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β-Arylaminoacrolein Derivatives. II.[1] Cyclodehydration of β-Arylaminoacrolein Derivatives

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The cyclodehydration of 4-arylamino-3-penten-2-one to 2,4-dimethylquinoline (Combes reaction) is markedly affected by the substituted group in the aromatic ring of the former compounds and is possible to occur only in a limited number of their derivatives.[3]

In the preceding paper[1] the syntheses of β-arylaminoacrolein derivatives for further studies of Combes reaction were reported. These compounds were expected to undergo cyclodehydration by acid because the aldehyde are generally of higher reactivity than the ketones.

When 4-anilino-3-buten-2-one (II) was heated in sulfuric acid II was sulfonated on the aromatic ring and no quinolines were detected from the reaction mixture,[1] while 4-anilino-3-penten-2-one (I) was cyclodehydrated to 2,4-dimethylquinoline under the same conditions.

β-Anilinoacrolein (III) gave only a trace of quinoline after heating in concentrated sulfuric acid. Although the isolation of β-(*p*-sulfoanilino)-acrolein (V) from the reaction mixture of III and concentrated sulfuric acid has not been successful, the sulfonation of III was proved by the following experiments. The compound III was warmed in concentrated sulfuric acid at 50° for 5 hours, and the reaction mixture was poured into ice-water and the resulting clear solution was allowed to stand overnight. Malonaldehyde dianil of sulfanilic acid (VI) was precipitated from the solution and was recrystallized from 2N hydrochloric acid to give VI as orange-yellow prisms melting at 313° (decomp.). The compound VI was also obtained by the reaction of malonaldehyde dianil (IV) and concentrated sulfuric acid or of sulfanilic acid and malonaldehyde bis (diethyl acetal) in 2N hydrochloric acid. The identity of the substances obtained by the above mentioned three methods was confirmed by the comparison of their infrared absorption spectra.

When III was heated in concentrated sulfuric acid at higher temperature (above 90°), carbon monoxide was developed and only the tarry material was found after the treatment of the reaction mixture.

The difference in chemical properties between I and II or III is attributable to the steric factor of the methyl group at β-position to the carbonyl group in I. The conformational analysis of I and II were carried out on their nuclear magnetic resonance spectra in the similar manner to that of III described in the preceding paper.[1] In the case of I only s-*cis* form was detected in either deuterochloroform, deuterodimethyl sulfoxide or deuteromethanol, while II was found only in s-*cis* form in deuterochloroform and in both s-*cis* and s-*trans* form in deuteromethanol. As reported previously[1] III was found in both s-*cis* and s-*trans* form in deuterochloroform and only in s-*trans* form in either deuterodimethyl sulfoxide or deuteromethanol. It is, therefore, believed that the tendency of these compounds to be in s-*cis* form is in the following order: I>II>III.

The cyclodehydration of anils in concentrated sulfuric acid is believed to proceed *via* diprotonated intermediate, while the most part of anil exists as monoprotonated form in the

1) Part I: S. Tamura and E. Yabe, *Chem. Pharm. Bull.* (Tokyo), **21**, 2105 (1973).
2) Location: *No. 542, Miyamacho, Funabashi.*
3) E. Roberts and E.E. Turner, *J. Chem. Soc.*, **1927**, 1832.

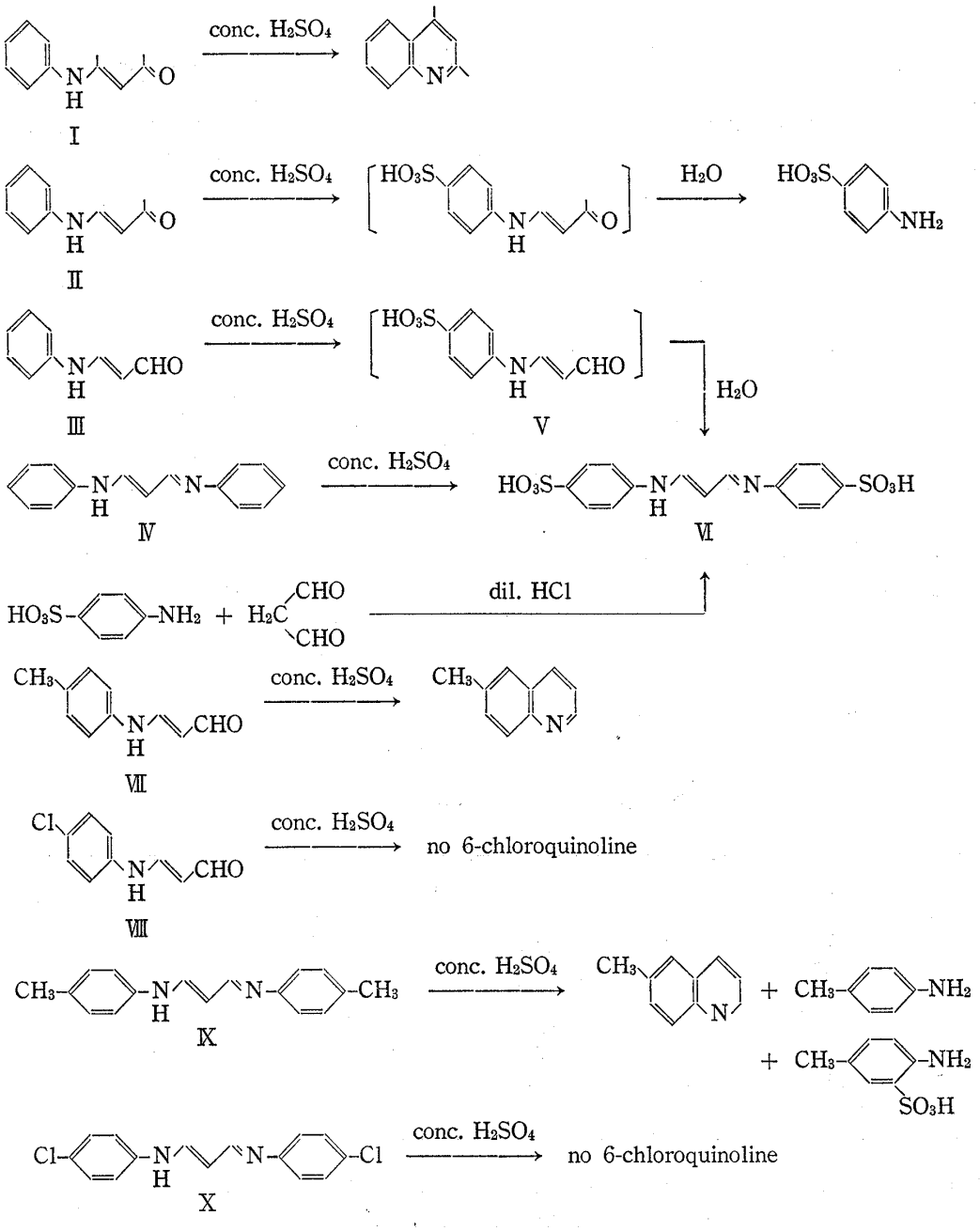
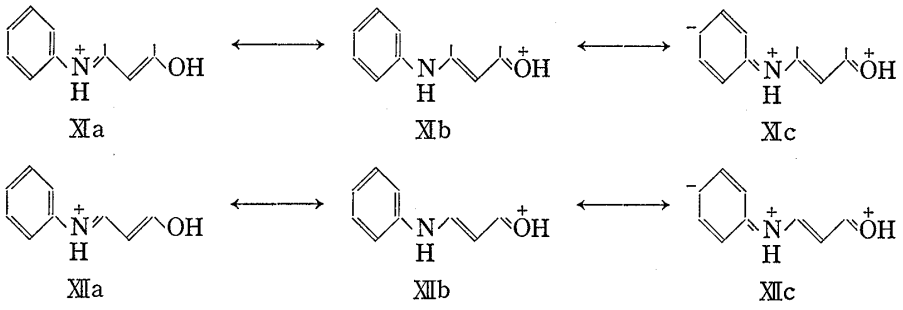


Chart 1

same medium.[4] The conjugated double bond system of monoprotonated I (XI, Chart 2) is unable to lie on the same plane for s-*trans* form owing to the repulsion between two methyl groups in XI. The resonance stabilisation of XI, therefore, may be less than that of monoprotonated form of III (XII, Chart 2). Further, aromatic ring of XI is difficult to lie in the plane of the conjugated double bond system owing to the repulsion of β-methyl group and *o*-hydrogen atom of aromatic ring. The resonance contribution of XIc is, therefore, less than that of XIIc. As the result, I is more readily cyclodehydrated to give 2,4-dimethylquinoline and III is more easily sulfonated at para position of aromatic ring in concentrated sulfuric acid. From the above consideration, the cyclodehydration of β-(*p*-substituted anilino)-acrolein was attempted on presumption that the compounds are insusceptible to the sulfonation.

4) T.G. Bonner, M.P. Thorne and J.M. Wilkins, *J. Chem. Soc.*, **1955**, 2351; T.G. Bonner and M. Barnard, *J. Chem. Soc.*, **1958**, 4176.



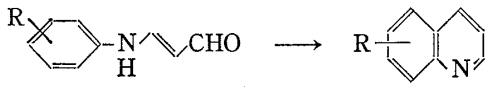
XIa XIb XIc

XIIa XIIb XIIc

Chart 2

β-(*p*-Toluidino)-acrolein (VII) was cyclodehydrated to give a excellent yield of 6-methylquinoline in concentrated sulfuric acid, whereas β-(*p*-chloroanilino)-acrolein (VIII) did not undergo the reaction to give 6-chloroquinoline under the same conditions, but *p*-chloroaniline was obtained in good yield after the usual treatment of reaction mixture. β-(*o*-Toluidino)-acrolein (XIII) and β-(*m*-toluidino)-acrolein (XIV) was cyclodehydrated in concentrated sulfric acid to give 8-methylquinoline (30%) and a mixture of 5- and 7-methylquinoline (43%), respectively. In the case of XIII, the reaction mixture was diluted with water, made alkaline and extracted with ether. The alkaline mother liquor showed positive diazo coupling reaction. This fact suggests that sulfonation of XIII took place in parallel with the cyclodehydration.

Table I. Cyclodehydration of β-Arylaminoacroleins in Concentrated Sulfuric Acid (at 120°, for 5 hr)

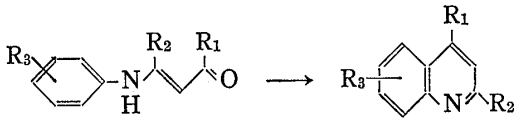


R	Yield of quinolines (%)	Recovered anilines (%)
H	trace	0
p-CH_3	89	0
m-CH_3	42	0
o-CH_3	30	0
p-C_2H_5	87	trace
p-Cl	trace	74
m-Cl	45	0

In the next series of experiments, polyphosphoric acid was employed as cyclodehydrating agent to prevent sulfonation of β-arylaminoacroleins. The maximal yield of quinoline (23%) was obtained when III was heated in polyphosphoric acid at 160° for 3 hours, but the yield of quinoline was less than the expected.

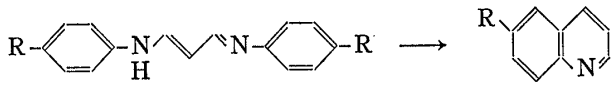
Lewis-type acid (*viz.* anhydrous aluminium chloride) as cyclodehydrating agent, however, showed a satisfactory result. Treatment of 4-(*p*-chloroanilino)-3-penten-2-one with three molar anhydrous aluminium chloride at 120° for 5 hours brought about its conversion to 6-chloro-2,4-dimethylquinoline in 73% yield. The compound II and III, which did not undergo the cyclodehydration owing to the sulfonation in concentrated sulfuric acid, were cyclodehydrated by heating them at 120° for 5 hours in the presence of anhydrous aluminium chloride to give lepidine (50%) and quinoline (64%), respectively. Similary, other β-arylaminoacrolein derivatives were cyclodehydrated to give the corresponding quinolines in good yield (Table II). Tetrachloroethane as solvent gave similar satisfactory result, but nitrobenzene generally caused lower yield of quinolines. In the case of VII, however, good yield was obtained either in the presence of tetrachloroethane or of nitrobenzene. The methyl group at para position may activate the reacting site to the electrophilic attack of the carbonyl group. It is not clear, whether aluminium chloride catalyzes the cyclodehydration as Lewis acid or as Brønsted

Table II. Cyclodehydration of β-Arylamino -α,β-unsaturated Carbonyl Compounds in the Presence of $AlCl_3$ (at 120°, for 5 hr)



R_1	R_2	R_3	Molar ratio of $AlCl_3$	Solvent	Yield of quinolines (%)	Recovered anilines (%)
CH_3	CH_3	H	3		90	0
CH_3	CH_3	H	3	$C_2H_2Cl_4$	93	0
CH_3	CH_3	H	2	$C_2H_2Cl_4$+HCl	86	10
CH_3	CH_3	H	3	$C_6H_5NO_2$	70	0
CH_3	CH_3	*p*-Cl	1		26	56
CH_3	CH_3	*p*-Cl	2		44	41
CH_3	CH_3	*p*-Cl	3		73	25
CH_3	H	H	3		50	12
CH_3	H	*p*-CH_3	3		52	20
H	H	H	3		64	trace
H	H	H	3	$C_2H_2Cl_4$	67	trace
H	H	*p*-CH_3	3		78	trace
H	H	*p*-CH_3	2		66	3
H	H	*p*-CH_3	3	$C_2H_2Cl_4$	63	3
H	H	*p*-CH_3	2	$C_2H_2Cl_4$+HCl	43	25
H	H	*p*-CH_3	3	$C_6H_5NO_2$	12	30
H	H	*m*-CH_3	3		81	0
H	H	*m*-CH_3	3	$C_2H_2Cl_4$	90	0
H	H	*m*-CH_3	3	$C_6H_5NO_2$	88	0
H	H	*o*-CH_3	3		80	trace
H	H	*p*-Cl	3		40	22

Table III. Cyclisation of Malonaldehyde Dianils in the Presence of $AlCl_3$



R	Reacting form	Molar ratio of $AlCl_3$	Yield of quinolines (%)
H	HCl salt	1	40
CH_3	free base	5	31
CH_3	HCl salt	2	27
Cl	free base	5	1
Cl	HCl salt	2	20
Br	HCl salt	2	13

acid of the type $HAlCl_4$, because the added hydrogen chloride caused no remarkable change in the yield of 6-methylquinoline from the reaction VII and aluminium chloride in tetrachloroethane.

Finally, the cyclization of malonaldehyde dianil derivatives to quinolines was investigated. Malonaldehyde dianil of aniline (IV) was readily sulfonated in concentrated sulfuric acid, while *p*-toluidine dianil (IX) was cyclized to give 6-methylquinoline (48%) and *p*-toluidine (23%) under the similar condition. A part of IX was sulfonated in parallel with cyclisation, and 2-amino-5-methylbenzenesulfonic acid (17%) was obtained after treatment of the reaction mixture. *p*-Chloroaniline dianil (X) did not undergo these reaction in concentrated sulfuric acid and only *p*-chloroaniline was obtained from the reaction mixture. Malonaldehyde dianils or their hydrochloride were cyclized to give corresponding quinolines in the presence

of anhydrous aluminium chloride, but the yield were rather unsatisfactory (Table III). Thus the cyclization of malonaldehyde dianil is difficult to occur compared with that of 2-methyl-3-ketobutanal dianils reported by Gagan and Lloyd.[5]

The kinetic study of the cyclodehydration of β-arylaminoacrolein derivatives will be reported latter.

Experimental

Preparation of VI——To a mixture of malonaldehyde bis (diethyl acetal) (1.10 g, 0.005 mole) and 2N HCl (20 ml) was added sulfanilic acid (1.73 g, 0.01 mole) at room temperature under stiring. The reaction mixture was allowed to stand overnight and the deposited precipitates (2.27 g) were collected and recrystallized from 2N HCl to give VI (1.18 g, 56%), yellow needles, mp 313° (decomp.). *Anal.* Calcd. for $C_{15}H_{14}O_6N_2S_2 \cdot 2H_2O$: C, 43.05; H, 4.34; N, 6.69. Found: C, 42.86; H, 4.21; N, 6.60.

Action of Concentrated Sulfuric Acid on III——A mixture of III (1.45 g, 0.01 mole) and concentrated sulfuric acid (6 g) was warmed at 50° for 7 hr. The reaction mixture was poured into ice-water (24 g) and the resulting red clear solution was allowed to stand overnight at room temperature. The deposited precipitates were collected and recrystallized from 2N HCl using charcoal to give VI (0.19 g, 9%), yellow needles, mp 313° (decomp.). Its infrared (IR) spectrum is identical with that of VI obtained by the reaction of sulfanilic acid and malonaldehyde bis (diethyl acetal).

Sulfonation of IV——A mixture of malonaldehyde dianil (1.11 g, 0.005 mole) and concentrated sulfuric acid (6 g) was allowed to stand for 2 days at room temperature. To the reaction mixture was added ice (24 g) and the deposited precipitates were collected and recrystallized from 2N HCl to give VI (0.84 g, 40%). Its IR spectrum is identical with that of VI obtained by the reaction of sulfanilic acid and malonaldehyde bis (diethyl acetal).

Cyclodehydration of β-Arylaminoacrolein Derivatives in Concentrated Sulfuric Acid——A mixture of β-arylaminoacrolein (0.01 mole) and concentrated sulfuric acid (15 g) was warmed at 80° for 5 hr, and then water (10 ml) was added and extracted with ether. The ethereal layer was dried over KOH and ether was removed. The residue was treated in the usual manner to separate quinoline derivatives and aromatic primary amines. The quinolines were identified by the comparison of their picrate with authentic samples.

Cyclodehydration of β-Arylaminoacrolein Derivatives in the Presence of $AlCl_3$——β-Arylaminoacrolein (0.01 mole) and powdered $AlCl_3$, after intimate mixing in a mortar, was heated at 120° for 5 hr. The viscous product was dissolved in 1N HCl, the solution was made alkaline with 2N NaOH and extracted with ether. The ethereal layer was dried over KOH and ether was removed. The residue was treated in the usual manner to separate quinoline derivatives and aromatic primary amines.

Action of Concentrated Sulfuric Acid on IX——A mixture of IX (1.25 g, 0.005 mole) and concentrated sulfuric acid (15 g) was heated at 150° for 5 hr. To the reaction mixture was added water and the solution was carefully treated with 2N NaOH. The precipitate separated was collected and recrystallized from water to give 2-amino-5-methylbenzenesulfonic acid (0.62 g, 17%), mp 280°. Its IR spectrum is identical with that of authentic sample. The mother liquor was further made alkaline and extracted with ether. The ethereal layer was dried over KOH and the ether was removed. The residue was worked up in the usual manner to separate 6-methylquinoline (0.34 g, 48%) and *p*-toluidine (0.17 g, as its acetate, 23%).

Cyclization of Malonaldehyde Dianils in the Presence of $AlCl_3$——A mixture of malonaldehyde dianil or its hydrochloride (0.2 mole), $AlCl_3$ and nitrobenzene (100 ml) was heated at 180° for 5 hr. To the reaction mixture was added 2N H_2SO_4 and nitrobenzene was removed by steam distillation. The residue made alkaline by the addition of 30% NaOH and distilled with steam. The amines were extracted with ether from the distillate and worked up by usual manner to saparate quinoline derivatives and aromatic primary amines.

5) J.M.F. Gagan and D. Lloyd, *J. Chem. Soc.*, (*C*), **1970**, 2488.