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Studies on Quinoline and Isoquinoline Derivatives. V.[1] Reaction of Isoquinoline 2-Oxide with Diketene[2]

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The reaction of isoquinoline 2-oxide with diketene afforded three products whose structures were assigned as 2,6-dimethyl-3-(1-isoquinolyl)-4-pyrone (II), 4-methyl-2-oxo-2*H*-benzo[*a*]quinolizine (III), and 1-acetonyl-4-acetoxy-2-acetyl-1,2-dihydroisoquinoline (IV), respectively.

Keywords——diketene; isoquinoline 2-oxide; addition reaction; benzo[*a*]quinolizine; 1,2-dihydroisoquinoline

Recently, Hamana and co-workers extensively investigated the reaction of quinoline 1-oxides with a variety of nucleophiles such as enamines and active methylene compounds in the presence of an appropriate acylating agent to introduce a carbon-substituent into the α-position of the quinoline ring. For example, they treated quinoline 1-oxide with ethyl cyanoacetate in the presence of acetic anhydride and obtained ethyl α-cyano-2-quinolineacetate in good yield.[3] Reactions of this type are now a standard method for the synthesis of 2-substituted quinoline derivatives.

Diketene is known to have an acylating ability together with a carbanion-like character. Thus, we decided to investigate the reaction of quinoline 1-oxide with diketene and obtained 2,6-dimethyl-3-(2-quinolyl)-4-pyrone,[4] as expected. Our interest was then focussed on the reaction of other heteroaromatic N-oxides with this reagent. The present paper deals with the reaction of isoquinoline 2-oxide (I) with diketene in acetic acid, to give characteristic products.

Treatment of I with an excess of diketene in acetic acid gave three products, colorless prisms of mp 147—148° ($C_{16}H_{13}NO_2$) (II), colorless prisms of mp 223—225° (dec.) ($C_{14}H_{11}$-

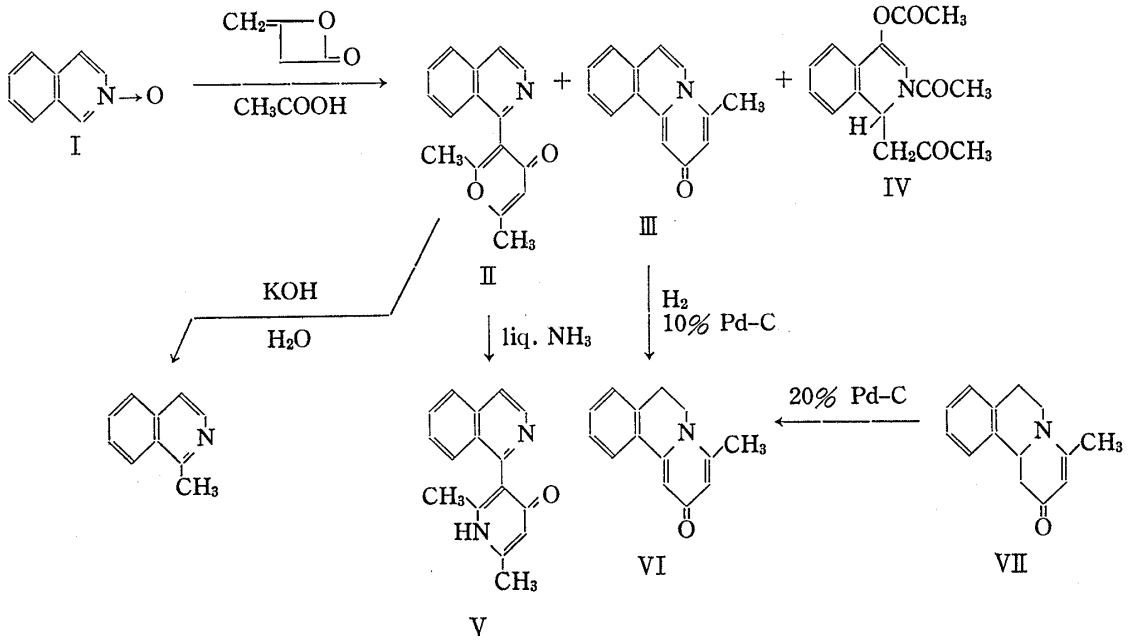

Chart 1

NO) (III), and colorless prisms of mp 132—133° ($C_{16}H_{17}NO_4$) (IV), in yields of 29.9, 9.6, and 13.2%, respectively (Chart 1).

The main product (II) was shown to have a 2,6-dimethyl-4-pyrone moiety on the basis of the nuclear magnetic resonance (NMR) and infrared (IR) spectra, which are similar to those of 2,6-dimethyl-3-(2-quinolyl)-4-pyrone.[3] Alkaline hydrolysis of II yielded acetone and 1-methylisoquinoline, which proved II to be a 1-substituted isoquinoline derivative. Accordingly, the 3-(1-isoquinolyl)-2,6-dimethyl-4-pyrone structure was assigned to the product II. The ready conversion of II into 3-(1-isoquinolyl)-2,6-dimethyl-4-pyridone (V) by the treatment of II in liquid ammonia also supported the proposed structure.

The structure of III was presumed to be 4-methyl-2-oxo-2*H*-benzo[*a*]quinolizine from the spectral data. This was chemically confirmed by the following experiments. On catalytic hydrogenation in the presence of palladium–charcoal, III was transformed into its dihydro derivative (VI), $C_{14}H_{13}NO$, mp 168—170° in good yield. Compound VI was identical with an authentic specimen prepared by dehydrogenation of the known benzoquinolizine derivative (VII).[5]

The IR spectrum ($CHCl_3$) of IV exhibits characteristic bands at 1770 and 1665, 1720, and 1685 cm^{-1}, which are due to an enol ester, an aliphatic ketone, and an amide carbonyl group, respectively. As shown in Fig. 1, the NMR spectrum of IV indicates the presence of three acetyl methyls at 1.5—2.1 ppm, a proton at the 3-position on the isoquinoline ring at 6.48 ppm, and a >CH–CH_2– group which gives signals at 2.4—3.0 and 6.4 ppm as an ABX-type multiplet, J_{AB}=15 Hz and $J_{AX}=J_{BX}$=9.2 Hz. The somewhat complicated splitting pattern of each signal might be explained by assuming the existence of a pair of rotamers owing to the double bond character of the N–C bond between the ring nitrogen and the amide carbonyl group. Based on the spectral data described above, the 1-acetonyl-4-acetoxy-2-acetyl-1,2-dihydroisoquinoline structure has been assigned to the product IV.

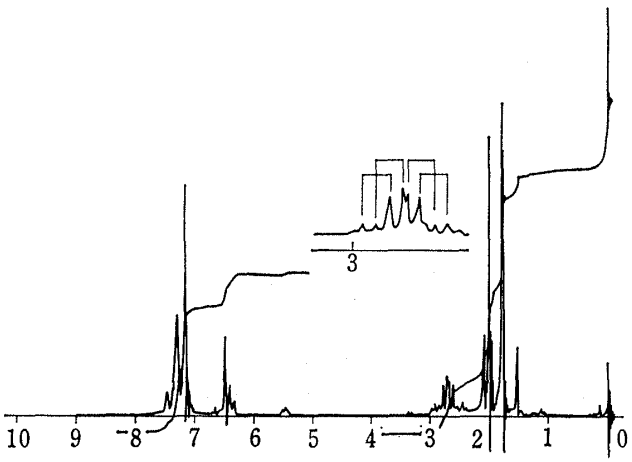

Fig. 1. NMR Spectrum of IV (100 MHz) in $CDCl_3$

The three reaction pathways (A, B, C) to the products (II, III, IV) are supported by some experimental evidence, as shown in Chart 2. The authors have already obtained a small amount of 2-acetonylquinoline from the reaction of quinoline 1-oxide with diketene and proved this compound to be an intermediate of the reaction. Although 1-acetonylisoquinoline (VIII) was not isolated in the present reaction, the compound VIII prepared alternatively from 1-methylisoquinoline and ethyl acetate was treated with diketene under conditions similar to those of the reaction of I with diketene. As a result of the above experiment, II and III were obtained in yields exceeding those observed on the direct formation of II and III from I.

The IR spectrum of the crude reaction mixture of I and diketene shows a characteristic acid anhydride band at 1820 cm^{-1}, which suggests the formation of a mixed anhydride from the reaction of diketene and acetic acid. It is well known[6] that the reaction of I with acetic anhydride affords 4-acetoxyisoquinoline (IX). The presence of the mixed anhydride may explain the formation of IX, although IX was not isolated from our reaction mixture. Further, it was confirmed that IX reacted with diketene to give IV in fairly good yield by an independent experiment.

In addition, it should be mentioned that the three pathways A′,B′ and C′ are conceivable for the formation of the intermediate (VIII), on the basis of the chemical properties of diketene

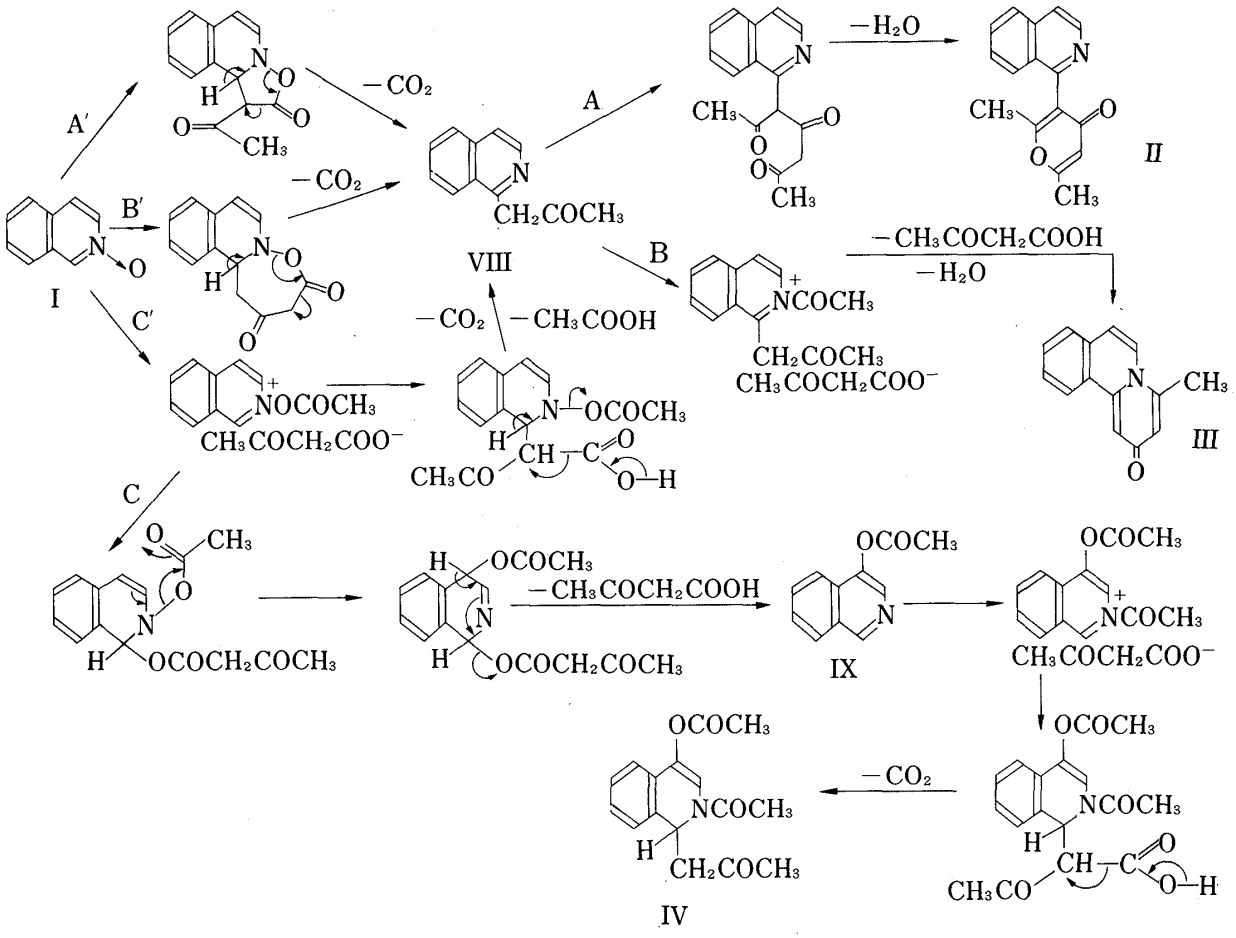

Chart 2

reported by Kato.[7]

Although the chemical properties of isoquinoline 2-oxides are in general considered to be similar to those of quinoline 1-oxides, there are reports of some differences of chemical reactivity of these N-oxides.[8] Our present results seem to represent an additional example in this category.

Experimental[9]

Reaction of Isoquinoline 2-Oxide (I) with Diketene——Diketene (42 g, 0.5 mol) was added dropwise at 55—60° to a solution of I (14.5 g, 0.1 mol) in AcOH (100 ml), and the mixture was stirred until the exothermic reaction ceased. The solution was concentrated under reduced pressure and the oily residue was dissolved in $CHCl_3$ (200 ml). Upon addition of 10% HCl (100 ml), a colorless crystalline solid separated out. The solid was filtered off and dissolved in 1 N Na_2CO_3. The resulting precipitate was extracted with $CHCl_3$ and dried over K_2CO_3. The chloroform solution was concentrated and the solid product was recrystallized from acetone, affording 2.0 g (9.6%) of 4-methyl-2-oxo-2*H*-benzo[*a*]quinolizine (III) as colorless prisms, mp 223—225° (dec.). *Anal.* Calcd for $C_{14}H_{11}NO$ (III): C, 80.36; H, 5.30; N, 6.69. Found: C, 80.86; H, 5.30; N, 6.61. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640 (4-pyridone). NMR (CD_3OD): 2.52 (3H, s, 4-CH_3), 6.51 (1H, d, J=3 Hz, 4-H), 6.88 (1H, d, J=7.5 Hz, 7-H), 7.06 (1H, d, J=3 Hz, 1-H), 7.2—7.55 (3H, m, 8,9,10-H), 7.64 (1H, d, J=7.5 Hz, 6-H), 7.8—8.1 (1H, m, 11-H). The aqueous layer was separated from the filtrate ($CHCl_3$–10% HCl), and the organic layer was extracted with 10% HCl. The combined aqueous extracts were made alkaline with K_2CO_3, and the resulting mixture was extracted with $CHCl_3$. The chloroform extracts were dried over K_2CO_3, and evaporated to dryness. The residue was chromatographed on alumina, eluting with ether. A crystalline solid was obtained from the eluates and recrystallized from AcOEt, yielding 7.5 g (30%) of 3-(1-isoquinolyl)-2,6-dimethyl-4-pyrone (II) as colorless prisms, mp 147—148°. *Anal.* Calcd for $C_{16}H_{13}NO_2$ (II): C, 76.49; H, 5.46; N, 5.75. Found: C, 76.66; H, 5.17; N, 5.66. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (4-pyrone). NMR ($CDCl_3$): 2.05 (3H, s, CH_3), 2.34 (3H, s, CH_3), 6.24 (1H, s, proton of pyrone ring), 7.5—7.95 (5H, m, protons of isoquinoline

ring), 8.56 (1H, d, J=6.0 Hz, proton of isoquinoline ring).

The chloroform layer separated from the filtrate ($CHCl_3$–10% HCl) was washed with 5% $NaHCO_3$, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on silica gel, eluting with benzene. The eluates were concentrated, and the crude product was recrystallized from benzene, affording 3.8 g (13.2%) of 1-acetonyl-4-acetoxy-2-acetyl-1,2-dihydroisoquinoline (IV) as colorless prisms, mp 132—133°. *Anal.* Calcd for $C_{16}H_{17}NO_4$ (IV): C, 66.86; H, 5.96; N, 4.88. Found: C, 66.77; H, 5.85, N, 4.77.

Hydrolysis of II——A solution of II (1.0 g, 4 mmol) and KOH (5 g) in 50% EtOH (50 ml) was heated on a water-bath for 1 hr. The mixture was then distilled, and 2,4-dinitrophenylhydrazine was added to the resulting distillate to give yellow needles of mp 125—126° (from EtOH), undepressed on admixture with authentic acetone 2,4-dinitrophenylhydrazone.

On the other hand, the distillation residue was extracted with ether, and the extract was dried (K_2CO_3), and evaporated to dryness. The oily residue was distilled under reduced pressure to give 0.12 g (21%) of 1-methylisoquinoline as a pale yellow liquid, bp 109—110° (18 mmHg), whose IR spectrum was identical with that of an authentic sample. Picrate mp 233—234° (dec.) (authentic mp 233—234° (dec.)).

Reaction of II with Liquid Ammonia——A mixture of II (1.25 g, 5 mmol), liq. NH_3 (10 ml) and EtOH (10 ml) was warmed at 50° for 24 hr in a sealed tube. After the removal of liq. NH_3 and EtOH by evaporation, the residue was recrystallized from MeOH–AcOEt giving 1.1 g (88%) of 3-(1-isoquinolyl)-2,6-dimethyl-4-pyridone (V) as colorless prisms, mp above 320°. *Anal.* Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.44; H, 5.74; N, 11.29. IR ν_{max}^{KBr} cm^{-1}: 3400, 1625 (4-pyridone). NMR (CF_3CO_2H): 2.54 (3H, s, CH_3), 2.90 (3H, s, CH_3), 7.49 (1H, s, proton of pyridine ring), 8.9—9.0 (6H, m, protons of isoquinoline ring).

4-Methyl-2-oxo-6,7-dihydro-2*H*-benzo[*a*]quinolizine (VI)——4-Methyl-2-oxo-1,6,7,11b-tetrahydro-2*H*-benzo[*a*]quinolizine (VII)[5] (2.13 g, 10 mmol) and 20% Pd–C (2.0 g) in xylene (40 ml) were heated under reflux for 30 hr. The catalyst was then removed and the solution was concentrated. The residue was recrystallized from benzene, affording colorless needles of mp 168—170°, 1.5 g (70%). *Anal.* Calcd for $C_{14}H_{13}NO$ (V): C, 79.59; H, 6.20; N, 6.63. Found: C, 79.34; H, 6.43; N, 6.49. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1630 (4-pyridone). NMR ($CDCl_3$): 2.49 (3H, s, 4-CH_3), 3.02 (2H, t, J=6.0 Hz, 7-CH_2), 4.01 (2H, t, J=6.0 Hz, 6-CH_2), 6.24 (1H, d, J=2.5 Hz, 3-CH), 6.79 (3H, d, J=2.5 Hz, 1-CH), 7.2—7.5 (3H, m, 8,9,10-CH), 7.5—7.8 (1H, m, 11-CH).

Hydrogenation of III——Compound III (0.42 g, 2 mmol) was hydrogenated over 10% Pd–C (0.5 g) in AcOH (20 ml)–10% HCl (10 ml) under atmospheric pressure at room temperature until 45 ml (2 mmol) of hydrogen had been taken up. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was made alkaline with 3 N Na_2CO_3, extracted with $CHCl_3$, and dried over K_2CO_3. The solvent was evaporated off, and the resulting product was recrystallized from benzene, yielding 0.30 g (70%) of colorless needles, mp 168—170°, which were identical with VI as judged by mixed melting point determination.

Reaction of 4-Acetoxyisoquinoline (IX) with Diketene in Acetic Acid——4-Acetoxyisoquinoline (IX) (1.87 g, 10 mmol) was treated with diketene (4.2 g, 50 mmol) in AcOH (10 ml) under conditions similar to those used for the reaction of isoquinoline. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in $CHCl_3$. The chloroform solution was washed with 5% $NaHCO_3$ and then 10% HCl, and dried over Na_2SO_4. The solvent was evaporated off and the resulting oil was chromatographed on silica gel, eluting with benzene. Concentration of the eluates gave a crystalline solid, which was recrystallized from benzene, to afford 0.80 g (28%) of colorless prisms, mp 132—133°, undepressed on admixture with IV.

The Reaction of 1-Acetonylisoquinoline (VIII) with Diketene——Diketene (1.0 g, 12 mmol) was added to a solution of VIII (0.93 g, 5 mmol) in AcOH (5 ml). The mixture was stirred at room temperature for 5 hr, and then allowed to stand overnight. The solution was worked up according to the procedure described in the case of isoquinoline 2-oxide, yielding 0.38 g (36.4%) of colorless prisms, mp 233—235° (dec.) (from acetone), and 0.43 g (34.3%) of colorless prisms, mp 147—148° (from AcOEt). The IR spectrum (KBr) of the former compound was identical with that of III, and the melting point of the latter was undepressed on admixture with II.

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References and Notes

1) Part IV: H. Yamanaka, H. Egawa, and T. Sakamoto, *Chem. Pharm. Bull.*, **27**, 1004 (1979).
2) A part of this work was reported in *Heterocycles*, **3**, 1065 (1975) as a short communication.
3) M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.*, **11**, 415 (1963).
4) T. Kato, H. Yamanaka, T. Sakamoto, and T. Shiraishi, *Chem. Pharm. Bull.*, **22**, 1206 (1974).
5) M. von Strandtmann, M.P. Cohen, and J. Shavel, Jr., *J. Org. Chem.*, **31**, 797 (1966).
6) M.M. Robinson and B.L. Robison, *J. Org. Chem.*, **21**, 1337 (1957).

7) T. Kato, *Accounts Chem. Res.*, 7, 265 (1974).
8) E. Ochiai and M. Ikehara, *Pharm. Bull.*, 3, 454 (1955).
9) All melting points are uncorrected. IR spectra measurements were performed with a JASCO IRA-1 spectrometer. NMR spectra were taken at 60 MHz with a Hitachi-Perkin-Elmer R-20 spectrometer and at 100 MHz with a JEOL JNM-PS-100 spectrometer. Chemical shifts are expressed in ppm downfield from TMS as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, and m=multiplet.