supernatant concentrated under reduced pressure. Paper chromatography in the solvent system isopropyl alcohol (75 ml.)–water (25 ml.)–trichloroacetic acid (5 g.)–ammonia[21] (0.25 ml.) showed the presence of a strong spot corresponding to inorganic pyrophosphate as well as two spots corresponding to higher polyphosphates. (b) A second portion was treated as above under (a) up to the point of alkaline hydrolysis of the acetyl group. After two evaporations of the aqueous solution to remove last traces of pyridine, dilute hydrochloric acid was added to *p*H 3. The ultraviolet-absorbing material was adsorbed onto Norite A by successive additions of small portions of the latter and the charcoal was collected by centrifugation and washed twice with 5-ml. portions of water. Four elutions were carried out in the centrifuge tube with 5-ml. portions of 50% ethyl alcohol containing 2% ammonia. The total eluate was concentrated under reduced pressure and examined in solvents A and B and isopropyl alcohol–1% aqueous ammonium sulfate (2:1) and 1 *M* ammonium acetate (*p*H 7.5)–ethyl alcohol (3:7.5, v./v.) and also by paper electrophoresis at acid and neutral *p*H. Thymidine-5′ phosphate was the only ultraviolet-absorbing material present.

Methanolysis of Reaction Mixtures Containing Phosphate Esters, Acetic Anhydride and Pyridine.—(a) Pyridinium thymidine-5′ phosphate (0.1 mmole) was treated with acetic anhydride (0.5 ml.) in pyridine (2 ml.). After 11 hr. at room temperature methyl alcohol (2 ml.) was added and the mixture kept overnight. Repeated evaporations under reduced pressure with water gave a gum which was treated with 0.1 *N* sodium hydroxide (2 ml.) for 30 minutes. An excess of pyridinium Dowex-50 ion exchange resin was then added and the supernatant solution chromatographed in solvent A. The only nucleotidic band present was that of thymidine-5′ phosphate.

(b) P^1,P^2-Di-(3′-*O*-acetylthymidine-5′) pyrophosphate (0.03 mmole) was treated in anhydrous pyridine (1 ml.) with 0.45 ml. of acetic anhydride for two days at room temperature. Methyl alcohol (2 ml.) was then added and after a further period of 2 hr. the reaction products treated and chromatographed as above under (a). A very strong band corresponding to thymidine-5′ phosphate, a weak band corresponding to dithymidine-5′ pyrophosphate, and another weak band (about 10%) corresponding approximately in mobility to methyl thymidine-5′ phosphate (R_f 0.52) were present. An extremely faint band close to the solvent front with ultraviolet spectrum of thymidine chromophore was also noticeable. A comparison of the band with R_f 0.52, after elution, with methyl thymidine-5′ phosphate showed it to have slightly lower mobility on paper chromatograms developed in solvents A and B as well as paper electrophoresis at *p*H 7.5. The substance on treatment with 0.5 *N* sodium hydroxide at 100° for 15 minutes gave thymidine-5′ phosphate and methylthymidine-5′ phosphate. A similar result was obtained on heating in 20% acetic acid for 15 minutes at 100°. Authentic methylthymidine-5′ phosphate was found to be completely stable during the above acidic and alkaline treatments. Incubation with a *Crotalus adamanteus* venum diesterase preparation[22] gave first thymine-5′ phosphate and methylthymidine-5′ phosphate and ultimately thymidine-5′ phosphate as the only ultraviolet-absorbing product. From these data the substance was concluded to be IX.

When, in the above reaction between the pyrophosphate II and acetic anhydride–pyridine, methyl alcohol was added after only 0.5 hr., the yield of IX was about the same, an appreciable amount (20–30%) of dithymidine-5′ pyrophosphate (I) was present and the remainder of the ultraviolet-absorbing material was thymidine-5′ phosphate.

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[21] J. P. Ebel, *Bull. soc. chim.* (*France*), 991 (1953).

[22] W. E. Razzell and H. G. Khorana, *J. Biol. Chem.*, **234**, 2114 (1959).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Rearrangement of Isopelletierene Oxime[1]

BY ROBERT L. AUGUSTINE

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Isopelletierene oxime, on treatment with phosphorus pentachloride in phenetole, gave the amidine, 2-methyl-1,3-diazabicyclo[4:3:0]-2-nonene (IX); IX is hydrolyzed to N-(2-pipicolyl)-acetamide and 2-pipicolylamine. In view of the pelletierene–isopelletierene identity recently proposed, these results are used in a re-evaluation of the evidence presented in the determination of the structure of pelletierene.

Pelletierene, one of several alkaloids found in *Punica granatum* L., was first assigned the structure β-(2-piperidyl)-propionaldehyde (I) by Hess in 1917.[2] Since that time numerous attempts have been made at the synthesis of this compound, all of which have ended in failure as the amino-aldehyde underwent self-condensation with great facility.[3] Thus, some doubt was shed on the reliability of the structure assigned to pelletierene as it was difficult to see how a material which was so unstable as to prevent synthesis could be the same material described as a relatively stable, mobile liquid with well defined physical characteristics.[4] In 1954, Galinovsky and Hollinger reported that treatment of a commercial sample of pelletierene hydrobromide with benzoyl chloride gave the benzamide of isopelletierene, 2-acetonylpiperidine (V), another of the alkaloids found in *Punica granatum* L.[5] It was known, however, that commercial samples of pelletierene salts contained various amounts of isopelletierene, pseudopelletierene, and other materials, as well as pelletierene.[3] Thus, the results tended to be inconclusive.

Confirmation of the identity of pelletierene with isopelletierene was accomplished somewhat later by Wibaut and Hirschel[3] who compared a sample of synthetic isopelletierene hydrobromide with a pure sample of pelletierene hydrobromide obtained from natural sources. They found no depression on mixed melting point determination and identical infrared spectra and X-ray powder patterns.

In the light of this evidence it would seem that a re-evaluation of the work described by Hess in determining the structure of pelletierene would be of some interest. His structure proof was based primarily on the following reaction sequence.

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[1] This work was supported by a grant from the University of Texas Research Institute.

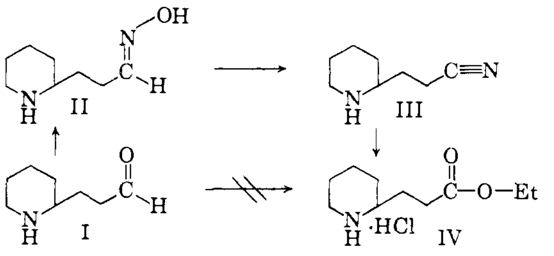
[2] K. Hess and A. Eischel, *Ber.*, **50**, 1192 (1917).

[3] J. P. Wibaut and M. J. Hirschel, *Rec. trav. chim.*, **75**, 225 (1956), and references cited therein.

[4] K. Hess, *Ber.*, **50**, 368 (1917).

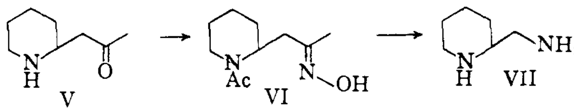
[5] F. Galinvosky and R. Hollinger, *Monatsh.*, **85**, 1012 (1954).

Treatment of pelletierene oxime (II) with phosphorus pentachloride in phenetole gave a liquid which analyzed for a $C_8H_{14}N_2$ compound and gave a picrate, melting point 175–176°. The amine was treated with alcoholic hydrogen chloride giving crystals, melting point 122°, which crystallized from acetone and analyzed for $C_{10}H_{20}NO_2Cl$. This compound was considered to be ethyl β-(2-piperidyl)-propionate hydrochloride (IV) on the basis of this analysis and the fact that the melting point obtained was the same as that reported for the synthetic material.[6] Thus reasoning from these results, the $C_8H_{14}N_2$ compound was assigned the structure β-(2-piperidyl)-propionitrile (III), and pelletierene, the structure I. However, in no way was a direct conversion of pelletierene into β-(2-piperidyl)-propionic acid accomplished.



Recently, Mortimer[7] had reported the isolation of isopelletierene from *Duborsia myoporides* R. Br. In this report[7b] he had compared the melting points of derivatives of pelletierene, synthetic isopelletierene and the isopelletierene he had obtained. In almost all cases similarity could be observed. A notable exception was in the melting points of the oximes. Two melting points were reported for pelletierene oxime, 80° and 96°[1] depending on whether recrystallization was accomplished from ether or petroleum ether, respectively. Mortimer, on the other hand, states that melting points of 90° and 105.5° were obtained for isopelletierene oxime, a considerable deviation, if indeed pelletierene and isopelletierene are identical.

Thus, one is faced with an interesting problem. If pelletierene and isopelletierene are identical, the conversion of a methyl ketoxime into a nitrile would involve a skeletal rearrangement heretofore unobserved. But, if a nitrile were not the rearrangement product, what, then, was the actual nature of the observed degradation product? Why, also, is there such a discrepancy in the reported melting points of the respective oximes? Thus, a study of the chemistry of isopelletierene oxime seemed called for to shed some light on the problem. This need was recognized by Mortimer who stated that an attempt to repeat Hess' work using isopelletierene oxime was unsuccessful. Beckmann rearrangement of N-acetylisopelletierene oxime (VI) gave a di-amide which on hydrolysis yielded 2-pipicolylamine (VII) thus showing that normal rearrangement had occurred when the ring nitrogen was blocked as the amide.[7b] However, nothing was known concerning the rearrangement of isopelletierene oxime. Thus, the following investigation was begun in an effort to clarify the situation.



Isopelletierene was prepared synthetically[8] and converted to the oxime VIII. Recrystallization of the product from petroleum ether gave an oxime (A) melting at 95–97°, unchanged after several recrystallizations. However, recrystallization of the oxime (A) from anhydrous ether raised the melting point to 104–105°. On one occasion one recrystallization of the crude oxime from anhydrous ether gave a solid which melted at 78–80°. Further recrystallization, however, raised this value to 104–105°. Thus, the discrepancy in the observed melting points of the oximes seemed to be resolved.

The oxime VIII was then rearranged using the same conditions as described by Hess. When the phosphorus pentachloride was warmed in phenetole, hydrogen chloride was liberated and an orange solution resulted. On further heating, hydrogen chloride evolution ceased and the solution became colorless. It has been shown that phosphorus pentachloride reacts with phenetole to form *p*-chloro- and 2,4-dichlorophenetole, phosphorus trichloride and HCl.[9] The orange color of the solution could be due to the formation of oxonium salts which decompose on further heating.

Addition of a phenetole solution of VIII to this orange solution resulted in the formation of a precipitate which on heating at 75–80° to remove the solvent was changed into a dark oil. Subsequent workup of the reaction mixture gave a dark brown liquid as the product. Treatment of this material with picric acid gave a picrate, which, on purification, melted at 174–175° and analyzed correctly for a $C_8H_{14}N_2$ amine picrate. Thus, it was considered that the product obtained was identical with that described as the "nitrile" III. Any deviation from the experimental description reported by Hess gave only intractible material from which none of the picrate of IX could be obtained. An infrared spectrum of the free amine, liberated from the picrate by treatment with base, showed no absorption between 4.0 and 5.0 μ, thus eliminating the possibility of the presence of a nitrile group in the compound.

Hydrolysis of the rearrangement product with aqueous acid gave 2-pipicolylamine, identified as its dipicrate which did not depress the melting point on admixture with an authentic sample. It was thus considered likely that the rearrangement product was the amidine, 2-methyl-1,3-diazabicyclo[4:3:0]-2-nonene (IX). Further evidence for this assumption lay in the fact that the infrared spectrum of this compound had a medium intensity peak at 6.27 μ which is in the region ascribed to the absorption of N,N'-trisubstituted benzamidines.[10] Final proof lay in its unambiguous synthesis.

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(6) K. Loffler and H. Kaim, *Ber.*, **42**, 94 (1909).

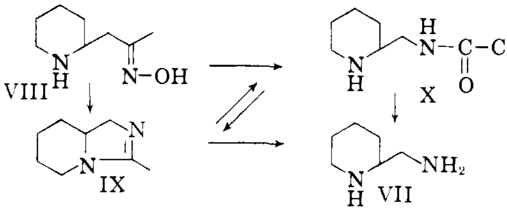
(7) (a) P. I. Mortimer and S. Wilkinson, *J. Chem. Soc.*, 3967 (1957); (b) P. I. Mortimer, *J. Aust. Chem.*, **11**, 82 (1958).

(8) J. Meisenheimer and E. Mahler, *Ann.*, **462**, 301 (1928).

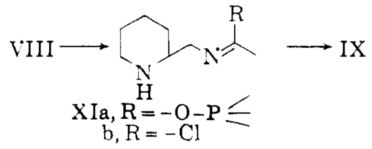
(9) W. Autenrieth and P. Mühlinghaus, *Ber.*, **39**, 4098 (1906).

(10) J. Fabian, V. Delaroff and M. Legrand, *Bull. soc. chim. France*, 287 (1956).

Since amidines can be prepared by heating amines and amides in phosphorus trichloride,[11] preparation of the normal Beckmann rearrangement product of VIII would give the necessary amino-amide X for conversion to the amidine IX. The rearrangement was accomplished by heating VIII in polyphosphoric acid. That the product obtained was the desired compound was shown by an amide absorption peak in the infrared at 6.15 μ, and by hydrolysis to 2-pipicolylamine. Dehydration of X with phosphorus trichloride gave IX, isolated as the picrate. No depression of melting point was observed with a mixture of this picrate with the picrate of the phosphorus pentachloride–phenetole rearrangement product.



Reasoning after the fact, the formation of the amidine was not too surprising in this reaction[12] since the first step in the Beckmann rearrangement is the formation of the imino compound XI which can very readily close to the amidine. It was thought that the precipitate first formed in the reaction was this imino compound, which during the heating necessary to remove the phenetole closed to the amidine. However, addition of water to the phenetole suspension did not give the amide, but yielded, instead, isopelletierene as the product.



Two facts are present which indicate that the imino-chloride XIb is the species which undergoes cyclization, rather than the imino-phosphorus compound XIa: (A) In the polyphosphoric acid rearrangement XIa must be present as an intermediate; however, no amidine is obtained from this reaction. (B) The use of the colorless phosphorus pentachloride – phosphorus trichloride – phenetole solution after the evolution of HCl had ceased, gave no amidine as the product. It was not, however, determined at this point whether any amide was formed. Thus, the rearrangement would seem to go through the sequence: VIII–XIb–IX.

There remains, then, one further question; that of the nature of the hydrolysis product obtained by Hess from his "nitrile." If this "nitrile" was actually the amidine IX, the amino ester hydrochloride IV could hardly have been the product obtained. In fact, none of the expected products from the hydrolysis of the amidine would give an analysis which would agree with the results reported in the original work. Treatment of IX with ethanolic hydrogen chloride was therefore attempted in an effort to obtain a material which would agree with the description given by Hess. Unfortunately, all that was obtained was a semicrystalline solid from which nothing could be obtained on extraction with hot acetone. In order to ascertain the nature of the hydrolysis product, the crude material was benzoylated and the resulting product chromatographed from alumina. Two crystalline products were obtained. One was shown to be the benzamide of X by the fact that there was no depression of melting point on admixture with an authentic sample. The second material, obtained in a small quantity, was identified as the di-benzamide of VII by the fact that its infrared spectrum was identical in every respect with that of the di-benzamide obtained by benzoylation of VII.

It was thought, then, that the final product obtained by Hess could have been the hydrochloride of X containing either some difficultly removable material or some solvent of crystallization which would account for the discrepancy in the analysis. To check this point, X was treated with anhydrous hydrogen chloride and the product recrystallized from acetone. A flocculent precipitate was obtained, which, on filtration, was found to be very hydroscopic. This crude material had a melting point of 115–120°, but no further characterization was accomplished. Thus, the exact nature of the final product obtained by Hess in the degradation of pelletierene (isopelletierene) cannot be defined with certainty, but if one accepts the pelletierene–isopelletierene identity as a fact, then, on the basis of the evidence presented here, one is also led to the conclusion that this final product was probably the hydrochloride of X and not ethyl β-(2-piperidyl)-propionate hydrochloride.

Experimental[13]

Isopelletierene Hydrobromide (V).—Twenty-five grams of isopelletierene, prepared from 1-(α-pyridyl)-2-propanol[14] by the method described by Meisenheimer and Mahler,[8] was neutralized with 10% hydrobromic acid and the resulting solution evaporated to dryness under reduced pressure on the steam-bath. Recrystallization of the residue from acetone gave 28 g. of I, m.p. 137–139°; reported m.p. for isopelletierene HBr, 135°[7b]; pelletierene HBr, 140°.[3]

Isopelletierene Oxime (VIII).—To a solution of 6.6 g. of V and 2.5 g. of hydroxylamine hydrochloride in 20 ml. of water was added a solution of 6.5 g. of sodium hydroxide in 10 ml. of water. The resulting solution was allowed to stand at room temperature overnight. The basic solution was

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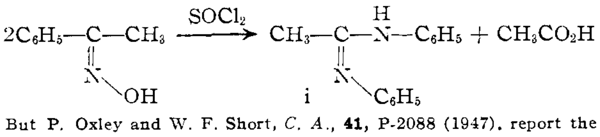
[11] R. L. Shriner and F. W. Newmann, *Chem. Revs.*, **35**, 351 (1944), and references cited there.

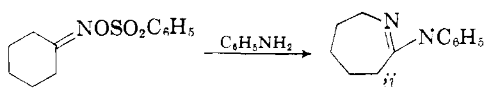
[12] H. Stephen and W. Bleloch, *J. Chem. Soc.*, 886 (1931), report the rearrangement of acetophenone oxime to an amidine (i) on treatment with thionyl chloride. However, this reaction is not analogous to the isopelletierene oxime rearrangement since two molecules of acetophenone oxime were involved.



$$2C_6H_5\text{—}\underset{\underset{\displaystyle N\diagdown OH}{\|}}{C}\text{—}CH_3 \xrightarrow{SOCl_2} CH_3\text{—}\underset{\underset{\displaystyle N\diagdown C_6H_5}{\|}}{C}\text{—}\overset{H}{N}\text{—}C_6H_5 + CH_3CO_2H$$

i

But P. Oxley and W. F. Short, *C. A.*, **41**, P-2088 (1947), report the formation of an amidine (ii) by heating the benzenesulfonate of cyclohexanone oxime with aniline, a more analogous case.



[13] All melting points are uncorrected.

[14] L. A. Walter, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 757.

neutralized by bubbling in carbon dioxide until the solution became cloudy. The cloudy solution was extracted with chloroform and the organic layer dried and evaporated. The oily residue was taken up in hexane and crystallized, giving 3.6 g. (77%) of VIII, m.p. 94–96°. Further recrystallization from cyclohexane raised the m.p. to 95–97°; reported[2] m.p. for pelletierene oxime, 96–97°. However, recrystallization from anhyrous ether raised the m.p. to 104–105°; reported[7] m.p. for isopelletierene oxime, 105.5°.

Anal. Calcd. for $C_8H_{16}N_2O$: C, 61.50; H, 10.32. Found: C, 61.42; H, 10.32.

N-α-Pipicolyl acetamide (X).—A mixture of 2 g. of VIII and 20g. of polyphosphoric acid was heated at 80° for six hours (two hours after the mixture became homogeneous) with frequent stirring. The warm sirup was poured into ice-water. After it had completely dissolved, the acidic solution was made basic with cold 50% aqueous potassium hydroxide and extracted with chloroform. The chloroform was dried and evaporated. The residue was dissolved in 80 ml. of ether and stored at 0° for 48 hours to precipitate any unreacted oxime. The ether was filtered and evaporated, giving 1.6 g. of X as a thick oil. The infrared spectrum of X had a strong peak at 6.15μ.

The benzamide of X had a m.p. of 135–136° after recrystallization from benzene–cyclohexane.

Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74. Found: C, 69.41; H, 7.73.

Two-tenths of a gram of X was taken up in acetone and dry HCl added. The mixture was evaporated to dryness and refluxed with 25 ml. of acetone, filtered while hot, and the filtrate cooled. A flocculent precipitate formed which, on filtration, was found to be very hydroscopic. The crude material had a m.p. of 115–120°.

2-Methyl-1,3-diazabicyclo[4:3:0]-2-nonene (IX). From VIII.—Nine grams of phosphorus pentachloride was dissolved in 30 ml. of phenetole by warming. The solution became deep orange and HCl fumes were evolved. The warming was stopped as soon as all of the phosphorus pentachloride dissolved. Heating after this point caused the solution to become colorless. Use of the colorless solution in the reaction did not give the desired product. A cold solution of 4.4 g. of VIII in 20 ml. of phenetole was added to the cold orange solution with cooling and swirling. A precipitate formed almost at once. After the reaction had ceased, the mixture was allowed to stand at room temperature for 15 minutes and the phenetole removed under vacuum at a bath temperature of 70–85°. The residue was taken up in 10 ml. of water and extracted with ether. The aqueous solution was made basic with cold 50% aqueous potassium hydroxide solution and the oil which separated was taken up in ether. The ether was dried and evaporated giving 2.7 g. of a dark oil. This was taken up in 10 ml. of ethanol and poured into a warm solution of 4.6 g. of picric acid in 70 ml. of ethanol and allowed to stand at room temperature overnight. Crystals formed on trituration. They were filtered and recrystallized from ethanol until a m.p. of 168–170° was obtained; yield 2.8 g. The picrate was then placed in a separatory funnel with 30 ml. of 50% potassium hydroxide solution and 20 ml. of ether and extracted thoroughly. The ether was separated and the process repeated with three further portions of ether. The ether solutions were combined, dried, and evaporated, giving 1.0 g. of IX as a dark red oil. The infrared spectrum of the oil had a medium intensity peak at 6.27μ.

The Picrate of IX had a m.p. of 174–175° on recrystallization from ethanol; reported[2] m.p. for the "nitrile" picrate obtained from pelletierene oxime, 175–176°.

Anal. Calcd. for $C_{14}H_{17}N_5O_7$: C, 45.78; H, 4.67. Found: C, 45.85; H, 4.74.

Addition of water to the reaction mixture before the removal of the phenetole caused the precipitate which was present to dissolve. The aqueous layer was separated and made basic with 50% potassium hydroxide solution. An oil separated which was taken up in ether. The ether was dried and evaporated and the oil treated with picric acid as before. The picrate melted at 146–147° and showed no depression on admixture with an authentic sample of isopelletierene picrate; reported[4] m.p. for isopelletierene picrate, 150–151°.

From X.—A mixture 0.35 g. of X and 10 ml. of phosphorus trichloride was refluxed for one hour and then evaporated to dryness under reduced pressure. The dark residue was dissolved in 5 ml. of water and the resulting solution was made basic with cold 50% potassium hydroxide solution. The cloudy mixture was extracted with ether and the organic solution was dried and evaporated. The residue was taken up in ethanol and treated with picric acid. The picrate precipitated and was recrystallized from ethanol with a m.p. of 174–175°. There was no depression in melting point on admixture of this picrate with the one obtained from the phosphorus pentachloride–phenetole rearrangement product.

Mild Hydrolysis of IX.—One gram of IX was heated on a steam-bath for a short time in 50 ml. of 5% ethanolic potassium hydroxide. The solution was made acidic with concentrated hydrochloric acid and evaporated to dryness. The residue was refluxed with ethanol, filtered while hot and the residue washed with more hot ethanol. The combined filtrates were evaporated to dryness and the residue was refluxed for one hour with ethanolic HCl. Evaporation of the reaction mixture to dryness gave a semi-crystalline residue. Refluxing this residue with acetone, filtering while hot and evaporation of the filtrate to a small volume did not result in the formation of a precipitate when the acetone was cooled. Treatment of the residue with benzoyl chloride in pyridine gave a semi-solid benzoate which was chromatographed from 50 g. of alumina. Elution with benzene, followed by 20% ether in benzene, gave a small amount of a crystalline material, which on recrystallization from acetone had a m.p. of 186–187°. This material had an infrared spectrum which was identical with that of the dibenzamide of 2-pipicolylamine.

Further elution of the column with ether gave 250 mg. of the benzamide of X as evidenced by the fact that there was no depression of the melting point of the authentic material in a mixed melting point determination.

2-Pipicolylamine (VII). **From IX.**—The product from the mild hydrolysis of IX (before benzoylation) was refluxed with 6 *N* hydrochloric acid for six hours and the solution evaporated to dryness. The residue dissolved readily in water. Addition of picric acid gave an insoluble picrate which on recrystallization from water had a m.p. of 199–200°; reported[7b] m.p. of the dipicrate of VII, 201°. There was no depression of the m.p. in a mixed melting point determination using a mixture of the dipicrate obtained from the hydrolysis product and an authentic sample.[7b]

From X.—One-half of a gram X was refluxed with 6 *N* hydrochloric acid for six hours and the solution evaporated to dryness. The residue was taken up in water and picric acid added. A picrate was obtained which had a m.p. of 199–200°, and did not depress the m.p. of an authentic sample.

The dibenzamide of VII had a m.p. of 186–187° on recrystallization from acetone.

Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.50; H, 6.88. Found: C, 74.26; H, 7.03.

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