55. **Shigehiko Sugasawa and Koji Oka:** Synthesis in the Benzoquinolizine Group. XX[1]. Synthesis of *rac*-C-Trisnoremetine.

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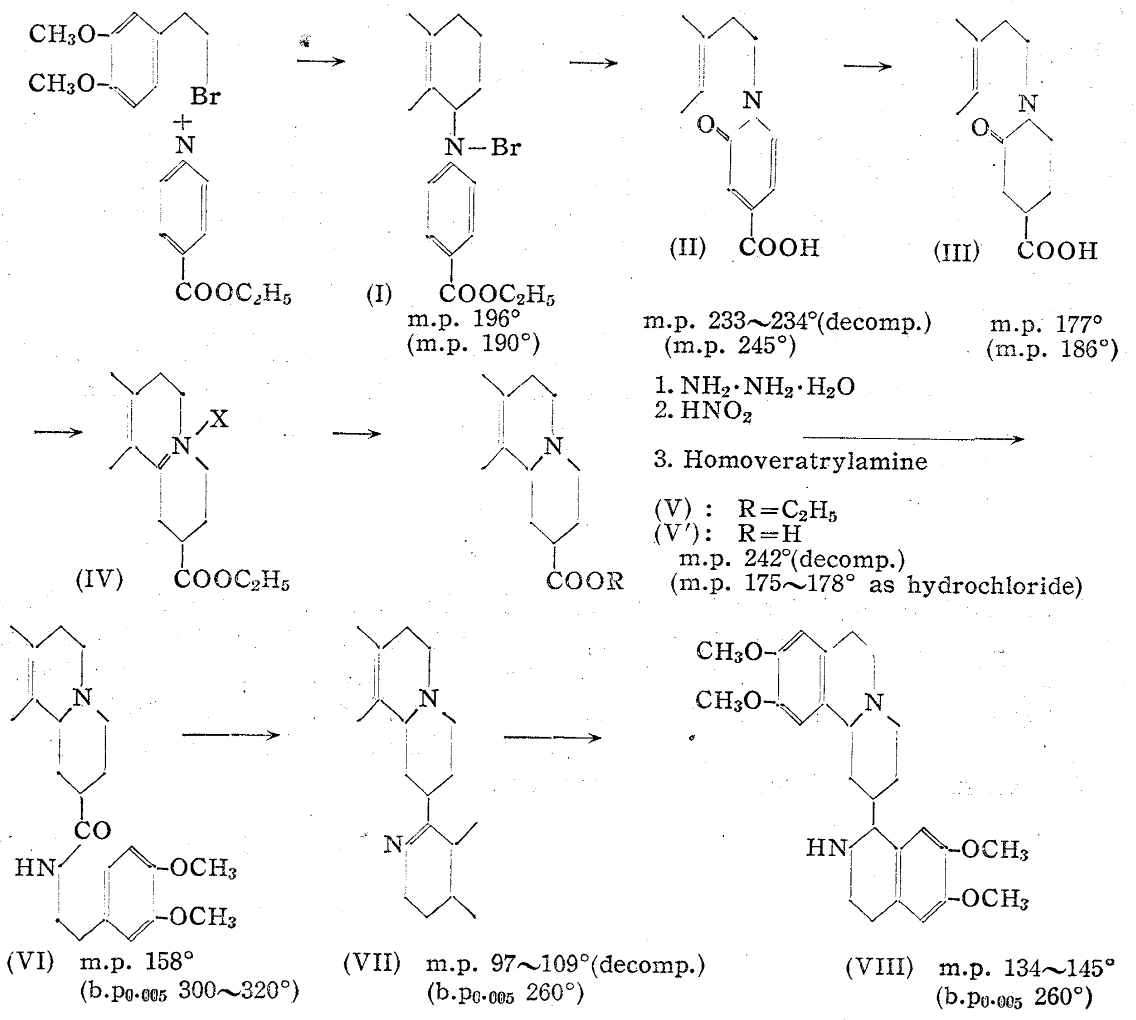
The abstract of paper by Pailer *et al.*, upon "Synthesis of compounds with constitutional reference to emetine, II." which appeared in the recent number[2] of the Chemical Abstracts has prompted as to publish the result of our experiments concerning the synthesis of *rac*-C-trisnoremetine, completed nearly a year ago, which we meant to publish jointly with other syntheses of *rac*-C-noremetines, now under progress in our hands.

Our method of synthesis of *rac*-C-trisnoremetine is essentially the same as that of Pailer, as is shown in the following chart:



Figures in parentheses show data given by Pailer, *et al.*

β-3,4-Dimethoxyphenethyl bromide and ethyl isonicotinate were heated in benzene, giving the quaternary salt (I), which was oxidized by means of alkaline potassium ferricyanide. The pyridone-carboxylic acid (II) thus obtained was reduced to the corresponding piperidone carboxylic acid (III), which was then ring-closed by heating with phosphoryl chloride. The solvent and excess of phosphoryl chloride were removed in vacuo and the

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[2] C. A., 47, 2186 (1953).

residue was treated with absolute ethanol, yielding carbethoxybenzoquinolizinium salt (IV), which was identified as its iodide. The corresponding chloride smoothly absorbed one mole of hydrogen, giving rise to the tertiary base (V), the azide of which gave the homoveratrylamide (VI) on being treated with homoveratryl amine in absolute ether. The ring-closure of (VI) followed by reduction furnished *rac*-C-trisnoremetine (VIII) as colorless amorphous powder with an indefinite melting point of 134~145°, which probably represents a mixture of diastereoracemates.

The melting points of some of the compounds prepared by us, however, do not agree with those of Pailer and the most striking difference exists in that our attempt to prepare the homoamide corresponding to (VI) by treating the diazoketone obtained from the acid (V) with homoveratrylamine, as the possible intermediate for the synthesis of *rac*-C-bisnoremetine, has so far failed, whereas Pailer, *et al.* reported the successful synthesis of this compound via the same route. We are as yet impossible to elucidate the reason of our failure, but mention will be made that our acid (V) melts at 242° with decomposition, whereas their acid as hydrochloride melts at 175~178°. Therefore, there is no material at present to speak of the identity of these two acids and they may possibly be diastereoisomers.

Our efforts are now being directed to the synthesis of *rac*-C-bisnoremetine and the result will be published in due course.

Our thanks are due to Messrs. Kaneko, Sekijima, and Fukuda for microanalytical data.

Experimental

N-β-3′,4′-Dimethoxyphenethyl-4-carbethoxypyridinium bromide (I)—3,4-Dimethoxyphenethyl bromide (17 g.), ethyl isonicotinate (10.4 g.), and pure dry benzene (34 cc.) (benzene was proved to be a preferred solvent) were refluxed on a steam bath for ca. 10 hrs. Yellow crystalline solid separated was filtered, washed with a little benzene, which was combined with the filtrate, and the whole was refluxed again, giving some more product. Repeating this procedure several times there was obtained 22 g. (or 80%) of (I), melting at 196°, which was pure enough for the next step. Purified from alcohol, forming yellow needles of m.p. 196°. *Anal.* Calcd. for $C_{18}H_{22}O_4NBr$: C, 54.6; H, 5.6; N, 3.5. Found: C, 54.2; H, 5.7; N, 3.2.

N-β-3′,4′-Dimethoxyphenethyl-2-pyridone-4-carboxylic acid (II)—To an aqueous solution of the foregoing bromide (10 g. of the bromide in 100 cc. of water) was added a solution of potassium hydroxide (7 g. in 5 cc. of water) dropwise with stirring under 10°. To the mixture was now introduced a solution of potassium ferricyanide (20 g.) in 120 cc. of water, followed by an aqueous solution of potassium hydroxide (63 g. in 45 cc. of water) with stirring. The mixture was then kept at 60~65° for 1 hr. while being stirred. On cooling, a large amount of inorganic salt separated which was filtered, and the filtrate was made HCl-acid, separating light brown amorphous solid, which was dissolved in aqueous sodium bicarbonate solution, treated with charcoal, and filtered. On acidifying the filtrate there was obtained 6.5 g. (or 85%) of (II) as brownish powder of m.p. 232°(decomp.), which was good enough for the next reaction. Purified from alcohol, forming colorless thin needles of m.p. 233~234° (decomp.). *Anal.* Calcd. for $C_{16}H_{17}O_5N$: C, 63.4; H, 5.6; N, 4.6. Found: C, 63.7; H, 5.7; N, 4.8.

N-β-3′,4′-Dimethoxyphenethyl-2-piperidone-4-carboxylic acid (III)—The pyridone-carboxylic acid (II) (6.5 g.) was dissolved in 2% sodium carbonate solution and was reduced catalytically over Raney nickel (1.5 g.). The filtrate from the catalyst was acidified with dil. HCl and the precipitate was filtered and purified from 80% alcohol (charcoal). Yield, 5.85 g. or 90%. Colorless grains of m.p. 177~178°. *Anal.* Calcd. for $C_{16}H_{21}O_5N$: C, 62.5; H, 6.8; N, 4.6. Found: C, 62.6; H, 6.9; N, 4.7.

4′,5′-Dimethoxy-7-carbethoxy-3,4,5,6,7,8-hexahydro-9,10-dehydro-(2′,1′:1,2-benzoquinolizinium) salt (IV)—The above-mentioned acid (5.8 g.), phosphoryl chloride (29 g.), and pure benzene (29 cc.) were boiled gently on a steam bath for 1.5 hrs. Excess of phosphoryl chloride and benzene were then evaporated in vacuo and the residue was refluxed with absolute alcohol (50 cc.) for 20 min. Alcohol was then removed in vacuo and the residue was dissolved in water (ca. 40 cc.), treated with charcoal, and the filtrate was added with potassiumiod ide (14 g.), separating crystalline solid, which was purified once from hot water. Yield, 6 g. or 75%. Repeatedly recrystallized for analysis, forming yellowish brown dices of m.p. 182~184°(decomp.) *Anal.* Calcd. for $C_{18}H_{24}O_4NI$: C, 48.5; H, 5.4; N, 3.1. Found: C, 48.6; H, 5.8; N, 3.5.

4′, 5′-Dimethoxy-7-carbethoxy-3,4,5,6,7,8-hexahydro-(2′,1′ : 1,2-benzoquinolizine) (V)—The foregoing iodide (5.9 g.) was converted into the corresponding chloride and the latter was reduced catalytically over Adams' Pt catalyst; one mole of hydrogen being smoothly absorbed. The filtrate from the catalyst was evaporated in vacuo and the residue (3.8 g.) was triturated with cold acetone, giving solid substance of m.p. 220° (3.4 g.). This was dissolved in water and basified with soda solution. The base separated was extracted with ether, dried, and evaporated, leaving (V) as oily substance. Yield, 2.6 g. or 62.5%.

4′,5′-Dimethoxy-3,4,5,6,7,8-hexahydro-(2′,1′ : 1,2-benzoquinolizyl)-7-carboxylic acid hydrazide—The ester (V) (2.5 g.) and hydrazine hydrate (1.5 g.) were heated together with amyl alcohol (10 cc.) at 130~140° (oil bath temp.) for 5 hrs. Crystalline solid, which separated on cooling, was collected on a filter, washed with a little cold alcohol, and dried. Yield, 2.26 g. or 95% of a substance melting at 204~206°, pure enough for the next step. Purified twice from alcohol forming colorless minute needles of m.p. 204~207°. *Anal* Calcd. for $C_{16}H_{23}O_3N_3$: C, 62.9; H, 7.6; N, 13.8. Found: C, 63.25; H, 7.7; N, 13.5.

[4′, 5′-Dimethoxy-3,4, 5,6,7,8-hexahydro-(2′,1′ : 1,2-benzoquinolizyl)-7]-carboxylic acid β-3″,4″-dimethoxyphenethylamide (VI)—The afore-mentioned hydrazide (1.7 g.) in water (29 cc.) was acidified with HCl (2.9 g. of 35%) and treated with aqueous sodium nitrite solution (0.56 g. in 5 cc. of water) under 5° with stirring. After being agitated at 5° for 30 min. the solution was basified with 5% soda solution and the azide separated was taken up in ether, dried over sodium sulfate for 1 hr. The dried ethereal solution was mixed with ethereal homoveratryl amine solution (1.5 g. in 7 cc. of absolute ether), crystalline solid separating immediately. The whole was stirred for 1 hr. and then was gently warmed in a tepid water bath for 2 hrs., cooled, and filtered. Purified once from alcohol, yielding 1.7 g. (or 67%) of colorless needles of m.p. 154~157°. Three times purified from alcohol for analysis forming colorless needles of m.p. 158~159°, which are sparingly soluble in ether, readily soluble in hot alcohol and dil. acetic acid. *Anal.* Calcd. for $C_{26}H_{34}O_5N_2$: C, 68.7; H, 7.5; N, 6.2. Found: C, 68.4; H, 7.5; N, 6.6.

4′, 5′-Dimethoxy-7-(6″,7″-dimethoxy-3″, 4″-dihydroisoquinolyl-1″)-3, 4, 5, 6, 7, 8-hexahydro-(2′, 1′ : 1,2-benzoquinolizine) = ***rac*-C-Trisnor-1, 2-dehydroemetine (VII)**—The foregoing amide (1.1 g.), phosphoryl chloride (2.2 cc.), and pure benzene (8.8 cc.) were refluxed on a steam bath for 3 hrs. On cooling, enough petroleum ether (b.p. 45~65°) was added to precipitate the reaction product. After standing for some time the supernatant layer was discarded and the residue was dissolved in water, filtered with a wet filter, and the filtrate was basified with sodium carbonate. The base separated was now taken up in benzene, washed, dried, and purified by filtering through an alumina column. The benzene eluate was evaporated below 70° in vacuo and the residue was triturated with ether, giving 0.8 g. (or 75%) of crystalline solid melting at 97~107° with decomposition, which was used directly for the following stage. This substance, though it can be crystallized from ethyl acetate forming a colorless crystalline solid of m.p. 97~109°(decomp.), is fairly unstable in the air, gradually turning red, which coloration proceeds more rapidly in a solution. Dipicrate: Yellow sandy grains from glacial acetic acid, decolorizes at 186°, darkens at 216°, and melts at 226° with decomposition. *Anal.* Calcd. for $C_{38}H_{38}O_{18}N_8$: C, 51.0; H, 4.3; N, 12.5. Found: C, 50.3; H, 4.3; N, 12.7. Dihydrochloride: Nearly colorless (very faint yellow-greenish) plates from alcohol-acetone; m.p. 231~234°(decomp.). *Anal.* Calcd. for $C_{26}H_{32}O_4N_2 \cdot 2HCl$: N, 5.5. Found: N, 5.8.

4′,5′-Dimethoxy-7-(6″,7″-dimethoxy-1″,2″,3″,4″-tetrahydroisoquinolyl-1″)-3, 4, 5, 6, 7, 8-hexahydro-(2′,1′ : 1,2-benzoquinolizine)=***rac*-C-Trisnoremetine (VIII)**—The foregoing base (0.2 g.) in alcohol (10 cc.) was reduced catalytically over Adams' Pt catalyst (0.05 g.); one mole of hydrogen was absorbed in ca. 1 hour. The filtrate from the catalyst was evaporated in vacuo, leaving 0.2 g. of syrupy substance, which came in colorless amorphous solid of m.p. 134~145° from acetic ester. *Anal.* Calcd. for $C_{26}H_{34}O_4N_2$: C, 71.1; H, 7.8; N, 6.4. Found (in substance dried at 20~30° in vac. for 40 hrs.): C, 70.8; H, 8.0; N, 6.2. When exposed to light this base turns red gradually, forms dipicrate of m.p. 191~205° with decomposition (from glacial acetic acid) and dihydrochloride of m.p. 263°(decomp.) after sintering at about 255° (from alcohol-acetone).

Summary

A synthesis of *rac*-C-trisnoremetine starting from ethyl isonicotinate and β-3,4-dimethoxyphenethyl bromide is described. The present method of synthesis is essentially the same as that of Pailer, *et al.*, but some discrepancies in the physical constants of the final product and also some of the intermediates were observed.

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