradiation in benzene. The former showed ultraviolet absorption maxima at 247.5 (11,200), 256 (12,500) and 340 mμ (ε 35,500) suggesting the presence of *cis* olefin and infrared absorption bands at 1614 and 1575 $cm^{-1}$ (conjugated diene) and 953 and 995 $cm^{-1}$ (*trans* -CH=CH-). The higher melting isomer (XVI) exhibited infrared absorption bands due to a diene and *trans* olefin, and a more intense ultraviolet absorption band at 341 mμ (ε 53,700) than XV. From the spectral data the lower melting isomer should be *cis-trans* and the higher, *trans-trans* compound. The spectral evidence of these two compounds did not show the presence of an acetylenic linkage, but the presence was demonstrated by reduction of XV using Lindler's catalyst to afford two triene compounds, XVIII, m.p. 92~93° and XIX, m.p. 174~175°. From mechanistic considerations the major product (XVIII) expected would be the *cis-trans-cis* triene isomer, and the minor product (XIX), the all-*trans* isomer which was also obtained in the reduction described below and has very intense ultraviolet absorption maximum at 355.5 mμ (ε 70,500) comparable to all-*trans*-diphenylhexatriene.[10,11]

Quinolizinium bromide also reacted with styrylmagnesium bromide in refluxing tetrahydrofuran to give two isomeric trienes. The one (XX) obtained as the major product was a pale yellow crystalline substance, m.p. 93~94°, which was photochemically isomerized into the other minor product, m.p. 174~175°. The latter melted undepressed on admixture with the Lindler's reduction product (XIX) of XV. The ultraviolet spectrum of XX showed absorption maxima at 262.5 (12,000), 253.5 (11,800), 356 mμ (ε 50,800) with

10) E. A. Braude : J. Chem. Soc., **1950**, 379.
11) K. Lunde, L. Zechmeister : J. Am. Chem. Soc., **76**, 2308 (1954).

close similarity to those of *cis-trans-trans*-diphenylhexatriene.[11] The infrared spectrum of XX exhibited conjugated triene absorption bands at 1640, 1628, 1608 $cm^{-1}$ and mono-substituted aromatic bands. From the spectral data and the reaction mechanism, XX should be *cis-trans-trans* triene isomer.

Although nucleophilic reactions of quaternary pyridinium compounds by anionoid reagents have been widely investigated, pyridinium ring opening has been only rarely observed except for the labile pyridinium derivatives.[12] On the other hand, these experiments prove that the nucleus of the quinolizinium ion was readily cleaved at the $C_4$ (or $C_6$)-N bond by attack of the anionic moiety of Grignard reagents. The probable mechanism for the formation of the pyridine derivatives is considered to be as follows: first the nucleophilic attack of the anionic moiety of Grignard reagent at the $C_4$ (or $C_6$)-position of the quinolizinium cation gives a 4-substituted-4*H*-quinolizine intermediate (Ⅳ) which rearranges, in next step, to the more stable pyridine compound. The shift of the nitrogen lone pair electrons to the ring juncture is similar to that in a dieneamine and would cause ring opening of the intermediate as shown below.



Ⅳ

Chart 6.

Part of the driving force for the carbon-nitrogen cleavage would be supplied by aromatization to the pyridine nucleus conjugated with the diene. The instability of such a quinolizine reaction intermediate would be supported by the fact that various syntheses of quinolizine itself have been unsuccessfully attempted giving instead other products.[13,14]

Prefferential attack by the anion would occur at $C_4$ (or $C_6$)-position closest to the positive nitrogen which is most favored by coulombic attraction[15] as compared with $C_2$ (or $C_8$)-position.

The quinolizinium ion will be treated by molecular orbital calculations later.

## Experimental

**Reaction of Quinolizinium Bromide (V) with Methylmagnesium Iodide**——To a stirred suspension of V (3.0 g.) in 50 ml. of dry $Et_2O$ was added at room temperature an ethereal solution of $CH_3MgI$ prepared from Mg (0.75 g.) and $CH_3I$ (4.35 g.) in 50 ml. of dry $Et_2O$. The mixture was refluxed for 18 hr. Aq. $NH_4Cl$ solution was added and the organic layer was separated. The aq. solution was extracted with $Et_2O$ several times and combined $Et_2O$ extract were washed with $H_2O$, dried over $Na_2SO_4$, and distilled, to yield after removal of the solvent, 1-(2-pyridyl)-1,3-pentadiene (Ⅵ, 0.3 g.), b.p. 85°/3 mm. (bath temp.). IR $\nu_{max}^{liq.}$ $cm^{-1}$: 1645, 1615 (conj. diene), 3020, 1590, 1560, 743 (pyridyl), 2940, 1450 ($CH_3$). UV $\lambda_{max}^{EtOH}$ mμ ($\varepsilon$): 293.5 (14,900), 265 (15,800).

The picrate of Ⅵ was prepared from $Et_2O$ solution and recrystallized from EtOH. m.p. 161~162°. *Anal.* Calcd. for $C_{16}H_{14}O_7N_4$: C, 51.34; H, 3.77; N, 14.97. Found: C, 51.05; H, 3.85; N, 15.01.

**Hydrogenation of VI**——A solution of 200 mg. of Ⅵ in 20 ml. of AcOH was hydrogenated absorbing 2 moles of $H_2$ with 5% Pd-C (20 mg.) as catalyst. After removal of the catalyst and solvent, $H_2O$ was added to the residue and the aq. solution was made alkaline with $Na_2CO_3$, extracted with $Et_2O$ and the $Et_2O$ extract, washed with $H_2O$ and dried over $Na_2SO_4$. The solvent was removed and the residue distilled to give 2-pentylpyridine (Ⅶ), b.p. 100°/20 mm. (bath temp.). It was redistilled for analysis. *Anal.* Calcd. for $C_{10}H_{15}N$: C, 80.48; H, 10.13; N, 9.39. Found: C, 80.18; H, 10.07; N, 9.63. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 3080, 1592, 1570, 748 (pyridyl). UV $\lambda_{max}^{EtOH}$ mμ ($\varepsilon$): 268.2 (3,000), 262 (4,100), 255.5 (3,900).

**Reaction of V with Phenylmagnesium Bromide**——To a stirred suspension of V (6.3 g.) in 50 ml. of abs. tetrahydrofuran was added at room temperature a solution of PhMgBr prepared from PhBr (9.6 g.) and Mg (1.46 g.) in 120 ml. of tetrahydrofuran. The insoluble bromide (V) reacted exothermically dissolving in the solution as the Grignard reagent was added. After the resulting solution was treated with

12) E. N. Shaw: "The Chemistry of Heterocyclic Compounds, Pyridine and Its Derivatives Part Ⅱ", Ed. by A. Weissberger, pp. 58~63 (1961), Interscience Publishers, New York.
13) V. Boekelheide, W. G. Gall: J. Am. Chem. Soc., **76**, 1832 (1954).
14) O. Diels, H. Schrum: Ann., **530**, 68 (1937).
15) M. Saunders, E. H. Gold: J. Org. Chem., **27**, 1489 (1962).

aq. $NH_4Cl$ and washed with $H_2O$, the organic layer was extracted with dil. HCl solution. The acidic solution was washed with $Et_2O$, made alkaline with $Na_2CO_3$; extracted with $Et_2O$ and the $Et_2O$ extract, washed with $H_2O$ and dried over $Na_2SO_4$. Removal of the solvent gave a crystalline substance which was chromatographed in benzene on silica gel to give two compounds, Ⅷ (4.15 g.) and Ⅸ (68 mg.). The former 1-*cis*-3-*trans*-1-(2-pyridyl)-4-phenyl-1, 3-butadiene was recrystallized from petr. benzin to give prisms, m.p. 91~92°. *Anal.* Calcd. for $C_{15}H_{13}N$ : C, 86.92; H, 6.32; N, 6.76. Found : C, 86.66; H, 6.54; N, 6.84. UV $\lambda_{max}^{EtOH}$ mμ ($\varepsilon$) : 330 (31,300), 247 (13,400), 240 (15,200). IR $\nu_{max}^{Nujol}$ $cm^{-1}$ : 1625, 1607 (conj. diene), 965, 992, 1000 (*trans* olefin), 1583, 1578, 1561, 748, 738, 707, 694 (pyridyl, phenyl).

The picrate of Ⅷ was prepared from $Et_2O$ solution and recrystallized from EtOH to give yellow needles, m.p. 168.0~168.5°. *Anal.* Calcd. for $C_{21}H_{16}O_7N_4$ : C, 57.80; H, 3.70; N, 12.84. Found : C, 57.74; H, 3.96; N, 13.10.

1-*trans*-3-*trans*-1-(2-pyridyl)-4-phenyl-1,3-butadiene (Ⅸ) was recrystallized from hexane to give colorless leaflets, m.p. 121~122°. *Anal.* Calcd. for $C_{15}H_{13}N$ : C, 86.92; H, 6.32; N, 6.76. Found : C, 86.73; H, 6.40; N, 7.05. UV $\lambda_{max}^{EtOH}$ mμ ($\varepsilon$) : 332 (53,000), 231 (9,000). IR $\nu_{max}^{Nujol}$ $cm^{-1}$ : 1624, 1610 (conj. diene), 993, 1000 (*trans* olefin), 1557, 1580, 750, 688 (pyridyl, phenyl).

The picrate of Ⅸ was prepared from EtOH solution and recrystallized from EtOH as golden needles, m.p. 217~218°. *Anal.* Calcd. for $C_{21}H_{16}O_7N_4$ : C, 57.80; H, 3.70; N, 12,84. Found : C, 57.61; H, 3.67; N, 12.72.

**Hydrogenation of VIII and IX**——A solution of Ⅷ (210 mg.) in 30 ml. of AcOH was hydrogenated with 5% Pd-C (50 mg.) absorbing 2 moles of $H_2$. Isolation as described in the reduction of Ⅵ gave 2-(4-phenylbutyl)pyridine (X) of b.p. 110°/$3\times10^{-5}$ mm. (bath temp.). *Anal.* Calcd. for $C_{15}H_{17}N$ : C, 85.26; H, 8.11; N, 6.63. Found : C, 84.95; H, 8.02; N, 6.75. UV $\lambda_{max}^{EtOH}$ mμ ($\varepsilon$) : 256.5 (3,660), 262 (4,150), 268.2 (3,100). IR $\nu_{max}^{liq.}$ $cm^{-1}$ : 3070, 3030, 1607, 1592, 1573, 748, 698 (pyridyl, phenyl).

The picrate of X was prepared from $Et_2O$ solution and recrystallized from EtOH. m.p. 113~114°. *Anal.* Calcd. for $C_{21}H_{20}O_7N_4$ : C, 57.27; H, 4.58; N, 12.72. Found : C, 57.27; H, 4.63; N, 12.80. The *trans-trans* diene (Ⅸ) gave the same tetrahydro derivative (X) and its picrate as Ⅷ. No depression in melting point was observed in admixture of these two picrates.

**Thermoisomerization of VIII to IX**——A solution of Ⅷ (200 mg.) in 10 ml. of *p*-cymene was refluxed for 1 hr. using 5% Pd-C (50 mg.) in a stream of $N_2$ in the dark. The solution was cooled and extracted with dil. HCl. The acidic solution was made alkaline with $Na_2CO_3$ and extracted with $Et_2O$. The $Et_2O$ extract was washed with $H_2O$ and dried over $Na_2SO_4$. Removal of the solvent gave the solid which was chromatographed in benzene on silica gel to afford the *trans-trans* isomer (Ⅸ, 71 mg.) and the unchanged *cis-trans* isomer (Ⅷ, 121. mg). They were confirmed by the admixture in melting point.

The thermoisomerization of Ⅷ to Ⅸ was also observed only on refluxing the *p*-cymene solution without the catalyst.

**Photoisomerization of VIII to IX**——A solution of Ⅷ (500 mg.) in 500 ml. of benzene was irradiated 12 hr. using a ultraviolet lamp in a stream of $N_2$ under cooling. The solution was concentrated and chromatographed on silica gel to give the *trans-trans* isomer (Ⅸ), 221 mg. and the unchanged *cis-trans* isomer, 242 mg.

**1-*trans*-1-(2-Pyridyl)-4-phenyl-1-buten-3-yne (XIII)**——A solution of phenylpropargyl aldehyde (50.0 g.) in 200 ml. of $Et_2O$ was added under cooling to a solution of picolyllithium prepared from Li (7.3 g.), PhBr (84.9 g.) and α-picoline (55.8 g.). The reaction mixture was stirred for 2 hr. at room temperature, and then acidified with glacial AcOH and $H_2O$ added. The organic layer was separated and the aqueous solution was extracted with $Et_2O$. The combined $Et_2O$ extracts were washed with $H_2O$ and dried over $Na_2SO_4$. Evaporation of the solvent gave a viscous oil which was reacted without purification because of partial decomposition on distillation *in high vacuo*. A solution of the crude oil in 500 ml. of pyridine containing 100 ml. of $POCl_3$ was allowed to stand at room temperature for 38 hr. and heated on a steam-bath for 1 hr. The reaction mixture was poured onto ice and extracted with $Et_2O$. The $Et_2O$ layer was extracted with dil. HCl solution, the acidic solution was washed with $Et_2O$, made alkaline with $Na_2CO_3$ and extracted with $Et_2O$. The $Et_2O$ extract was washed with $H_2O$ and dried over $Na_2SO_4$. After removal of the solvent, the residue in benzene was chromatographed on silica gel to give an oil (7.3 g.) which was distilled to afford a colorless oil (XIII), b.p. 140°/$4\times10^{-5}$ mm. (bath temp.). The oil crystallized on standing, m.p. 49~50°. *Anal.* Calcd. for $C_{15}H_{11}N$ : C, 87.77; H, 5.40; N, 6.82. Found : C, 87.51; H, 5.37; N, 7.12. UV $\lambda_{max}^{EtOH}$ mμ ($\varepsilon$) : 320 (37,600), 221 (10,000). IR $\nu_{max}^{liq.}$ $cm^{-1}$ : 2180 (C≡C), 1617 (C=C), 993, 957 (*trans* olefin).

**1-*trans*-3-*cis*-1-(2-Pyridyl)-4-phenyl-1,3-butadiene (XIV)**——A solution of XIII (734 mg.) in 30 ml. of AcOEt was hydrogenated to absorb 1 mole of $H_2$ using Pd-$CaCO_3$ (300 mg.). Removal of the catalyst and the solvent gave an oil which was chromatographed in benzene on silica gel to give XIV (480 mg.) and a trace of the *trans-trans* isomer-like substance. The *trans-cis* isomer was distilled at b.p. 125~130°/$2\times10^{-4}$ mm. *Anal.* Calcd. for $C_{15}H_{13}N$ : C, 86.92; H, 6.32; N, 6.76. Found : C, 86.68; H, 6.22; N, 6.91. UV $\lambda_{max}^{EtOH}$ mμ ($\varepsilon$) : 325 (28,500), 243.5 (15,000), 238 (14,000). IR $\nu_{max}^{liq.}$ $cm^{-1}$ : 1630, 1604 (conj. diene), 950, 992 (*trans olefin*). The picrate of XIV was prepared from $Et_2O$ solution and recrystallized from EtOH,

fine yellow needles, m.p. 172~173°. *Anal.* Calcd. for $C_{21}H_{16}O_7N_4$ : C, 57.80; H, 3.70; N, 12.84. Found : C, 57.71; H, 3.77; N, 12.92.

The free base was very labile in the absence of solvent and gave the crystalline *trans-trans* isomer (IX) on standing under ordinary light.

**Reaction of V with Phenylethynylmagnesium Bromide-Formations of 1-*cis*-3-*trans*-(XV) and 1-*trans*-3-*trans*-1-(2-Pyridyl)-6-phenyl-1,3-hexadien-5-yne (XVI)**——To a stirred suspension of V (5.25 g.) in 50 ml. of tetrahydrofuran was added with stirring a solution of phenylethynylmagnesium bromide prepared from Mg (1.22 g.), $C_2H_5Br$ (5.7 g.) and phenylacetylene (5.1 g.) in the usual manner. The mixture was refluxed 1 hr., and then treated with aq. $NH_4Cl$ solution and extracted with $Et_2O$. The $Et_2O$ layer was extracted with dil. HCl, and the aqueous extract made alkaline with $Na_2CO_3$ and extracted with $Et_2O$. The $Et_2O$ extract was washed with $H_2O$ and dried over $Na_2SO_4$. Removal of the solvent gave an oil which was chromatographed in benzene on silica gel to give two crystalline compounds, XV (4.27 g.) and XVI (0.237 mg.). The former was recrystallized from hexane to give plates of m.p. 63~64°. *Anal.* Calcd. for $C_{17}H_{13}N$ : C, 88.28; H, 5.67; N, 6.06. Found : C, 88.54; H, 5.67; N, 6.35. UV $\lambda_{max}^{EtOH}$ mμ ($\varepsilon$) : 340 (35,500), 356 (12,500), 247.5 (11,200). IR $\nu_{max}^{Nujol}$ $cm^{-1}$ : 1614, 1575 (conj. diene), 953, 995 (*trans* olefin).

The second compound (XVI) was recrystallized from petr. ether to give pale yellow needles, m.p. 91~92°. *Annl.* Calcd. for $C_{17}H_{13}N$ : C, 88.28; H, 5.67; N, 6.06. Found : C, 88.01; H, 5.53; N, 6.09. UV : $\lambda_{max}^{EtOH}$ 341 mμ ($\varepsilon$ 53,700). IR $\nu_{max}^{Nujol}$ $cm^{-1}$ : 1620, 1576 (conj. diene), 968, 995 (*trans* olefin).

**Hydrogenation of XV and XVI**——A solution of XV (462 mg.) in 50 ml. of AcOH was hydrogenated using 5% Pd-C (50 mg.) with 4 mole uptake of $H_2$. Work-up in the usual manner gave a colorless oil 6-phenyl-1-(α-pyridyl)-hexane (XVIII), b.p. 115~120°/$4\times10^{-5}$ mm. (bath temp.). *Anal.* Calcd. for $C_{17}H_{21}N$ : C, 85.30; H, 8.84; N, 5.85. Found : C, 84.95; H, 8.77; N, 6.01. UV $\lambda_{max}^{EtOH}$ mμ ($\varepsilon$) : 268.4 (3,300), 261.7 (4,500), 256.5 (3,900).

The *trans-trans* isomer (XVI) was similarly hydrogenated giving the same octahydro derivative (XVIII) as that obtained from the reduction of XV.

**Hydrogenation of XV with Lindler's Catalyst**——A solution of XV (465 mg.) in 30 ml. of AcOEt was hydrogenated using Pd-$CaCO_3$ as catalyst to a 1 mole uptake of $H_2$. After removal of the catalyst the filtrate was evaporated and the residue was chromatographed in benzene on silica gel to give 1-*cis*-3-*trans*-5-*cis*-1-(2-pyridyl)-6-phenyl-1,3,5-hexatriene (XVIII, 325 mg.) and the all-*trans* triene (XIX, 77.7 mg.). The former was recrystallized from hexane giving plates, m.p. 92~93°. *Anal.* Calcd. for $C_{17}H_{15}N$ : C, 87.51; H, 6.48; N, 6.00. Found : C, 87.42; H, 6.37; N, 6.00. UV : $\lambda_{max}^{EtOH}$ 339 mμ ($\varepsilon$ 44,100). IR $\nu_{max}^{Nujol}$ $cm^{-1}$ : 1625, 1610, 1585 (sh) (conj. triene), 1003, 992, 962 (*trans* olefin).

All-*trans* isomer (XIX) was recrystallized from $Et_2O$ giving pale yellow leaflets, m.p. 174~175°. *Anal.* Calcd. for $C_{17}H_{15}N$ : C, 87.51; H, 6.48; N, 6.00. Found : C, 87.48; H, 6.69; N, 6.06. UV $\lambda_{max}^{EtOH}$ mμ ($\varepsilon$) : 355.5 (70,500), 371 (55,300). IR $\nu_{max}^{Nujol}$ $cm^{-1}$ : 1637, 1612, 1597 (conj. triene), 1009, 994 (*trans* olefin).

**Photoisomerization of XVIII to XIX**——A stirred solution of XVIII (500 mg.) in 500 ml. of benzene was irradiated for 40 hr. using ultraviolet lamp. The solution was concentrated and chromatographed on silica gel giving the isomerized product (XIX, 214 mg.) and unchanged XVIII (203 mg.).

**Reaction of V with Styrylmagnesium Bromide**——To a stirred tetrahydrofuran solution of V (4.2 g.) was added at room temperature a solution of styrylmagnesium bromide prepared from β-bromostyrene (7.4 g.) and Mg (0.97 g.) in tetrahydrofuran. The mixture was refluxed for 1 hr. The reaction mixture was worked up as described in the reaction of V with phenylethynylmagnesium bromide giving 1.4 g. of a dark brown oil. It was chromatographed in benzene on silica gel affording two crystalline compounds, 1-*cis*-3-*trans*-5-*trans*-1-(2-pyridyl)-6-phenyl-1,3,5-hexatriene (XX, 1.15 g.) and the all-*trans* triene (XIX, 40 mg.). The former was recrystallized from hexane m.p. 93~94°. *Anal.* Calcd. for $C_{17}H_{15}N$ : C, 87.51; H, 6.48; N, 6.00. Found : C, 87.66; H, 6.40; N, 6.07. UV $\lambda_{max}^{EtOH}$ mμ ($\varepsilon$) : 356 (50,800), 262.5 (12,000), 253.5 (11,800). IR $\nu_{max}^{Nujol}$ $cm^{-1}$ : 1640, 1628, 1608 (conj. triene), 1003, 993, 963 (*trans* olefin).

The latter compound (XIX) was recrystallized from $Et_2O$ to give pale yellow leaflets, m.p. 174~175°, which melted undepressed on admixture with sample obtained in Lindler's reduction of XV.

**Photoisomerization of XX to XIX**——A solution of XX (118 mg.) in 20 ml. of benzene was irradiated for 24 hr. using a ultraviolet lamp. The solution was concentrated to a small volume and chromatographed on silica gel giving the isomerized XIX (45 mg.) and unchanged XX (44.7 mg.).

Low pressure mercury lamp was used in the above photoisomerizations of *cis* olefin compounds to *trans* isomers.

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**Summary**

Quinolizinium bromide (V) reacts with various Grignard reagents giving two geometric isomers of ring opened products respectively. The reaction intermediate would be a 4-substituted-4*H*-quinolizine derivative (IV) which rearranges to the more stable pyridine derivative (*i.e.*, VIII).

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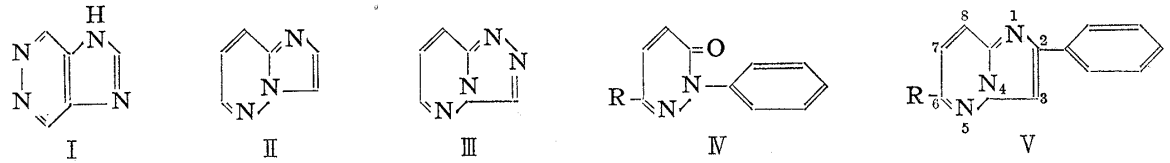
## 188. Fumio Yoneda, Takayuki Ohtaka, und Yoshihiro Nitta : Pyridazin-derivate. VI.*1 Synthese der Derivate des Imidazo[1,2-*b*]pyridazins.

(*Forschungslaboratorium, Chugai Pharmaz. A. G.**2)

Während einige Untersuchungen über Synthesen von Imidazo[4,5-*d*]pyridazinen (I)[1~4] bisher ausgeführt worden sind, finden sich über ihre isomeren Körper, Imidazo[1,2-*b*]-pyridazine (II) in der Literatur keine Angaben. Die Azaloga von II, *s*-Triazolo[4,3-*b*]-pyridazine (III) wurden aber durch mehrere Forscher bereits hergestellt,[5~8] um ihre tumorhemmende, antiprotozoische oder pharmakodynamische Wirkung zu prüfen. Salle, *et al.*[7] haben berichtet, um ein Beispiel anzuführen, daß 8-methylamino-*s*-triazolo[4,3-*b*]-pyridazin eine cardiovasculäre Wirkung besitzt.

Imidazo[1,2-*b*]pyridazine (II) sind die Deazakörper der oben erwähnten III und überdies können 2-Phenyl-derivate (V) von II chemischstrukturell als Viniloga der von Druey, *et al.* hergestellten 2-Phenyl-6-substituierten-3(2*H*)-pyridazinonen (IV)[9] angesehen werden. Also ließ sich bei den Verbindungen vom Strukturtypus V das Erscheinen der pharmakodynamischen Wirkung erwarten.



I II III IV V

Schema 1.

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