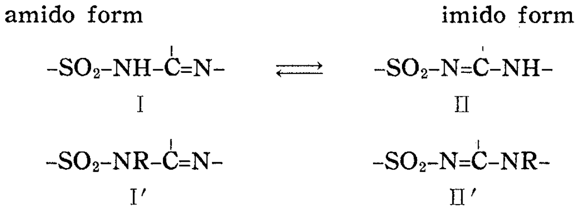
UDC 615.778.25-011 : 543.422.4

120. Toyozo Uno, Katsunosuke Machida, Kazuhiko Hanai, Michihiro Ueda, and Shigeru Sasaki : Infrared Spectra of Sulfonamide Derivatives. I. Pyridine, Thiazole, and Pyrimidine Derivatives.

(*Faculty of Pharmacy, Kyoto University*[*1])

Several N-glucuronides of monosubstituted sulfanilamides have been revealed to occur in the metabolic products of the sulfa-drugs.[1,2] Since these sulfanilamides usually involve a heterocyclic ring containing nitrogen, the tautomerism between the amido form (I) and the imido form (II) is considered. Accordingly, there are two conceivable forms I′ and II′ which differ from each other with respect to the position of the substituent, R, introduced in place of the amide hydrogen atom.



$$\begin{array}{ccc} \text{amido form} & & \text{imido form} \\ -SO_2-NH-\overset{|}{C}=N- & \rightleftarrows & -SO_2-N=\overset{|}{C}-NH- \\ I & & II \\ -SO_2-NR-\overset{|}{C}=N- & & -SO_2-N=\overset{|}{C}-NR- \\ I' & & II' \end{array}$$

The syntheses of the structural isomers, I′ and II′, have been reported for the methyl derivatives of sulfapyridine[3] and sulfathiazole.[3,4] However, it seems that similar syntheses are very difficult for such complex substituents as in the case of glucuronides.

In the ultraviolet spectra, it has been revealed that there are one maximum for the form I or I′ and two maxima for the form II or II′.[3,5,6] This empirical criterion seems to be useful to distinguish the form I and II, as well as I′ and II′.

On the other hand, Sheinker, *et al.* have examined the difference between the amido and the imido form in the infrared spectra, and reported that these two forms can be distinguished empirically by several spectral differences in the 1000～900 cm^{-1} region.[6]

In the NH compounds the hydrogen atom is bonded to the different nitrogen atoms for the amido and the imido form. Thus, the remarkable differences in the infrared spectra of these compounds may be expected with respect to the bands due to the vibrations of the hydrogen atom. Naturally, the hydrogen frequencies can be detected by the comparison with the deuterated compounds.

In this respect, the present paper deals with the infrared spectra of monosubstituted sulfonamides, their N-deuterated compounds and N^1- or ring N-methylsulfonamide derivatives.

Experimental

Materials[*2]

Methanesulfonanilide (MSAn)[*3]——This compound was prepared by reaction of methanesulfonyl chloride and aniline, recrystallized from EtOH. m.p. 99.5～101°.

[*1] Yoshida-Konoe-cho, Sakyo-ku, Kyoto (宇野豊三, 町田勝之輔, 花井一彦, 上田道広, 佐々木 滋).

[*2] All melting points are uncorrected.

[*3] Abbreviations in the parentheses are hereafter used.

1) T. Uno, M. Kono : Yakugaku Zasshi, **80**, 201 (1960) ; *Idem* : *Ibid.*, **82** 1660 (1962).

2) T. Uno, M. Ueda : *Ibid.*, **80**, 1785 (1960).

3) R.G. Shepherd, A.C. Bratton, K.C. Blanchard : J. Am. Chem. Soc., **64**, 2532 (1942).

4) M. Hartmann, J. Druey : Helv. Chim. Acta, **24**, 536 (1941); K.A. Jensen : *Ibid.*, **24**, 1249 (1941).

5) S.J. Angyal, S.R. Jenkin : Australian J. Sci. Research, **3A**, 461 (1950) (C.A., **45**, 7041 (1951)).

Benzenesulfonanilide (BSAn)*3——The commercially available material was recrystallized from 50% EtOH, m.p. 110$\sim$110.5°.

2-Phenylsulfonamidopyrimidine (PSPm)*3——2-Aminopyrimidine (4.8 g.) in 50 ml. dry pyridine was treated dropwise with benzenesulfonyl chloride (9.2 g.) with cooling in icewater. After removing the solvent under the reduced pressure to 0.5 volume, reaction product was poured into HCl acidified ice water. The crude product was separated, washed with H_2O and recrystallized from EtOH and lastly from dioxane. m.p. 227$\sim$228°. *Anal.* Calcd. for $C_{10}H_9O_2N_3S$: C, 51.05; H, 3.86; N, 17.86. Found : C, 51.13; H, 3.98; N, 17.77.

2-Methylsulfonamidopyridine (MSPy)*3——This compound was prepared according to Kostsova's method,7) and crystallized from H_2O or Me_2CO, m.p. 199$\sim$200.5° (194° reported by Kostsova7)).

2-Phenylsulfonamidopyridine (PSPy)*3——This compound was prepared by reaction of benzenesulfonyl chloride and 2-aminopyridine, recrystallized from benzene, m.p. 171$\sim$172.5°.

2-Methylsulfonamidothiazole (MST)*3——A solution of methanesulfonyl chloride (3 g.) in 20 ml. of dry benzene was added gradually to 2-aminothiazole (5 g.) in 140 ml. of dry benzene. Reddish brown syrup was separated by decantation, and recrystallized three times from EtOH, m.p. 219.5$\sim$221°. *Anal.* Calcd. for $C_4H_6O_2N_2S_2$: C, 26.96; H, 3.39; N, 15.72. Found : C, 27.01; H, 3.52. N, 16.02.

2-Phenylsulfonamidothiazole (PST)*3——Benzenesulfonyl chloride (10 g.) was added dropwise to a solution of 2-aminothiazole (5 g.) in 40 ml. dry pyridine under cooling with icewater. After standing overnight at room temperature, solvent was removed under the reduced pressure. Water was poured into the residue, and the crude product was separated by filtration, washed with H_2O and recrystallized three times from dil. EtOH and from dioxane, m.p. 169$\sim$170°. *Anal.* Calcd. for $C_9H_8O_2N_2S_2$: C, 44. 98; H, 3.36. N, 11.66. Found : C, 45.27; H, 3,39; N, 11.76.

N-Methylsulfanilamide derivatives——These compounds were prepared by methylation of sulfanilamides with CH_2N_2 and then separation of N^1-methyl derivatives and ring N-methyl derivatives, according to Shepherd's method.3) The former was crystallized from MeOH, the latter from 6*N* AcOH or EtOH.

N^1-Methyl-N^1-(2-pyridyl)sulfanilamide——m.p. 86$\sim$87.5°.

N^1-(1-Methyl-1,2-dihydro-2-pyridylidene)sulfanilamide——m.p. 232$\sim$233°.

N^1-Methyl-N^1-(2-thiazolyl)sulfanilamide——m.p. 109.5$\sim$111°.

N^1-(3-Methyl-4-thiazolin-2-ylidene)sulfanilamide——m.p. 245$\sim$246° (250$\sim$251°, from 6*N* AcOH, given by Shepherd3) and 244$\sim$245°, from EtOH, given by Tsuda8)).

N-Deuterated species were prepared by the exchange reaction with deuterium oxide in Me_2CO or dioxane. The infrared spectra of these deuterated compounds were compared with those of ordinary compounds which were treated with hydrogen oxide under the same conditions as the case of deuteration.

Measurements

The Koken DS 301 IR spectrophotometer was used with NaCl (3600$\sim$650 cm^{-1}) prisms. Ammonia, polystyrene and acetonitrile were used for the frequency calibration. The measurements of IR spectra were carried out for hexachlorobutadiene (3600$\sim$1800 and 1500$\sim$1300 cm^{-1}) and Nujol (1800$\sim$1500 and 1300$\sim$650 cm^{-1}) pastes.

Results and Discussion

Spectral change on N-Deuteration——The spectral change on N-deuteration may be complicated for sulfanilamide derivatives, because they contain *p*-amino group. Therefore, the simpler sulfonamides in Table I were synthesized and their infrared spectra were measured for NH compounds and ND compounds (Figs. 1, 2, 3 and 4*4).

It is clear from their structure that sulfonanilides take the amido form. In sulfonanilides, a prominent spectral change occurs on N-deuteration in the region 1000$\sim$700 cm^{-1}. As seen in Figs. 1 and 2, PSPm shows similar spectral change to sulfonanilides on N-deuteration. For these compounds, the bands around 1600 cm^{-1} are hardly affected by N-deuteration. On the other hand, in the spectra of MSPy, PSPy, MST, and PST, a strong band around 1600 cm^{-1} disappears and a new strong band appears near 1500 cm^{-1} on N-deuteration, but the bands below 1000 cm^{-1} are almost unchanged.

---

*4 See the Experimental part for the abbreviations.

6) Yu. N. Sheĭnker, I. Ya. Postovskiĭ, N. M. Voronina, V. V. Kushkin : J. Phys. Chem. U. S. S. R., **31**, 1745 (1957); Yu. N. Sheinker, I. K. Kuznetsova : *Ibid.*, **31**, 2657 (1957).

7) A. G. Kostsova : Zhur. Obshcheĭ Khim., **22**, 1428 (1952) (C. A., **47**, 4862 (1953)).

8) K. Tsuda, *et al.* : Yakugaku Zasshi, **70**, 425 (1950).

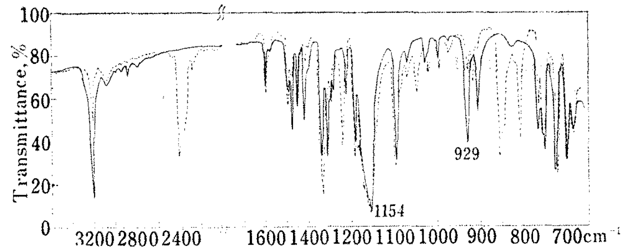


Fig. 1. Infrared spectra of BSAn (solid line) and BSAn-*d* (broken line)

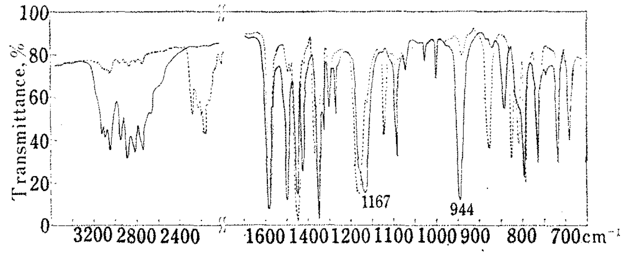


Fig. 2. Infrared spectra of PSPm (solid line) and PSPm-*d* (broken line)

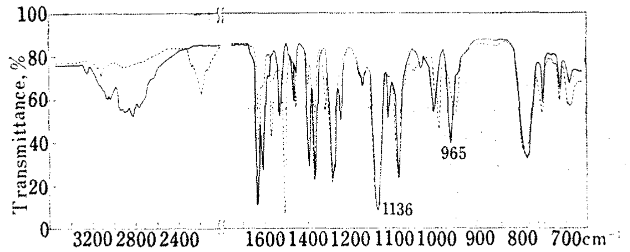


Fig. 3. Infrared spectra of PSPy (solid line) and PSPy-*d* (broken line)

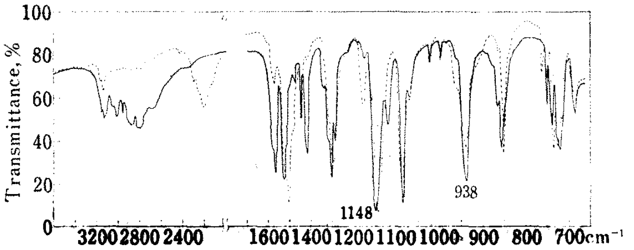


Fig. 4. Infrared spectra of PST (solid line) and PST-*d* (broken line)

The disappearance of a band near 1600 cm^{-1} on N-deuteration has been reported for 2(1*H*)-pyridone[9] which has a ring NH bond whose nature might be similar to that of the imido form.

Thus, these spectral changes on N-deuteration suggest that PSPm takes the form involved in sulfonanilides, that is, the amido form, while MSPy, PSPy, MST and PST take the imido form.

We have carried out the deuteration measurement also for sulfadiazine and sulfathiazole, and revealed that the former shows, but the latter does not show the spectral change on N-deuteration below 1000 cm^{-1}. Thus, these *p*-amino compounds seem to be in the form involved in the corresponding benzene- and methanesulfonamide derivatives.

---

9) K. Nakamura: Nippon Kagaku Zasshi, 80, 231 (1959).

In addition, one maximum peak (265 mμ) in ultraviolet spectra is observed in sulfadiazine in butanol solution. This fact suggests that sulfadiazine is also in the amido form in solution.

These results agree with Sheinker's conclusions[6] for N-(2-pyridyl)- and N-(2-thiazolyl)-sulfonamide derivatives, but do not agree with for N-(2-pyrimidinyl)-sulfonamide derivatives. Sheinker and his coworkers[6,10] have reported that in PST, sulfapyridine, sulfathiazole, sulfadiazine and their heterocyclic ring N-methyl derivatives, a fairly strong band is observed in the region 970～910 cm^{-1}, but in N^1-methyl derivatives this band is not observed. Therefore, attributing the 940 cm^{-1} band to the structure $-SO_2-N=\overset{|}{C}-N-$, these authors concluded that sulfadiazine is also in the imido form in the solid state.

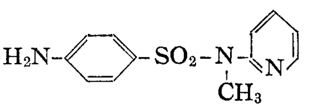
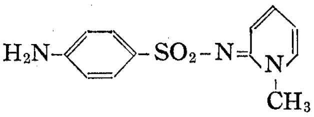
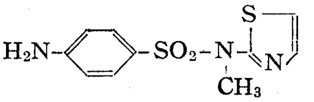
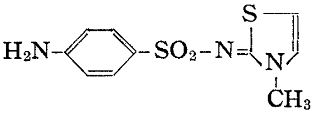
However, as described above, the 940 cm^{-1} band found in PSPm and sulfadiazine was not observed in their N-deuterated species, but the corresponding band found in MSPy, PSPy, MST, PST and sulfathiazole did not disappear on N-deuteration. Therefore, for pyridine and thiazole derivatives the band in 940 cm^{-1} region does not seem to be related with vibration of hydrogen atom. But, 940 cm^{-1} band in pyrimidine derivatives is related with vibration of hydrogen atom, and the band which differs from those of pyridine and thiazole derivatives. In this connection, it is incorrect to give the imido form to pyrimidine derivatives on basis of the presence of 940 cm^{-1} band.

Table I. SO_2 symmetric stretching frequencies of mono-substituted sulfonamides (in cm^{-1})

	SO_2 sym. stretch.
Methanesulfonanilide	1152
Benzenesulfonanilide	1154
2-Methylsulfonamidopyrimidine	
2-Phenylsulfonamidopyrimidine	1167
Sulfadiazine (N^1-(2-pyrimidinyl)sulfanilamide)	1155
2-Methylsulfonamidopyridine[a]	1119
2-Phenylsulfonamidopyridine[a]	1136
Sulfapyridine (N^1-(pyridyl)sulfanilamide)[a]	1125
2-Methylsulfonamidothiazole[a]	1141
2-Phenylsulfonamidothiazole[a]	1148
Sulfathiazole (N^1-(2-thiazolyl)sulfanilamide)[a]	1135

a) The usual names were used, although our results indicate that these compounds take the imido form.

Table II. SO_2 symmetric stretching frequencies and the 940 cm^{-1} band of N-methyl derivatives of sulfapyridine and sulfathiazole (in cm^{-1})

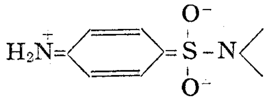
	SO_2 sym. stretch.	940 cm^{-1} band
	1150	—
	1125	975
	1159	—
	1137	939

---

[10] Yu. N. Sheĭnker, I. Ya. Postov: Doklady Akad. Nauk. S.S.S.R., **113**, 1080 (1957). (C.A., **51**, 14718 (1957).

SO_2 Symmetric Stretching Bands——For the most of sulfonamides, one of the strongest absorptions in the infrared spectra is the SO_2 symmetric stretching band occurring in the region 1170~1130 cm^{-1}.[11] The wave numbers of SO_2 symmetric stretching vibrations are shown in Table I and II, where the frequencies of the 940 cm^{-1} band are also shown.

Table II shows that this region can be divided into the two regions, 1170~1145 cm^{-1} and 1145~1130 cm^{-1}, corresponding to the form I′ and the form II′, respectively. Furthermore, as seen in Table I, sulfanilamides which take the amido form absorb in the region 1170~1145 cm^{-1} while sulfanilamides which take the imido form absorb in the region 1145~1130 cm^{-1}. As shown in Table I, the SO_2 symmetric stretching bands of sulfanilamides are always lower than those of the corresponding benzenesulfonamides. This may be due to the contribution from the resonance structure[12,13]. In the same way, the effects on the SO_2 symmetric stretching band are naturally expected to be different for the amido and the imido form.



Thus, the difference in the SO_2 symmetric stretching frequency between the amido form and the imido form may be attributed to the difference in the S=O double bond character between the two forms. In this connection, the difference between the two forms may also be expected for the SO_2 antisymmetric stretching vibration in the region 1370~1330 cm^{-1}.[11] However, the SO_2 antisymmetric stretching band is always weaker than the symmetric stretching band, and more than one band often appear in this region. Therefore, it is difficult to investigate the difference between the two forms by the SO_2 antisymmetric stretching bands.

Conclusion

N-(2-pyridyl)- and N-(2-thiazolyl)-sulfonamide derivatives, that is, MSPy, PSPy, MST and PST, as well as sulfapyridine and sulfathiazole are in the imido form in solid state, while N-(2-pyrimidinyl)-sulfonamide derivatives, that is, PSPm and sulfadiazine are in the amido form.

Infrared spectra of monosubstituted sulfonamides which take the imido form show the prominent spectral change on N-deuteration in the region 1600 to 1200 cm^{-1}. Contrarily, the spectra of sulfonamides which take the amido form show the remarkable spectral change on N-deuteration in the region 1000 to 700 cm^{-1}.

The SO_2 symmetric stretching frequencies of sulfanilamides studied in this paper are divided into the two regions, 1170 to 1145 cm^{-1} and 1145 to 1130 cm^{-1}, corresponding to the amido form and the imido form, respectively.

Summary

The infrared spectra of N-(2-pyridyl)-, N-(2-thiazolyl)-, N-(2-pyrimidinyl)- and N-phenyl-sulfonamide derivatives and their N-deuterated compounds, as well as N^1- or ring N-methylsulfonamide derivatives were measured. The spectral changes on N-deuteration suggest that pyrimidine derivatives take the amido form, while pyridine and thiazole derivatives take the imido form.

The SO_2 symmetric stretching bands of sulfanilamide derivatives may be divided into the two regions, 1170 to 1145 cm^{-1} and 1145 to 1130 cm^{-1}, according to the amido form and the imido form, respectively.

(Received December 8, 1962)

---

[11] L.J. Bellamy: "The Infrared Spectra of Complex Molecules," 2nd Ed., 363 (1958), Methuen & Co., Ltd., London.

[12] T. Momose, Y. Ueda, T. Shoji: This Bulletin, **6**, 669 (1958).

[13] J.N. Baxter, J. Cymerman-Craig, J.B. Willis: J. Chem., Soc., **1955**, 669 (1955).