dioxane. Deuteriochloride of deuterated pyridinecarboxylic acids was prepared by decomposition of the chloride of each carboxylic acid with heavy water and distillation of heavy water *in vacuo.*

Summary

Infrared absorption spectra of pyridine- and pyrazine-carboxylic acids have following characteristic absorptions.

1) There are broad absorption bands with peaks at 2450 and 1900 cm^{-1}. The former shifts to around 1900 cm^{-1} by deuteration but the latter does not.

2) Absorptions for O–H in-plane deformation and C–O stretching vibration are present at 1340∼1300 cm^{-1} and 1310∼1260 cm^{-1}, and shift respectively to 1360∼1340 cm^{-1} and 1080∼1020 cm^{-1} by deuteration.

3) There is no absorption band for O–H out-of-plane deformation and that for $\delta_{\mathrm{C}\genfrac{}{}{0pt}{}{\nearrow\mathrm{O}}{\searrow\mathrm{O}}}$ is present at around 700 cm^{-1}.

These characteristic absorptions can be explained by the structure (II) with intramolecular hydrogen bonding for nicotinic and isonicotinic acids, and the structures (VI and VII) with intramolecular hydrogen bonding for picolinic and pyrazinic acids possessing a carboxyl in the position *alpha* to ring nitrogen. The hydrochloride of pyridinecarboxylic acids and 2,6-disubstituted isonicotinic acid derivatives possess the structure (II) same as that of ordinary carboxylic acids.

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〔Added in proof〕 A report on the spectra of benzoic acid and deuterated benzoic acid mixed with pyridine (1 : 1) became available during printing of this paper (D. Hadži, M. Pintar : Spectrochim. Acta, **12**, 162(1958)) and following points listed by these workers are similar to the results described in the foregoing pages.

1) The band due to OH out-of-plane vibration near 900 cm^{-1} does not appear.

2) The band near 1420 cm^{-1} is not detectable.

3) The band at 1275 cm^{-1} shifts to 1330 cm^{-1} on deuteration.

UDC 547.734

33. **Ryuichi Kimura and Takahiro Yabuuchi** : Studies on Thiophene Derivatives. II.[1] Optical Resolution of 3-Piperidino-1,1-di(2-thienyl)-1-butene.

(*Scientific Research Institute for Practical Life, University of Kyoto**)

In 1950, dithienyl-amino-butene derivatives were synthesized by Adamson and Green,[2,3] and their potent analgesic and antispasmodic actions were demonstrated. Of these derivatives, *dl*-3-piperidino-1,1-di(2-thienyl)-1-butene hydrochloride (*dl*-PBN-HCl) gave especially potent antitussive action by "Coughing Dog method" as reported by Kasé.[4]

This compound was also synthesized by the present authors and was recognized in the clinical application as a new potent antitussive, which was effective in a dose of

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[1] Part I : This Bulletin, **6**, 159(1958).

[2] D. W. Adamson, A. F. Green : Nature, **165**, 122(1950).

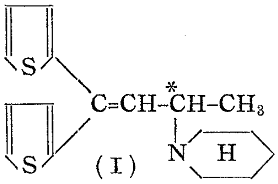
[3] D. W. Adamson, W. H. Duffin, A. F. Green : *Ibid.*, **167**, 153(1951).

[4] Y. Kasé, *et al.* : This Bulletin, **3**, 394(1955).

2~4 mg. for adults and had no untoward side effect.[5]

In general, a variation in the pharmacological activity with optical properties has been observed between the dextrorotatory and the levorotatory forms. For example, though the levorotatory 3-methoxy-N-methylmorphinan shows potent analgesic, antispasmodic, and antitussive actions, its dextrorotatory form shows only a potent antitussive action.

3-Piperidino-1,1-di(2-thienyl)-1-butene (I) has one asymmetric carbon atom in its side chain and the above-mentioned interesting facts prompted further studies on the optical resolution of this compound.



(I)

It has been reported by Green[6] that in the optical isomers of 3-dimethylamino-1,1-di(2-thienyl)-1-butene hydrochloride and 3-morpholino-1,1-di(2-thienyl)-1-butene hydrochloride, the corresponding dextrorotatory compound shows a more potent pharmacological activity than the levorotatory form, but the method of optical resolution of these compounds has not been reported yet. In this paper the optical resolution of *dl*-PBN salts is described.

In spite of variety of conditions tried, attempted optical resolution of *dl*-PBN-HCl was unsuccessful in conversion to diastereoisomers, using *d*-tartaric acid, dibenzoyl-*d*-tartaric acid monohydrate, or *d*-camphor-β-sulfonic acid. If the crystals of *dl*-PBN-HCl were a racemic mixture, conglomerate, crystals of each optical isomer might be picked up separately by means of a pair of tweezers and a hand lens, but there could be found no difference in the appearance of these crystals. Therefore, a modified, the so-called preferential recrystallization by inoculation of one isomer was applied and the procedure is described in detail in the Experimental Section. The optical resolution of *dl*-3-piperidino-1,1-di(2-thienyl)-1-butene hydrobromide (*dl*-PBN-HBr) was carried out by the above-mentioned method. The melting points and specific rotation of these crystals are shown in Table I. The melting points of the optical isomers were 5~7° higher than those of the racemate crystals. The fact that *l*-PBN-HBr obtained from *l*-PBN-HCl, having $[\alpha]_D^{31.5}$ $-117.8°$ in ethanol was $[\alpha]_D^{13}$ $-127.4°$ in chloroform, which value was equal to that in Table I, showed that the optical resolution had taken place completely in the above procedure.

Table I. Optical Isomers of PBN Salt

Compound	Optical Isomer	Appearance	m.p. (°C)	Specific Rotation (Solvent) (c=20)
PBN-HCl	*dl*	Prism	190 ~190.5	
	d	〃	195.5~169	$[\alpha]_D^{31.5}$ +117.8°(EtOH)
	l	〃	195.5~196	$[\alpha]_D^{31.5}$ −117.8°(EtOH)
PBN-HBr	*dl*	〃	179.5~180	
	d	〃	187	$[\alpha]_D^{13}$ +127.4°($CHCl_3$)
	l	〃	187	$[\alpha]_D^{13}$ −127.4°($CHCl_3$)

In order to distinguish three types of racemic modifications, i.e. racemic mixture, racemic compounds, and solid solution, melting point-composition diagrams and infrared spectra were examined and the results are shown in Figs. 1~5. In the melting point-composition diagram of PBN-HCl (Fig. 1), the melting point of pure dextrorotatory form is lowered by the addition of levorotatory form until the content of levorotatory form reaches 50%. The eutectic point is equal to the melting point of the racemate and there is only one.

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[5] Part III: This Bulletin, 7, 175(1959).

[6] A.F. Green: Brit. J. Pharmacol., 8, 2(1953).

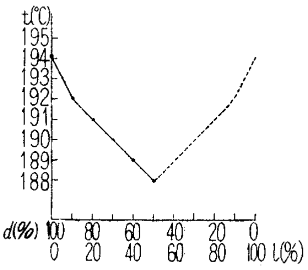

Fig. 1. Melting Point-Composition Diagram of PBN-HCl

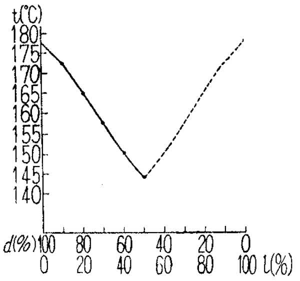

Fig. 2. Melting Point-Composition Diagram of PBN-HCl with Naphthalene

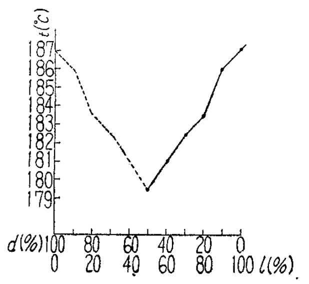

Fig. 3. Melting Point-Composition Diagram of PBN-HBr

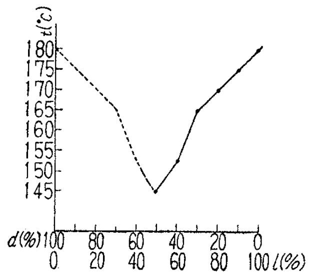

Fig. 4. Melting Point-Composition Diagram of PBN-HBr with Naphthalene

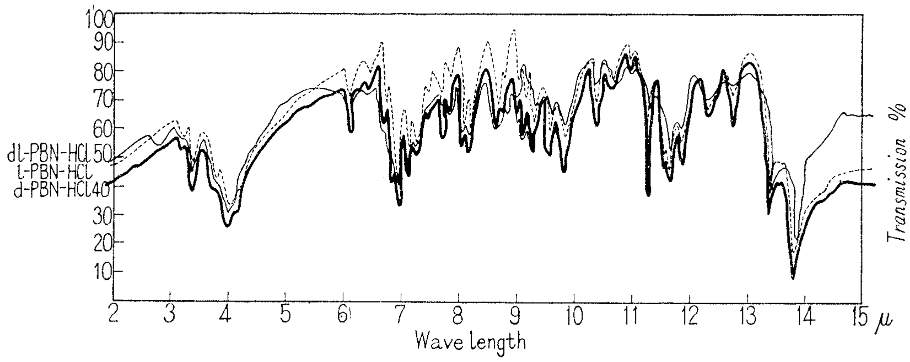

Fig. 5. Infrared Absorption Spectra of PBN-HCl

Therefore, the racemic modification of *dl*-PBN-HCl is considered to be a racemic mixture. This result is observed more clearly in Fig. 2, in which a definite weight of naphthalene is added to each composition of the two optical forms. The racemic modification of PBN-HBr is also a racemic mixture as shown in Figs. 3 and 4 in the same manner. Moreover, the infrared spectra of *d*-, *l*-, and *dl*-PBN-HCl are as shown in Fig. 5 and above-mentioned result also agrees with these infrared spectral data, the position of absorption bands in the region of 2.5~15 μ being the same in these isomers. If the racemic modification of *dl*-PBN-HCl were a racemic compound, it is anticipated that absorption bands of *dl*-PBN-HCl would be slightly different from that of pure dextro- or levorotatory compounds by molecular interaction.

The pharmacological properties of these isomers, examined by Dr. H. Fujimura of the Pharmacological Institute, University of Kyoto, were of considerable interest. Antitussive and analgesic activities of dextro-isomer were respectively 5 and 2 times more powerful than those of the levo-isomer. Detailed pharmacological results will be reported elsewhere.

The authors express their gratitude to Professor H. Saikachi of Pharmaceutical Institute, Medical Faculty, University of Kyushu, for his guidance and encouragement throughout this work. The authors' thanks are also due to Mr. K. Nakamura for the measurement of infrared absorption spectra and to the members of the Analysis Room of the Pharmaceutical Institute, University of Kyoto, for elementary analysis.

Experimental

Optical Resolution of *dl*-PBN-HCl—Some pieces of well-formed crystals were selected from *dl*-PBN-HCl crystals and after crushing, it was inoculated in a hot supersaturated solution which was prepared by adding 10 cc. of AcOEt to a hot solution of 10 g. of *dl*-PBN-HCl dissolved in 20 cc. of $CHCl_3$. After 2 hrs., crystals which grew rapidly from the solution were collected. These crystals

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7) This value was variable according to the optical property of the crystal selected and that of the residual solution.

were slightly optical active, e. g. $[\alpha]_D^{31.5}$ −12° in EtOH.7) Some of these crystals were inoculated in a hot supersaturated solution of these crystals by the above-mentioned method. The crystals grown from this hot supersaturated solution usually had more optical activity than that of seed grain crystals. The crystals used for inoculation and the crystals used for preparation of supersaturated solution would have the same direction of optical rotation.8) This procedure was repeated a number of times until the optical activity of crystals increased no longer. Finally, the specific rotation of *l*-PBN-HCl reached $[\alpha]_D^{31.5}$ −117.8° in EtOH and that of *d*-PBN-HCl reached $[\alpha]_D^{31.5}$ +117.8° in EtOH.

Once the two optical isomers of PBN-HCl were obtained in a pure form, the optical resolution of *dl*-PBN-HCl was carried out only a few times by preferential recrystallization, using these pure optical isomers.

Optical Resolution of *dl*-PBN-HBr—Optical resolution of *dl*-PBN-HBr was also carried out in the same manner as that of *dl*-PBN-HCl. The optical rotation of dextro- and levo-rotatory compounds were $[\alpha]_D^{13}$ −127.4° and +127.4° in $CHCl_3$, respectively. *Anal.* Calcd. for $C_{17}H_{22}NBrS_2$: C, 53.09; H, 5.771; N, 3.646. Found : C, 53.08; H, 5.783; N, 3.487.

Melting Point-Composition Diagram—Melting points were measured of various compositions of *d*-PBN-HCl-*dl*-PBN-HCl mixture and on adding 150 mg. of naphthalene to 50 mg. of each sample of *d*-PBN-HCl-*dl*-PBN-HCl, and the results are shown in Figs. 1 and 2, respectively. Figs. 3 and 4 are mixed melting point diagrams obtained on plotting various compositions and melting points of admixture of *l*-PBN-HBr and *dl*-PBN-HBr, respectively.

Infrared Spectra—The infrared absorption spectra of *d*-, *l*-, and *dl*-PBN-HCl were measured with the Perkin-Elmer Model 21 Infrared Spectrometer and the result is shown in Fig. 5.

Summary

Optical resolution of 3-piperidino-1,1-di(2-thienyl)-1-butene hydrochloride and hydrobromide, which had interesting pharmacological properties, was carried out by the preferential recrystallization method, because these could not be resolved by a method for diastereomers. Thus, specific rotation of these isomers was found to be $[\alpha]_D^{31.5}$ ±117.8° in ethanol for isomers of hydrochloride and $[\alpha]_D^{13}$ ±127.4° in chloroform for those of hydrobromide. Moreover, it was recognized that the racemic modifications of these salts were racemic mixtures and not racemic compounds, by the investigation of the melting point-composition diagrams and infrared absorption spectra.

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8) It was observed, however, that frequently the crystals grown had less optical activity than that of crystals used in the other cases.