Herstellung der 3-Alkoxy-6-benzylaminopyridazine (Nr. 19～Nr. 21)——5 g 3-Chlor-6-benzylaminopyridazin wurde zusammen mit den entsprechenden anhyd. Na-Alkoholaten in 100 ccm Xylol 12 Stunden lang unter Rückfluß erhitzt. Nach dem Abdampfen des Lösungsmittels wurde der Rückstand mit H_2O versetzt. Die so ausgeschiedenen Kristalle wurden abgesaugt, mit H_2O gewaschen und aus $MeOH+H_2O$ umgelöst, wobei man farblose Nadeln der 3-Alkoxy-6-benzylaminopyridazine in ziemlich guter Ausbeute erhielt.

Zun Pchluß sei gesagt, daß wir Herrn G. Tatsui dem Direktor unseres Laboratoriums für die Anregung zu dieser Arbeit zu großem Dank verpflichtet sind

Zusammenfassung

Durch die Einwirkung von Anilinen auf 3,6-Dichlorpyridazin wurden verschiedenartige 3-Chlor-6-anilinopyridazine dargestellt. Die letzteren lieferten durch Einwirkung von Natrium-Benzylalkoholat 3-Benzyloxy-6-anilinopyridazine, die durch Zersetzung mit Salzsäure in 6-Anilino-3(2*H*)-pyridazinone übergeführt wurden. Die so erhaltenen 6-Anilino-3(2*H*)-pyridazinone lieferten beim Einwirkenlassen von Methyljodid 2-Methyl-6-anilino-3(2*H*)-pyridazinone. 3-Chlor-6-anilinopyridazine ergaben bei der katalytischen Hydrierung mit Palladium-Kohle 3-Anilinopyridazine. Ferner wurden einige 3-Alkoxy-6-benzylaminopyridazine hergestellt.

(Eingegangen am 19 Mai, 1962)

UDC 547.852.2.07

128. Yoshihiro Nitta, Reiko Tomii, and Fumio Yoneda : Pyridazine Derivatives. IV.[*1] The Structures of Aminopyridazines.

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A number of investigations[1~4] have been made upon the infrared spectra of monoaminopyridines, namely 2-, 3-, and 4-aminopyridines. However, the study of infrared spectra of pyridazine derivatives analogous to pyridines has not been reported as yet, except that of pyridazine itself.[5,6]

Here it is of interest to study whether introduction of one nitrogen atom into the nucleus of aminopyridines to give aminopyridazines causes any change or not in the infrared spectra comparing with those of the parent aminopyridines. This in turn may be provided useful informations concerning the structures of aminopyridazines having two heteroatoms in a nucleus. From such a point of view, the infrared spectra of 3- and 4-aminopyridazines and 2-, 3-, and 4-aminopyridines have now been examined. Consequently, we have confirmed for the first time that aminopyridazines exist in the amino-form as in the case of aminopyridines. Furthermore, it was also found that the

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[*1] Part Ⅲ : This Bulletin, **11**, 740 (1933).

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1) S.T. Angyal, C.L. Angyal : J. Chem. Soc., **1952**, 1461.
2) J.D.S. Goulden : *Ibid.*, **1952**, 2939.
3) L.C. Anderson, N.V. Seeger : J. Amer. Chem. Soc., **71**, 340 (1949).
4) C.L. Angyal, R.L. Werner : J. Chem. Soc., **1952**, 2911.
5) M. Ito, R. Shimada, T. Kuraishi, W. Mizushima : J. Chem. Phys., **25**, 597 (1956).
6) R.C. Lord : Spectrochemica Acta, **9**, 113 (1957).

position of substituent correlates with its nature. These results will be mentioned most conveniently in three sections as follows :

a) Spectral Evidence for Amino-form——In general, it has been demonstrated that bands arising from the NH_2 stretching vibrations occur in the 3000 cm^{-1} region while the corresponding bending vibration causes on absorption in the 1800～1600 cm^{-1} region. In this particular problem therefore both the 3000 cm^{-1} and the 1800～1600 cm^{-1} regions have been investigated and for convenience the results in each will be discussed separately.

In the 3000 cm^{-1} region, 3- and 4-aminopyridazines give similar spectra in the solid state, consisting of three peaks between 3110～3350 cm^{-1}, a pattern characteristic of hydrogen-bonded NH groups (Fig. 1). These bands changed to three bands near 2257, 2385 and 2465 cm^{-1} on deuteration. In chloroform solution, thesecompounds show four bands near 3530, 3420, 3300, and 3100 cm^{-1}. However, in dilute solution, the latter two bands have disappeared, while the former two bands are still remaining in the same positions. Moreover, the positions and relative intensities of these two bands were not altered on dilution of the chloroform solution, thus showing that two bands near 3530 and 3420 cm^{-1} are assigned to the nonbonded asymmetric and symmetric vibrations of the amino group, and two bands near 3300 and 3100 cm^{-1} are assigned to the corresponding bonded NH stretching modes. From these results, it can be reasonably assumed that 3- and 4-aminopyridazine present as the amino-form.

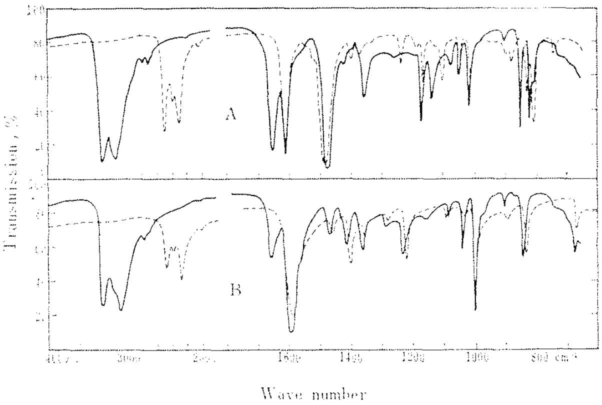

Fig. 1. Infrared Spectra of Aminopyridazines (——) and Deuterated Aminopyridazines (------)

A : 3-aminopyridazine
B : 4-aminopyridazine
(in KBr disc)

This conclusion is also supported by results reached in the 1800～1600 cm^{-1} region. The NH_2 scissor deformation bands in aminopyridazines appear as a band near 1640 cm^{-1}, completely disappearing on deuteration in the solide state. In the acetylated compounds, the original NH_2 deformation bands disappear and new strong bands appear near 1700 and 1520 cm^{-1}; the former band is obviously due to the C=O stretching vibration, and the later is attributed to the amide (II) band arising from the CH_3CONH-group.

TABLE I.

Compound	Antisymmetric			Symmetric		
	ν	E_{max}	I	ν	E_{max}	I
3-Aminopyridiazine	3530	56	3360	3415	77	3465
2-Aminopyridine	3510	45	2925	3405	63	3150
4-Aminopyridazine	3530	56	3080	3420	108	4320
4-Aminopyridine	3530	43	2580	3420	79	3160
Aniline	3460	20	1600	3380	25	1250
3-Aminopyridine	3495	26	2340	3400	38	2280

The positions (ν : cm^{-1}) and the intensities (I : 1 $mole^{-1}$ cm^{-2}) of the symmetric and antisymmetric N-H stretching vibration bands of aminopyridazines, aminopyridines and aniline in $CHCl_3$. The intensities (I) are given as the product of the maximum extinction coefficient (1 $mole^{-1}$ cm^{-1}), $E_{max}=(1/cl)\log_{10}(T_0/T)\,\nu_{max}$, and the band half-width.

From these results of infrared study, it is clear that aminopyridazines exist predominantly in the amino-form both in the solid state and in solution. Further evidence is given on the base of the spectral similarity of these compounds with the known compounds of the amino form such as 2- and 4-aminopyridine, as will be described in the following sections.

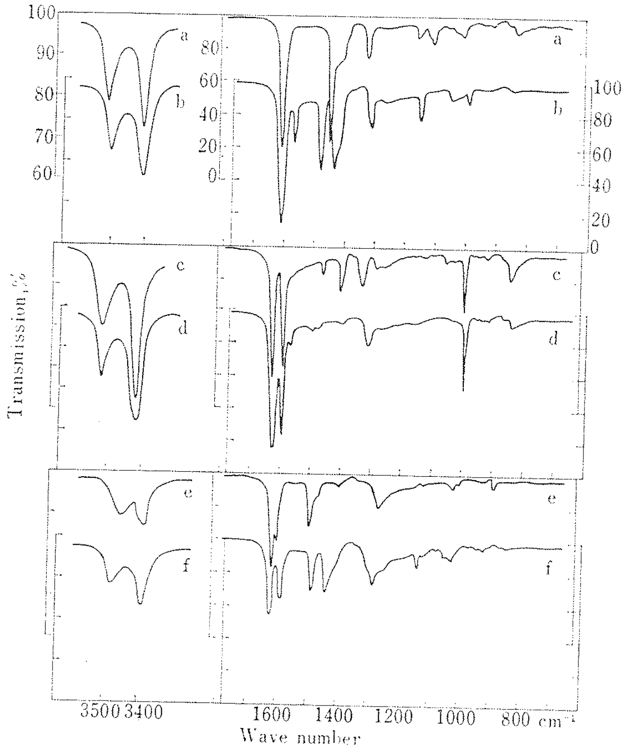

Fig. 2. Infrared Spectra in the 3000 cm^{-1} and 1800~700 cm^{-1} Rigions

a : 3-aminopyridazine
b : 2-aminopyridine
c : 4-aminopyridazine
d : 4-aminopyridine
e : aniline
f : 3-aminopyridine
(0.016*M* $CHCl_3$ solution lmm. cell)

b) The Close Resemblance of the Absorption Spetra of Aminopyridazines to those of Aminopyridines——It is felt of interest to examine whether 4-aminopyridazine is structurally analogous to either 3-aminopyridine or 4-aminopyridine. In order to solve this question, we compared the infrared spectra of aminopyridazines with those of aminopyridines. This attempt resulted to indicate that the spectra of 3-aminopyridazine and 4-aminopyridazine do closely resemble those of 2-aminopyridine and 4-aminopyridine, respectively. Contrary to a possible consideration, the spectrum of 4-aminopyridazine is not close to that of 3-aminopyridine which is well close to that of the aniline having benzene ring. This interesting resemblance will be described below in detail.

The results given in Table I indicate that, in a pair of 3-aminopyridazine and 2-aminopyridine, both the antisymmetric band and the symmetric band present slightly lower frequencies than those of 4-aminopyridazine and 4-aminopyridine, and the difference between the intensities of $\nu_{a(NH_2)}$ and $\nu_{s(NH_2)}$ in the former pair is obviously smaller than that of later pair. On the other hand, in the case of 3-aminopyridine and aniline, the intensities of the antisymmetric stretching frequencies conversely is larger than those of the symmetric stretching frequecies; the same observation has been done for the aromatic amines such as aniline and three isomers of toluidine.⁷⁾

Moreover, in the 1800~700 cm^{-1} region, further aspect of these close resemblance is given (Fig. 2). In solution, the NH_2 deformation bands of 4-aminopyridazine and 4-aminopyridine appear at same position (1627 cm^{-1} and 1625 cm^{-1}), respectively, while in the case of 3-aminopyridazine and 2-aminopyridazine the NH_2 deformation bands

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7) R. Soda : Bull. Chem. Soc. Japan, **30**, 499 (1957).

are similarly present at 1613 cm^{-1} and 1615 cm^{-1}, respectivly, these bands being coupling with the ring vibration.

In addition, in the region of 1600～1400 cm^{-1}, these compounds give four bands, which must be assigned to the ring vibration. This assignment can be supported by the fact that these bands do not change on deuteration[*3] and by the data of the pyridazine itself reported by Lord,6) who noted that four bands at 1572, 1565, 1444 and 1414 cm^{-1} are assigned to the ring vibration in the region of 1600～1400 cm^{-1}. 4-Aminopyridazine shows the presence of four bands at 1588, 1560, 1457 and 1400 cm^{-1}, corresponding to four bands at 1605, 1573, 1503 and 1430 cm^{-1} for the 4-aminopyridine. The latter two bands are characteristically weak in each one. On the other hand, 3-aminopyridazine shows four bands at 1613, 1590, 1452 and 1405 cm^{-1} corresponding to four bands at 1615, 1573, 1487 and 1442 cm^{-1} for the 2-aminopyridine, of those, the band at 1452 cm^{-1} and the corresponding one at 1487 cm^{-1} being strong contrast to those of 4-aminopyridazine and 4-aminopyridine. From the above discussion, we concluded that 3- and 4-aminopyridazines have the structual similarity with 2- and 4-aminopyridines, respectively. Consequently it is to be expected that the chemical reactions and the electronic nature of the amino group in 3- and 4-aminopyridazine seem to be close to those of 2- and 4-aminopyridine, respectively. These relation is also shown by the results of ultraviolet spectra study of these compounds, which will be reported elsewhere.

c) **Correlation between the Position and the Nature of Substituent**——Hitherto, in the study of the structure of aminopyridines it has been known that the nature of amino group of 3-aminopyridine is different from that of 2- or 4-aminopyridine. However, little has been reported about the difference between 2- and 4-aminopyridines, at least in the study of the infrared spectra. It has now been verified that some difference exists between the nature of amino groups of 3-aminopyridazine and 4-aminopyridazine as well as between those of 2-aminopyridine and 4-aminopyridine. The result will be reported below.

That the difference exists between the absorption data of 3-aminopyridazine and 4-aminopyridazine is shown by a comparison of the intensity ratio and of the wavenumber for the absorption frequencies of the antisymmetric and the symmetric stretching vibrations of the amino group. In the chloroform solution, the antisymmetric stretching vibration band of 3-aminopyridazine shows larger intensity than that of 4-aminopyridazine, and the symmetric band of 3-aminopyridazine shows smaller intensity than that of 4-isomer, as can be seen from Table I.

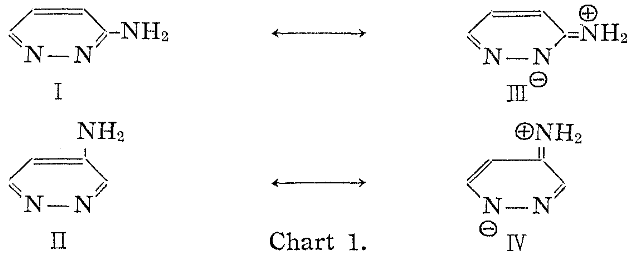

Chart 1.

Similar relationship between absorptions and intensities is also found in the spectra of 2-aminopyridine and 4-aminopyridine (Table I). These results seem to suggest that the $=\overset{+}{N}H_2$ type structure is more contributing in 4-aminopyridazine than in 3-aminopyridazine (see Chart I). This view in accounting for changes in absorption would be supported by the results of the investigations of Mason8) who concluded that the inten-

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[*3] Infrared spectra study of deuterated aminopyridazines in solution will be reported elsewhere.

8) S.F. Mason : J. Chem. Soc, **1959**, 1281.

sity of the symmetric band is larger the greater the conjugation between the nitrogen atom of the nucleus and the amino group, and the intensity of the antisymmetric band increases with the H-N-H bond angle.[*4] Same conclusion is also shown by the spectra in the solid state; 4-aminopyridazine shows the slightly lower frequencies and the wider absorption band of the NH stretching vibrations than those of 3-aminopyridazine as shown in Fig. 1.

Additional evidence is given from the position and strength of the NH_2 deformation bands for these compounds under consideration. In the solid state, the NH_2 deformation band for 4-aminopyridazine is stronger in intensity than that for 3-aminopyridazine, as shown in Fig. 1. The intensity of the band can be probably correlated with the electronic nature of NH_2 group. It can be reasonably expected that the conjugation between the nitrogen atom of the nucleus and the amino group is larger the smaller is the intensity of the NH_2 deformation band. Moreover, the fact that the NH_2 deformation band of 4-aminopyridazine appears at higher frequency (ca. $10\,cm^{-1}$) than that of 3-aminopyridazine in solution as mentioned above, is expected from the same reason. Accordingly, these spectra both in solution and in solid state are presumably explained as due to the difference in the electronic state of the NH_2 structure between the 3- and 4-aminopyridazines.

Seemingly, the structures of aminopyridazines involve resonance between the two structures in the excited state, as shown in Chart 1; the similarity of infrared spectra between 4-aminopyridazine and 4-aminopyridine and between 3-aminopyridazine and 2-aminopyridine shows that polar structures of aminopyridazines are similar to those of corresponding aminopyridines, thus ruling out the structures (3) and (4). And, the results of infrared spectra mentioned above indicate that in the case of 4-aminopyridazine the contribution to the structure of (4), being *p*-quinoid in nature, is larger than that to the polar structure of (3) in the 3-aminopyridazine, this conclusion being in good agreement with the result already afforded in the $3000\,cm^{-1}$ region.

Such conclusion in turn can be drawn that 3- and 4-aminopyridazines are regarded as α- and γ-isomer, respectively.

Experimental

Materials——Aniline, 2-, 3- and 4-aminopyridines were commercial samples; 3- and 4-aminopyridazines were prepared according to Grundmann[9] and to Kuraishi.[10] All these substances were redistilled or recrystallised within a few hours before measurement and were examined with KBr discs and in $CHCl_3$ solution. The spectra of aminopyridazines could not be measured in CCl_4 or CS_2 solution, because of their low solubilility. N-Deuterated aminopyridazines were prepared from purified aminopyridazines. Replacement of the amino hydrogen by deuterium was accomplished by adding an excess of D_2O, evaporating the D_2O in vacuum, and repeating this procedure four times.

Apparatus——The spectra were recorded on a Hitachi EPI 2 with NaCl optics.

The authors wish to thank Mr. G. Tatui of director of this Laboratory for his encouragement during this work.

Summary

The infrared absorption spectra of the two aminopyridazines were observed and compared with those of the three aminopyridines and aniline. The amino-form of the two aminopyridazines was confirmed, and at the same time the structural similarity of 4-aminopyridazine with 4-aminopyridine was shown by their infrared spectra. Similarly, the spectrum of 3-aminopyridazine was close to that of 2-aminopyridine. In addition, the correlation between the position and the nature of substituent was discussed.

(Received May 19, 1962)

[*4] The Mason's conclusion is based on a correlation between the force constant for N-H stretching vibrations in primary aromatic amines and the electron density on nitrogen.

9) C. Grundmann : Chem. Ber., **81**, 1 (1948).

10) T. Kuraishi : This Bulletin, **4**, 137 (1956).