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.

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

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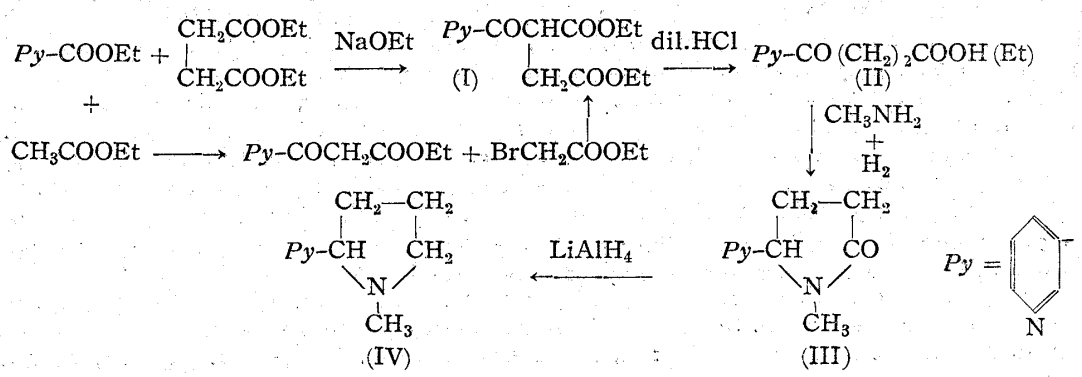
There are already several methods of synthesizing nicotine described in the literature.[1] In the foregoing paper[2] we described the synthesis of *rac*-γ-nicotine for the first time, and it appeared to us not without interest to see whether this method will also be available for the synthesis of *rac*-nicotine,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

ethyl nicotinoylacetate. However, when ethyl bromoacetate was used instead of the chloro compound, the reaction proceeded smoothly at a lower temperature with the exclusion of alcoholysis and thus the compound (I) was produced in a fair yield.

The hydrogenation of ethyl nicotinoylpropionate (II) in the presence of methylamine was carried out under pressure as in the former case, furnishing 5-(3′-pyridyl)-1-methylpyrrolid-2-one (III, cotinine). This compound has already been described by Pinner,[3] who gave m.p. 220° (decomp.) for its platinic salt, but we found our cotinine platinum salt to melt at about 10 degrees higher. This compound was characterized as a gold salt because this salt was found to be more crystallizable than the corresponding platinum salt.

The reduction of cotinine by means of lithium aluminum hydride was carried out smoothly in the tetrahydrofuran solution, giving *rac*-nicotine (IV), which was proved to be identical with the one obtained through racemization of natural nicotine.

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

Experimental

Diethyl Nicotinoylsuccinate (I)—(a) A pure benzene (40 cc.) solution of ethyl nicotinate (20 g.) and diethyl succinate (21 g.) was added with alcohol-free sodium ethoxide (prepared from 4 g. as usual) with ice cooling and then the mixture was refluxed on a steam bath with stirring for 3 hrs., giving a dark red solution. On cooling, water (25 cc.) was added, the aqueous layer was extracted with benzene. From the benzene solution, combined with the original benzene layer, ethyl nicotinate was recovered.

The aqueous layer was acidified with hydrochloric acid, extracted with benzene, and again basified with sodium carbonate, separating an oily substance which was taken up in benzene, dried and evaporated, leaving a red oil which came over at 152~154° (0.08 mm.); yield, 4.2 g. The picrate was prepared in ethereal solution and purified from methanol-ether, forming yellow needles of m.p. 94~95°. *Anal.* Calcd. for $C_{20}H_{20}O_{12}N_4$: C, 47.2; H, 4.0; N, 11.0. Foud: C, 47.4; H, 3.7; N, 10.8.

(b) Potassium ethoxide (prepared from 1.8 g. of potassium) was added dropwise into the alcoholic solution of ethyl nicotinoylacetate (11 g.), gradually separating white crystalline substance. To the mixture was now added an alcoholic solution of ethyl bromoacetate (5 g.) with ice cooling and stirring. Then the whole was stirred at a room temperature (about 25°) for 10 hrs., during which time the original white solid disappeared and faint yellow precipitate newly separated. From the filtrate alcohol was now removed, the residue was dissolved in benzene, dried, and evaporated. The residual oil was distilled, giving a fraction of $b.p_{0.08}$ 152~157°; yield, 8.1 g. or 67 %, when the recovered ethyl nicotinoylacetate was taken into account. Gives yellow needle-shaped picrate of m.p. 94~95°, which was identical with the one obtained above.

Ethyl β-Nicotinoylpropionate (II)—The foregoing ketosuccinate (8.1 g.) was dissolved in hydrochloric acid (80 cc. of 5 %) and the mixture was boiled in an oil bath until the evolution of carbon dioxide had ceased (ca. 3 hrs.). The reaction mixture was now evaporated *in vacuo*, the residue was mixed in toluene-alcohol (2:1), and the solvent was distilled off. The dried product was then dissolved in absolute alcohol (20 cc.) and esterified by saturating dry hydrogen chloride, while being refluxed. On cooling most of alcohol was evaporated *in vacuo*, and the residue was dissolved in water (ca. 20 cc.), basified with sodium carbonate, and then extracted with benzene. The benzene layer was washed with salt solution, dried, and evaporated. Colorless liquid of $b.p_4$ 142~145° was obtained; yield, 5 g. or 80 %.

Picrate: Yellow needles from alcohol, m.p. 107~109°. *Anal.* Calcd. for $C_{17}H_{16}O_{10}N_4$: C, 46.8; H, 3.7; N, 12.8. Found: C, 46.6; H, 3.9; N, 12.3.

5-(3′-Pyridyl)-1-methylpyrrolid-2-one (III)—The ketoester (II, 5 g.) in alcohol (15 cc.) was added with alcoholic solution of methylamine (7.2 g. amine in 20 cc. of alcohol) and was reduced with hydrogen (initial pressure 65 atm.) over Raney nickel (3 g.) at 140~150° for 1.5 hrs. On cooling the filtrate from the catalyst was evaporated and the residue was taken up in benzene which was washed, dried, and evaporated, leaving a reddish viscous liquid, which distilled at 160~180° (0.03~0.04 mm.). This was again dissolved in benzene and purified through alumina column (25 g.). The solvent was removed from the benzene eluate, leaving a faint yellow oil (1.1 g.), which gave

3) Pinner: Ber., 26, 297 (1893).

crystalline chloroplatinate of m.p. 232° (decomp.), this being about 10° higher than that given by Pinner for the same substance. For analysis the chloroaurate was prepared and purified from alcohol, acidified with a little hydrochloric acid, forming yellow pillars of m.p. 215° (decomp.). *Anal.* Calcd. for $C_{10}H_{12}ON_2HCl \cdot AuCl_3$: C, 23.3; H, 2.5; N, 6.1; Au, 38.2. Found: C, 23.3; H, 3.1; N, 6.1; Au, 39.4.

***rac*-Nicotine (IV)**—The pyrrolidone (III: 0.8 g.) in tetrahydrofuran (20 cc.) was added dropwise into the solution of lithium aluminum hydride (0.2 g.) in the same solvent (15 cc.) with ice cooling and the mixture was then refluxed for 40 hrs. on a steam bath, depositing yellowish precipitate. Worked up as usual, the product yielded an oily substance (0.5 g.) having a nicotine-like odor. Pure base was obtained by purifying through alumina column. Gives a dipicrate of m.p. 216~218° (decomp.), which was proved to be identical with the one obtained from *rac*-nicotine prepared by racemizing natural nicotine.

Summary

A new synthesis of *rac*-nicotine is described. Ethyl β-nicotinoylpropionate, which was obtained by boiling diethyl nicotinoylsuccinate with dilute hydrochloric acid was catalytically reduced in the presence of methylamine, giving cotinine. This was then reduced by means of lithium aluminum hydride in tetrahydrofuran solution to give *rac*-nicotine in a fair yield. For the preparation of diethyl nicotinoylsuccinate the condensation of ethyl nicotinoylacetate with ethyl bromoacetate was recommended.

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12. Kôzô Hayashi, Tatsuo Noguchi, und Yukihide Abe: Studien über Anthocyane. XXIV[1]. Karacyanin, ein Farbstoffprinzip in den feuerroten Blüten von *Canna generalis*.***

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Ein leuchtend feuerroter Farbstoff in den Blüten von *Canna generalis* Bailey (Cannaceae) ist unseres Wissens noch nicht genauer untersucht worden. Wir fanden nur eine kurze Angabe von G. M. Robinson und R. Robinson[2], die unter Benutzung ihrer eigenen Arbeitstechnik gefunden haben, dass die Blüten von *Canna indica* ein Pentoseglykosid des Cyanidins enthält. Ob ihre Versuchspflanze mit der unseren identisch war, können wir zur Zeit nicht entscheiden, da die Bezeichnung *Canna indica* bisweilen auch den kultivierten *Canna*-Arten gegeben wird.

Im August, 1952, hat uns Herr N. Sasaki, Obergärtner im städtischen Garten „Shinjuku-gyoen", ein beträchtliche Menge von feuerroten Blüten (aus einer Gartensorte „Louisiana") im frisch gepflückten Zustand zur Verfügung gestellt, wodurch die Durchführung unserer Arbeit ermöglicht wurde.

Unsere vorläufig durchgeführten papier-chromatographischen Untersuchungen schienen darauf hinzuweisen, dass der Hauptfarbstoff der genannten Pflanze vorzugsweise auf das Cosmocyanin[3], d.h. ein Rhamnoglucosid des Cyanidins, zurückzuführen ist.

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*** Mitteilung aus der Forschungsanstalt für Naturerzeugnisse, Nr. 661.
1) XXIII. Mitteil.: Misc. Repts. Research Inst. Natural Resources, 29, 1 (1953).
2) G. M. Robinson, R. Robinson: Biochem. J., 28, 1714 (1934).
3) K. Hayashi: Acta Phytochim., 12, 83 (1941).