stannous chloride in concentrated hydrochloric acid to produce 2'-aminopyrido-3,4 : 4',5'-thiazole. When 3-nitro-4-thiocyanopyridine was heated with glacial acetic acid, 3-nitro-4-aminopyridine was obtained. The change of the thiocyano radical of 3-nitro-4-thiocyanopyridine to the amino group is considered to be of great interest.

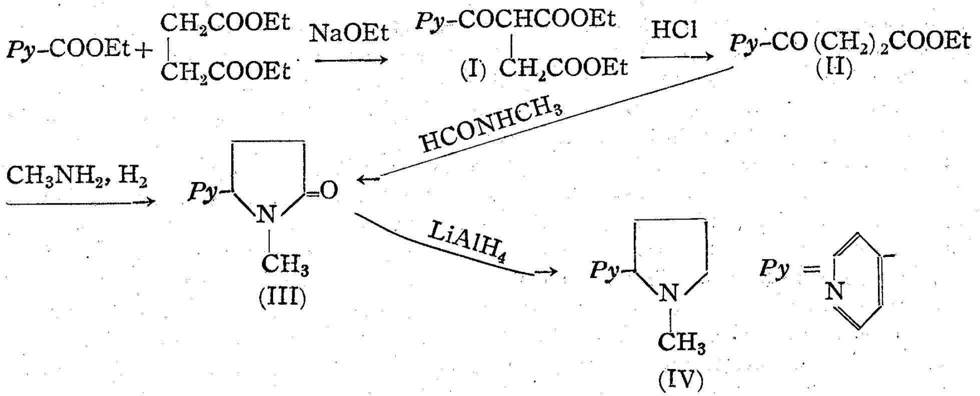
(Received November 30, 1953)

## 10. Shigehiko Sugasawa, Takashi Tatsuno, and Takashi Kamiya: A Synthesis of *rac*-4-(N-methylpyrrolid-2'-yl)-pyridine.

(*Pharmaceutical Institute, Medical Faculty, University of Tokyo**)

In connection with other synthetical works now going on in our hands, we needed 4-(N-methylpyrrolid-2'-yl)-pyridine (*rac*-γ-nicotine) as one of the starting materials, whose synthesis is not described in any literature.

Our first attempt to prepare this compound according to Späth's synthesis[1] of *rac*-nicotine ended fruitless but the synthesis by the following scheme turned out to be successful.



Ethyl isonicotinate was condensed with diethyl succinate by means of sodium ethoxide, giving diethyl isonicotinoylsuccinate (I) in 40~50% yield. The latter was hydrolyzed by boiling with dilute hydrochloric acid, followed by esterification, yielding ethyl β-isonicotinoylpropionate (II) in 25~30% yield. This was then subjected to hydrogenation in the presence of methylamine over Raney nickel under pressure,[2] yielding 5-(pyrid-4'-yl)-1-methylpyrrolid-2-one (III) in a fair yield. The latter was then reduced with lithium aluminum hydride preferably in tetrahydrofuran[3] to give the ultimate product (IV) in excellent yield.

*rac*-γ-Nicotine thus prepared comes as colorless liquid with an odor like that of natural nicotine. It forms crystalline *l*-γ-nicotine *d*-tartrate, when treated with *d*-tartaric acid and physiological properties of this salt is now being investigated.

The authors' thanks are due to members of the analysis room of this Institute for microanalytical data.

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[1] Späth, *el al.*: Ber., 61, 327 (1928).

[2] cf. Org. Syntheses, 27, 28.

[3] Moffet, White: J. Org. Chem., 17, 407 (1952).

## Experimental

**Ethyl β-Isonicotinoylpropionate (II)**—Alcohol-free sodium ethoxide was prepared from 5 g. of sodium (0.22 atom) and this was mixed with ethyl isonicotinate (25 g., 0.15 mole), diethyl succinate (26 g., 0.14 mole), and pure benzene (50 cc.), and the mixture was heated with stirring, giving orange yellow slurry. After being refluxed for two hrs., the whole was added with water (30 cc.), and the aqueous layer was extracted with benzene to remove the unreacted starting materials. After being acidified with hydrochloric acid, the aqueous layer was again extracted with benzene. The separated aqueous solution was basified with sodium bicarbonate and the oily substance that separated out was extracted with benzene, washed, dried, and evaporated, furnishing an oily liquid (20∼22 g. or ca. 50%), which gives minute needle-shaped picrate of m.p. 100∼102°. From the first benzene extract a mixture of the starting materials (4∼5 g.) was recovered and the second benzene extract gave needle-shaped crystals, m.p. 125°, of diethyl succinylsuccinate formed as a by-product.

The oily substance thus obtained (12 g.) was dissolved in hydrochloric acid (40 cc. of 8%) and the whole was refluxed in an oil bath (120∼140°) until the evolution of carbon dioxide had ceased. The reaction product was then evaporated to dryness *in vacuo*. Absolute alcohol (30 cc.) was added to the residue and solution was saturated with dry hydrogen chloride. The whole was now refluxed on a water bath for 3 hrs., during which dry hydrogen chloride was introduced. Most of alcohol was now evaporated and the residue was poured on to crushed ice, salted out with potassium carbonate, and the liberated base was taken up in ether which was dried and evaporated. The residue distilled at 145∼147° (4 mm.), forming faint yellow viscous oil; yield, 5.5 g. or 29%. Gives yellow leaflet-shaped picrate of m.p. 136∼138° from methanol.

Oxime: Colorless rhombs of m.p. 92∼93° from alcohol. *Anal.* Calcd. for $C_{11}H_{14}O_3N_2$: C, 59.4; H, 6.35; N, 12.6. Found: C, 59.2; H, 6.4; N, 12.5.

**5-(Pyrid-4′-yl)-1-methylpyrrolid-3-one (III)**—(a) The foregoing keto ester (5.5 g., 0.2 mole) was mixed with alcoholic methylamine solution (3 g. or 0.8 mole of amine in 15 cc. of alcohol) and the mixture was reduced with hydrogen (initial pressure: 70∼100 atm.) over Raney nickel (2 g.) at 140∼150° for 40 min. On cooling the filtrate from the catalyst was evaporated *in vacuo*, leaving viscous liquid, to which absolute benzene was added, filtered, and the filtrate was evaporated. The residue distilled at 148∼151° (0.04∼0.05 mm.) as yellowish oil, which solidified on standing, forming rhombic crystals of m.p. 42∼45°. Yield, 3 g. or 64%.

Picrolonate: Yellow needles of m.p. 222∼224° from alcohol.

Picrate: Yellow needles of m.p. 187∼188° (decomp.) from alcohol. *Anal.* Calcd. for $C_{16}H_{15}O_7N_5$: C, 47.4; H, 3.7; N, 17.25. Found: C, 47.3; H, 3.8; N, 17.3.

(b) By the Leuckart Method: The same pyrrolidone can be obtained by subjecting the keto ester (II) to the Leuckart reaction. The keto ester (2 g., 0.02 mole) was mixed with formmethylamide (prepared from 2.5 g. of 80% formic acid or 0.04 mole) and the mixture was refluxed at 220∼230° until the cessation of carbon dioxide generation (ca. 6 hrs.). The reaction product was poured on to crushed ice, left standing over night, and salted out with potassium carbonate, separating dark red oil which was taken up in benzene (ca. two-thirds remained undissolved), dried, and evaporated. The residue distilled at 150∼152° (0.04 mm.) forming reddish oil. Yield, 0.6 g. or 35%. Gives a picrate of m.p. 185∼188° (decomp.) and a picrolonate of m.p. 220∼223° (decomp.), which were found to be identical with those obtained above.

***rac*-γ-Nicotine (IV)**—The foregoing pyrrolidone can be reduced to *rac*-γ-nicotine with lithium aluminum hydride either in ether or in tetrahydrofuran, but the latter is the solvent of choice, giving much higher yield of (IV). The yield of (IV) was about 15% when ether was used as a solvent.

A solution of the pyrrolidone (3.5 g., 0.02 mole) in tetrahydrofuran (50 cc.) was added dropwise into the tetrahydrofuran solution of lithium aluminum hydride (0.6 g., 0.016 mole in 20 cc. of the solvent) and then the whole was refluxed 40 hrs., depositing a large amount of the double salt. The solvent was now evaporated and ether was added to the residue. The double salt was then decomposed by adding water and acidified with dilute sulfuric acid. The aqueous layer was now basified and salted out with potassium carbonate, separating the free base, which was taken up in ether, dried, and evaporated, yielding an oily residue. It came over at 94∼95° (7 mm.) forming colorless liquid of nicotine-like odor. Soluble in water and common organic solvents. Yield, 2.7 g. or 79%.

Dipicrate: Yellow needles of m.p. 195° (decomp.) from alcohol. *Anal.* Calcd. for $C_{22}H_{20}O_{14}N_8$: C, 42.6; H, 3.25; N, 18.0. Found: C, 43.1; H, 3.3; N, 18.25. Bis-bitartrate: Colorless feather-like crystals from hydrated acetone, m.p. 88∼89°. *Anal.* Calcd. for $C_{10}H_{14}N_2 \cdot 2C_4H_6O_6 \cdot 2H_2O$: C, 43.4; H, 6.1; N, 5.6. Found: C, 43.3; H, 5.65; N, 5.7.

## Summary

The synthesis of *rac*-γ-nicotine was described for the first time. It forms a colorless liquid of b.p$_7$ 94~95°, having a nicotine-like odor. Gives a dipicrate of m.p. 195° (decomp.) and a dipicrolonate of m.p. 217° (decomp.). *l*-γ-Nicotine *d*-tartrate (m.p. 88~89°) was also prepared and its physiological properties are being examined.

(Received December 15, 1953)

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## 11. Shigehiko Sugasawa, Takashi Tatsuno, and Takashi Kamiya: A New Synthesis of *rac*-Nicotine.

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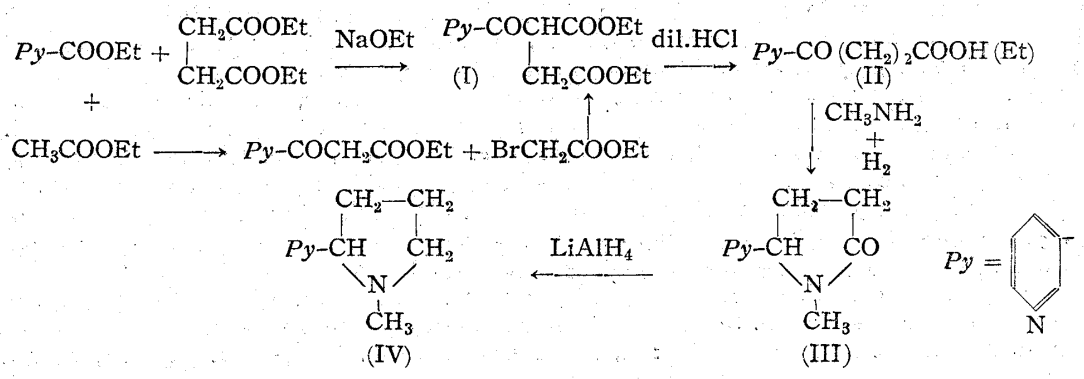
There are already several methods of synthesizing nicotine described in the literature.[1] In the foregoing paper[2] we described the synthesis of *rac*-γ-nicotine for the first time, and it appeared to us not without interest to see whether this method will also be available for the synthesis of *rac*-nicotine, since, as was shown in the foregoing paper, the method of synthesizing nicotine by Späth was proved inapplicable for the preparation of γ-nicotine.

The result of our experiments showed that the method is useful for the synthesis of nicotine, but for better results, some modification was found to be necessary, as is shown in the following chart.



The condensation of ethyl nicotinate with diethyl succinate by means of sodium ethoxide gave diethyl nicotinoylsuccinate (I), only in 20% yield at the best, so far inferior than the former case; diethyl succinylsuccinate being the main product. The compound (I) gave β-nicotinoylpropinonic acid (II) by being boiled with dilute hydrochloric acid.

In order to obtain (I) in better yield we next investigated the condensation of ethyl nicotinoylacetate with ethyl chloroacetate by means of sodium ethoxide, when a large amount of ethyl nicotinate was recovered, probably due to the alcoholysis of

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[1] Pictet, Rotschy: Ber., **37**, 1225 (1904); Späth: *Ibid.*, **61**, 327 (1928); Craig: J. Am. Chem. Soc., **55**, 2854 (1933). For the synthesis of α-nicotine cf. Wibaut: Rec. trav. chim., **42**, 1033 (1923).

[2] This Bulletin, **2**, 37 (1954).