alkaline with aq. 15% potassium hydroxide. The solution was extracted three times with chloroform, the aq. layer reacidified with 2 N sulfuric acid and the brown solid filtered (1.2 g.). The product XXVII was purified by dissolving it in dil. base, treating with Norit, and reprecipitating with sulfuric acid (0.52 g., 20%, m.p. 210–213° dec.). An analytical sample, m.p. 213° dec., was prepared by crystallization from aq. acetic acid; infrared bands: 3.7–4.4, 5.1–5.6, 5.70(m), 5.87(s), 6.08(m), 6.70(m) μ.

Anal. Calcd. for $C_{12}N_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.07; H, 4.67; N, 13.20.

Treatment of the hydroxyester XXVI with concd. sulfuric acid at room temperature for 1 hr. and the same work-up as above did not give a precipitate on reacidification. The acidified solution was therefore extracted three times with chloroform and the chloroform evaporated under reduced pressure. The residue was an almost colorless powder (50%) which was recrystallized from small amounts of ethanol to give the colorless hydroxyacid XXXI, m.p. 171–173°; infrared bands: 2.86, 3.7–4.4, 5.0–5.6, 5.85 (broad) μ.

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.08; H, 5.30; N, 11.94.

An attempt to dehydrate XXVI by heating with acetic anhydride on the steam-bath for 15 hr. gave a liquid which could not be crystallized. Base hydrolysis of the liquid led to the formation of both the hydroxyacid XXXI and the α,β-unsaturated acid XXVII. Treatment of XXVI with thionyl chloride on the steam-bath for 1 hr. gave an intractable dark oil which was not further investigated.

2,3-Dimethylquinoxaline–Chloral Addition Compounds, XXXIII and XXXIV. A solution of the quinoxaline (7.0 g., 44 mmoles) in pyridine (50 ml.) was heated to 60° on the steam-bath and chloral (6.0 g., 40 mmoles) was added dropwise with vigorous swirling. The solution was heated for 50 min., and then freed of pyridine under reduced pressure. The dark residue was dissolved in ethanol and somewhat less than one volume of water was added (too much water gives very impure product). The nearly colorless solid that slowly separated (5.1 g., m.p. 131–143°) was recrystallized from carbon tetrachloride (2.3 g., 19%, m.p. 143–146°; second crop, 13%, m.p. 139–144°). An analytical sample of XXXIII, m.p. 147.5–148°, was obtained as a colorless powder.

Anal. Calcd. for $C_{12}H_{11}N_2OCl_3$: C, 47.15; H, 3.62; N, 9.16; Cl, 34.81. Found: C, 46.98; H, 3.56; N, 9.22; Cl, 35.37.

When an excess of chloral and a small amount of pyridine were used, a mixture of two compounds (m.p. 148–151°) was obtained from which the dichloral addition compound XXXIV could be separated by several crystallizations from benzene and benzene-pentane. The product crystallized as colorless solid kernels, m.p. 175–179° dec. (depending upon the rate of heating). The material in the mother liquors was a mixture, which could nevertheless be used for the preparation of XXVII.

Anal. Calcd. for $C_{14}H_{12}N_2O_2Cl_6$: C, 37.11; H, 2.67; N, 6.18; Cl, 46.94. Found: C, 37.64; H, 2.88; N, 6.10; Cl, 46.81.

The monochloral addition product was readily converted to the dichloral addition product on treatment with chloral and pyridine. The infrared bands distinguishing between the two compounds are at 8.63, 8.80, 9.11 (sharp), and 13.18 μ for XXXIII and at 8.74, 8.84, 8.98 and ca. 9.17 and 13.10 μ for XXXIV.

Base Treatment of XXXIII: Formation of XXVII. When an aqueous solution of sodium hydroxide (2.4 g., 60 mmoles, in 10 ml. of water) was slowly added to a gently boiling ethanolic solution (12 ml.) of XXXIII (3.4 g., 11 mmoles), vigorous ebullition occurred. The dark solution was cooled, treated with charcoal, and acidified with dil. sulfuric acid to pH 3. The resulting light brown precipitate (1.7 g.) was recrystallized from aq. acetic acid and then was the same in all respects as the acid, m.p. 213° dec., obtained from the hydroxyester XXVI.

Hydrogenation of XXVII: Formation of XXVIII.—A solution of XXVII (1.1 g., 5.1 mmoles) in ethyl acetate (200 ml.) was stirred with hydrogen in the presence of 5% Pd/C (200 mg.) until 1.04 equiv. (132 ml.) was consumed. The same color changes took place as were observed in the formation of XIX. The catalyst was filtered, and the solvent was removed under reduced pressure. The residue was crystallized from ethyl acetate and then had m.p. 148–167° which did not change on repeated crystallization from the same solvent or from ethanol–pentane; infrared bands: 3.6–4.4, 5.75(sh), 5.81 μ. The analytical sample was dried at room temperature and 0.05 mm. for 12 hr.

Anal. Calcd. for $C_{12}H_{12}N_2O_2 \cdot 0.25\,EtOAc$: C, 65.53; H, 5.92; N, 11.76. Found: C, 65.55, 65.74; H, 5.99, 5.90; N, 11.75, 11.91.

When the acid was sublimed under reduced pressure it became yellow and then had m.p. 167–168°. After crystallization from ethyl acetate it was colorless and had m.p. 152–168°. It was dried at 80° and 0.025 mm. for 24 hr.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.09; H, 5.86; N, 12.28.

The methyl ester XXXII of XXVIII was prepared with ethereal diazomethane and purified by sublimation (80–90°, 0.04 mm.) to fine colorless needles, m.p. 97–98°; infrared band: 5.78(s) μ.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.78; H, 6.16; N, 12.24.

Cyclization of XXVIII to XXIX.—The finely powdered acid XXVIII (0.50 g.) was added to hot (70°) acetic anhydride (40 ml.) containing a few drops of concd. sulfuric acid, and the solution was heated for 20 min. on the steam-bath. It was then concentrated to a small volume, the residue was thoroughly cooled, and water was added. When 10% KOH was added to pH 5, an orange fluffy material precipitated. After filtration and air-drying, the compound was bright red (0.47 g.). It was recrystallized several times from acetic acid (a small amount of dark compound insoluble in hot acetic acid was filtered and discarded) to give orange-yellow needles, m.p. >340°, darkens above 190°. The analytical sample was dried at 100° and 0.20 mm. for 12 hr. and then was deep orange. After standing for several weeks, the compound became brown; infrared bands: 3.11, 3.17, 3.24, 3.6–4.4, 6.00(w), 6.17, 6.23, 6.38(s), 6.56(s), 6.70 μ.

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13; C–CH₃, 7.6. Found: C, 72.52; H, 5.12; N, 13.94; C–CH₃, 1.9.

Photochemical Dimerization of 2-Aminopyridines and 2-Pyridones[1,2]

BY EDWARD C. TAYLOR AND ROBERT O. KAN

Ultraviolet irradiation of 2-aminopyridine, 2-amino-5-chloropyridine, 2-amino-3-methyl-, 4-methyl-, 5-methyl- and 6-methylpyridines, and of N,6-dimethyl-2-iminopyridine in hydrochloric acid solution resulted in the formation of 1,4-dimers. A similar series of photodimers (XIII) has been prepared from the corresponding 2-pyridones, and the two series have been directly interrelated by alkaline hydrolysis of the tetrahydro dimer of 2-aminopyridine to the tetrahydro dimer of 2-pyridone. Assignment of the *anti-trans* configuration to all dimers has been made on the basis of a detailed study of their n.m.r. spectra. The unusual chemical and physical properties of these dimers are discussed.

Valence-bond tautomerism is now a well-established phenomenon, and although most examples involve the bridging of a seven-membered ring to give a bicyclo-(3.2.0)heptene or heptadiene system, several instances of the conversion of cyclic hexadienes incorporated into rigid polycyclic systems into bicyclo(2.2.0)hexenes

have been reported.[3] It seemed to us that a possible monocyclic system which upon irradiation might be expected to undergo valence-bond tautomerism in the above sense would be a salt of 2-aminopyridine, since the formation of a cyclic amidine salt (2-aminopyridine is known to protonate on the ring nitrogen rather than on the exocyclic amino group)[4] might give partial diene

(1) This work was supported by grants to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service (Grant No. CY-2551) and from the American Cancer Society.

(2) A part of this work has been summarized in a recent communication: E. C. Taylor, R. O. Kan and W. W. Paudler, *J. Am. Chem. Soc.*, **83**, 4484 (1961).

(3) (a) W. H. Schuller, R. N. Moore, J. E. Hawkins and R. V. Lawrence, *J. Org. Chem.*, **27**, 1178 (1962); (b) W. G. Dauben and G. J. Fonken, *J. Am. Chem. Soc.*, **81**, 4060 (1959).

(4) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen and Co., Ltd., London, 1962, p. 143.

character to the remaining aromatic bonds. The present paper describes the outcome of these studies.

Chemistry.—Photolysis of a solution of 2-amino-5-chloropyridine (I) in N hydrochloric acid resulted in the gradual separation of large, colorless crystals which proved to be isomeric with 2-amino-5-chloropyridine hydrochloride. With slow heating, this material (II) melted at the same temperature as the hydrochloride of I (192–194°), and a mixture melting point with the latter compound was undepressed. However, the photoproduct melted considerably higher (207°) upon rapid heating. The most striking physical characteristic of the photoproduct II was its transparency to ultraviolet light. An aqueous solution showed only end absorption below 260 mμ, in contrast to 2-amino-5-chloropyridine hydrochloride, which exhibited strong maxima at 238 and 315 mμ. However, the spectrum of the latter compound was gradually restored when the solution of II was allowed to stand at room temperature, and reconversion of II to I upon treatment with strong base was essentially instantaneous and quantitative. Furthermore, the photoproduct II was approximately 10,000 times a stronger base than I (pK_a of 8.4 $vs.$ 4.7), giving further confirmation of the destruction of the aromatic ring present in I.

Catalytic reduction of the photoisomer II resulted in the hydrogenolysis of the C–Cl bond and the formation of a compound ($C_5H_8N_2\cdot HCl)_x$ (Va) in which a double bond originally present in II had been saturated. The absorption spectrum of the reduction product reflected this loss of unsaturation, for this material now was transparent to ultraviolet light above 240 mμ, with only end absorption below 240 mμ.

Photolysis of 2-aminopyridine (III) in N hydrochloric acid solution yielded a similar photoisomer (IV), which upon catalytic reduction gave a "dihydro" derivative (as its hydrochloride) identical with Va.

At this point, a disturbingly large number of structures could be envisaged for the photoproducts II and IV, compatible with the loss of aromatic character, increased base strength and ease of re-aromatization. Fortunately, the n.m.r. spectrum of II (Fig. 4b) made it possible to distinguish unequivocally among several of these possibilities. The spectrum showed an equal intensity doublet in the vinyl hydrogen region with a coupling constant of 7.5 c.p.s., the components of which were further split into doublets with a coupling constant of 2 c.p.s. This effectively excludes from further consideration provisional structures A, B, D, E and F.

When an aqueous solution of the hydrochloride of the reduced photoproduct Va was made slightly alkaline
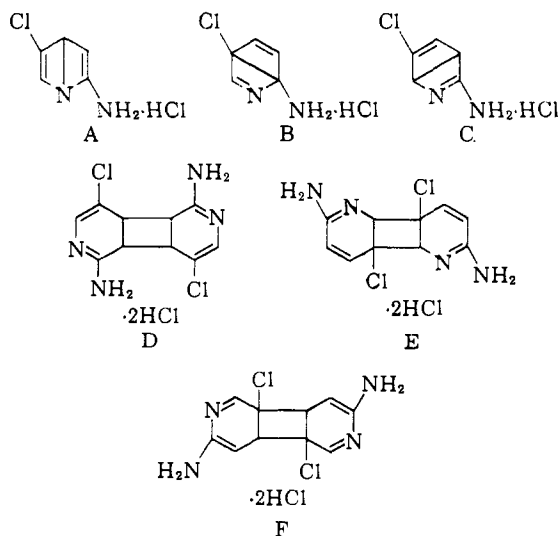

Figure 1.

with sodium bicarbonate or sodium hydroxide, a colorless, stable hydrate (Vb) immediately separated. The anhydrous material V could be obtained by prolonged vacuum drying at 100°, and could be reconverted both to the hydrate and to the hydrochloride upon treatment with water or dilute hydrochloric acid, respectively. However, prolonged refluxing of V with concentrated aqueous potassium hydroxide resulted in the evolution of ammonia and the formation of a solid product *identical in every respect with the tetrahydro derivative* (VI) *of the photodimer* (VII) *of 2-pyridone*. The structure of VII (through its N-methyl derivative VIII, with which it has been related by direct methylation), has been shown by two independent groups[5,6] to be a 1,4-dimer, and thus the interconversions described above may be represented as shown in Fig. 1.[7] It thus follows that the 2-amino-5-chloro- and 2-aminopyridine hydrochloride photoproducts (II and IV) are also 1,4-dimers possessing the same stereochemistry as the 2-pyridone dimer.

The resistance of the tetrahydro dimer V to hydrolysis, even with hot concentrated alkali, is remarkable, since a monocyclic model compound, 2-amino-3,4,5,6-tetrahydropyridine (2-iminopiperidine), is unknown as the free base because of hydrolysis even with water to 2-piperidone.[8] The apparently anomalous stability of V would appear to be due to steric crowding in the transition state leading to hydrolysis, since conversion of C_2 from sp^2 to sp^3 bonding by addition of hydroxyl ion in the initial hydrolysis step forces the amino group into a space already occupied by the methylene protons of the second ring.

The effect of reaction medium and the light source on the photodimerization of the 2-aminopyridines and 2-

(5) W. A. Ayer, R. Hayatsu, P. deMayo, S. T. Reid and J. B. Stothers, *Tetrahedron Letters*, **18**, 648 (1961).

(6) G. Slomp, F. A. MacKellar and L. A. Paquette, *J. Am. Chem. Soc.*, **83**, 4473 (1961).

(7) For purposes of clarity, only the correct configurations of the 1,4-dimers are given in Fig. 1, but justification for these assignments is presented in the latter part of this discussion under the heading *Stereochemical Configuration*.

(8) T. B. Grave, *J. Am. Chem. Soc.*, **46**, 1460 (1924).

TABLE I[a]

Dimer of	3-H	6-H	4-H	5-H	CH_3	$N\text{-}CH_3$	$\delta_6-\delta_3$	$\delta_5-\delta_4$	$J_{3,6}$	$J_{4,5}$	$J_{3,5}$	$J_{4,6}$	$J_{3,4}$	$J_{5,6}$
2-Aminopyridine·HCl[d]	5.89	5.32	3.65	3.10	..	..	0.57	0.55	9.5	7.5	1.5	1.5	6.5	6.5
2-Amino-3-methylpyridine·HCl[d]	..	5.88	3.94	3.11	8.30	..	..	.83	..	7.5	..	1.5	..	7.5
2-Amino-4-methylpyridine·HCl[d]	6.21	5.38	..	3.63	8.08	..	.83	..	10	..	1.5	..	..	7.5
2-Amino-5-methylpyridine·HCl[d]	5.97	5.62	4.15	..	7.96	..	.35	..	10	..	..	1.5	7.5	..
2-Amino-6-methylpyridine·HCl[d]	6.23	..	3.66	3.38	8.27	..	..	.28	..	8	1.5	..	7	..
2-Amino-5-chloropyridine·HCl[d]	5.63	5.25	3.66	..	..	..	.38	..	10	..	..	2	7.5	..
N,6-Dimethyl-2-iminopyridine·HCl[e]	6.15	..	3.48 or	3.40	8.17	6.92	..	.08	..	..	..	..	..	..
2-Benzylaminopyridine·HCl[d]	5.80	5.30	3.73	3.18	..	..	.50	.55	10	8	1.5	1.5	7	6.5
2-Pyridone[b]	6.08	5.50	3.72	3.14	..	..	.58	.58	10	8	1.5	1.5	6.5	6.5
3-Methyl-2-pyridone[b]	..	6.08	4.03	3.21	8.42	..	..	.82	..	8	..	1.5	..	6.5
4-Methyl-2-pyridone[b]	6.41	5.70	..	3.59	8.15	..	.71	..	10	..	2	..	..	6
5-Methyl-2-pyridone[b]	6.20	5.78	4.21	..	7.95	..	.42	..	9.5	..	..	1.5	7	..
6-Methyl-2-pyridone[c]	6.47	..	3.71	3.46	8.30	..	..	.25	..	8	2	..	6.5	..
N-Methyl-2-pyridone[b]	5.92	5.62	3.68	3.19	..	7.30	.30	.49	10	7.7	1.5	1.5	6	..
N,6-Dimethyl-2-pyridone[c]	6.94	..	4.09 or	4.02	8.65	7.49	..	.07	..	..	..	..	..	..

[a] Chemical shifts (τ) are relative to tetramethylsilane. All spectra were determined on a Varian A-60 spectrometer, and in the following solvents: [b] CF_3COOH, [c] CD_3COOD, [d] D_2O, [e] $CD_3COOD\text{-}D_2O$.

pyridones investigated is rather specific. Optimum conditions for the dimerization of 2-aminopyridines were found to be irradiation of concentrated solutions in concentrated hydrochloric acid solution through Pyrex glass with an AH-6 high pressure mercury arc. Excellent yields are obtained within a few hours, and the crystalline product must be repeatedly scraped from the sides of the irradiation vessel to permit further passage of light to the solution. Under the same conditions, however, a large number of 2-pyridones investigated failed to dimerize. Instead, optimum conditions for the latter series appeared to be the use of alcohol as a solvent and a low pressure mercury vapor immersion lamp.

a, A, B, C, D = H
b, A = CH₃; B, C, D = H
c, B = CH₃; A, C, D = H
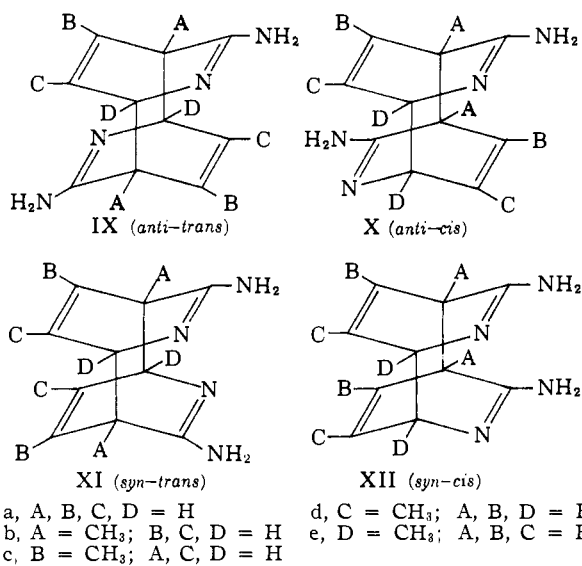d, C = CH₃; A, B, D = H
e, D = CH₃; A, B, C = H

Figure 2.

The effect of substituents in the pyridine ring upon the ease of dimerization is also worthy of note. Although chlorine and bromine in the 5-position of 2-aminopyridine seem to have little effect on the ease of dimerization, a methyl group in that position facilitates the photochemical dimerization, while nitro, amino, carboxy and carboxamido groups prevent dimerization completely. These data point to the generalization that electron-withdrawing groups in the 5-position hinder the dimerization, while electron-donating groups facilitate it. In both the 2-aminopyridine and 2-pyridone series, some localization of the $N_1\text{-}C_2$ π-electrons (through amidine or amide resonance, respectively) exists, and this condition appears to be necessary for dimerization, since 2-methoxypyridine is inert to ultraviolet irradiation in ethanol. On the other hand, 2-benzylaminopyridine readily gave a photodimer upon

irradiation in hydrochloric acid solution, and presumably other 2-substituted aminopyridines would behave similarly upon irradiation. An attempt to relate the structure of the 2-benzylaminopyridine hydrochloride dimer to the dimer of 2-aminopyridine by reduction to V failed, for the benzyl group resisted hydrogenolysis. This is not unexpected, however, for 2-benzylaminopyridine itself upon catalytic reduction gives only 3,4,5,6-tetrahydro-2-benzylaminopyridine, with retention of the benzyl group.[9]
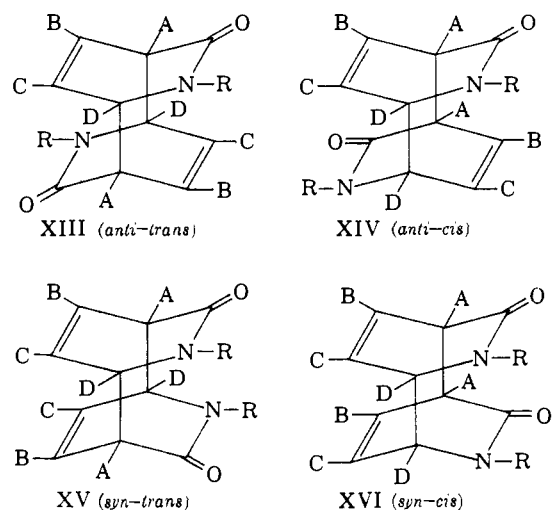

a, R, A, B, C, D = H
b, A = CH₃; R, B, C, D = H
c, B = CH₃; R, A, C, D = H
d, C = CH₃; R, A, B, D = H
e, D = CH₃; R, A, B, C = H
f, R = CH₃; A, B, C, D, = H
g, R, D = CH₃; A, B, C = H

Figure 3.

Stereochemical Configuration.—With the interrelationship of the dimers obtained by photolysis of 2-amino-5-chloro- and 2-aminopyridine, and of N-methyl-2-pyridone and 2-pyridone, well established, we turned to the question of the precise stereochemistry of the dimers. As an aid in this investigation we prepared the photodimers of 2-amino-3-methyl-, -4-methyl-, -5-methyl- and -6-methylpyridine hydrochloride, as well as the photodimers of the corresponding 2-pyridones, not only to study the individual proton signals in the n.m.r. spectra but also to examine the possibility that a change in configuration might accompany a change in substitution pattern.

For the dimer of 2-aminopyridine hydrochloride four 1,4-dimeric structures (IXa, Xa, XIa and XIIa) may be written (Fig. 2). Inspection of these four configurations reveals that IXa and XIa may be distinguished from Xa and XIIa by the fact that the latter two possess two
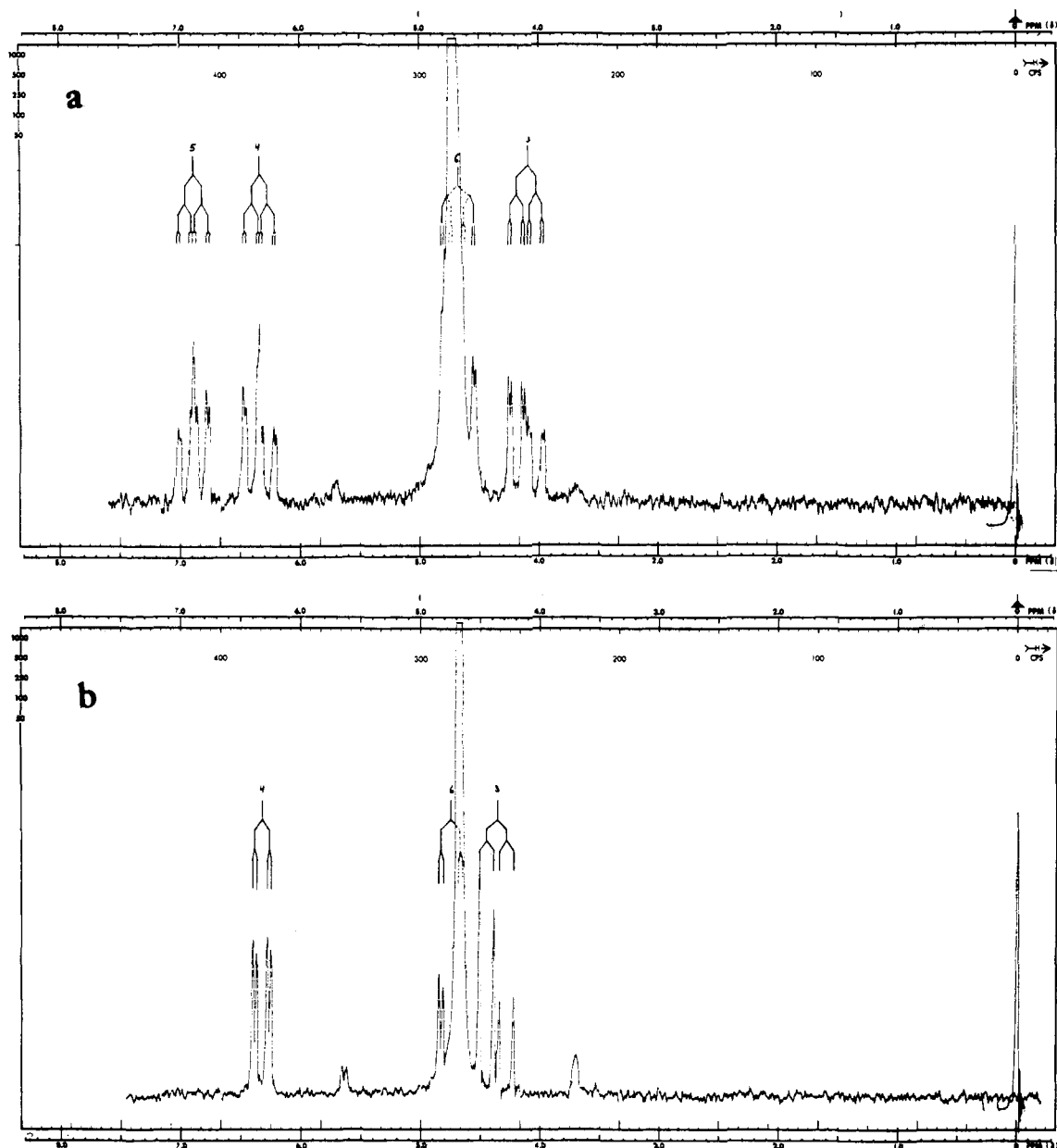
(9) L. Birkofer, Ber., 75B, 429 (1942).

Fig. 4a and b.—N.m.r. spectra: a, dimer of 2-aminopyridine hydrochloride (IV, IXa); b, dimer of 2-amino-5-chloropyridine hydrochloride (II).

equivalent bridgehead methine hydrogens neighboring each other, which will reduce the order of splitting of these hydrogens by one. Thus the two methine hydrogens in IXa and XIa would be expected to exhibit four doublets each, whereas the two methine hydrogens in Xa and XIIa should exhibit only two doublets each.

Figures 4a–g give the n.m.r. spectra of a series of 2-aminopyridine hydrochloride dimers. Examination of the spectrum of the 2-aminopyridine hydrochloride. dimer (Fig. 4a) shows the presence of four doublets for the 3-hydrogen[10] (5.89 τ) and four doublets for the 6-hydrogen (5.32 τ), although the latter are partly hidden under the solvent signal. Structures Xa and XIIa may thus

(10) The numbering system for the dimer is that of the monomer; i.e., i.
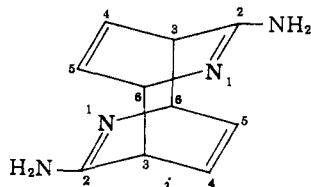
be eliminated. It should be noted that this spectrum represents a normal ABX pattern $\left(\begin{array}{ccc} CH{=}CH{-}CX \\ | \quad\ | \quad\ | \\ A \quad\ B \quad\ X \end{array} \right)$ and that the coupling constants listed (Table I) are in full agreement with the expected values. This observation holds for all the other 2-aminopyridine hydrochloride dimers listed in Table I.

Of the two remaining structures IXa and XIa, the latter would seem to be eliminated, since dimerization was carried out with 2-aminopyridine hydrochloride, and the formation of XIa would have involved an extremely unfavorable proximity of the two positively charged amidine functions in adjacent rings. Preliminary X-ray measurements of the Cl–Cl bond distance in the dimer of 2-amino-5-chloropyridine hydrochloride appear to confirm the correctness of structure IXa (and II).[11]

Several groups of workers[6,8] have commented recently on the stereochemistry of the photodimer of N-methyl-

(11) We are indebted to Professor R. A. Jacobson for this information. Full details of these X-ray studies will be published independently.
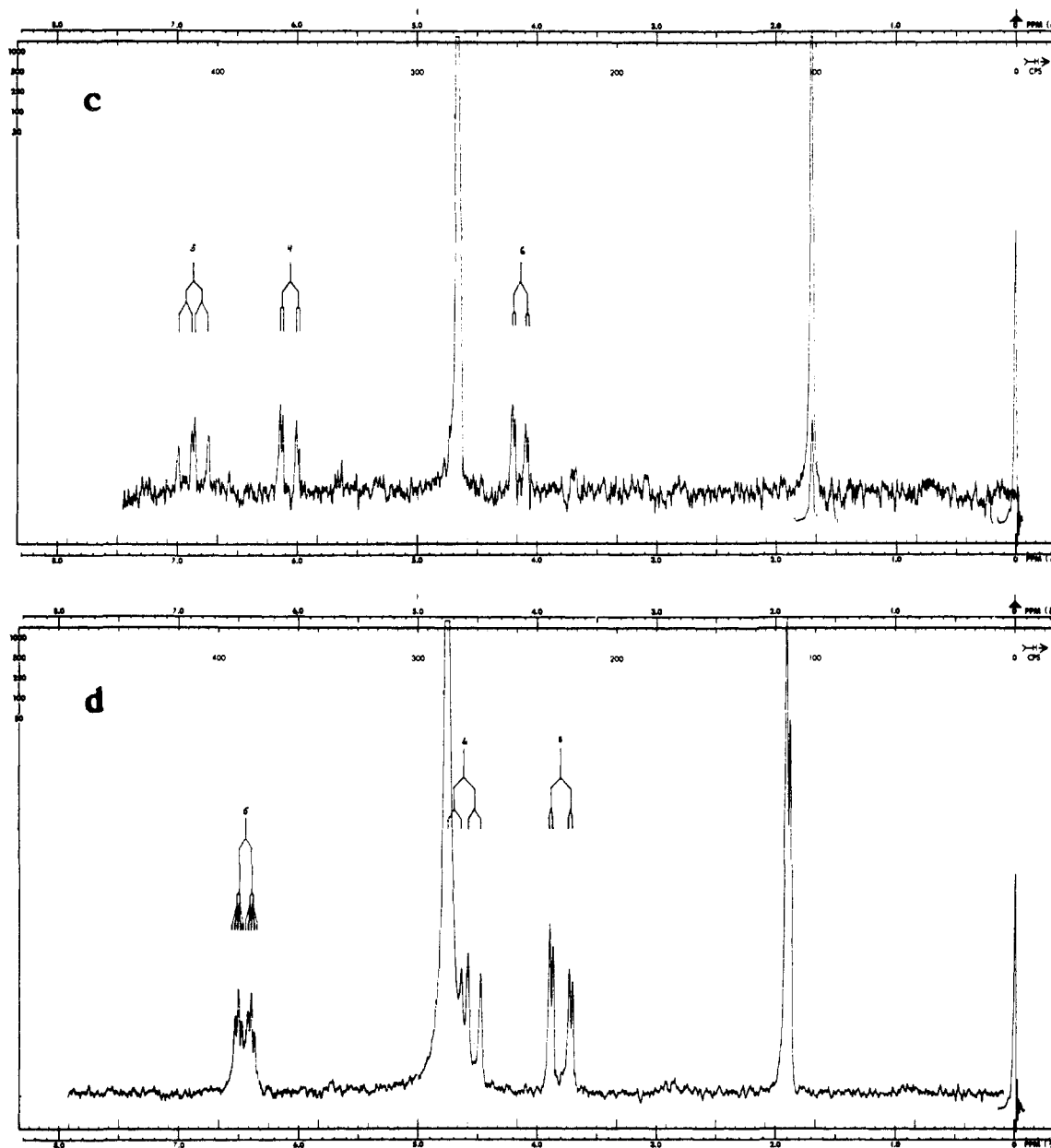
Fig. 4c and d.—N.m.r. spectra: c, dimer of 2-amino-3-methylpyridine hydrochloride (IXb); d, dimer of 2-amino-4-methylpyridine hydrochloride (IXc).

2-pyridone, which has been related chemically (*vide supra*) to the 2-aminopyridine hydrochloride dimer IXa. The measured negligible dipole moment (about 0.1 D. in chloroform) for the former compound[12] was considered convincing evidence for the *anti-trans* structure XIIIf (Fig. 3), since calculations indicated[13] that structures XIVf and XVIf should have dipole moments well in excess of 4 D., structure XVf a dipole moment in the order of 3 D. and structure XIIIf a negligible dipole moment. However, one cannot place absolute reliance upon the observed (in chloroform) dipole moment in selecting structure XIIIf, for errors as large as 2 D. may result from measurements taken in chloroform because of severe solvation effects.[13] It would therefore be more accurate to say that the measured dipole moment for the N-methyl-2-pyridone dimer is probably less than 2 D., and arguments selecting structure XIIIf in preference to XVf should be reviewed with this limitation in mind.

(12) E. C. Taylor and W. W. Paudler, *Tetrahedron Letters*, **25**, 1 (1960).

(13) Professor Norman Allinger, Wayne State University; private communication.

In this connection, it might be noted that Slomp, MacKellar and Paquette[6] examined the n.m.r. spectrum of the tetrahydro derivative of the N-methyl-2-pyridone dimer and noted that the newly formed methylene hydrogens cause the adjacent methine hydrogens to split into triplets, pointing to equivalence of the two methylene hydrogens at carbons 4 and 5. This equivalence was attributed to easy ring-interconversion between two boat forms of two six-membered rings, and was used as an additional argument in favor of structure XIIIf. However, models showed that such interconversion is equally possible with the tetrahydro derivative of XVf, and thus this argument becomes irrelevant in the ultimate choice between XIIIf and XVf.

Since the photodimer of N-methyl-2-pyridone has been related chemically to the dimer of 2-aminopyridine hydrochloride, it thus appears that 2-aminopyridine hydrochloride, 2-amino-5-chloropyridine hydrochloride, 2-pyridone and N-methyl-2-pyridone all dimerize in the *anti-trans* configuration.

An assignment of structure to the dimers of 2-amino-4-methyl- and 5-methylpyridine hydrochlorides can
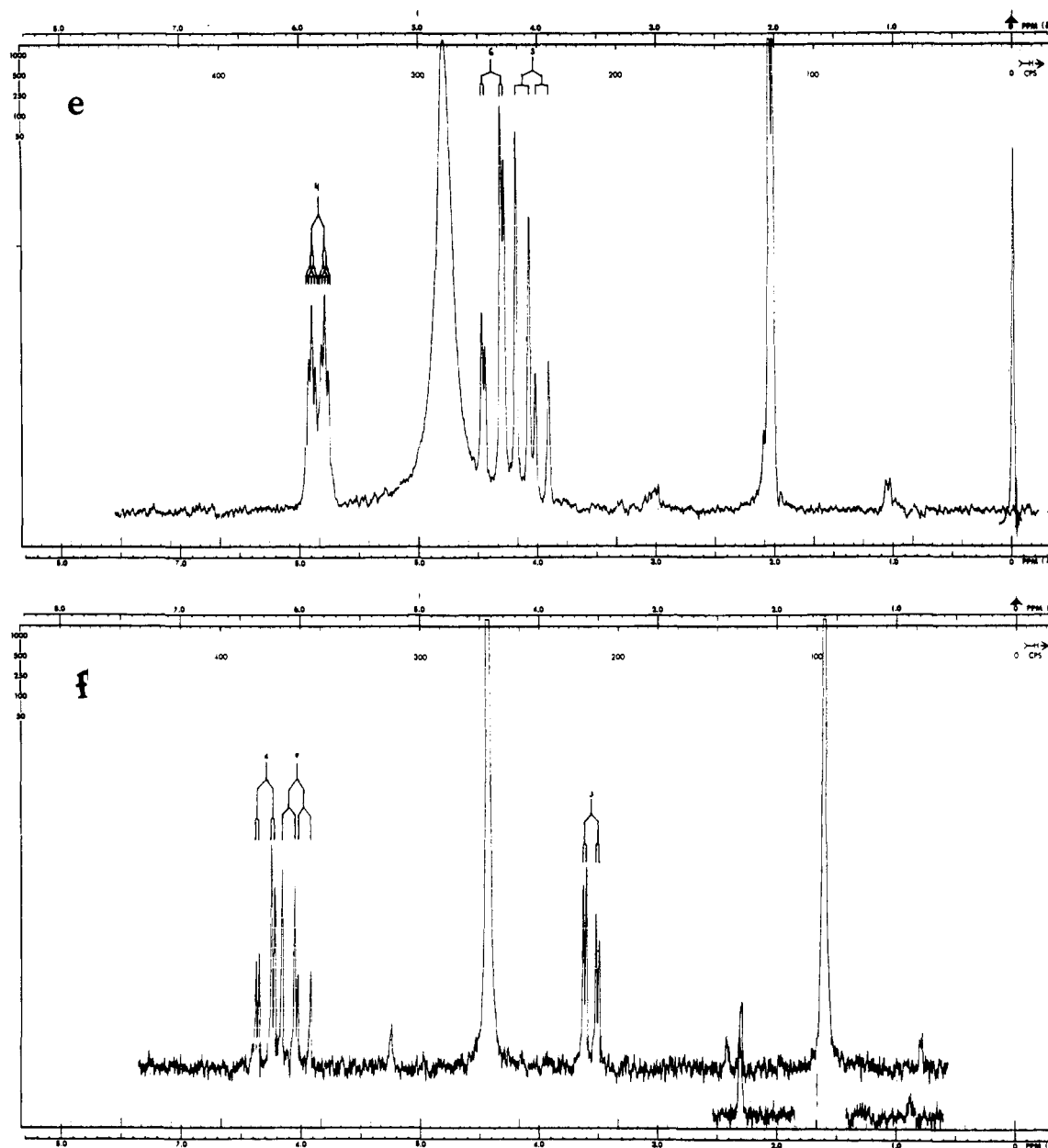
Fig. 4e and f.—N.m.r. spectra: e, dimer of 2-amino-5-methylpyridine hydrochloride (IXd); f, dimer of 2-amino-6-methylpyridine hydrochloride (IXe).

also be made by analysis of their n.m.r. spectra. First, it may be noted that in structures IXc and XIc the 3-hydrogen should produce two doublets, while the 6-hydrogen should give rise to a quartet. In structures IXd and XId, the situation is exactly reversed. In structures X (c and d), and XII (c and d), on the other hand, the 3-hydrogen should result in a doublet, while the 6-hydrogen should also give rise to a doublet. The spectrum of 2-amino-4-methylpyridine hydrochloride dimer (Fig. 4d) shows two doublets (6.19 τ) for the 3-hydrogen and a quartet (5.48 τ), partly obscured by the solvent signal, for the 6-hydrogen, while the spectrum of 2-amino-5-methylpyridine hydrochloride dimer (Fig. 4e) shows a quartet (5.97 τ) for the 3-hydrogen and two doublets (5.62 τ) for the 6-hydrogen. These spectra are clearly inconsistent with structures X (c and d) and XII (c and d).

We feel that the difference between the chemical shifts of the 5-hydrogen in the 2-amino-4-methylpyridine hydrochloride dimer and the 4-hydrogen in the 2-amino-5-methylpyridine hydrochloride dimer should be the same as the difference between the chemical

shifts of the 4- and 5-hydrogens in the unsubstituted 2-aminopyridine hydrochloride dimer, *provided that all have the same stereochemistry*. Table I shows these differences to be 0.52 and 0.55 p.p.m., respectively. Structure XI (c and d), which differs in stereochemistry from the *anti-trans* configuration IXa established for the 2-aminopyridine hydrochloride dimer, thus becomes improbable.

Similar reasoning applied in selecting the *anti-trans* configuration for the corresponding 4-methyl- and 5-methyl-2-pyridone dimers (XIIIc and d).

Turning now to the structures of the photodimers of 2-amino-3-methyl- and 2-amino-6-methylpyridine hydrochloride, examination of their n.m.r. spectra (Fig. 4c and 4f) reveals that a distinction between IX (b and e) and XI (b and e), on the one hand, and X (b and e) and XII (b and e), on the other hand, cannot be made on the basis of methine proton signals, for in the former case the protons are adjacent to a methyl group, and in the latter case adjacent to an equivalent proton, with the net result that two doublets would be expected in each case.
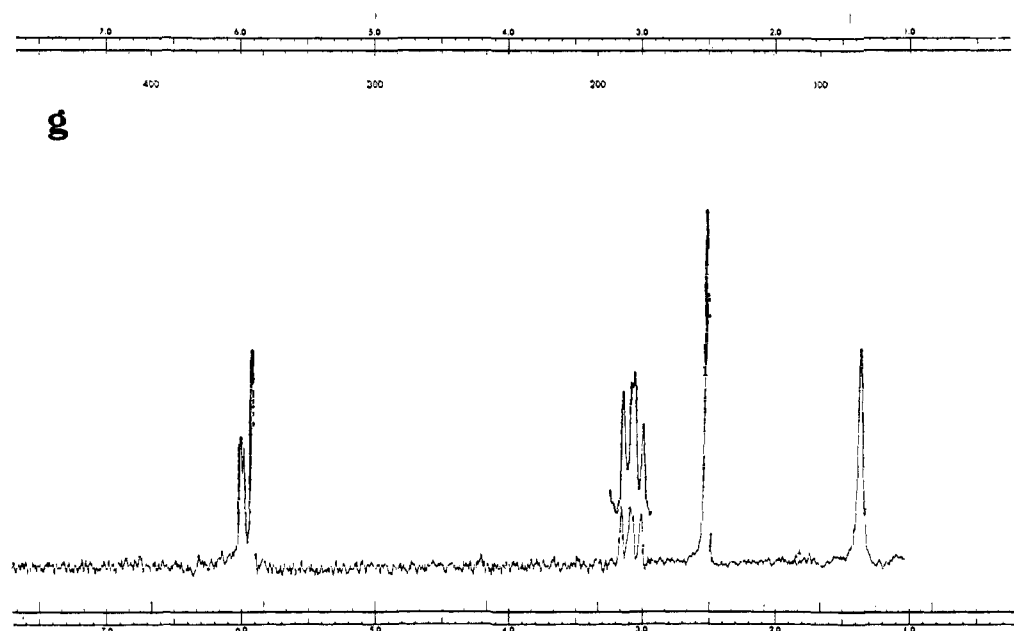
Fig. 4g.—N.m.r. spectrum of dimer of N,6-dimethyl-2-pyridone (XIIIg).

Ayer and co-workers[5] noted that the dimer of N,6-dimethyl-2-pyridone (XIIIg), in addition to possessing a dipole moment of "less than 2 D.," also displayed a markedly reduced difference between the chemical shifts of the olefinic protons (the 4- and 5-hydrogens) relative to N-methyl-2-pyridone, and concluded that in this case the *syn-trans* configuration XVg had been obtained. Inspection of Table I reveals that a similar but diminished change is observed for the dimers of 2-amino-3-methyl- and 2-amino-6-methylpyridine as compared to 2-aminopyridine, which must be due to the influence of the adjacent methyl group. It is seen that the chemical shift of the olefinic proton adjacent to the methyl group increases approximately 0.28 p.p.m., while the remaining olefinic proton is insensitive to the presence of the methyl group. With 2-amino-3-methyl-pyridine dimer, this results in an increase in the difference between the chemical shifts of the 4- and 5-protons to 0.83 p.p.m., whereas with 2-amino-6-methyl-pyridine dimer this difference is decreased to 0.28 p.p.m. These observations point to a mutually similar structure for the two dimers. Furthermore, since the position of the signal of the olefinic proton not adjacent to the 3- or 6-methyl group is almost identical with that in the 2-aminopyridine hydrochloride dimer itself, it seems reasonable to suggest that all three dimers possess the same configuration. Entirely similar reasoning may be applied to the dimers of 3-methyl-(XIIIb) and 6-methyl-2-pyridone (XIIIe) in assigning to them the *anti-trans* configuration.

It is interesting to point out that the changes in chemical shifts accompanying the introduction of a 3, 4, 5- or 6-methyl group are almost identical in the 2-aminopyridine hydrochloride and 2-pyridone series. This is not at all compatible with the role ascribed to the amide carbonyl group by Ayer, *et al.*,[5] who suggested that it was responsible for the difference between the chemical shifts of the 4- and 5-hydrogens by influencing the hydrogen immediately above it. One can hardly expect an amide carbonyl group and a protonated amidine function to have exactly the same effect.

The n.m.r. spectra obtained from the dimers of N,6-dimethyl-2-pyridone (XIIIg) (Fig. 4g) and N,6-dimethyl-2-iminopyridine hydrochloride (XVII) depart rather widely from the spectra of those dimers which do not bear an N-methyl group.

XVII
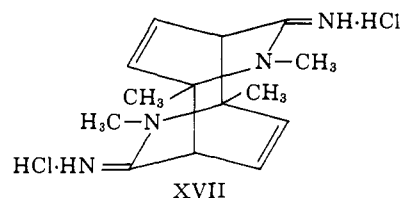
As mentioned above, the almost identical chemical shift of the 4- and 5-protons in the former case caused Ayer, *et al.*,[5] to suggest that no carbonyl group could be located below an olefinic proton, and they thus proposed structure XVg for the N,6-dimethyl-2-pyridone dimer. Apparently the N-methyl group alone is not responsible for this phenomenon, since the spectra of the dimers of 2-pyridone and N-methyl-2-pyridone are identical except for the presence of an N-methyl signal in the spectrum of the latter. We have been assured[14] that the "deviating" spectra do indeed still conform to the characteristic ABX pattern, but that the almost identical chemical shifts of the olefinic protons may be due to a combination of effects. For example, the 6-methyl group in structure XIIIg eclipses the adjacent methine hydrogen, which in turn may deform or alter the shape of the amide function. The net effect is directed toward equal shielding of the protons. The N-methyl group may serve to enhance the deformation with a resulting overlap of the olefinic proton signals, as observed.[14]

It thus appears that the N,6-dimethyl-2-pyridone and N,6-dimethyl-2-iminopyridine hydrochloride dimers again possess the *anti-trans* configuration. An attempt was made to prove this structural assignment experimentally by direct methylation of the tetrahydro dimer of 6-methyl-2-pyridone to the tetrahydro dimer of N,6-dimethyl-2-pyridone, but the results were inconclusive.

In conclusion, all 2-aminopyridines and 2-pyridones examined dimerize to give the *anti-trans* configuration, regardless of the nature or position of substituents.

Experimental[15]

Dimerization of 2-Aminopyridines.—The preparation of the photodimer of 2-aminopyridine hydrochloride is illustrative of the method employed. A solution of 30 g. of 2-aminopyridine in 40

(14) Dr. James Burdon and Professor J. D. Roberts, Department of Chemistry, California Institute of Technology; private communications.

(15) Melting points are uncorrected. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

TABLE II

Dimer

Starting material	Formula	M.p., °C.[a]	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2-Aminopyridine	$C_{10}H_{14}N_4Cl_2$	215 d.	45.99	5.41	21.46	45.89	5.35	21.59
2-Amino-3-methylpyridine	$C_{12}H_{18}N_4Cl_2$	179 d.	49.83	6.28	19.37	49.97	6.17	19.58
2-Amino-4-methylpyridine	$C_{12}H_{18}N_4Cl_2$	207 d.	49.83	6.28	19.37	49.72	6.34	19.55
2-Amino-5-methylpyridine	$C_{12}H_{18}N_4Cl_2$	221 d.	49.83	6.28	19.37	49.68	6.04	19.41
2-Amino-6-methylpyridine	$C_{12}H_{18}N_4Cl_2$	182 d.	49.83	6.28	19.37	50.14	6.33	19.44
2-Amino-5-chloropyridine	$C_{10}H_{12}N_4Cl_4$	207 d.	36.39	3.67	16.98	36.44	3.56	17.11
N,6-Dimethyl-2-iminopyridine	$C_{14}H_{22}N_4Cl_2$	255–255.5 d.	52.98	6.99	17.67	53.19	6.89	17.58
2-Pyridone[12]	$C_{10}H_{10}N_2O_2$	225.5–227.5	63.15	5.30	14.73	62.79	5.27	14.98
N-Methyl-2-pyridone	$C_{12}H_{14}N_2O_2$	222–222.5	66.04	6.47	12.84	66.25	6.41	12.95
3-Methyl-2-pyridone	$C_{12}H_{14}N_2O_2$	192–194	66.04	6.47	12.84	66.00	6.63	12.79
4-Methyl-2-pyridone	$C_{12}H_{14}N_2O_2$	243	66.04	6.47	12.84	65.86	6.65	12.77
5-Methyl-2-pyridone	$C_{12}H_{14}N_2O_2$	222	66.04	6.47	12.84	65.92	6.60	12.62
6-Methyl-2-pyridone	$C_{12}H_{14}N_2O_2$	180–182	66.04	6.47	12.84	65.99	6.67	12.87
N,6-Dimethyl-2-pyridone	$C_{14}H_{18}N_2O_2$	195–196	68.27	7.37	11.37	68.38	7.26	11.49
2-Benzylaminopyridine	$C_{24}H_{26}N_4Cl_2$	198–199	65.30	5.94	12.70	65.51	6.01	12.71

Tetrahydro dimer

Formula	M.p., °C.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$C_{10}H_{18}N_4Cl_2$	333–335	45.29	6.84	21.12	45.32	6.85	21.13
$C_{10}H_{16}N_4$	252	62.47	8.39	29.15	62.58	8.15	29.08
$C_{12}H_{22}N_4Cl_2$	346	49.15	7.56	19.11	49.06	7.59	19.19
$C_{12}H_{20}N_4$	224	65.42	9.15	25.44	65.49	9.04	25.45
$C_{12}H_{22}N_4Cl_2$	>360	49.15	7.56	19.11	49.20	7.42	19.24
$C_{12}H_{20}N_4$	257	65.42	9.15	25.44	65.50	9.14	25.59
$C_{12}H_{22}N_4Cl_2$	>360	49.15	7.56	19.11	48.88	7.52	19.09
$C_{12}H_{20}N_4$	237	65.42	9.15	25.44	65.61	8.97	25.51
$C_{12}H_{22}N_4Cl_2$	295	49.15	7.56	19.11	49.25	7.68	18.99
$C_{12}H_{20}N_4$	212–213	65.42	9.15	25.44	65.15	9.38	25.40
$C_{14}H_{26}N_4Cl_2$	>360	52.33	8.16	17.46	52.54	8.25	17.52
$C_{10}H_{14}N_2O_2$	>360	61.84	7.26	14.42	61.87	7.12	14.26
$C_{12}H_{18}N_2O_2$	285–286	64.84	8.16	12.60	64.85	8.20	12.42
$C_{12}H_{18}N_2O_2$	>360	64.84	8.16	12.60	64.90	8.19	12.52
$C_{12}H_{18}N_2O_2$	>360	64.84	8.16	12.60	64.86	8.15	12.62
$C_{12}H_{18}N_2O_2$	>360	64.84	8.16	12.60	65.00	8.08	12.52
$C_{12}H_{18}N_2O_2$	>360	64.84	8.16	12.60	64.84	8.20	12.44
$C_{12}H_{18}N_2O_2$	>360	64.84	8.16	12.60			
$C_{14}H_{22}N_2O_2$	255–256	67.17	8.86	11.20	67.17	8.61	11.21
$C_{24}H_{30}N_4Cl_2$	331 d.	64.71	6.79	12.58	64.64	6.90	12.39

[a] All melting points were strongly dependent upon the rate of heating.

ml. of concentrated hydrochloric acid contained in a 250-ml. Pyrex erlenmeyer flask was immersed in a 1500-ml. Pyrex beaker fitted with an inlet and an outlet for continuous water cooling. The beaker was placed in front of a G.E. AH-6 high pressure mercury arc. After two hours of irradiation large white crystals had formed along the walls of the flask. These were removed in

order to allow further passage of light into the solution, and irradiation was continued. In this manner the photoproduct was regularly "harvested" from the irradiation solution until the decrease in concentration of the starting material (readily assayed by observing the decrease in the ultraviolet absorption maximum at 310 mμ) made further irradiation unfruitful. In a typical experiment, 20 g. (66%) of the dimer of 2-aminopyridine hydrochloride was obtained after about 20 hr. of irradiation. The product was recrystallized from aqueous ethanol, and melted (rapid heating) at 215° dec. Other members of the series were obtained in a similar manner; their physical and microanalytical data are given in Table II.

Dimerization of 2-Pyridones.—The preparation of the photodimer of 2-pyridone is illustrative of the method employed. A solution of 69 g. of 2-pyridone in 100 ml. of ethanol was placed in a long, narrow tube designed to fit around a large Hanau low pressure immersion lamp. After 5 days of irradiation 19.5 g. (28%) of the dimer of 2-pyridone had separated at the bottom and sides of the tube, and irradiation was discontinued. In an alternative preparation, a solution of 20 g. of 2-pyridone in 125 ml. of ethanol, contained in a 250-ml. Pyrex erlenmeyer flask, was immersed in a 1500-ml. Pyrex beaker fitted with an inlet and an outlet for continuous water cooling, which was placed in front of a G.E. AH-6 high pressure mercury arc. After 1 day of irradiation, considerable solid product had collected on the walls of the flask and was removed to allow further passage of light into the solution. After 3 days the total yield of product was 8 g. (40%). The dimer was recrystallized from glacial acetic acid and melted at 225.5–227.5°. Other dimers in this series were obtained similarly except for the dimer of N-methyl-2-pyridone, which was most conveniently prepared by irradiation of the neat liquid by means of a Hanovia lamp (type 30600). Table II lists the physical and microanalytical data for the 2-pyridone dimers prepared.

Hydrogenation of 2-Aminopyridine Dimers.—The following procedure is illustrative of the method employed for the conversion of the 2-aminopyridine dimers to their tetrahydro derivatives. A solution of 20.0 g. of the dimer of 2-aminopyridine hydrochloride in 300 ml. of water was hydrogenated for 12 hours at room temperature under 40 p.s.i. of hydrogen, using 0.3 g. of platinum oxide as catalyst. Filtration of the reduction mixture followed by evaporation under reduced pressure left 17.8 g. (88%) of a white solid, m.p. 333–335°. The compound could be recrystallized from aqueous ethanol. A dihydrate of the free base could be obtained quantitatively by the addition of cold 10% sodium hydroxide solution to an aqueous solution of the dihydrochloride of the tetrahydro dimer; the extremely insoluble dihydrate separated immediately from the neutralized solution as a white solid, m.p. 252°. It could be reconverted to the hydrochloride by the addition of dilute hydrochloric acid, and to the anhydrous free base by thorough drying. All other members of the series were converted into their tetrahydro derivatives similarly except for the dimer of 2-amino-5-chloropyridine hydrochloride, which suffered hydrogenolysis of the C–Cl bond upon hydrogenation to give the tetrahydro derivative of the dimer of 2-aminopyridine hydrochloride. Physical constants and microanalytical data for these derivatives are given in Table II.

Hydrogenation of 2-Pyridone Dimers.—The above procedure was followed except that glacial acetic acid was used as the solvent for the hydrogenation. All tetrahydro derivatives were recrystallized from glacial acetic acid. Physical constants and microanalytical data for these derivatives are given in Table II.

Preparation of C-Methyl-2-pyridones.—The following procedure was employed for the preparation of 3-methyl-, 4-methyl-, 5-methyl- and 6-methyl-2-pyridone. A solution of 50 g. of the appropriate C-methyl-2-aminopyridine in 200 ml. of water and 80 ml. of concentrated sulfuric acid was cooled to 15°, 180 g. of crushed ice added, and a solution of 37 g. of sodium nitrite in 92 ml. of water was added slowly at such a rate that the temperature of the reaction mixture was maintained below 10°. After addition was complete, the mixture was slowly heated to boiling on a hot-plate and then boiled for 15 minutes. The pH of the cooled mixture was adjusted to 7 by the addition of solid sodium carbonate. Extraction with chloroform (at least 7 times), followed by drying of the extracts and evaporation of the solvent gave the desired C-methyl-2-pyridone which was recrystallized from benzene (charcoal). The yields ranged from 40–70%; melting points of the products agreed well with the literature values.

Conversion of the Tetrahydro Dimer of 2-Aminopyridine into the Tetrahydro Dimer of 2-Pyridone.—A mixture of 0.55 g. of the tetrahydro dimer of 2-aminopyridine, 1.0 g. of potassium hydroxide and 20 ml. of water was heated under reflux for 8 hours. Filtration of the cooled reaction solution yielded a white solid, and an additional quantity was obtained by evaporation of the mother liquor under a stream of air. The total yield of white solid was 0.2 g. (36%) which was recrystallized from boiling water; m.p. > 360°. The infrared spectrum of this material was superimposable upon that of the tetrahydro derivative of 2-pyridone.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.26; N, 14.42. Found: C, 61.61; H, 7.53; N, 14.71.

Conversion of the Dimer of 2-Pyridone to the Dimer of N-Methyl-2-pyridone.—A mixture of 1.0 g. of the dimer of 2-pyridone, 50 ml. of water, 10 ml. of dimethyl sulfate and 4 g. of sodium hydroxide was stirred at room temperature for 6 hours and then filtered to remove unreacted starting material. Extraction of the filtrate with chloroform, followed by drying of the extract over anhydrous sodium sulfate and evaporation to dryness, yielded a small amount of a colorless solid, m.p. 225–226°, identical with an authentic sample of the dimer of N-methyl-2-pyridone, as determined by a mixture melting point determination and by a comparison of infrared spectra.

N,6-Dimethyl-2-pyridone was prepared essentially as described by Adams and Schrecker.[16] Recrystallization from diethyl ether gave colorless crystals, m.p. 56°.

Anal. Calcd. for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.39; H, 7.34; N, 11.39.

N,6-Dimethyl-2-iminopyridine.—A mixture of 23 g. of 2-amino-6-methylpyridine and 34 g. of methyl iodide was warmed on a steam-bath until a violent exothermic reaction set in. After the reaction had subsided, the mixture was cooled and the hygroscopic solid so obtained was recrystallized from ethanol to give 28 g. (53%) of N,6-dimethyl-2-iminopyridine hydroiodide. The free base was prepared by dissolving the salt in 100 ml. of water and shaking vigorously for 15 minutes with thoroughly washed silver oxide, prepared from 32 g. of silver nitrate and 10 g. of sodium hydroxide. Filtration of the mixture followed by evap-

oration of the filtrate under reduced pressure yielded a green, viscous liquid which could not be induced to crystallize. It was characterized as a picrate, which upon recrystallization from ethanol melted at 162–163°.

Anal. Calcd. for $C_{13}H_{14}N_5O_7$: C, 44.33; H, 4.01; N, 19.88. Found: C, 44.50; H, 3.87; N, 19.80.

The hydrochloride of N,6-dimethyl-2-iminopyridine was obtained by addition of concentrated hydrochloric acid to the above filtrate prior to evaporation. Subsequent concentration under reduced pressure yielded hygroscopic needles, m.p. 246–250°, which were used directly in the irradiation experiments without further purification.

The structure of this material was confirmed by treatment with nitrous acid (under the conditions described above for the conversion of 2-aminopyridines to 2-pyridones), followed by conversion to the picrate, m.p. 128°. Mixture melting point determinations and comparison of infrared spectra confirmed that the product of diazotization was N,6-dimethyl-2-pyridone.

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# Intramolecular Hydrogen Bonding Studies with Semi-rigid Molecules. I. Derivatives of 5,10b-Ethanophenanthridine

By H. M. FALES AND W. C. WILDMAN

Spectroscopic examination of the hydroxyl stretching frequencies of 32 compounds derived from the 5,10b-ethano-8,9-methylenedioxy-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (crinane) nucleus has demonstrated the utility of this technique for the determination of hydroxyl configurations. Evidence is cited for the occurrence of interactions of hydroxyl groups with each other, with favorably situated alkoxyl, epoxy and carbonyl groups, and with the π-electrons of double bonds and aromatic rings. A useful technique for O-deuteration within the infrared cell is described.

Beyond the immediate goal of structural constitution, the study of natural products may yield unique series of compounds through which physical phenomena can be investigated and clarified. Detection of intramolecular hydrogen bonding by spectroscopic methods has proved to be particularly fruitful in structural studies of a great variety of complex organic compounds.[1–5] In previous papers on the alkaloids of the Amaryllidaceae, this technique provided a means of differentiating haemanthamine (I, R = OH, R' = H) from epihaemanthamine (I, R = H, R' = OH). The hydroxyl group in haemanthamine interacts with π-electrons of the C_1–C_2 double bond and in epihaemanthamine with those of the aromatic ring. Catalytic reduction of the isolated double bond caused a change in frequency of hydroxyl absorption in haemanthamine but not in epihaemanthamine.[6] The hydrogen bonding of vicinal methoxy alcohols within a semi-rigid ring system was discussed in connection with the structures of monotanine (II, R = OCH_3, R_1 = OH, R_2 = H) and coccinine (II, R = H, R_1 = OH, R_2 = OCH_3).[7] In the present paper,

spectral studies are reported on oxygenated derivatives of the 5,10b-ethano-8,9-methylenedioxy-1,2,3,4,4a,5,6,-10b-octahydrophenanthridine (crinane) nucleus. The preparation and structures of these compounds have been presented in earlier papers of the Amaryllidaceae series.[8]
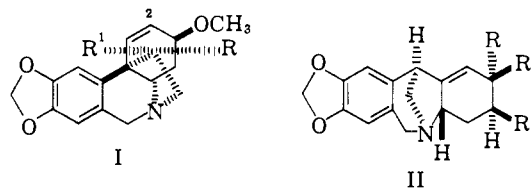
Experimental

A Beckman IR-7 spectrophotometer with prism-grating interchange was employed in all studies. Usually, a spectral slit-width of 5 cm.$^{-1}$ was used, furnishing an error in peak absorbance of less than 3%. The spectra were obtained by scanning at such a speed that tracking error was negligible. Most of the frequencies are considered accurate within 1–2 cm.$^{-1}$. The spectrophotometer was purged with dry air and calibrated against ammonia or water vapor in the region employed.

All substances were run in carbon tetrachloride in 0.1–5-cm. salt or silica cells under double-beam conditions. To ensure that intermolecular association was not occurring in samples showing more than one sharp band, the spectra were rerun at higher dilution (0.001–0.005 M) using a proportionately longer path length or proportionately increased ordinate scale. Insolubility became a severe problem with several of the diols, and it was necessary to

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