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STUDIES ON QUINOLIZINIUM SALTS—VI[1]

THE REACTION OF QUINOLIZINIUM ION WITH ANILINE[2]

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Abstract—Quinolizinium bromide and the 3-methyl analogue (I and II) react with boiling aniline to give quinolines (III–V), and other minor products (VI–XII) with expulsion of 2-picoline and 2,5-lutidine respectively. The reaction of I with ^{14}C-labelled aniline shows that the substituted quinolines (IV and V) are produced from two molecules of aniline and a fragment from I. It appears likely that all these products are derived from a possible intermediate (XXIV). In connection with a mechanistic assumption, the acid-catalysed reaction of 2-vinylpyridine and its aniline adduct (XXI and XXII) was carried out to give 2-picoline and fragmentation products (VI, VIII and X–XII).

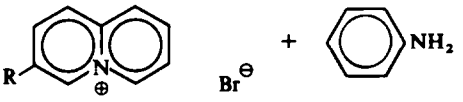
QUINOLIZINIUM bromide (I) was previously shown to undergo Grignard reactions[3] and metal hydride reductions[1] with the formation of butadienylpyridines and quinolizine derivatives. Apparently these nucleophilic reactions involve 4*H*-quinolizine or its derivatives as the reaction intermediate, although they were not isolated. As evident from sodium borohydride reduction of I,[1] the parent 4*H*-quinolizine sustains a ring opening reaction in aprotic solvents and, in contrast, undergoes protonation and subsequent reduction in protic solvents without ring opening. The present paper is concerned with the reaction of I and aniline leading to quinoline derivatives and other minor products, possibly *via* a quinolizine derivative.

Aniline is a useful nucleophilic reagent in the investigation of reactivity of electron-deficient heterocycles. For instance, quinoline hydrochloride, isoelectronic with quinolizinium ion, undergoes reaction with aniline giving 2-(*p*-aminophenyl)-quinoline (IV).[4] It is of interest that the product IV is identical with one of the products obtained from I and aniline, in spite of great difference between the two reaction mechanisms.

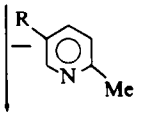
Heating a solution of I in aniline in a nitrogen atmosphere afforded a mixture which showed numerous spots on thin layer chromatograms. The reaction mixture was steam-distilled and then the residue was chromatographed on silica gel with 9:1 benzene–ethyl acetate as eluent to give two isomeric quinolines (IV and V) in yields of 28 and 7% and other minor products (VI–XII). Preparative gas chromatography of the steam distillate afforded 2-picoline and a small amount of quinoline (III).

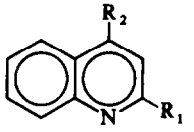
The molecular formula $C_{15}H_{12}N_2$ was assigned for the two isomeric quinolines (IV and V) on the basis of elemental analyses and most prominent molecular ion peak at *m/e* 220 in the mass spectra. The IR spectra showed the presence of a primary aromatic amine in 3200–3500 cm^{-1} region. The minor substituted quinoline (V) was characterized as 4-(*p*-aminophenyl)quinoline on the basis of the NMR spectrum which showed an A_2B_2 pattern ($J_{A,B}$ = 8·3 c/s) centred at 2·95 τ, two doublets at 1·09 and 2·71 τ (J = 4·5 c/s) assignable to C-2 and C-3 protons respectively. The

CHART 1

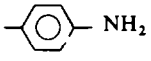


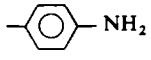
I: R = H
II: R = Me

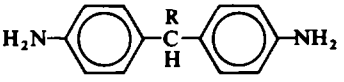




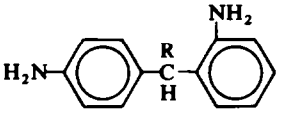
III: $R_1 = R_2 = H$

IV: R_1 = 
$R_2 = H$

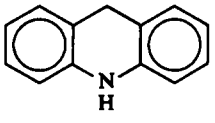
V: $R_1 = H$
R_2 = 



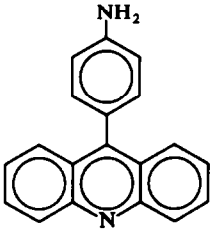
VI: R = H
VII: R = Me



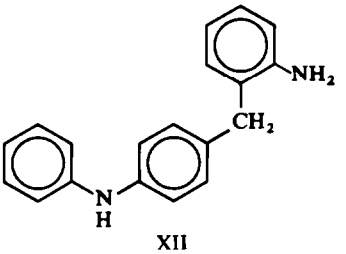
VIII: R = H
IX: R = Me



X



XI



XII

remaining four aromatic protons appeared as multiplets in aromatic region. Similarly, the NMR spectrum suggested that the major isomeric quinoline (IV) should be 2-(*p*-aminophenyl)quinoline. IV showed the absence of the deshielded C-2 proton in quinoline ring, but instead a doublet of doublets centred at 1·94 τ ($J_{3,4}$ = 8·5 c/s, $J_{4,8}$ = 0·7 c/s) due to C-4 proton, and a C-3 proton doublet at 2·27 τ. In this case, aromatic protons in the aniline moiety appeared as an A_2X_2 pattern at 2·01 and 3·26 τ. Final proof of the structures of IV and V was obtained by IR spectral comparison with authentic samples independently prepared.

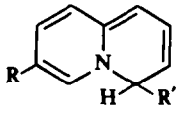
The quinolizinium ion-aniline reaction involves fragmentations with the formation of alkylidenedianilines (VI–IX), a diphenylamine (XII) and acridine derivatives (X and XI) as the minor products. Although the yields of the products except VII were

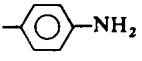
insufficient to isolate in pure form, extention of mechanistic studies suggested the possibility of the production of all these compounds. Thus, the minor products were characterized by thin layer chromatographic comparison with the samples obtained by another procedure. The alkylidenedianilines were separated as a 1:2·1 mixture of 4,4′-alkylidenedianilines (VI and VII) and a 1:2·7 mixture of the 2,4′-isomers (VIII and IX). Of these alkylidenedianilines only VII was isolated by repeated recrystallization and identified by direct comparison with an authentic sample. The structures of the remaining three were, without isolation, assigned by the NMR and IR spectral comparison with samples obtained from acid-catalysed reaction of paraformaldehyde and acetaldehyde with aniline.[5]

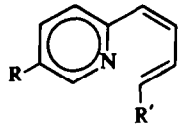
From a mechanistic point of view, the reaction of 3-methylquinolizinium bromide (II) with aniline was carried out to give the same products as described above. In this case, however, 2,5-lutidine was isolated from the steam distillate of the reaction mixture. Gas chromatography of the distillate showed that 2-picoline and 2,5-lutidine were produced in a ratio of about 5:95.

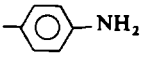
Aniline is expected to attack at C-4 of I yielding a butadienylpyridine (XV or XVI) *via* a 4-substituted 4*H*-quinolizine (XIII or XIV) as in Grignard reactions.[3] It appears likely that the elimination of 2-picoline follows the ring opening and subsequent addition of aniline. This mechanistic assumption is in accord with the reaction of II with aniline affording 2,5-lutidine as the major pyridine base, since a nucleophilic reaction of II occurred preferentially at C-6 with the formation of 2,5-disubstituted pyridine.[6]

CHART 2



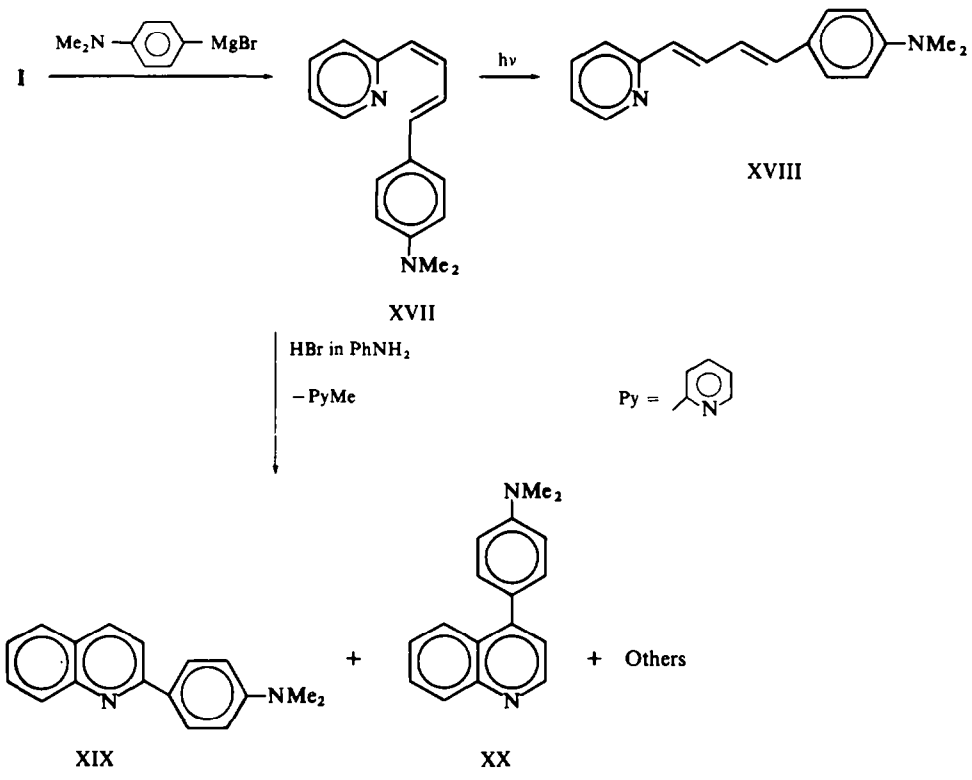
R = H or Me
XIII: R′ = —NHPh
XIV: R′ = 



R = H or Me
XV: R′ = —NHPh
XVI: R′ = 

If the ring opening isomerization follows immediately the nucleophilic attack of aniline, 2-(4-anilino-1,3-butadienyl)pyridine (XV) should be formed. This pathway is more probable than the other plausible one involving the formation of 4-*p*-aminophenyl-4*H*-quinolizine (XIV) and subsequent isomerization to the butadiene (XVI). In order to confirm the mechanistic assumption, the butadiene (XVII) of the latter type was prepared from I and *p*-dimethylaminophenylmagnesium bromide and submitted to acid-catalysed reaction with aniline. The structure of XVII was assigned by photochemical isomerization to the *trans–trans* isomer (XVIII) which was identified by direct comparison with the sample independently prepared. The geometry of XVII was assumed to be 1-*cis*–3-*trans* by analogy with Grignard reactions.[3] The butadiene (XVII) thus prepared was reacted with aniline in the presence of one mole-equivalent of aniline hydrobromide. The reaction afforded numerous products with expulsion of 2-picoline as in the quinolizinium ion-aniline reaction. We focused on

CHART 3



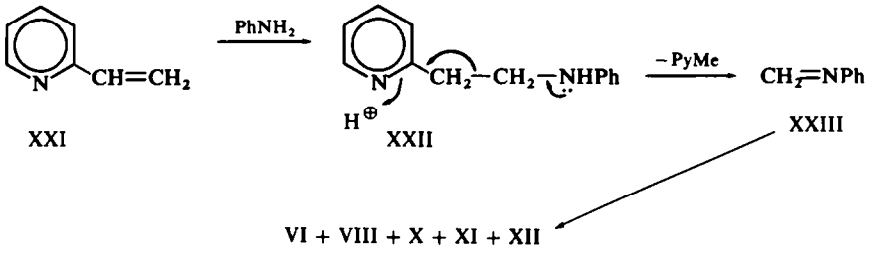
only two quinolines (XIX and XX), although the acid-catalysed reaction of XVII with aniline seemed to involve the formation of many fragmentation products and their related compounds. The major product was shown to be 4-(*p*-dimethylaminophenyl)-quinoline (XX) by spectral comparison with the corresponding amino derivative (V). The UV spectrum closely resembles that of V and the NMR spectrum showed a similar pattern in the corresponding regions. On the other hand, 2-(*p*-dimethyl-aminophenyl)quinoline (XIX) was obtained in trace amounts and identified by direct comparison with an authentic sample. The results are in contrast to the reaction of I and aniline leading to the major 2-substituted quinoline (IV). Thus, it is concluded that the main reaction of I and aniline should proceed *via* the intermediates (XIII and XV) rather than XIV and XVI.

Yoshida *et al.*[7] have obtained dihydroquinoline *via* 2-(1,3-butadienyl)pyridine by pyrolysis of 2-(1-acetoxy-3-butenyl)pyridine at higher temperatures. In our reaction, however, it is unlikely that such cyclization on the pyridine ring of XV would have taken place with the formation of quinoline. This assumption is based on the fact that I and II yielded the same products with expulsion of 2-picoline and 2,5-lutidine respectively. Furthermore, the radioactive-tracer experiment ruled out the possibility of the cyclization at C-3 of the pyridine ring and provided a strong indication that

two molecules of aniline were incorporated into IV and V. Aniline uniformly labelled with ^{14}C ($1{\cdot}08 \times 10^9$ dpm/mole) was reacted with I to give IV and V of $2{\cdot}22 \times 10^9$ and $2{\cdot}31 \times 10^9$ dpm/mole respectively. This fact indicates that the reaction proceeded by a pathway involving the formation of IV and V with elimination of 2-picoline.

The elimination of 2-picoline is thought to be initiated by C-2 addition of aniline to the butadiene intermediate (XV). If this is true, such fragmentation is to occur in 2-vinylpyridine (XXI) or its aniline adduct (XXII) under similar conditions. For confirmation of this assumption, XXI and XXII were heated under reflux in aniline involving one mole-equivalent of aniline hydrobromide. Column and preparative gas chromatography afforded fragmentation products (VI, VIII and X–XII), together with 2-picoline. All these products except 2-picoline were identical with those obtained from the acid-catalysed reaction of paraformaldehyde and aniline.[5] The fragmentation

CHART 4

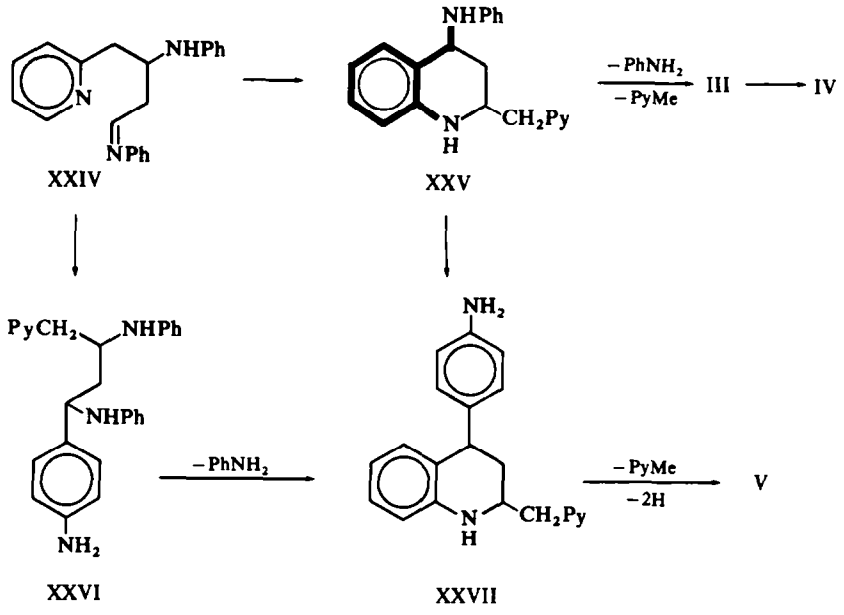


seems to be catalysed by acid, since 2-picoline was not formed to any great extent in the absence of hydrogen bromide. Hence, the fragmentation can be considered as proceeding with the formation of N-methyleneaniline (XXIII) as shown in Chart 4. Thus, it seems quite reasonable that fragmentation follows addition of aniline to the butadiene leading to 2-picoline and N,N′-1-propen-1-yl-3-ylidenedianiline (XXVIII). However, this pathway could not be the predominant one, since XXVIII undergoes preferred fragmentation leading to the products such as VI–XII.[5]

Possibly as a main reaction, XXIV may be cyclized, followed by elimination of 2-picoline and aniline from XXV to form quinoline (III). The resultant quinoline can undergo further acid-catalysed reaction with aniline to give IV.[4] However, the HBr-catalysed reaction of quinoline with aniline was shown by TLC not to produce the 4-substituted quinoline (V). This fact led us to the postulate that V may be formed from a precursor of quinoline. It is known that N-methyleneaniline (XXIII) is readily converted to N-(*p*-aminobenzyl)aniline, followed by rearrangement to methylenedianilines (VI and VIII).[8] Analogously, the intermediate (XXIV) possessing anil structure may have a chance to be led in part to a *p*-aminobenzylaniline derivative (XXVI). V may reasonably be produced from the intermediate (XXVI) structurally related to the aniline adduct of XVII. Following cyclization of XXVI, elimination of 2-picoline and dehydrogenation leads to V.

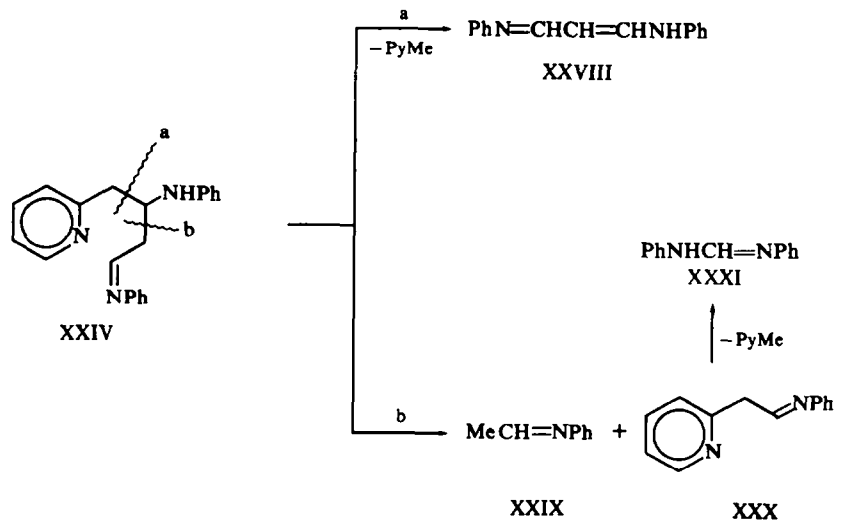
Alternatively, XXVII may be formed from acid-catalysed rearrangement of the anilino group in XXV just as in the rearrangement of N-(aminobenzyl)aniline[8] (partial

CHART 5



structure illustrated in heavy line corresponds to N-(*o*-aminobenzyl)aniline). The above postulate indicates the possibility of the formation of V in the acid-catalysed reaction of acrolein with aniline. Indeed, acrolein was shown to afford the expected quinoline (V) as the minor product, together with the 2-substituted isomer (IV).[5]

CHART 6



In addition, we have found that acrolein undergoes in part fragmentation involving C-2—C-3 bond cleavage of a possible intermediate, γ-anilinopropylideneaniline. The fragmentation products were identical with those obtained from acid-catalysed reaction of paraformaldehyde and acetaldehyde with aniline.[5]

As described above, the minor products (VI–XII) are derived from the acid-catalysed fragmentation of a possible fragment (XXVIII) in aniline. Alternative fragmentation is expected in the intermediate (XXIV), since XXIV can be regarded as a γ-substituted ö-anilinopropylideneaniline. The fragmentation of XXIV may proceed with the formation of N-ethylideneaniline (XXIX) and 2-pyridylacetaldehyde anil (XXX) in a manner similar to that of γ-anilinopropylideneaniline. The fragment XXX resembles XXVIII in partial structure, —N=C—CH_2—CH=NPh, and thus possibly undergoes further fragmentation to give 2-picoline and N,N'-diphenylamidine (XXXI). A successive paper[5] discusses the fragmentation mechanism and the formation of VI–XII and other products from the possible fragments XXIII, XXVIII, XXIX and XXXI.

EXPERIMENTAL

All m.p's were uncorrected. NMR spectra were obtained with a Varian A-60 and H-100 spectrometer using $CDCl_3$ solns with TMS as an internal standard. IR spectra were measured with a Perkin–Elmer 221 spectrophotometer and UV spectra were recorded on a Beckmann DK-2A ratio recording spectrophotometer. Measurements of radioactivity were made with a Packard Tri-Carb model 3275 scintillation spectrometer, with dimethyl POPOP in dioxane and toluene (8:2). TLC was performed on silica gel G (Merck, Darmstadt) with benzene–EtOAc (3:1) as developer. Spots were revealed with Dragendorff's reagent. Column chromatography was carried out on silica gel (>100 mesh, Kanto Chemical Co. Inc.). Preparative gas chromatography was performed on an F & M model 775 gas chromatograph (Column. 160 in × ¼ in 20% XE-60 on Chromosorb P (60–80 mesh); flow rate of He carrier gas, 0·7 l./min; bridge current, 100 mA; oven temp was programmed from 200 to 250°, 5°/min, and then maintained at 250° for 15 min.

Reaction of quinolizinium bromide (I) *with aniline.* A soln of I (3·0 g) in 30 ml aniline was refluxed for 7·5 hr in a stream of N_2. The mixture was steam-distilled and the residue made alkaline with Na_2CO_3 and extracted with $CHCl_3$. After the organic layer was dried over Na_2SO_4, evaporation of the extract left a viscous oily residue. Column chromatography of the residue on silica gel with benzene–EtOAc (9:1) as eluent afforded the following products in the order:

9,10-Dihydroacridine (X, trace) containing diphenylamine derived from two molecules of aniline. The crude X was identical by TLC with the sample which was prepared from the reduction of acridine.[9]

4-(*o*-Aminobenzyl)diphenylamine (XII, trace). The identity of this material as XII was shown by TLC with those of the sample obtained from the acid-catalysed reaction of XXI with aniline. The structural determination is described in the following paper.

9-(*p*-Aminophenyl)acridine (XI, trace). This was also identified by TLC with the sample which was prepared from the acid-catalysed reaction of acridine and aniline.[10]

2-(*p*-Aminophenyl)quinoline (IV, 887 mg). Recrystallization from EtOH gave pure IV as pale yellow crystals, m.p. 138·5–139°; ν_{max}^{Nujol} cm^{-1}: 3460, 3310, 3190 (NH_2); λ_{max}^{EtOH} mμ (ε): 223 (36,100), 279 (16,600), 306 (15,000), 353 (15,800). Its IR spectrum was identical with that of an authentic sample prepared from quinoline hydrochloride and aniline.[4]

A 1:2·7 mixture of VIII and IX (82 mg) on the basis of the NMR spectrum.

A 1:2·1 mixture of VI and VII (224 mg). VII was isolated in pure form by repeated recrystallization from ether as colourless crystals, m.p. 119–120°, and identified by comparison with an authentic sample. Although VI was not isolated, the mixture was proved to contain VI on the basis of the NMR spectrum.

4-(*p*-Aminophenyl)quinoline (V, 226 mg). Recrystallization from benzene gave analytically pure V as pale yellow leaflets, m.p. 156–157°; ν_{max}^{Nujol} cm^{-1}: 3460, 3320, 3190 (NH_2); λ_{max}^{EtOH} mμ (ε): 230 (35,400), 242–270 (sh), 300–310 (sh), 317 (9000), 337 (9800). This was identical with an authentic sample which was prepared by reduction of 4-(*p*-nitrophenyl)quinoline with zinc and hydrochloric acid.[11]

From the steam distillate 2-picoline and quinoline (III) were isolated by preparative gas chromatography and identified as the picrate, m.p. 164–165° (1·41 g) and 199–200° (230 mg) respectively.

Reaction of 3-methylquinolizinium bromide (II) *with aniline.* A soln of 3·0 g of II in 30 ml aniline was refluxed for 7·5 hr in a stream of N_2. The reaction mixture was steam-distilled and the residue worked up as described above. The oil thus obtained was chromatographed on silica gel with benzene–EtOAc (9:1) as eluent. IV (253 mg) and V (32 mg) were eluted, recrystallized and identified by direct comparison with the samples obtained before. Other minor products were chromatographically identical with those resulting from the I-aniline reaction.

Gas chromatography of the steam distillate of the reaction mixture showed the formation of 2,5-lutidine and 2-picoline in a ratio of 95:5 (Shimazu GC-1B Gas Chromatograph; 2·25-m column packed with 25% PEG-6000 on Shimalite (30–60 mesh); isothermal, 156°; He flow 54 ml/min). The steam distillate was extracted with ether and the extract dried over Na_2SO_4. Evaporation of ether afforded an oily residue which were acetylated with AcOH. The resulting mixture was poured into water, made alkaline with NaOH and extracted with ether. From the organic layer basic products were extracted with dil HCl. The acidic soln was washed with ether, made basic with NaOH and extracted with ether. The extract was dried over K_2CO_3 and distilled, after removal of the solvent, to give a colourless oil which was purified as the picrate, m.p. 171–172° (from EtOH), yield, 1·4 g. The picrate was identical with an authentic 2,5-lutidine picrate.

2-(4-p-*Dimethylaminophenyl*-cis-1,trans-3-*butadienyl*)*pyridine* (XVII). *p*-Dimethylaminophenylmagnesium bromide was prepared from 7·14 g of *p*-dimethylaminophenyl bromide and 0·955 g of Mg in 50 ml THF. To a suspended soln of I (3·0 g) in 30 ml THF, a soln containing the Grignard reagent was added dropwise. After addition, the mixture was stirred at room temp for 3 hr. The excess of Grignard reagent was decomposed by the addition of NH_4Cl aq. The resulting soln was extracted with ether. The organic layer was washed with sat NaCl aq, dried over Na_2SO_4, and evaporated *in vacuo* to give a brown oily product. The pure diene XVII was obtained as yellow needles, m.p. 79–81°, by chromatography on silica gel with benzene in the dark and subsequent recrystallization from n-hexane, yield, 2·81 g (79%). Found: C, 81·71; H, 7·30; N, 11·19. $C_{17}H_{18}N_2$ requires: C, 81·56; H, 7·25; N, 11·19%; λ_{max}^{EtOH} mμ (ε): 235 (10,500), 279 (12,100), 382 (30,400); ν_{max}^{Nujol} cm^{-1}: 1617, 1600 (conj. diene). The geometry of XVII was assumed to be 1-*cis*-3-*trans* by analogy with other Grignard reaction products. The diene XVII in n-hexane was photochemically isomerized to the *trans–trans* isomer XVIII, m.p. 165–166°, on standing. Found: C, 81·37; H, 7·51; N, 11·33. $C_{17}H_{18}N_2$ requires: C, 81·56; H, 7·25; N, 11·19%. This was identical with sample which was prepared as described below.

2-(4-p-*Dimethylaminophenyl*-trans-1,trans-3-*butadienyl*)*pyridine* (XVIII). To an ice-cold and stirred soln of 2-picolyllithium prepared from 1·4 g Li, 15·7 g bromobenzene and 11·2 g 2-picoline in 200 ml of ether, a soln of 17·5 g *p*-dimethylaminocinnamaldehyde in 180 ml THF was added dropwise. After addition, the mixture was stirred for 30 min and poured into ice-water. The ether layer was dried over Na_2SO_4 and evaporated to give an oily residue. The residue was dissolved in 200 ml Ac_2O, a few drops of conc H_2SO_4 added and the mixture refluxed for 30 min. The resulting soln was evaporated *in vacuo* to give an oily residue. Water was added and the mixture made alkaline with Na_2CO_3 and extracted with ether. After evaporation of the solvent, the residue was chromatographed on silica gel. XVIII was eluted with benzene and recrystallized from EtOH as yellow needles (1·52 g), m.p. 165–166°.

Hydrogen bromide-catalysed reaction of XVII *with aniline.* A soln of XVII (3·0 g) and 2·09 g aniline hydrobromide in 30 ml aniline was refluxed for 7·5 hr under N_2. The resulting soln was worked up as described above to give an oily product which showed numerous spots on silica gel thin layer chromatogram. Column chromatography on silica gel with benzene–EtOAc (9:1) as eluent afforded a trace of XIX, m.p. 179–180°, identical with an authentic sample, and 283 mg of XX, m.p. 179–179·5° (from benzene). Found: C, 82·08; H, 6·59; N, 11·31. $C_{17}H_{16}N_2$ requires: C, 82·22; H, 6·50; N, 11·28%; λ_{max}^{EtOH} mμ (ε): 228 (35,700), 263 (16,500), 358 (12,000), 300–325 (sh); NMR ($CDCl_3$): τ 1·06 (doublet, J = 4·6 c/s, C-2 H), 2·67 (doublet, J = 4·6 c/s, C-3 H), 2·84 (A_2B_2 pattern, J = 9·1 c/s, *p*-substituted phenyl protons).

The steam distillate was worked up as described for the separation of 2,5-lutidine to give 2-picoline picrate.

Acid-catalysed reaction of 2-(2-*anilinoethyl*)*pyridine* (XXII) *in aniline.* A soln of XXII (5·94 g) and 5·22 g aniline hydrobromide in 50 ml aniline was refluxed for 14 hr under N_2. The reaction mixture was steam-distilled and the residue worked up as described above. The oil thus obtained was chromatographed on silica gel with benzene–EtOAc (9:1) as eluent. The following crystalline products were eluted and then recrystallized from EtOH or benzene. (i) a mixture of X and diphenylamine (90 mg), (ii) XII (322 mg), m.p. 134–135 (from EtOH), (iii) XI (170 mg), m.p. 271–272° (from EtOH), (iv) VIII (1·63 g), m.p. 88° (from

benzene), (v) VI (784 mg), m.p. 92° (from benzene). These products were identified by IR spectral comparison and mixed m.p. with samples obtained by the acid-catalysed reaction of paraformaldehyde and aniline.[5]

Preparative gas chromatography of the steam distillate afforded 2-picoline. This was purified as the picrate (1·22 g) and identified by comparison with an authentic sample.

Acid-catalysed reaction of XXI and aniline in the presence of HBr resulted in the formation of the same products with expulsion of 2-picoline.

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