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A Kinetic Study of Cyclodehydration of β-(*p*-Toluidino)-acrolein. I

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The cyclodehydration of β-(*p*-toluidino)-acrolein (I) in sulfuric acid was studied kinetically in relation of that of 4-(*p*-toluidino)-3-penten-2-one (VII).

Reversible sulfonation of I at α-position and cyclodehydration to 6-methylquinoline (II) proceeded in parallel.

The difference in reactivity between β-arylaminoacrolein and 4-arylamino-3-penten-2-one was discussed.

Keywords——kinetic study; cyclodehydration; protonation; reversible sulfonation; β-(*p*-toluidino)-acrolein; 6-methylquinoline

In the previous paper[2] we have reported the action of concentrated sulfuric acid on β-arylaminoacrolein derivatives. β-(*p*-Toluidino)-acrolein (I) was cyclodehydrated to give 6-methylquinoline (II) quantitatively, while β-anilinoacrolein (III) was mainly sulfonated at *para* position of the benzene ring and only a trace of quinoline was detected in the reaction mixture.

A kinetic study by Bonner, *et al.*[3,4] revealed that the experimental first order rate constant k_1 of the cyclodehydration of 4-arylamino-3-penten-2-one (IV) is related to Hammett's acidity function H_0 as expressed by the equation, $\log k_1 + H_0 = \text{constant}$. They concluded that the bulk of IV is a monoprotonated form (V) in sulfuric acid, and the cyclodehydration proceeds *via* diprotonated intermediate (VI).

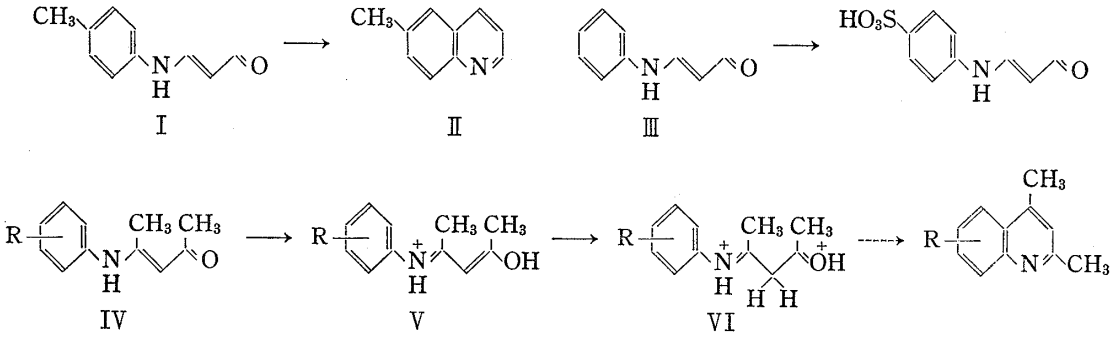

Chart 1

In the previous paper[2] we presumed that the difference in reactivities of III and IV is attributable to the steric effect of methyl group at 4-position of V. In the present work a kinetic study of cyclodehydration of I was attempted to obtain further insight into the problem of the steric effect of methyl group. Bonner, *et al.*[3,4] measured unchanged IV as ferric complex of acetylacetone after the dilution of reaction mixture with water. This method is not applicable to our purpose becouse I is converted to malonaldehyde dianil in diluted mineral acid solution.[5]

1) Location: *No 542, Miyamacho, Funabashi.*
2) S. Tamura and E. Yabe, *Chem. Pharm. Bull.* (Tokyo), **22**, 2982 (1974).
3) T.G. Bonner, M.P. Thorne, and J.M. Wilkins, *J. Chem. Soc.*, **1955**, 2351.
4) T.G. Bonner and M. Barnard, *J. Chem. Soc.*, **1958**, 4176.
5) S. Tamura and E. Yabe, *Chem. Pharm. Bull.* (Tokyo), **21**, 2105 (1973).

A direct measurement of I and II by the optical density of the reaction mixture was attempted, and for comparison, cyclodehydration of 4-(*p*-toluidino)-3-penten-2-one (VII) to 2,4,6-trimethylquinoline (VIII) was followed by the same method. This method was expected to have an advantage that the influence of the dissolution of amines on the acidity of sulfuric acid was minimized owing to the lower concentrations of reaction mixture compared with Bonner's method.

The ultraviolet absorption (UV) spectra of I, II, VII and VIII in sulfuric acid were shown in Fig. 1. In the kinetic study of cyclodehydration of VII at 25°, optical densities of reaction mixture were measured at 241, 242, 287 and 288 nm and the concentrations of VII and VIII were calculated by the least square method, and an isosbetic point was observed at 254 nm. Excellent first order rate constants were obtained in the range of media studied and the results were shown in Table I. Bonner, *et al.*[3] showed the value of −12.52[6] for log k_1+H_0 in the case of VII at 25° and we have obtained the value of −12.36 for the same equation. This means that the reaction proceeded slightly faster in our condition, and is consistent with the above-mentioned conception.

In the case of I at 25°, however, the result of the least square method was rather unsatisfactory, *i. e.*, the sum of the concentrations of I and II was inconsistent with the initial concentration of I in each measurement and isosbestic point was not observed. These tendencies were found to be more remarkable at higher concentration of sulfuric acid. But after the prolonged time of standing, UV spectrum of reaction mixture was completely consistent with that of II in all concentrations of sulfuric acid examined. This result, together with the fact that the yield of II was nearly quantitative when I was treated with concentrated sulfuric acid,[2] suggests I was converted ultimately to II completely.

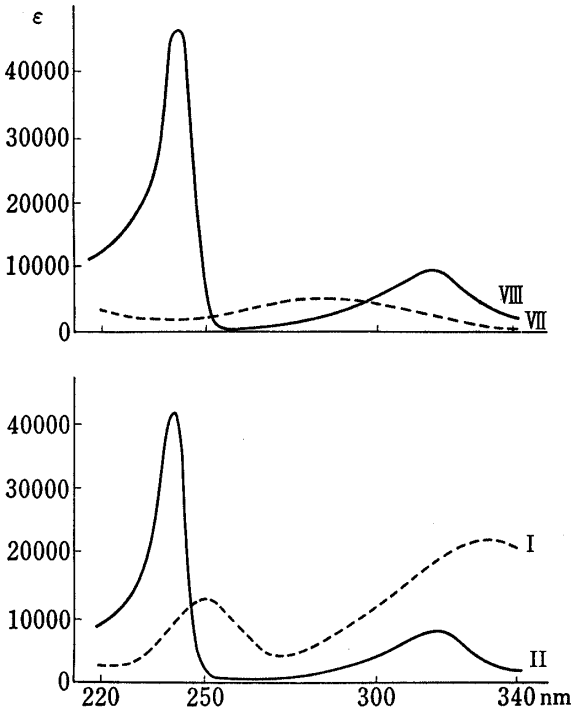

Fig. 1. UV Spectra of I (in 81.3% H_2SO_4), II (in 81.3% H_2SO_4), VII (in 75.7% H_2SO_4) and VIII (in 86.9% H_2SO_4)

Table I. Rates of Cyclodehydration of VII in H_2SO_4 at 25°

%H_2SO_4	H_0	10^5k_1(sec^{-1})	logk_1+H_0
83.7	−7.90	3.59	−12.34
85.6	−8.20	7.22	−12.34
86.2	−8.30	8.95	−12.35
88.4	−8.69	18.72	−12.42

Table II. Rates of Cyclodehydration of I in H_2SO_4 at 60°

%H_2SO_4	H_0	10^5k_1(sec^{-1})	log k_1+H_0
81.4	−7.51	0.470	−12.84
83.1	−7.80	1.65	−12.58
84.6	−8.05	2.98	−12.58
86.1	−8.30	5.89	−12.53

6) After the publication of Bonner's work, Jorgenson (*J. Am. Chem. Soc.*, **88**, 878 (1963)) had reinvestigated the acidity of aqueous sulfuric acid and submitted a new values of H_0. The value designated is calculated from Bonner's experimental rate constants and Jorgenson's H_0 values by us.

When the cyclodehydration of I was carried out in sulfuric acid of relatively low concentration (81—86%) at 60°, the above-mentioned method gave a satisfactory result, *i. e.*, the sum of the concentrations of I and II was consistent with initial concentration of I within the experimental error, and an isosbestic point was observed at 248.5 nm. The results were shown in Table II and a value of −12.63 for log k_1+H_0 was obtained. The cyclodehydration of I in sulfuric acid, therefore, proceeds much slower than that of VII, but precise comparison can not be made because of the reaction temperature difference.

β-(*p*-Chloroanilino)-acrolein (IX),[2] 4-(*p*-chloroanilino)-3-buten-2-one (X) and 4-(*p*-chloroanilino)-3-penten-2-one (XI)[7] don't undergo cyclodehydration in sulfuric acid. For the purpose of elucidating the behavior of the three compounds in sulfuric acid, their proton magnetic resonance (PMR) spectra were measured in the same medium (Fig. 2). The PMR spectrum of XI in 83% sulfuric acid showed a singlet signal (2H) of 3-position at δ 4.42 which disappeared in sulfuric acid-d_2. Therefore, the protonation of XI takes place not at oxygen atom but at 3-position. The PMR spectrum of IX in 83% sulfuric acid showed a triplet signal (1H) of α-position at δ 6.30 and that of X in the same medium showed two doublet signals (1H) of 3-position at δ 5.87 and 6.03. Therefore, the protonation of IX and X takes place at each oxygen atom and in the case of X two conformational isomers of monoprotonated form are present in sulfuric acid. These signals disappeared in sulfuric acid-d_2. The PMR spectra of *p*-toluidino-analogs of IX, X and XI in the same medium are similar to those of

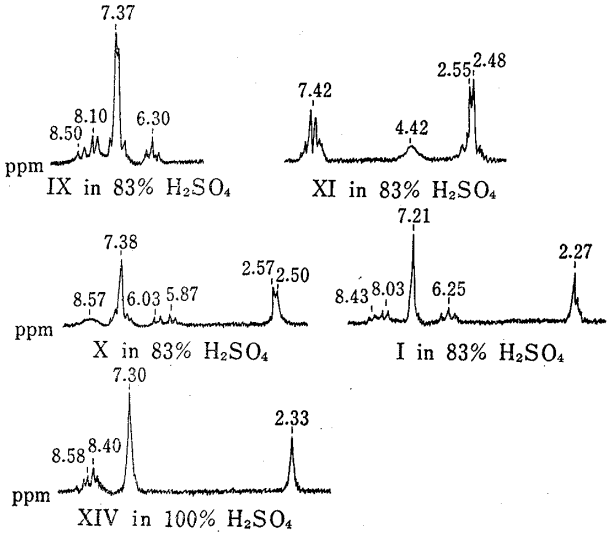

Fig. 2. PMR Spectra of IX, X, XI, I and XIV in H_2SO_4

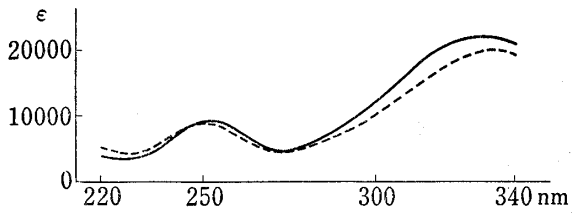

Fig. 3. Change of UV Spectrum of the Solution of IX in 96% H_2SO_4

——: at the first time (identical with that of IX in 83% H_2SO_4).
------: after 4 hr standing.

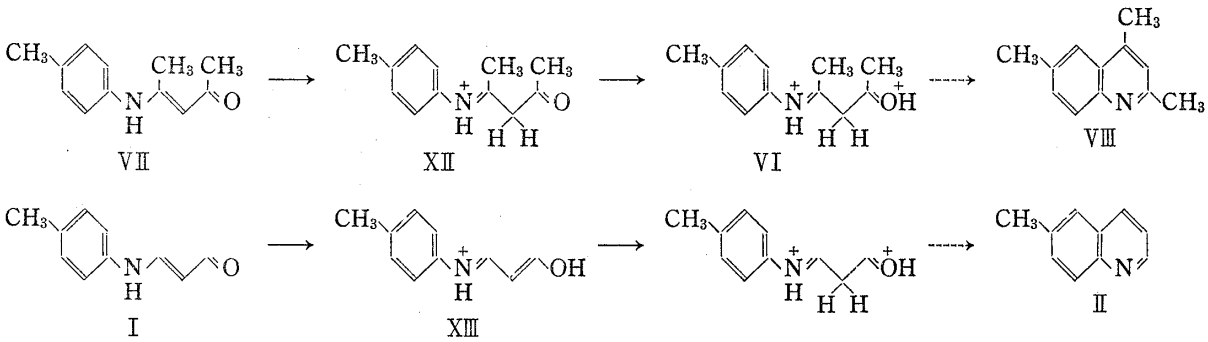

Chart 2

7) E. Roberts and E.E. Turner, *J. Chem. Soc.*, **1927**, 1832.

the original compounds. This fact also explains that the absorption maximum of UV spectrum of VII is present at shorter wave length and extinction coefficient is lower compared with those of I in sulfuric acid.

Consequently, Bonner's scheme (Chart 1) must be corrected as Chart 2, and from the above observations it is concluded that the difference of reactivity in cyclodehydration of I and VII is attributable to the difference in the position at which protonation takes place. The cyclodehydration of I and VII proceeds *via* each diprotonated form, and monoprotonated I (XIII, Chart 2) is expected to stand against diprotonation for its resonance stability, while monoprotonated VII (XII, Chart 2) is diprotonated more easily.

The PMR spectrum of IX in 100% sulfuric acid was first similar to that observed in 83% sulfuric acid, but afterward the signal at δ 6.30 disappeared slowly and simultaneously the signals in the region δ 8—9 (β-position and aldehyde) shifted toward a lower magnetic field (Fig. 2). After this change completed the solution was diluted to 83% sulfuric acid by adding 50% sulfuric acid. The PMR spectrum of this solution was changed slowly to the original pattern. Similar reversible change was observed in UV spectrum of IX in 83 and 96% sulfuric acid (Fig. 3).

From the above observations it was concluded that β-arylaminoacrolein derivatives undergo some reversible change in sulfuric acid, and this change was found to be sulfonation at α-position by the following experiments. The compound I was dissloved in 100% sulfuric acid under ice-cooling and the solution was allowed to stand for 1 hr at room temperature. Then the reaction mixture was poured onto ice and the resulting precipitate was collected and washed successively with ether, acetic acid, ether, ethanol and ether. A pale yellow crystalline mass (XIV), $C_{10}H_{11}NO_4S$, was obtained. When XIV was added into diluted aqueous sodium carbonate, a clear solution was obtained and then from that solution sodium salt of XIV (XV) precipitated gradually as pale yellow crystals.

The nuclear magnetic resonance spectrum of ^{13}C (CMR spectrum) of XIV in sulfuric acid-d_2 showed two singlet signals of α-carbon at δ 112.2 and 112.4, and these signals didn't split under offresonance condition suggesting that neither hydrogen nor deuterium atom is combined with the α-carbon of XIV, and that XIV is present as a mixture of two conformational isomers in sulfuric acid. The PMR spectrum of XV in dimethyl solfoxide-d_6 showed signals at δ 9.22 (1H, singlet, aldehyde), δ 7.90 (1H, doublet, J=13 Hz, β-position), δ 10.25 (1H, doublet, J=13 Hz, NH) and no signal of α-position was observed. From the above observations the structure of XIV was determined to be 3-(p-toluidino)-1-oxo-2-propen-2-sulfonic acid (XIV, Chart 3).

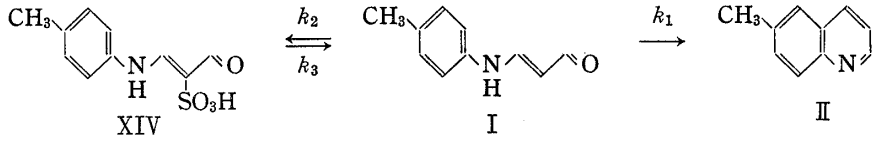

Chart 3

The UV spectrum of XV in 100% sulfuric acid showed two absorption maximum at 250 nm (ε=14800) and 340 nm (ε=17000) immediately after dissolution and gradually changed so that extinction coefficient at 340 nm slightly decreased whereas the optical density at 241 nm (the absorption maximum of II) showed no increase. This means that II was not produced directly from XIV and that the decrease of extinction coefficient at 340 nm is probably due to the slow comformational isomerisation of XIV. The UV spectrum of XIV in 83% sulfuric acid had at first a similar pattern to that of XIV in 100% sulfuric acid, but changed gradually to form that of I in 83% sulfuric acid (UV spectrum of I in 83% sulfuric acid showed no change for 24 hr at room temperature). The UV spectrum of XIV in 96% sulfuric acid, however, changed to form that of II in the same medium after the long period of time.

The PMR spectrum of XIV in 83% sulfuric acid showed at first signals at δ 8.58 and 8.68 (singlet, aldehyde) and δ 8.32 and 8.40 (singlet, β-position) and no signal of α-position, but the spectrum changed gradually and finally showed the signals at δ 8.43 (doublet, J=11 Hz, aldehyde), δ 8.03 (doublet, J=11 Hz, β-position) and δ 6.25 (triplet, J=11 Hz, α-position). This final pattern is identical with that of I in the same medium. These observations suggest that XIV is hydrolysed to form I in 83% sulfuric acid. The suggestion was confirmed by the recovery of I from the solution of XV in 83% sulfuric acid.

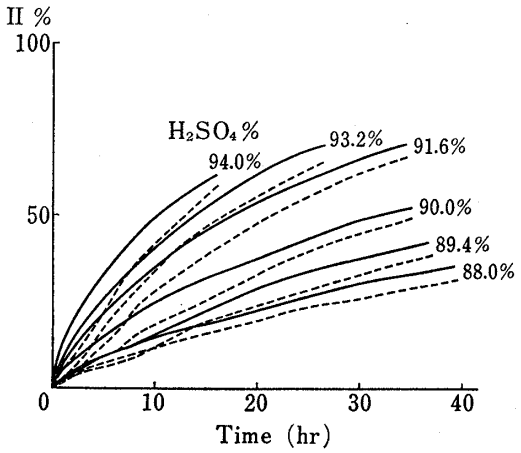

Fig. 4. Formation of II in H_2SO_4
——, starting material: I.
------, starting material: XV.

The kinetic experiment of formation of II from I and XV in sulfuric acid at 25° (Chart 3) was carried out as follows: At the definite time intervals, the aliquot part of the reaction mixture was diluted to 83% by the addition of 50% sulfuric acid under ice-cooling and allowed to stand for 24 hr at 25°. The concentrations of I and II were calculated from the optical densities of the solution at 241, 242, 332 and 333 nm by the least square method. A satisfactory result was obtained and an isosbestic point was observed at 248.5 nm. The results were shown in Fig. 4.

When XV and I was employed as the starting material, the rate equations are represented by 1), 2) and 3), 4), respectively.

$$x_S = \frac{k_3}{2\sqrt{\alpha^2-\beta}}(e^{r_1 t}-e^{r_2 t}) \tag{1}$$

$$y_S = 1 + \frac{1}{2\sqrt{\alpha^2-\beta}}(r_2 e^{r_1 t}-r_1 e^{r_2 t}) \tag{2}$$

$$x_M = \frac{r_1+k_3}{2\sqrt{\alpha^2-\beta}}e^{r_1 t} - \frac{r_2+k_3}{2\sqrt{\alpha^2-\beta}}e^{r_2 t} \tag{3}$$

$$y_M = 1 + \frac{k_1(r_1+k_3)}{2r_1\sqrt{\alpha^2-\beta}}e^{r_1 t} - \frac{k_1(r_2+k_3)}{2r_2\sqrt{\alpha^2-\beta}}e^{r_2 t} \tag{4}$$

where x_S and y_S represent the portion of I and II when XV was the starting material, x_M and y_M represent the portion of I and II when I was the starting material, and

$$2\alpha = k_1 + k_2 + k_3, \quad \beta = k_1 k_3$$

$$r_1 = -\alpha + \sqrt{\alpha^2-\beta}, \quad r_2 = -\alpha - \sqrt{\alpha^2-\beta}.$$

The non-leanear least square method to evaluate each rate constant afforded rather unsatisfactory result. Only the values of y_S and y_M were measured in the present experiments, and the measurement of x_S and x_M is necessary to obtain more precise result. Although the measurement of x_S and x_M is presumably difficalt owing to the similarity of UV spectra of I and XIV and to the slow conformational isomerisation of XIV in sulfuric acid, experiments are continued to obtain the values of x_S and x_M.

Experimental

UV spectra were measured on Hitachi spectrophotometer model 139 and PMR spectra were recorded on JNM-PMX 60 NMR spectrometer. PMR spectra in sulfuric acid and CD_3SOCD_3 were recorded using sodium β-trimethylsilylpropionate-d_4 and tetramethylsilane as internal standard, respectively.

Materials——I and IX were prepared according to the previous paper,[5] the melting points of I and IX were 122° and 160.5°, respectively. VII and XI were prepared by the method of Roberts and Turner,[7] the melting points of VII and XI were 66° and 60°, respectively. β-(*p*-Toluidino)-3-buten-2-one (XVI) and X were prepared by the method of Thielepape,[8] the melting points of XVI and X were 116—118° and 115°, respectively.[9] VIII was prepared by the method of Bonner, *et al.*,[3] the melting point of VIII was 43—45°.

Preparation of XIV——1.61 g (0.01 mol) of I was added gradually to 15 g of 100% H_2SO_4 under ice-cooling, and the resulting clear solution was allowed to stand for 1 hr at room temperature. The reaction mixture was poured onto 15 g of ice and the deposited precipitate was collected and washed successively with ether, AcOH, ether, EtOH and ether. 1.54 g (63.9%) of pale yellow crystalline mass (XIV) was obtained. mp 166° (dec.). *Anal.* Calcd. for $C_{10}H_{11}NO_4S$: C, 49.78; H, 4.60; N, 5.81. Found: C, 49.52; H, 4.66; N, 5.63.

Sodium Salt of XIV (XV)——0.95 g (0.0039 mol) of XIV dissolved in 50 ml of 0.9% aqueous Na_2CO_3 and filtered. From the filtrate pale yellow crystals precipitated under ice-cooling. The precipitate was collected and washed with cold water. 0.45 g (43%) of XV was obtained. It darkened at 215°. *Anal.* Calcd. for $C_{10}H_{10}NO_4SNa$: C, 45.63; H, 3.83; N, 5.32. Found: C, 45.63; H, 3.40; N, 4.84.

Recovery of I from XIV——0.53 g (0.002 mol) of XV was dissolved in 6 g of 83% H_2SO_4 under ice-cooling and the resulting solution was allowed to stand for 1 hr at room temperature. The reaction mixture was poured onto 6 g of ice and the deposited precipitate was collected and added in portions into 10 ml of 6% aqueous Na_2CO_3 and extracted with benzene. The extract was dried over K_2CO_3 and evaporated under reduced pressure. The residue was recrystallized from benzene. 0.11 g (34%) of I was obtained which was identified with authentic sample by the mixed melting point measurement and the comparison of their IR spectra.

CMR Spectra of I, XIV and XVI——All measurements were carried out in D_2SO_4 and tetramethylsilane was used as standard. The CMR spectrum of XVI was measured as the model compound of I and XIV. CMR spectrum of I in 86% D_2SO_4: aldehyde C, δ 177.6 and 180.1; β-C, δ 163.2 and 167.7; α-C, δ 104.8 (triplet). CMR spectrum of XIV in 100% D_2SO_4 (containing some H_2SO_4): 2-C, δ 112.2 and 112.4 (these signals showed no spliting under offresonance condition); 1-C, δ 176.6 and 179.5; 3-C, δ 153.4 and 158.4. CMR spectrum of XVI in 86% D_2SO_4: 2-C, δ 187.0 and 189.3 (these signals showed no spliting under offresonance condition); 4-C, δ 156.6 and 159.6; 3-C, δ 96.7 (triplet).

Acknowledgement The authors are indebted to Mr. K. Fujita, LEOL LTD., for the measurements of CMR spectra.

8) E. Thielepape, *Ber.*, **55**, 127 (1922).
9) H. Boehme, G. Berg, and H. Schneider (*Arch. Pharm.*, **297**, 321 (1964)) reported the values of 112° and 115° as the melting points of XVI and X, respectively.