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242. Yoshiro Kobayashi[*1,2] and Eitatsu Chinen[*1] : Studies on Organic Fluorine Compounds. I. Syntheses and Infrared Absorption of Bis(trifluoromethyl)pyridines.[*3]

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All six isomers of bis(trifluoromethyl)pyridine were synthesized by the reaction with corresponding pyridine dicarboxylic acid and SF_4. The characteristic infrared absorption frequencies of this series of compounds were compared with those of similar compounds and the fact that the symmetrical vibration frequencies of aromatic compounds with two trifluoromethyl groups generally shift to the lower side compared with the compounds with a trifluoromethyl group was found.

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Owing to the strong electronegativity of the trifluoromethyl group, compounds with this group are expected to have interesting behaviors electronically. Besides, since a trifluoromethyl and methyl group have similar spacial sizes, compounds mentioned above are worth much attention as antimetabolite in relation to chemotherapeutic drugs. To get systematic information about the physical and chemical behaviors of these compounds must be useful for the future application. However, in spite of many literatures on the aromatic compounds with a trifluoromethyl group (or groups) as substituent, there are very few on the behaviors of heterocyclic compounds with it. As regards pyridines with it, no report has been published on the systematic comparison of the isomers; especially, concerning the pyridine derivatives with two trifluoromethyl groups, three out of the six isomers have not even been synthesized.

The authors synthesized all the isomers of pyridines with one or two trifluoromethyl groups, nine in total, and carried out instrumental analyses on them to know their characters. In this paper, the synthetic methods and the results about the infrared absorption spectra are described, whereas in the following paper,1) the results of mass-spectrometry are to be treated.

To prepare this series of compounds, chlorine atoms of the trichloromethyl group obtained by the chlorination of the methyl group have usually been substituted by fluorine atoms using hydrogen fluoride.2) But when the isomers have two trifluoromethyl groups, the method was not practicable except for the 2,4- and 2,6-isomers. That trifluoromethylpyridines (Ⅰ, Ⅱ, Ⅲ) are obtained by the reaction of pyridine-monocarboxylic acids with sulfur tetrafluoride has been reported by Raasch.3) A similar method has been reported in the case of 2,3-pyridinedicarboxylic acid,4) but the paper is not explicit on the yield nor other details.

We succeeded in obtaining all the six isomers of bis(trifluoromethyl)pyridines (Ⅳ～Ⅸ) by the reaction of corresponding pyridine-dicarboxylic acids with sulfur tetrafluoride using anhydrous hydrogenfluoride as both catalyst and solvent.

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[*3] Most part of this work was presented at the Annual Meeting of the Chemical Society of Japan, Kyoto, April 1965.

1) Y. Kobayashi, F. Nakano, E. Chinen : This Bulletin, **15**, 1901 (1967).

2) J.H. Brown, C.W. Suckling, W.B. Whalley : J. Chem. Soc., **1949** (Suppl. Issue No. 1), 95.

3) M.S. Raasch : J. Org. Chem., **27**, 1406 (1962).

4) Soon Ng, C.H. Senderholm : J. Chem. Phys., **40**, 2090 (1964).

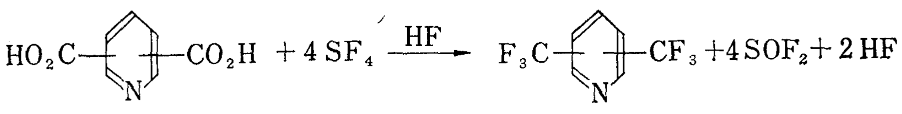

Chart 1.

The reaction was carried out in a "Hastelloy-C"-lined autoclave at 150° for 16~20 hours; the yield was better as the reaction time was longer in every case. Even if the products had contained some compounds having carboxyl groups or fluoroformyl groups on them owing to the imperfect fluorination, such compounds were easily eliminated by making the reaction mixture alkaline and extracting it with ether, and only the desired product was given.

Due to the remarkable volatility of this series of compounds, the loss of the products during distillation of the solvent was comparatively large; the yield of the product based on gas chromatographical analysis of extracted solution before distillation showed to be better than the actual yield by nearly 10% in every case. Purification of the product was carried out by sublimation when they were solids at room temperature, and by using the preparative gas chromatography when liquids. All these substances lack the band corresponding to the carbonyl-group on infrared absorption spectra. As will be discussed below, they showed characteristic absorptions of the trifluoromethyl group and were positive to the oxygen flask combustion method for detecting fluorine.[5] And as reported in the following paper,[1] the parent peaks of all these substances showed molecular weight 215 on mass spectra, and therefore, they are surely bis(trifluoromethyl)pyridine. Because of the remarkable volatility, elemental analysis was impracticable for this series of compounds; the result of analysis concerning 2,6-isomer, which seemed easiest to handle among them, showed the approximate agreement to the desired product. Their boiling points, melting points, and yields were as shown in Table I. Because the trifluoromethyl group is powerfully electron-attracting, these products showed very low basicity and did not form picrate nor hydrochloride.

TABLE I.

	Bis(trifluoromethyl)pyridine	m.p. (°C)	b.p. (°C)	Yield (%)
IV	2,3-	−2	158	75.3
V	2,4-		121~122	72.0
VI	2,5-	27~28	130~131	78.5
VII	2,6-	55~56	152~154	66.8
VIII	3,4-		132~133	70.2
IX	3,5-	35~36	117~118	77.1

A similar reaction was carried out with pyridinemonocarboxylic acid at 120° for 13 hours and at 150° for 2 hours, and almost the same yield as Raasch's reported in the cases of α- and γ-isomers (I and III) resulted, whereas a far better yield compared with that of Raasch was the result in the case of β-isomer (II).

For the purposes of massspectrometry analysis in the following paper, the same reaction was carried out with nicotinic acid-2,6-d_2 and 3-trifluoromethylpyridine-2,6-d_2 (X) was obtained. From the NMR spectrum (Fig. 1.) of this product in carbon tetrachloride, it is clear that 2- and 6-positions remained deuterated at the rate higher than 95% without being exchanged by hydrogen.

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[5] W. Schöniger: Mikrochim. Acta, **1956**, 869.

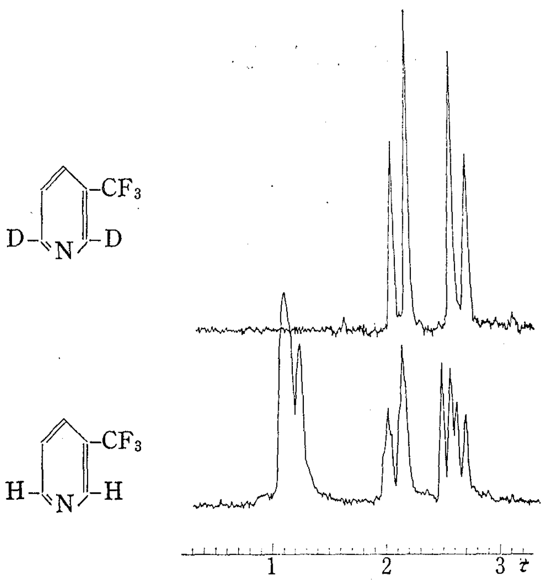

Fig. 1. NMR Spectra of X and II

Spectra were measured in CCl_4 and the chemical shifts were represented by τ-values.

Next, infrared absorption spectra of the above series of products were studied. About the frequencies of the three characteristic absorption bands of the trifluoromethyl groups on aromatic products have been studied by Randle, *et al.*,[6] who obtained the average values of those 26 kinds of the derivatives of benzotrifluoride, which have been widely quoted.[7] That is, as for C–F stretching vibrations, a symmetrical vibration and two antisymmetrical vibrations correspond respectively to the frequenciès at 1321±9 cm^{-1}, 1179±7 cm^{-1}, and 1140±9 cm^{-1}.

As regards the absorption of the trifluoromethyl group on the aromatic compounds with two trifluoromethyl groups, namely, $\alpha,\alpha,\alpha,\alpha',\alpha',\alpha'$-hexafluoroxylene isomers (*o,m,p*) and their derivatives, no interpretation has been published, though they appear in some charts. On the other hand, concerning trifluoromethylpyridine, there are reports on α-isomer only,[8,9] where all three characteristic absorptions are shown to be within the extent of Randle's average values.

The authors measured the infrared absorption spectra of the six isomers of bis(trifluoromethyl)pyridine, three isomers of trifluoromethylpyridine, three isomers of $\alpha,\alpha,\alpha,\alpha',\alpha',\alpha'$-hexafluoroxylenes and others (XI, XII, XIII), and comparatively examined the characteristic absorptions of the trifluoromethyl groups referring to some of the charts in Sadtler Standard Spectra.[10]

As is shown in Table II, concerning trifluoromethylpyridine the three characteristic absorption frequencies were near Randle's average values, with not only α-isomer but also β- and γ-isomers. But in the cases of benzene derivatives and pyridine with two trifluoromethyl groups, though antisymmetrical vibration frequencies almost agreed with Randle's average values with few exceptions, symmetrical vibration frequencies generally shifted to the lower side than Randle's average values; especially, concerning the compounds with two trifluoromethyl groups in the meta position to each other, frequencies shifted over 40 cm^{-1} (V, IX, XII, XIV, XV, XVI, XVII). In the case of 2,6-bis(trifluoromethyl)pyridine (VII), with nitrogen atom in between, the meta relationship of the two trifluoromethyl groups was broken, thereby not showing much shift.

The tendency of the symmetrical vibration frequencies to shift to the lower side, if there are strongly electron-attracting groups beside one trifluoromethyl group, can be assumed from the compounds with nitro groups among those chosen by Randle.

From the above consideration it was concluded that Randle's average values are not applicable to the symmetrical vibration frequencies of bis-substituted compounds.

In Table II, the frequencies in the parentheses are included, because no strong absorption owing to other causes in this neighborhood is probable, though whether it

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6) R.R. Randle, D.H. Whiffen: J. Chem. Soc., **1955**, 1311.

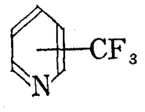
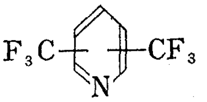
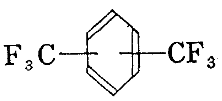
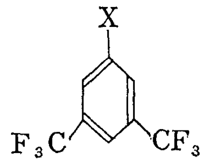
7) L.J. Bellamy: "The Infrared Spectra of Complex Molecules," 2nd ed., 332 (1958). John Wiley & Sons, New York.

8) J.M.S. Jarvie, W.E. Fitzgerald, G.J. Jand: J. Am. Chem. Soc., **78**, 978 (1956).

9) G.J. Jang, M.A. de Crescente: J. Org. Chem., **23**, 765 (1958).

10) Sadtler Research Laboratories, Philadelphia 2, Penna., U.S.A.

Table II. Characteristic Infrared Absorption Frequencies (cm^{-1})

Compound	Formula	Positions of CF_3	X	Frequencies		
				ν_s C–F	ν_{as} C–F	
I		α		1300	1175	1134
II		β		1328	1157	1129
III		γ		1320	1160	1132
IV		2,3		1308	1165	1112
V		2,4		1268 (1307)	1182 (1175)	1150
VI		2,5		1319	1162	1144
VII		2,6		1316 (1357)	1190	1153
VIII		3,4		1310	1167	1132
IX		3,5		1272	1168	1146
XI		o		1309	1177	1158
XII		m		1273	1178	1136
XIII		p		1315	1170	1135
XIV			NO_2	1285	1174	1131
XV			NH_2	1280 (1297)	1174	1129
XVI			Br	1274 (1348)	1179	1139
XVII			OH	1280 (1387)	1175	1135
Randle's average values				1321±9	1179±7	1140±9

can be assigned to the second absorption owing to the trifluoromethyl groups is not certain.

Finally, gas chromatographical analysis of this series of compounds is mentioned.

Three isomers of mono-trifluoromethylpyridines were analyzed using a conventional silicon grease column. However, in the analysis of six isomers of bis(trifluoromethyl)-pyridines, it was very difficult to separate 2,5- and 2,4-isomers completely with usual stationary phases. Satisfactory results were obtained using a column of Benton-34, an organo-clay complex as a stationary phase, in addition to the conventional silicon grease column.

Experimental

Materials——Of the pyridine-dicarboxylic acids used, 2,3-, 2,4-, and 2,6-isomers were obtained from Tokyo Kasei Co., 3,4-isomer was prepared by oxydation of isoquinoline with HNO_3, and 3,5-isomed by oxydation of 3,5-lutidine with $KMnO_4$.

SF_4 (purity : 90~94%) was obtained from the Matheson Co., U.S.A.

The weight of SF_4 was calculated from the volume of liquid condensed in a graduated "Pyrex" glass trap, kept at −60° and put between SF_4 cylinder and autoclave.

General Procedure of Preparing Bis(trifluoromethyl)pyridine——In a 100 ml. "Hastelloy-C"-lined autoclave with magnetic stirrer, pyridine-dicarboxylic acid (13.4 g., 0.08 mole), anhydrous HF (16.0 g., 0.8 mole), and SF_4 (54 g., 0.5 mole) were heated at 150° for 16 hr. with stirring. After having been cooled to room temp., gases were discharged and the remaining HF solution was made alkaline with 10% NaOH under cooling and extracted with ether; the etherial layer was dried over anhydrous Na_2SO_4. After gas chromatographic analysis, ether was removed *in vacuo* without heating. When the residue was crystallized, crystals were filtered and purified by sublimation *in vacuo*. When the residue was a liquid, it was distilled carefully, and the main fraction which still contained a small amount of ether was purified using the preparative gas chromatograph[11] with a silicon grease column.

Example of Elemental Analysis——*Anal.* Calcd. for $C_7H_3NF_6$ (2,6-bis(trifluoromethyl)pyridine : C, 39.05; H, 1.39; F, 53.07. Found : C, 38.62; H, 1.34; F, 52.27.

Nicotinic Acid-2,6-d_2——A mixture of nicotinic acid (1.0 g.) and D_2O (10 ml.) was heated in a sealed tube at 210~215° for 5 hr. After the solvent was distilled off, another portion of D_2O (10 ml.) was added to the residue and the same procedure was repeated. And the whole procedure was repeated again. By crystallization of the residue from H_2O, 0.92 g. of nicotinic acid-2,6-d_2 (m.p. 228°) was obtained. NMR spectrum in 2% NaOH showed clearly that only 2- and 6-positions were deuterated at the rate higher than 95%.

3-Triflyoromethylpyridine-2,6-d_2 (X)——Nicotinic acid-2,6-d_2 (1.0 g.), HF (8.0 g.), and SF_4 (17.0 g.) in a "Hastelloy-C"-lined autoclave were heated at 120° for 13 hr. and 150° for 3 hr. The reaction mixture was worked up according to the general procedure mentioned above.

By purification with preparative gas chromatograph, 0.77 g. (65.0%) of the product (b.p. 114~116°) was obtained. NMR spectrum in CCl_4 and mass spectrum proved that the product was 3-trifluoromethylpyridine-2,6-d_2. NMR spectra were measured by a JNM-317-60 spectrometer (Japan Electron Opitcs Laboratory Co.) operating at 60 Mc.p.s.

Infrared Spectra——The spectra were measured in CS_2 sol. by a Perkin-Elmer Model 521 Grating Spectrometer.

Gas Chromatographical Analysis——A Yanagimoto GCD-30 gas chromatograph was used.

Gas chromatograph of bis(trifluoromethyl)pyridines

isomer	3,5-	2,4-, 2,5-	3,4-	2,6-	2,3-
retention time (min.)	6.5	8.0	9.8	11.3	16

Column : silicon grease 20 wt % on chromosorb-W; 4 m.
Flask temp. : 165°; Column temp. : 80°
Flow rate : He 75 ml./min.

Gas chromatographic separation of 2,5- and 2,4-bis(trifluoromethyl)pyridines

isomer	2,5-	2,4-	3,4-
retention time (min.)	3	5.3	6

Column : Benton-34 5 wt % and Squalane 0.5 wt % on Diasolid : 7 m.
Flask temp. : 165°; Column temp. : 100°
Flow rate : He 60 ml./min.

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11) Beckman "MEGACHROM."