*Studies on Pelletierine. I. Isolation of Pelletierine from Pomegranate Root Bark**

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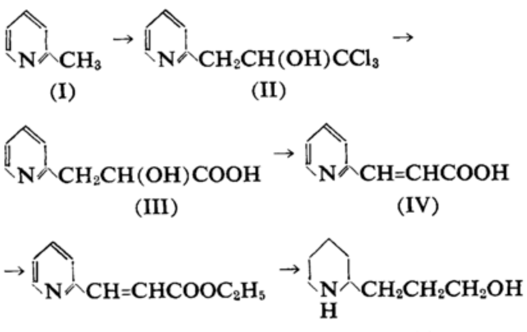
(Received November 28, 1959)

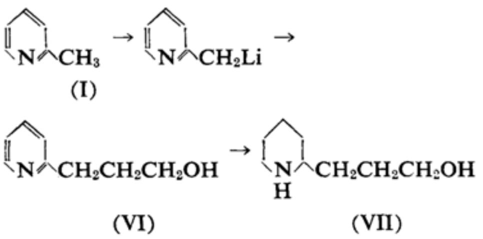
Pelletierine, an alkaloid which was found in pomegranate bark together with isopelletierine, methylisopelletierine and pseudopelletierine, and long regarded as the most anthelmintic component of the bark-extracts, was assigned the structure 3-(2-piperidyl)-propionaldehyde by Hess and Eichel already in 1917[1]. But no one has been able to succeed in the synthesis of this compound in spite of its very simple structure. This fact has been shedding some doubt upon the reliability of this structure.

According to Hess and Eichel, pelletierine is stable to oxidation and the corresponding propionic acid has never been obtained by the action of chromic acid in sulfuric acid, while part of the base is recovered unchanged and the rest is decomposed under the liberation of ammonia. From general properties of primary alcohol it will be expected that, when 3-(2-piperidyl)-1-propanol is oxidized with chromic acid, the corresponding aldehyde would be formed at least at the first oxidation step, and if this aldehyde is pelletierine as has been assumed, this may not be oxidizable further and must be isolated from the oxidation products. In order to scrutinize this idea, 3-(2-piperidyl)-1-propanol, which was prepared in the scheme of Eq. 1 or 2, was treated with chromic acid. This material, on being oxidized with chromic acid just sufficient to convert it into the aldehyde, gave no product corresponding to the aldehyde either at room temperature or at a higher one. By more drastic conditions using excess chromic acid, a colorless crystalline product was isolated as hydrochloride, which proved to be 3-(2-piperidyl)-propionic acid hydrochloride. These results show apparently that it is very difficult to assign the aldehyde structure to pelletierine.

Equation 1



Equation 2



The alternatively suggested structure for this alkaloid is 1-(2-piperidyl)-2-propanone, i. e., isopelletierine[2-7]. For instance, Galinovsky and Vogl[2], or Wibaut and Hirschel[7] asserted the identity of pelletierine with isopelletierine by comparing the derivatives of both compounds.

But it should be mentioned that the isolation of pelletierine, the most important material for these discussions, has never been attempted by tracing the reports of Hess and Eichel as closely as possible, and its physical properties or chemical behaviors have never been re-examined. Therefore one has been compelled to rely on their reports regarding the properties of this alkaloid. On re-examining their reports, however, a few descriptions are found unacceptable in some respects. For instance, constants of isopelletierine and its derivatives used for the comparison with those of pelletierine and its derivatives[8] are considerably different from those given later by

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* This work was partly presented at the 10th and 11th Annual Meetings of the Chemical Society of Japan, April 6, 1957 and April 5, 1958.

[1] K. Hess and A. Eichel, *Ber.*, **50**, 1192 (1917).

[2] F. Galinovsky and O. Vogl, *Monatsh.*, **83**, 1055 (1952).

[3] F. Galinovsky and R. Höllinger, ibid., **85**, 1012 (1954).

[4] O. Vogl and G. Bianchetti, ibid., **86**, 1024 (1955).

[5] J. P. Wibaut et al., *Rec. trav. chim.*, **73**, 102 (1954).

[6] J. P. Wibaut and U. Hollstein, *Konincl. Ned. Akad. Wetenshap., Proc. Ser.*, **B59**, 426 (1956): *Chem. Abstr.*, **51**, 11364i (1957).

[7] J. P. Wibaut and M. I. Hirschel, *Rec. trav. chim.*, **75**, 225 (1956).

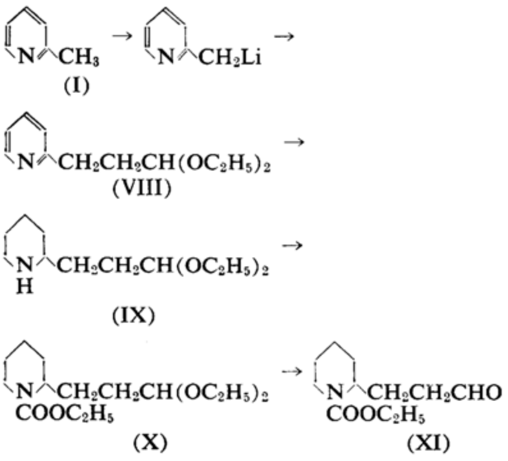
[8] K. Hess and A. Eichel, *Ber.*, **50**, 1386 (1917).

Hess himself[9] or by other researchers[10,11].

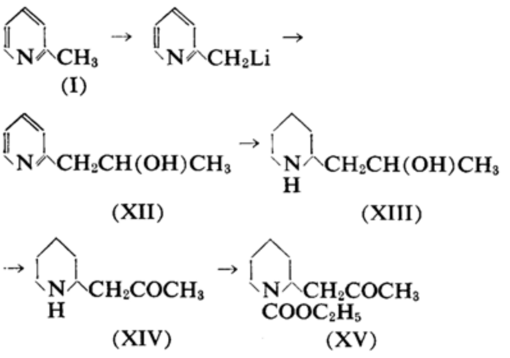
In order to compare pelletierine with isopelletierine decidedly, it will be most necessary to isolate the same sample of pelletierine as that which was obtained by Hess, and to reexamine its properties in the first step. Therefore the tracing of the Hess' experiment by using 60 kg. of powder of pomegranate root bark was attempted. The method of isolation was essentially the same as that which had been adopted by Hess and Eichel[8,12], and "pelletierine" was isolated in the form of urethane, having the same boiling point (b. p. 164～166°C at 20 mmHg; lit.[8] b. p. 169～170°C at 21 mmHg). In this method, some procedures were modified with the same results, and these could be confirmed by the preliminaly paper chromatographic test.

3-(2-Piperidyl)-propionaldehyde urethane and isopelletierine urethane, the partners for the comparison, were prepared according to Eqs. 3 and 4, respectively.

Equation 3



Equation 4



Now, "pelletierine urethane", thus obtained from natural sources, was compared with the synthetic samples of 3-(2-piperidyl)-propionaldehyde urethane and isopelletierine urethane.

TABLE I. PHYSICAL CONSTANTS OF THE THREE URETHANES

Urethane	B. p., °C mmHg	n_{D}^{20}
3-(2-Piperidyl)-propionaldehyde urethane	122～124 (2.5)	1.4792
1-(2-Piperidyl)-2-propanone urethane	131～132 (3.5)	1.4715
Pelletierine urethane from natural sources	131～131.5 (3.5)	1.4711

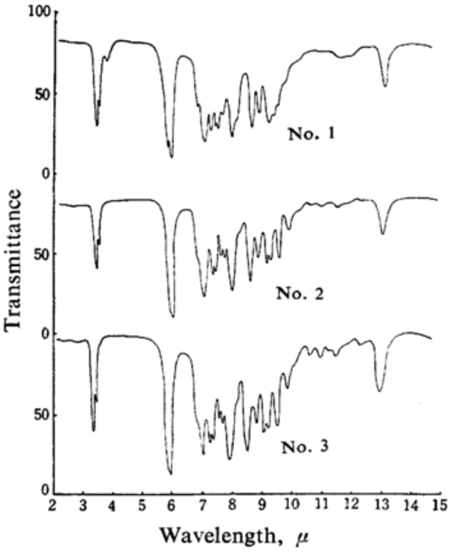


Fig. 1. I. R. of three urethanes.
No. 1: 3-(2-Piperidyl)-propionaldehyde urethane
No. 2: Pelletierine urethane from natural sources
No. 3: 1-(2-Piperidyl)-2-propanone urethane

The physical constants of these urethanes are listed in Table I.

From Table I, it may be recognized that the constants of urethane of pelletierine isolated from natural sources agree well with those of isopelletierine urethane but not with those of 3-(2-piperidyl)-propionaldehyde urethane.

In Fig. 1, in which the infrared spectra of these three urethanes are shown, the spectrum of pelletierine urethane agrees well with that of isopelletierine urethane[13], and not with that of 3-(2-piperidyl)-propionaldehyde urethane. It is remarkable that it never shows

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9) K. Hess and O. Littmann, *Ann.*, **494**, 7 (1932).

10) J. Meisenheimer and E. Mahler, ibid., **462**, 301 (1928).

11) P. I. Mortimer and W. Wilkinson, *J. Chem. Soc.*, **1957**, 3967.

12) Another method of isolating pelletierine was also reported by Hess, *Ber.*, **52**, 1005 (1919).

13) This result agrees with the one obtained using hydrobromide by J. P. Wibaut and M. I. Hirschel: Ref. 7.

peaks at 2700 cm^{-1} and 1710 cm^{-1} corresponding to the aldehyde group. Further, these peaks are recognizable in the spectrum of neither the fore-running nor the after-running of " pelletierine urethane ".

This fact shows that, in this sample, the compounds having the aldehyde group are never contained even in a small amount. This may be a decided bit of evidence for the absence of 3-(2-piperidyl)-propionaldehyde in the pomegranate bark.

Thus, from the above mentioned points, the author concludes that what has been named pelletierine is nothing but isopelletierine.

Experimental

1, 1, 1-Trichloro-2-hydroxy-3-(2-pyridyl)-propane (II). — 1) 2-Picoline (I) (93 g.) and anhydrous chloral (14 g.) were heated in amyl- or butylacetate (310 g.) for 11∼12 hr. at 120∼130°C according to Einhorn[14]. The product formed into colorless needle crystals (from ethanol); m. p. 201∼202°C (decomp.) (lit.[14] 201∼202°C (decomp.)). The yield was 40%.

2) Excess I (1000 cc.) and anhydrous chloral (500 g.) were heated to 110∼113°C for 40 hr. according to Tullock and McElvain[15]. The same compound as the above was obtained in 65% yield.

3-(2-Pyridyl)-lactic Acid (III).—The compound II was hydrolysed with sodium carbonate as described by Einhorn[14]. III formed into colorless prismatic crystals, m. p. 124∼125°C (from ethanol) (lit.[14] m. p. 124∼125°C). The yield was 80%.

3-(2-Pyridyl)-acrylic Acid (IV).—1) III was dehydrated as described by Einhorn[14]. IV formed into colorless needles, m. p. 204∼205°C (decomp.) (lit.[14] m. p. 204∼205°C (decomp.)). The yield was 81%.

2) The same compound was obtained from II according to the method of King[16] with some modifications.

A solution of II (341 g.) in ethanol (1100 cc.) was added dropwise with stirring during 5 hr. to a boiling solution of potassium hydroxide (408 g.) in ethanol (2600 cc.). After potassium chloride was filtered off, the filtrate was dried up and kept at 75∼79°C at 11∼12 mmHg for 24 hr. The cake obtained was dissolved in water and acidified to pH 4 with hydrochloric acid. The precipitate, after being collected and washed with water, gave the acid IV. The yield was 163 g.

Ethyl 3-(2-pyridyl)-acrylate (V). — The acid IV was esterified in 67% yield as described in the literature[14]; b. p.$_{14}$ 152.5∼153°C; b. p.$_{11}$ 143∼147°C (lit.[14] b. p.$_{11}$ 142∼145°C).

3-(2-Pyridyl)-1-propanol (VI).—2-Picolyl lithium prepared from I (23 g.) and phenyl lithium, which was, in turn, prepared from phenyl bromide (40 g.) and lithium (3.5 g.) in dry ether (200 cc.), was condensed with ethylene oxide (10 g.) as described in Org. Synth.[17]; b. p.$_7$ 128∼131°C (lit.[17] b. p.$_4$ 116∼118°C). The yield was 32%.

3-(2-Piperidyl)-1-propanol (VII).—1) The ester V was reduced in 28% yield with metallic sodium and ethanol according to Tullock and McElvain[15]. Replacing ethanol with cyclohexanol gave the same result without varying the yield of the reduction product; b. p.$_3$ 102∼105°C (lit.[15] b. p.$_3$ 102∼105°C).

2) The alcohol VI (21.5 g.) in dioxane (10 cc.) was hydrogenated over Raney nickel (ca. 0.2 g.) at 130∼140°C with hydrogen at an initial pressure of 90 kg./cm^2 for about 4 hr.; b. p.$_5$ 121∼125°C, n_D^{25} 1.4866 (lit.[18] n_D^{25} 1.4863). The yield was 14 g.

Oxidation of VII with Chromic Acid.—*1) Mild Oxidation.*—To the propanol VII (8.6 g., 0.06 mol.) in glacial acetic acid (80 cc.) was added chromic acid (4 g., 0.04 mol. = 0.06 equivalent of O) in water (4 cc.) dropwise with stirring at room temperature (30°C), then stirred for 2 hr. more at this temperature. No change of color was observed during this period. The bath temperature was gradually raised, and at about 80°C the color promptly turned green. After being stirred for 10 min. at 80°C and 2 hr. at 50°C, the acetic acid was evaporated. Then the residue was dissolved in water, made alkaline with sodium hydroxide when a considerable amount of tarry material, which dissolved neither in ether nor in water, was separated and the aqueous solution was extracted with ether. After drying, the ether extract was distilled in the stream of hydrogen under reduced pressure. There was obtained 1.7 g. of the fraction of b. p.$_{21}$ 143∼145°C, and its refractive index (n_D^{25} 1.4848) was found to be the same as that of the starting material. The residue (2.7 g.) could not be distilled in an oil-bath at 250°C under a pressure of 5 mmHg. No fore-running fraction, the boiling point of which corresponds to that of pelletierine could be recognized.

2) Violent Oxidation. — The propanol VII (4 g.) was added dropwise to a mixture of chromic acid (4 g.), concentrated sulfuric acid (16 g.) and water (50 cc.) with shaking. A considerable amount of heat was evolved and the color immediately turned green. Then it was heated with occasional shaking for 1 hr. at 90∼100°C. After the inorganic ions were removed by the method of Koenig and Hoppe[19], the aqueous solution was acidified with hydrochloric acid, decolorized and concentrated to dryness. An alcoholic extract of the residue was evaporated in vacuo. From the syrupy residue were separated needle crystals after being allowed to stand in a refrigerator overnight. The crystals were filtered from extremely viscous liquid, washed thoroughly with ethanol and recrystallized from ethanol. The needle crystals thus obtained melted at 186∼187°C and were not depressed by admixture with an authentic sample of 3-(2-piperidyl)-propionic acid hydrochloride.

1, 1-Diethoxy-3-(2-pyridyl)-propane (VIII).—According to Spielman et al.[20] VIII was synthesized

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[14] A. Einhorn, *Ann.*, **265**, 208 (1891).

[15] C. W. Tullock and S. M. McElvain, *J. Am. Chem. Soc.*, **61**, 961 (1939).

[16] J. A. King et al., *J. Org. Chem.*, **16**, 1100 (1951).

[17] L. A. Walter, "Organic Syntheses" **23**, 83 (1943).

[18] R. R. Burtner and J. M. Brown, *J. Am. Chem. Soc.*, **69**, 631 (1947).

[19] W. Koenig and G. Hoppe, *Ber.*, **35**, 1348 (1902); **36**, 2906 (1903).

[20] M. A. Spielman et al., *J. Org. Chem.*, **6**, 780 (1941).

with the reaction of 2-picolyl lithium and bromoacetal, which was prepared by the method of Org. Synth.[21]; b. p.$_7$ 128~129°C (lit.[20] b. p.$_8$ 128°C). The yield was 15% (based on lithium).

1, 1-Diethoxy-3-(2-piperidyl)-propane (IX).—The acetal VIII (30 g.) in ethanol (200 cc.) was hydrogenated over Raney nickel (ca. 5 g.) at 130~140°C with hydrogen at an initial pressure of 105 kg./cm^2 for about 2 hr.; b. p.$_6$ 117~120°C, n_D^{20} 1.4540 (lit.[20] b. p.$_3$ 101~106°C, b. p.$_1$ 91~92°C, n_D^{25} 1.4568). The yield was 20 g.

***N*-Ethoxycarbonyl-1, 1-diethoxy-3-(2-piperidyl)-propane(X).**—The acetal IX was converted into its urethane with ethyl chloroformate and sodium hydroxide by Spielman's method[20]; b. p.$_{3.5}$ 152~156°C, n_D^{20} 1.4612 (lit.[20] b. p.$_2$ 146~147°C, n_D^{25} 1.4580). The yield was 74%.

***N*-Ethoxycarbonyl-3-(2-piperidyl)-propionaldehyde (XI).**—The acetal X was hydrolyzed in 95% acetic acid by Spielman's method[20]; b. p.$_{2.5}$ 122~124°C, n_D^{20} 1.4792 (lit.[20] b. p.$_1$ 119~121°C, n_D^{25} 1.4771). The yield was 69%.

1-(2-Pyridyl)-2-propanol (XII).—According to Org. Synth.[17] the propanol XII was prepared by the condensation of acetaldehyde with 2-picolyl lithium; b. p.$_{17}$ 114~119°C (lit.[17] b. p.$_{17}$ 116~117°C). The yield was 56% based on I.

1-(2-Piperidyl)-2-propanol (XIII).—The propanol XII (184.5 g.) in dioxane (100 cc.) was hydrogenated over Raney nickel (ca. 12 g.) at 130°C with hydrogen at an initial pressure of 120 kg./cm^2 for 3 hr.; b. p.$_{13}$ 108~113°C (lit.[10] b. p.$_{16}$ 115~120°C). The yield was 158.5 g.

1-(2-Piperidyl)-2-propanone (Isopelletierine) (XIV).—The propanol XIII (11.4 g.) was oxidized to isopelletierine with chromic anhydride (6 g.) in glacial acetic acid (80 cc.) by the method of Meisenheimer and Mahler[10]. The fraction distilling below 105°C at 15 mmHg was collected (8 g.). Rectification yielded the fraction of b. p.$_7$ 79~80°C, b. p.$_{21}$ 101.2°C, n_D^{20} 1.4661, d_4^{20} 0.9587 (lit. b. p.$_{10}$ 86°C[10], b. p.$_{14}$ 91~92°C[9], n_D^{20} 1.46687[9], d_4^{20} 0.9624[9]).

Found: N, 10.05. Calcd. for $C_8H_{15}ON$: N, 9.92%.

Hydrobromide; colorless needles (from acetone), m. p. 139~140°C (lit. m. p. 137°C[5,10], 138°C[11]).

Picrate; yellow needles (from ethanol), m. p. 151.5~152°C (lit. m. p. 148~149°C[2], 149~150°C[11]).

***N*-Ethoxycarbonyl-1-(2-piperidyl)-2-propanone (XV).**—The pure isopelletierine, obtained by treating the pure hydrobromide with sodium hydroxide and rectifying the free base, was treated with ethyl chloroformate in the presence of sodium hydroxide by the usual method; colorless viscous liquid, b. p.$_{3.5}$ 131~132°C, b. p.$_{20}$ 165~166°C, n_D^{20} 1.4715.

Found: N, 6.60. Calcd. for $C_{11}H_{19}O_3N$: N, 6.57%.

" Pelletierine "

The samples of the pomegranae bark used in this experiment were as follows:

Powder of Pomegranate Root Bark (Sample I):—Gathered at the north-bank of the River Yoshino, in Tokushima Prefecture, Japan; dried for several days and ground to fine powder.

Powder of Pomegranate Root (Sample II).—From the pomegranate cultured in this laboratory; used immediately after gathering.

Powder of Pomegranate Bark (Sample III).—Purchased from drug store; when it was gathered was unknown.

Preparation of the Sample for Paper-chromatography.—*1) Method of Wibaut et al.*[5]*:*—Sample (common to I, II and III) was boiled with methanol, filtered and methanol was distilled off under diminished pressure. The residue was warmed with 10% hydrochloric acid at about 60°C and filtered. The filtrate was washed with chloroform and, after alkalifying with sodium hydroxide extracted with chloroform. The extract was shaken with 10% hydrochloric acid again, then the aqueous layer was condensed under reduced pressure.

2) Hydrochloric Acid-Methanol Extraction.—Sample was boiled with methanol containing hydrochloric acid, filtered and condensed under reduced pressure. The syrup thus obtained was extracted with 10% hydrochloric acid and treated as above.

3) Method of Hess and Eichel[8],**.—The mixture of sample and sodium hydroxide solution was placed in Soxhlet's apparatus and extracted with ether. The ether extract was treated with 10% hydrochloric acid and the hydrochloric acid extract was condensed.

Chromatography.—*Paper:*—Toyo filter paper No. 50 for chromatography (paper was allowed to stand over 24 hr. with saturated vapor of developer before use).

Developer.—*n*-Butyl alcohol: con. hydrochloric acid: water=100:8:ca. 20 (in volume) (the upper layer of the mixture was used as developer).

Method of Development.—Descending method.

Colorizing Agent:—Dragendorf's resgent.

The experimental results are shown in Table II.

TABLE II. RESULTS OF PAPER CHROMATOGRAPHIC ANALYSES

Sample	Method of preparation	R_f			
I	1		0.37	0.45	0.57
I	2		0.37	0.46	
I	3		0.39	0.46	
II	1		0.39	0.49	
III	1		0.35	0.42	
Root bark[5]		0.16	0.34	0.43	
Pseudopelletierine[5]			0.32~0.34		
dl-Methylisopelletierine[5]				0.41~0.45	
dl-Isopelletierine[5]					0.48~0.53

Isolation of Pelletierine.—Sixty kg. of sample I was extracted by boiling methanol three times, each for 10 hr. The extracts were condensed to syrup and warmed for some time with 10% hydrochloric acid on 60°C and filtered from resinous material. The filtrate was washed with chloroform, the residual aqueous layer was made alkaline with

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[21] S. M. McElvain and D. Kundiger, *Organic Syntheses*, **23**, 8 (1943).

** Instead of calcium hydroxide and chloroform, sodium hydroxide and ether were used, respectively.

sodium hydroxide and extracted with chloroform. The chloroform extract was treated with 10% hydrochloric acid, the aqueous solution was, after condensing, dried up in a desiccator, and thus the mixture of alkaloidhydrochlorides was obtained. The yield was 160 g. This hydrochloride was dissolved in water, and after weakly alkalifying with aqueous sodium bicarbonate solution, extracted with ether. From this ether extract pseudopelletierine was obtainable. The aqueous solution was strongly alkalified with sodium hydroxide and extracted with ether repeatedly until the ether layer became colorless. After drying with sodium hydroxide and distilling off the solvent, the ether extract was distilled under reduced pressure in the atmosphere of hydrogen, then the fraction of 102∼113°C at 20 mmHg was collected. The yield was 64.1 g. (The greater part of this fraction was distilled at 104∼105°C at 20 mmHg, and, when rectified, the liquid of b. p.$_{9}$ 86∼86.2°C and n_D^{20} 1.4665 was obtained. During distillation in the atmosphere of hydrogen, this liquid kept completely colorless, but it became pink at once when it was allowed to make a contact with air, and then turned dark red in time).

The mixture of the fraction of b. p.$_{20}$ 102∼113°C (31.9 g.), sodium hydroxide (45 g.) and water (160 cc.) was stirred and cooled below 10°C. To this suspension, ethyl chloroformate (36 g.) was added gradually. The reaction product was extracted with ether and the extract dried with sodium hydroxide freed from the solvent, and distilled under reduced pressure; thus the fraction which boils at 164∼166°C at 19 mmHg was obtained (lit.8) b. p.$_{21}$ 169∼170°C). The yield was 13.3 g. After rectification, viscous colorless liquid of b. p.$_{3.5}$ 131∼131.5°C and n_D^{20} 1.4711 was obtained.

Infrared Absorption Spectra.—These measurements were taken with a Perkin-Elmer spectrophotometer, Model 21 with sodium chloride prism).

Phase: liquid
Thickness: ca. 0.01 mm.

The author desires to state with sincere thanks that this work was commenced under the direction of the late Professor Ryuzaburo Nodzu and he wishes to express his profound gratitude to Professor Ryozo Goto of Kyoto University and to Professor Hiroshi Watanabe of Kōnan-University for thier invaluable advice and cordial encouragement throughout the work. He also thanks the Research Laboratory of Takeda Pharmaceutical Industries for infrared measurements and Miss. T. Nagahama and Mr. Y. Kaneko for their collaboration with him in the experiments.

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