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β-Arylaminoacrolein Derivatives. I. The Investigation of Combes Reaction and the Syntheses of β-Arylaminoacrolein Derivatives as the Possible Reactant

Shinzo Tamura and Emiko Yabe

Faculty of Pharmaceutical Sciences, Toho University[1]

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The limitations of Combes reaction were reinvestigated. 4-(*p*-Chloroanilino)-3-penten-2-one (III), hitherto believed to be insusceptible to cyclodehydration in sulfuric acid, reacted at a higher temperature to give 2,4-dimethyl-6-chloroquinoline (IV). 4-Anilino-3-buten-2-one (V), however, was sulfonated in concentrated sulfuric acid and no quinolines were detected in the reaction mixture. 4-(*p*-Chloroanilino)-3-buten-2-one (VI) was cyclodehydrated to give 6-chloroquinaldine (VIII) in dioxane containing sulfuric acid in low yield.

β-Anilinoacrolein (X), a possible reactant of Combes reaction, and its derivatives were synthesised for further studies, and their structure was confirmed by chemical evidences and by their infrared and nuclear magnetic resonance (NMR) spectra. The conformational analysis of β-arylaminoacroleins in three solvents was carried out using their NMR spectra.

Roberts and Turner[2] found that cyclodehydration of 4-(arylamino)-3-penten-2-one (I) to 2,4-dimethylquinoline (II) in sulfuric acid (Combes reaction) takes place in alkyl- or *m*-chloro-derivatives of I, while the reaction does not occur in *p*-chloro-derivative (III). They pointed out that the reaction is markedly affected by the substituted group in the aromatic ring of I, and is possible to occur only in a limited number of derivatives of I. Thielpape[3] failed to ob tain lepidine from 4-anilino-3-buten-2-one (V).

A kinetic study by Bonner, *et al.*[4] revealed that the experimental first order rate constant k_1 of the cyclodehydration is related to Hammett's acidity function H_0 as expressed by the equation, $\log k_1 + H_0 = \text{constant}$. The cyclodehydration of III and V is, therefore, expected to be achieved in more acidic medium or at higher temperature than in the studies so far unless a side reaction takes place. In the present study the cyclodehydration of III and V was first attempted from the above point of view. The compound (III) was cyclodehydrated by heating it at 140° in concentrated sulfuric acid giving 49% yield of 2,4-dimethyl-6-chloroquinoline (IV), whereas V did not undergo the reaction to give lepidine by heating at various temperatures ranging at 60—90° in concentrated sulfuric acid or in oleum, but sulfanilic acid was precipitated after the reaction mixture was poured into ice water and allowed to stand overnight indicating that V is sulfonated at the aromatic ring in concentrated sulfuric acid and the sulfo group substituted hinders the cyclodehydration.

In the next series of experiment the cyclodehydration of 4-(*p*-chloroanilino)-3-buten-2-one (VI) was studied, which is presumably insusceptible to the sulfonation since the sulfonation at the aromatic ring takes place mainly at *para* position to amino group. Heating VI did not give the quinolines in concentrated sulfuric acid or in oleum, but gave a small amount of 6-chloroquinaldine (VIII) in dioxane containing sulfuric acid. This fact suggests that a

1) Location: *No. 542, Miyamacho, Funabashi.*
2) E. Roberts and E.E. Turner, *J. Chem. Soc.*, **1927**, 1832.
3) E. Thielpape, *Ber.*, **55**, 127 (1922).
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.

part of VI was first hydrolysed into *p*-chloroaniline and acetoacetaldehyde, and both compounds thus formed were recombined to *β*-(*p*-chloroanilino)-crotonaldeyde (VII), which was cyclodehydrated to form VIII. On the basis of the above observations as well as a fact that the aldehyde are generally of higher reactivity than the ketones as to the cyclodehydration, *β*-arylaminoacrolein derivatives were synthesized for further studies.

The preparation of *β*-anilinoacrolein (X) was carried out as follows: aniline and *β*-ethoxyacrolein (IX) were mixed in ice-cold methanol, the reaction mixture was kept in an ice box overnight, the solvent was removed under reduced pressure, and the residue was subjected to recrystallization from benzene to give pale yellow crystals of *β*-anilinoacrolein, mp 121—122°.[5] The compound (X) reduced neither Tollen's reagent nor Fehling's solution, but its infrared absorption (IR) spectrum showed two bands for aldehyde (C–H stretching) at 2820 and

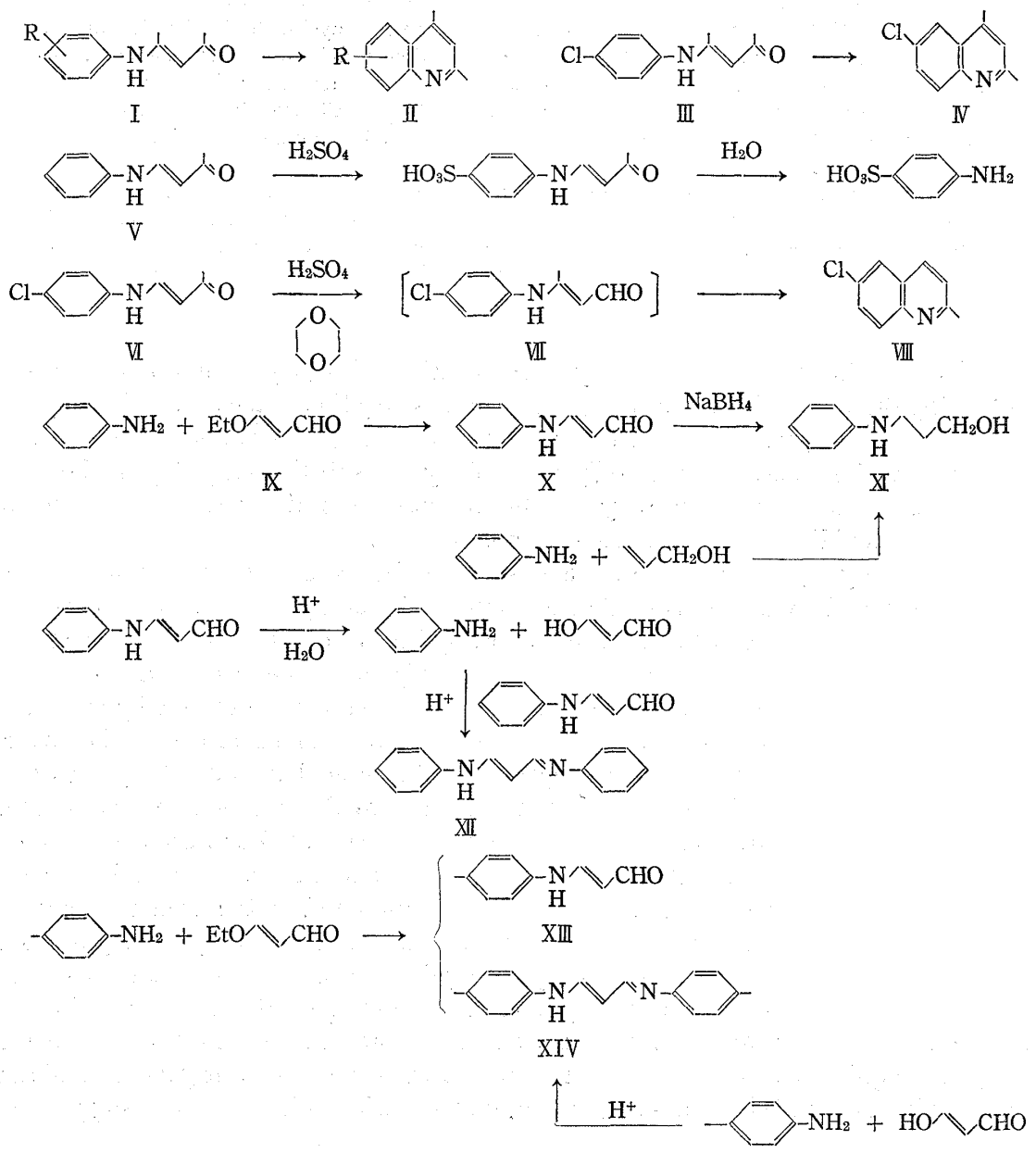


Chart 1

5) X may be identical with so-called enol form of malonaldehyde monoanil, mp 122—123°, prepared from propargyl aldehyde and aniline by I. Ya. Postovsky, R.O. Materosyan, and Yu. N. Sheinker [*J. Gen. Chem. USSR* (Eng. Transl.), **26**, 1623 (1956)].

2760 cm^{-1}, and the nuclear magnetic resonance spectrum was indicative of the structure of X. The reduction of X with sodium borohydride gave known 3-anilinopropanol-1 (XI), of which infrared absorption spectrum was identical with that of authentic sample prepared in a route of Hromatka.[6]

The conformational analyses of β-arylaminoacroleins were carried out on their nuclear magnetic resonance spectra, two of which obtained with X in deuterochloroform and in deuterodimethyl sulfoxide are shown in Fig. 1 and 2. In deuterochloroform the signals of *s-cis* H_α and *s-trans* H_α are found at 5.30 (quartet, J=7.5, 2 cps) and 5.70 ppm (quartet, J=13, 8.5 cps), respectively. The relative integrated intensities of both signals indicate that X consists of both the *s-cis* and the *s-trans* form (1.5: 1) in deuterochloroform. A signal at 7.60 ppm, which is apparently a split into triplet, is believed to be of *s-trans* H_β since the spin-spin coupling constant of H_β and H_α is same as that of H_β and NH proton (J=13 cps). The signals of *s-cis* H_α (quartet, J=3.5, 2 cps) and *s-trans* H_α (doublet, J=8.5 cps) are shifted to nearly the same position (approximately 9.3 cps) resulting in a complicated set of signals. The signals of *s-trans* NH proton and *s-cis* NH proton are located at 9.00 and 11.60 ppm, respectively, the latter of which is a result of the shift to a lower magnetic field owing to the intramolecular hydrogen bonding. The assignment of these two signals was comfirmed by double irradiation under conditions sufficient to destroy each proton's spin-spin splitting in X.

On the other hand, the signals of X in deuterodimethyl sulfoxide were found at 5.56 (*s-trans* H_α, quartet, J=8.5, 13 cps), 8.00 (*s-trans* H_β, triplet, J=13 cps), 9.25 (*s-trans* H_α, doublet, J=8.5 cps) and 10.00 ppm (*s-trans* NH, doublet, J=13 cps), and no signal from *s-cis* form was detected by the present method indicating that almost entire part of X is in *s-trans* form in deuterodimethyl sulfoxide. That is the case also in deuteromethanol (Table I). The conformation of β-(*p*-toluidino)-acrolein (XIII) was analyzed to be similar to that of X in each of the above-mentioned three solvents. In the case of β-(*p*-chloroanilino)-acrolein, however, only *s-cis* form was detected in deuterochloroform whereas *s-trans* form alone either in deuterodimethyl sulfoxide or in deuteromethanol.

Kramer[7] analyzed a conformation of β-(benzylamino)acrolein on the basis of chemical shift and split of each signal, and concluded that the compound is a mixture of *s-cis* and *s-trans* forms (3: 1) in deuterochloroform while is almost entierly in *s-trans* form in deuterodimethyl sulfoxide.

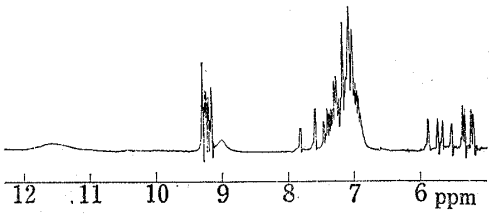


Fig. 1. NMR Spectrum of β-Anilinoacrolein (X) in $CDCl_3$ (60 Mc)

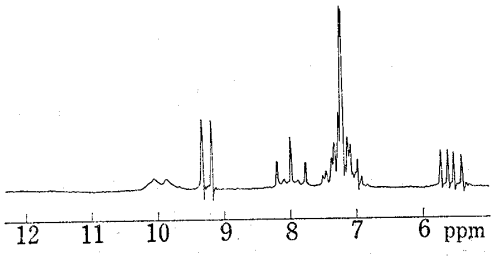
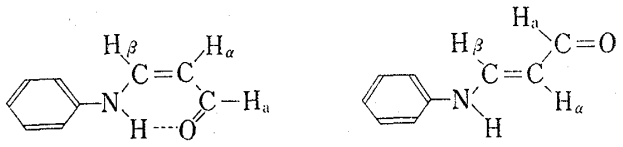


Fig. 2. NMR Spectrum of β-Anilinoacrolein (X) in CD_3SOCD_3 (60 Mc)

When the etheral solution of X was shaken with 2N sodium hydroxide, X was partitioned into both layers in a ratio of approximately 1: 1, showing that X is a weakly acidic substance. The compound (X) was recovered remaining unchanged by immediate addition of sodium bicarbonate to the above mentioned alkaline layer followed by the extraction with ether, whereas X was hydrolyzed to form aniline after being in the alkaline medium for a long period of time.

6) O. Hromatka, *Ber.*, **75**, 379 (1942).
7) H.E.A. Kramer, *Ann.*, **696**, 15 (1966).

TABLE I. Nuclear Magnetic Resonance Spectra of β-Anilinoacrolein Derivatives in ppm Relative to Tetramethylsilane



s-cis form *s-trans* form

R	Solvent	NH (*J*, cps) *s-cis*	NH (*J*, cps) *s-trans*	H_a (*J*, cps) *s-cis*	H_a (*J*, cps) *s-trans*
H	$CDCl_3$	11.60	9.00	9.29[a] (H_α2, H_β3.5)[b]	9.30[c] (H_α8.5)[b]
	CD_3SOCD_3		10.00[c] (H_β13)		9.25[c] (H_α8.5)
	CD_3OD				9.10[c] (H_α8.5)
CH_3	$CDCl_3$	11.66	8.90	9.22[a] (H_α2, H_β3.5)	9.20[c] (H_α8.5)
	CD_3SOCD_3		9.86[c] (H_β13)		9.20[c] (H_α8.5)
	CD_3OD				9.04[c] (H_α8.5)
Cl	$CDCl_3$	11.50		9.30[a] (H_α2, H_β3.5)	
	CD_3SOCD_3				9.20[c] (H_α8.5)
	CD_3OD				9.10[c] (H_α8.5)

R	Solvent	H_α (*J*, cps) *s-cis*	H_α (*J*, cps) *s-trans*	H_β (*J*, cps) *s-cis*	H_β (*J*, cps) *s-trans*
H	$CDCl_3$	5.30[a] (H_a2, H_β7.5)	5.70[a] (H_a8.5, H_β13)	[d]	7.60[e] (NH13, H_α13)
	CD_3SOCD_3		5.56[a] (H_a8.5, H_β13)		8.00[e] (NH13, H_α13)
					8.00[e] (H_α13)[f]
	CD_3OD		5.64[a] (H_a8.5, H_β13)		7.84[e] (H_α13)
CH_3	$CDCl_3$	5.26[a] (H_a2, H_β7.5)	5.66[a] (H_a8.5, H_β13)	[d]	7.56[e] (NH13, H_α13)
	CD_3SOCD_3		5.46[a] (H_a8.5, H_β13)		7.90[e] (NH13, H_α13)
					7.90[c] (H_α13)[f]
	CD_3OD		5.58[a] (H_a8.5, H_β13)		7.84[e] (H_α13)
Cl	$CDCl_3$	5.30[a] (H_a2, H_β7.5)		[d]	
	CD_3SOCD_3		5.54[a] (H_a8.5, H_β13)		7.92[c] (H_α13)
	CD_3OD		5.64[a] (H_a8.5, H_β13)		7.90[c] (H_α13)

a) quartet *b*) Observed apparently as quintet because the signals of *s-cis* H_α and *s-trans* H_α are in very near position. Each ppm and *J* value was measured by double irradiation method. *c*) doublet *d*) Masked by the signals of phenylprotons. *e*) triplet *f*) The most part of the signal split into triplet by the spin-spin coupling with NH proton and H_α, while a part of the signal split into doublet owing to rapid exchange of NH proton (Fig. 2).

The compound (X) is soluble in dilute hydrochloric acid. When the solution was allowed to stand, it was colored gradually after which orange-yellow crystals of malonaldehyde dianil hydrochloride was precipitated. It is already known that aniline and malonaldehyde interact in acidic aqueous solution to give malonaldehyde dianil (XII).[8] It is, therefore, reasonable to assume that a part of X in dilute hydrochloric acid is hydrolyzed to aniline and malonaldehyde, and aniline thus formed is combined with unchanged X to give XII by acid catalysis. An appreciable amount of XII or its derivative was formed as a by-product in the synthesis of β-arylaminoacroleins, and the quantities of these by-products varied with the purity of β-ethoxyacrolein used. The presumption is in agreement with an observed fact that a crystalline mass sometimes separated in the condenser in distilling raw β-ethoxyacrolein, and the substance recrystallized from benzene was identified with known β-ethoxyacrylic acid, mp 110°.

8) C.F. Jelinek and R.F. Kleinschmidt, U.S. Patent 2549097 (1951) [*C.A.*, **45**, 8035 (1951)].

On the basis of the above observations, the preparation procedure of β-arylaminoacroleins was improved as follows: after the fractional distillation, β-ethoxyacrolein dissolved in ether is shaken with 7% sodium bicarbonate solution, and the etheral layer is separated and dried over anhydrous potassium carbonate. After the solvent is evaporated, the residue is distilled under reduced pressure, and immediately afterwards the distillate is mixed with methanolic solution of amine in the presence of a small amount of sodium bicarbonate in order to neutralize possible acidic impurities.

In the most cases, the improved precedure largely reduced the by-product of dianils and definitely gave satisfactory results. The amount of dianil formed changed with amine used, and was still relatively large in some cases, so that many steps of purifying procedure were

Table II. β-Anilinoacrolein Derivatives and Malonaldehyde Dianil Derivatives

$$Ar\text{-}NH_2 + EtO\text{-}CH{=}CH\text{-}CHO \longrightarrow Ar\text{-}NH\text{-}CH{=}CH\text{-}CHO + Ar\text{-}NH\text{-}CH{=}CH\text{-}N\text{-}Ar$$

Ar	mp (°C)	Yield (%)	Appearance (recrystn. solv.)	Formula	Analysis Calcd. C	H	N	Found C	H	N
β-Anilinoacrolein derivatives										
Phenyl	121—122	63	pale yellow prisms (benzene)	C_9H_9ON	73.45	6.16	9.52	73.77	6.34	9.56
o-Methylphenyl	81—82	47	pale yellow leaflets (benzene–hexane)	$C_{10}H_{11}ON$	74.51	6.88	8.69	74.55	6.86	8.62
m-Methylphenyl	117—119	62	pale yellow prisms (benzene)	$C_{10}H_{11}ON$	74.51	6.88	8.69	74.48	6.90	8.68
p-Methylphenyl	121—122	65	pale yellow prisms (benzene)	$C_{10}H_{11}ON$	74.51	6.88	8.69	74.60	7.07	8.60
p-Ethylphenyl	101—103	54	pale yellow leaflets (benzene–hexane)	$C_{11}H_{13}ON$	75.40	7.48	7.99	75.22	7.62	8.01
m-Chlorophenyl	152	44	pale yellow leaflets (benzene)	C_9H_8ONCl	59.52	4.44	7.71	59.96	4.11	7.45
p-Chlorophenyl	161—162	53	colorless needles (benzene)	C_9H_8ONCl	59.52	4.44	7.71	59.24	4.49	7.76
m-Bromophenyl	141	30	pale yellow prisms (benzene)	C_9H_8ONBr	47.81	3.57	6.20	48.12	3.63	6.24
p-Bromophenyl	176—177	39	pale yellow needles (benzene)	C_9H_8ONBr	47.81	3.57	6.20	48.03	3.48	6.18
p-Iodophenyl	171—172	39	pale yellow needles (benzene)	C_9H_8ONI	39.58	2.95	5.13	39.59	2.96	5.22
p-Methoxyphenyl	124	48	pale yellow prisms (benzene)	$C_{10}H_{11}O_2N$	67.78	6.26	7.91	67.89	6.21	7.97
α-Naphthyl	125	22	pale yellow prisms (benzene)	$C_{13}H_{11}ON$	79.16	5.62	7.10	79.15	5.42	6.90
β-Naphthyl	161	43	pale yellow prisms (benzene)	$C_{13}H_{11}ON$	79.16	5.62	7.10	79.19	5.61	7.02
Malonaldehyde dianil derivatives										
p-Methylphenyl	164—165 (decomp.)	2.5	yellow leaflets (benzene)	$C_{17}H_{18}N_2$	81.56	7.24	11.15	81.56	7.18	10.96
p-Chlorophenyl	155—156 (decomp.)	1.4	yellow needles (benzene)	$C_{15}H_{12}N_2Cl_2$	61.87	4.15	9.62	62.06	4.16	9.60
p-Bromophenyl	167 (decomp.)	3.4	yellow needles (ethanol)	$C_{15}H_{12}N_2Br_2$	47.40	3.18	7.37	47.62	3.22	7.49
p-Iodophenyl	217 (decomp.)	4.1	yellow needles (benzene)	$C_{15}H_{12}N_2I_2$	38.00	2.55	5.91	38.00	2.56	5.98
p-Methoxyphenyl	183—185	1.5	yellow leaflets (benzene)	$C_{17}H_{18}O_2N_2$	72.32	6.43	9.92	72.54	6.38	9.96
β-Naphthyl	184	1.4	orange plates (benzene)	$C_{23}H_{18}N_2$	85.68	5.63	8.69	85.67	5.54	8.73

required. The following presentation describes some examples concerning the dianil formation: β-(*p*-toluidino)acrolein (XIII) was prepared from *p*-toluidine and β-ethoxyacrolein with good yield being accompanied by the almost undetectable amount of dianil in the reaction mixture. The compounds β-anilino-, β-(*p*-ethylanilino)- and β-(α-naphthylamino)-acrolein were obtained also with good yield owing partly to the large solubilities of corresponding dianils. On the other hand, β-(*p*-chloroanilino)-acrolein showed relatively low yield due to a considerable amount of dianil formed and to only a small difference in the solubility of both compounds.

Experimental

Malonaldehyde bis(Diethyl Acetal)——Malonaldehyde bis(diethyl acetal) was prepared by a modification of method described by Tsukamoto.[9]

To a mixture of 1184 g (8 moles) of ethyl orthoformate and 10 g of anhyd. $FeCl_3$ was added 300 g (3 moles) of ethyl vinyl ether under stirring at such a rate that the temperature of the reaction mixture did not exceed 30°. Stirring was continued for about 5 hours at 60—65° after addition of the last of the ethyl vinyl ether. Then the mixture was cooled to room temperature and 17 g of anhyd. Na_2CO_3 was added, stirred for 30 minutes and allowed to stand overnight. The reaction mixture was filtered and the filtrate was distilled under reduced pressure. The distillate was redistilled through a fractionating column 25 cm long. The fraction boiling at 114—116°/30 mmHg was collected. 670 g (76%) of malonaldehyde bis(diethyl acetal) was obtained.

β-Ethoxyacrolein (IX)——β-Ethoxyacrolein was prepared by a modification of method described by Yanovskaya, *et al.*[10]

A mixture of 110 g (0.5 mole) of freshly distilled malonaldehyde bis(diethyl acetal), 10 g of 3% aqueous *p*-toluenesulfonic acid solution and 20 ml of EtOH was heated on a boiling water bath with stirring until a clear solution resulted, which required about 5 minutes. Heating was then continued for 20 minutes longer, whereupon the mixture was cooled by a mixture of ice and water and 1 g of $NaHCO_3$ was added, stirred for 30 minutes. The reaction mixture was filtered and the filtrate was distilled under reduced pressure. The distillate was redistilled through a fractionating column 25 cm long. The fraction boiling at 86—88°/30 mmHg was collected. 21—23 g (42—46%) of β-ethoxyacrolein was obtained.

For the preparation of β-arylaminoacroleins the above fraction was further purified as follows: the etheral solution of β-ethoxyacrolein was washed with 7% aqueous $NaHCO_3$, dried over K_2CO_3. The ether was evaporated *in vacuo* and the residue was distilled under reduced pressure and collected the fraction boiling at 88°/30 mmHg.

β-Anilinoacrolein (X)——To a stirred mixture of 11 g (0.11 mole) of freshly distilled β-ethoxyacrolein (IX) and 0.2 g of $NaHCO_3$ in 50 ml of MeOH was added a solution of 9.3 g (0.1 mole) of aniline in 70 ml of MeOH in portions with cooling by a mixture of ice and water. The mixture was allowed to stand overnight in an ice box. MeOH was evaporated *in vacuo* and to the residue was added about 10 ml of benzene and the resulting crystals were filtered with suction. The crystals were recrystallized from benzene to yield X (9.45 g, 63%) as pale yellow prisms, mp 121—122°.

β-(*p*-Toluidino)-acrolein (XIII)——To a stirred mixture of 11 g (0.11 mole) of freshly distilled β-ethoxyacrolein (IX) and 0.2 g of $NaHCO_3$ in 50 ml of MeOH was added a solution of 10.7 g (0.10 mole) of *p*-toluidine in 150 ml of MeOH in portions with cooling by a mixture of ice and water. The reaction mixture was allowed to stand overnight in an ice box and then concentrated until 50 ml under reduced pressure, and 100 ml of benzene was added. The solution was concentrated under reduced pressure and the precipitated crystals were collected and recrystallized from benzene to give XIII as pale yellow needles, mp 121—122°. The mother liquor was further evaporated under reduced pressure and to the residue was added 20 ml of benzene and the resulting crystals were filtered with suction to give a mixture of XIII and XIV. The crystals were fractionally recrystallized from benzene to give XIII and XIV, the latter is yellow leaflets, mp 164—165° (decomp.), and weighed 0.63 g (2.5%). The total yield of XIII was 10.49 g (65%). XIV was identified with authentic sample by IR spectrum comparison and mixed melting point.

The Reduction of β-Anilinoacrolein (X) with $NaBH_4$——To a stirred solution of 1.47 g (0.01 mole) of β-anilinoacrolein (X) in 40 ml of MeOH was added 3.0 g (0.08 mole) of $NaBH_4$ in portions and allowed to stand overnight in an ice box. To the mixture was added 10 ml of AcOH in order to decompose the excess $NaBH_4$, and the solvent was removed *in vacuo* and the residue was dissolved in water and neutralized with Na_2CO_3

9) T. Tsukamoto, Japan Patent 4773 (1953) [*C.A.*, **49**, 6994 (1955)].
10) L.A. Yanovskaya and V.F. Kucherov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1962**, 667 [*C.A.*, **57**, 16378 (1962)].

and separated oil was extracted with ether, dried over K_2CO_3. The ether was removed *in vacuo* and the residue was distilled under reduced pressure, bp 138°/4 mmHg. 1.0 g of crude XI was obtained. This crude amine was added, with cooling, to a solution of 2 ml of concentrated hydrochloric acid (*d* 1.18) in 7 ml of water. The solution of the hydrochloride was cooled in an ice bath, and stirred rapidly, while a solution of 0.83 g (0.012 mole) of $NaNO_2$ in 3 ml of water was added slowly. After all $NaNO_2$ had been added, the mixture was allowed to stand for 10 minutes and then extracted with ether. The ether was evaporated from the extract. The crude nitroso compound was added gradually, with continuous shaking, to a solution of 13.5 g (0.06 mole) of $SnCl_2$–$2H_2O$ in 15 ml of concentrated hydrochloric acid (*d* 1.18). After standing for 30 minutes the mixture was heated at 60° for 1.5 hours and was made strongly alkaline by the cautious addition of a cold 50% aqueous solution of NaOH. The resulting milky suspension was shaken with ether. The etheral layer was separated and dried over Na_2SO_4 and after removal of the solvent, the amine was distilled under reduced pressure, bp 140°/5 mmHg, 0.29 g of pure XI was obtained. XI was identified with authentic sample[6] by infrared spectrum comparison.

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