With Methanol: 0.3 g. of methyl thiocarbamate was refluxed with 6 cc. of methanol on a water bath for 19 hrs. After the reaction was complete, the reaction mixture was treated with 10% NaOH solution and extracted with ethyl acetate. After removal of the solvent, the residue was washed with ether and yielded 60 mg. of the amino compound, m.p. 200°.

Summary

In general, when 3-nitro-4-thiocyanopyridine is allowed to react with aliphatic alcohols, four kinds of products are formed, namely, the alkyl thiocarbamates, 3-nitro-4-aminopyridine, 3,3′-dinitrodipyridyl 4,4′-disulfide, and 3,3′-dinitrodipyridyl 4,4′-monosulfide, and this reaction mechanism was considerated.

(Received December 24, 1953)

22. Shigehiko Sugasawa and Koji Oka: Synthesis in the Benzoquinolizine Group. XXIII.[1] Synthesis of *rac*-C-bisnoremetine.

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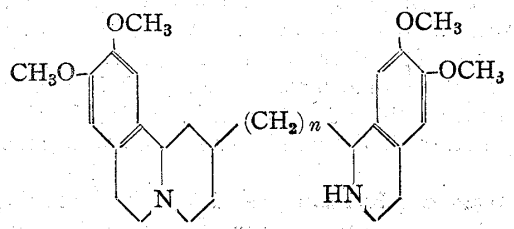
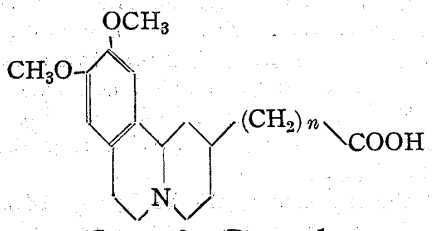
The preceding paper[1] of this series described a synthesis of *rac*-C-trisnoremetine (A). The compound (C), which formed one of the intermediates in the above synthesis, appeared to be also a suitable material for the synthesis of *rac*-C-bisnoremetine (B) in case the corresponding homoacid (D) is obtainable from (C) by Arndt-Eistert method. Our efforts to this end, however, ended fruitless because of the difficulty of preparing the chloride of the acid (C) pure enough, so that the Arndt-Eistert reaction can be carried out satisfactorily. This difficulty is probably due to the amphoteric character of the acid (C).



(A): n=0; (B): n=1



(C): n=0; (D): n=1

So we next turned our attention to N-β-3′,4′-dimethoxyphenethylpyrid-2-one-4-carboxylic acid (I), the precursor of (C), whose chloride is expected to be obtainable in higher state of purity because of the nonbasic character of the nitrogen present in the molecule. However, the preparation of the chloride first met with some difficulty, which was, however, overcome by using an excess of oxalyl chloride as the chlorination agent in the presence of a small amount of pure pyridine at an ordinary temperature. The crude diazoketone, which was prepared by the usual method from this acid, was directly treated with β-3,4-dimethoxyphenethylamine in the presence of silver nitrate, giving the amide (III), which was then reduced catalytically to yield the corresponding piperidone derivative (IV) as colorless needles of m.p. 130~131°.

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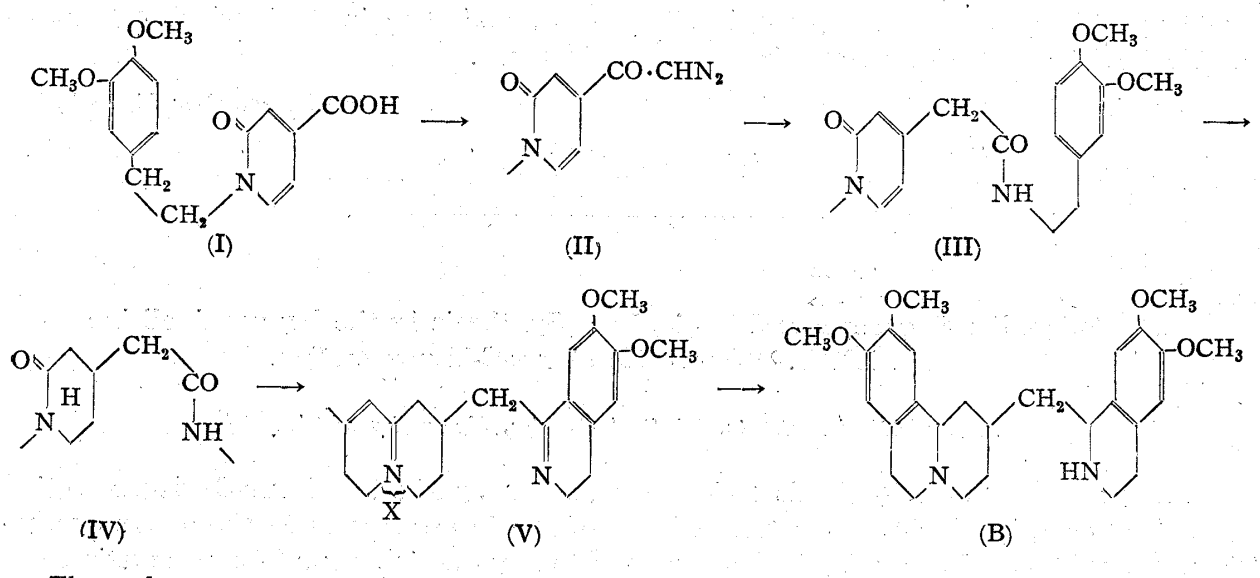
1) This Bulletin, 1, 230 (1953).

Some time ago, Tomimatsu[2] prepared the same compound but by a different method and described it as an oily substance, which was not induced to crystallize. This discrepancy is probably due to the higher state of purity of the compound prepared by the present method.

The ring closure of (IV) and reduction of the cyclization product (V) proceeded smoothly, giving *rac*-C-bisnoremetine (B) as an oily substance from which crystalline dipicrate and dipicrolonate were obtained, probably representing the salts of one of the four possible diastereoracemates.



The authors are grateful to the Ministry of Education for the research grants which enabled them to carry out this work. They are also thankful to the members of the central analysis room of this Institute for microanalytical data.

Experimental

Chloride of N-β-3′,4′-Dimethoxyphenethylpyrid-2-one-4-carboxylic acid (I)—A mixture of the acid (I; 4 g.), oxalyl chloride (12 g.) and 2 drops of pure pyridine was allowed to stand for 72 hrs. at about 30°. Pure chloroform (25 cc.) was then added and the whole was warmed on a water bath for 20 min., giving an almost clear solution. On cooling, the excess of oxalyl chloride and chloroform were evaporated *in vacuo* at room temperature, leaving yellowish brown crystalline solid, which represents the hydrochloride of the acid (I) chloride. Since the purification of this substance was only possible with a great loss of material, the crude substance was used directly for the next step.

N-β-3′,4′-Dimethoxyphenethylpyrid-2-one-4-diazomethyl ketone (II)—The foregoing material (ca. 4.7 g.) was mixed with pure chloroform (30 cc.) and to this mixture was added pure pyridine with cooling until clear solution resulted (1～2 cc. of pyridine was needed). The solution thus obtained was now introduced dropwise into the benzene (250 cc.) solution of diazomethane (generated from 20 g. of nitrosomethylurea and 70 g. of potassium hydroxide in 75 cc. of water) at 0° to 10°, giving yellowish solution, which gradually turned brown. After being stirred at this temperature for 0.5 hr., the whole was left standing over night at a room temperature (ca. 20°). The excess of diazomethane was now decomposed by adding 2% of aq. acetic acid, filtered, and the separated supernatant benzene layer was washed with water, dried, and evaporated *in vacuo* at below 30°. The residual brown syrup was again dissolved in benzene and purified through alumina column, giving faint yellow solution which was evaporated under a diminished pressure at below 30°, leaving faint yellow needles, which were washed with a little cold benzene. Yield 2.3 g. or 53% of the crude substance (II) of m.p. 116° (decomp.). This substance decomposes with effervescence when treated with dilute hydrochloric acid. The diazoketone is sparingly soluble in ether, soluble in cold alcohol and benzene, and readily so in chloroform. It gradually turns brown on exposure to light.

N-β-3′,4′-Dimethoxyphenethylpyrid-2-one-4-aceto-β-3″,4″-dimethoxyphenethylamide (III)—The above diazoketone (1 g.), homoveratrylamine (5 g.), and absolute alcohol (40 cc.) were mixed

2) Tomimatsu: J. Pharm. Soc. Japan, 73, 75 (1953).

and the mixture was warmed on a water bath. To this solution was added silver nitrate (2 cc. of 10% aq. alcoholic solution), causing a slight effervescence. Half an hour later, an additional 1 cc. of the same silver nitrate solution was added. This manipulation was repeated twice more and the whole was then refluxed for 1 hr. On cooling, alcohol was evaporated and the residual brown syrup was dissolved in cold 5% hydrochloric acid and washed twice with benzene. From the aq. acid solution the amide was now taken up in chloroform, which was washed with sodium bicarbonate solution, dried, and evaporated, leaving a brown syrup. The latter was dissolved in warm acetic ester (ca. 3 cc.) and cooled, separating crystalline solid, which was collected on a filter, washed with a little cold acetic ester, and was used for the next reaction.

For analysis, this was purified from the same solvent, forming colorless needles of m.p. 136~138°. *Anal.* Calcd. for $C_{27}H_{32}O_6N_2$: C, 67.5; H, 6.7; N, 5.8. Found: C, 67.5; H, 6.95; N, 5.5.

N-β-3′,4′-Dimethoxyphenethylpiperid-2-one-4-aceto-β-3″,4″-dimethoxyphenethylamide (IV)—The afore-said pyridone (III: 0.5 g.) was dissolved in ethanol and was reduced over Raney Ni (0.5 g.); 2 moles of hydrogen being smoothly absorbed. The reduction product was obtained as colorless syrup, which was dissolved in a little warm acetic ester, separating crystalline solid on cooling. Yield, 0.45 g. or 90% of the substance of m.p. 125~130°. For analysis, it was recrystallized twice from acetic ester, forming colorless needles of m.p. 130~131°. *Anal.* Calcd. for $C_{27}H_{33}O_6N_2$: C, 66.9; H, 7.5; N, 5.8. Found: C, 66.8; H, 7.6; N, 5.8. The molecular weight determination by micro-Rast method also gave the right value.

4′,5′-Dimethoxy-7-(6″,7″-dimethoxy-3″,4″-dihydroisoquinolylmethyl)-3,4,5,6,7,8-hexahydro-9,10-dehydro-(2′,1′ : 1,2-benzoquinolizinium) Salt (V)—The foregoing substance (0.34 g.) and phosphoryl chloride (5 cc.) were gently boiled in an oil bath for 1.5 hrs. On cooling, petroleum ether (40 cc.) was added, separating a light brown syrup. The supernatant layer was discarded and the residue was washed several times with petroleum ether. This was then dissolved in dil. hydrochloric acid, treated with charcoal, filtered, and the filtrate was added with potassium iodide, causing syrupy iodide to separate, which was not induced to crystallize. So the iodide was taken up in chloroform, dried, and evaporated. The residue was changed to the corresponding chloride and then was added with picrolonic acid in aq. alcohol, separating yellow picrolonate, which comes as yellow powder when purified from aq. alcohol. This salt is not stable towards heat and turns red at 136°, darkens at about 205°, and melts with decomposition at 220~221°. *Anal.* Calcd. for $C_{27}H_{33}O_4N_2 \cdot C_{10}H_8O_5N_4 \cdot C_{10}H_7O_5N_4 \cdot 3H_2O$: C, 54.7; H, 5.3; N, 13.6. Found (in substance dried at 20~30° for 48 hrs. *in vacuo*): C, 54.7; H, 5.75; N, 13.95.

When dried at 75°, in order to remove the water of crystallization in this salt, considerable browning was observed.

***rac*-C-Bisnoremetine (B)**—The syrupy chloride (0.3 g.) prepared as usual from the foregoing iodide was reduced catalytically in alcohol (30 cc.) over Adams' Pt-catalyst; two moles of hydrogen being absorbed in ca. 2 hrs. The reduction product was dissolved in water, basified with ammonia and the liberated base was taken up in ethyl acetate, dried, and evaporated, leaving a faint yellow syrupy base. Its dipicrolonate and dipicrate were obtained crystalline, probably representing salts of one of the four racemic forms. Dipicrolonate: Yellow minute pillars from 80% acetic acid. *Anal.* Calcd. for $C_{27}H_{36}O_4N_2 \cdot 2C_{10}H_8O_5N_4 \cdot 4H_2O$: C, 53.6; H, 5.7; N, 13.3. Found (in substance of m.p. 245° (decomp.) dried at 20~30° for 48 hrs. *in vacuo*): C, 53.7; H, 5.7; N, 13.25. Calcd. for $C_{27}H_{36}O_4N_2 \cdot 2C_{10}H_8O_5N_4 \cdot 2H_2O$: C, 55.5; H, 5.55; N, 13.8. Found (in substance of m.p. 245° (decomp.) dried at 115~120° for 20 hrs. *in vacuo*): C, 55.0; H, 5.4; N, 14.1. Dipicrate: Yellowish brown powder from 80% alcohol. Darkens at 148~153° and melts at 213~214° with decomp. *Anal.* Calcd. for $C_{27}H_{36}O_4N_2 \cdot 2C_6H_3O_7N_3$: C, 51.4; H, 4.65; N, 12.3. Found: C, 51.15; H, 4.6; N, 12.5.

(Addendum)

In the course of the present work, we prepared N-benzyl-2,4-dioxopiperidine (VI) as a model substance of the possible intermediate for the synthesis of *rac*-C-bisnoremetine. The compound (VI) was identified as its phenylhydrazone, which forms yellow sandy grains of m.p. 155~158° from alcohol.

Our attempt to condense this ketone with ethyl cyanoacetate under Cope condition was not effected because this compound was found to undergo bimolecular self-condensation fairly rapidly at a room temperature (ca. 20°) to give compound (VII).

When the distillation of (VI) was attempted in high vacuum (0.05 mm., oil bath temperature, ca. 200°) most of the substance turned into a brown viscous tar, from which some trimolecular self-condensation product (VIII) was isolated.

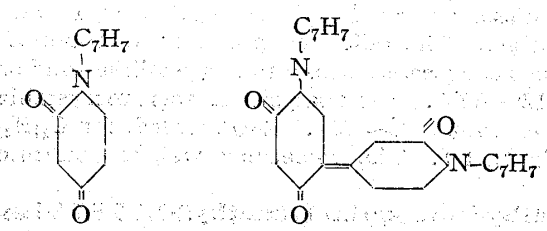
This tendency of the easy intermolecular self-condensation of (VI) is so remarkable when com-

pared with the stability of the corresponding 5-ethyl derivatives (IX[3] and X[4]), which suffer no change when kept in a stoppered bottle at room temperature for a long time. Efforts are now being made to synthesize *rac*-emetine from the latter compound (X).

(VI) Phenylhydrazone: Yellow grains from alcohol, m.p. 155~158°. *Anal.* Calcd. for $C_{18}H_{19}ON_3$: C, 73.7; H, 6.5; N, 14.3. Found: C, 73.2; H, 6.3; N, 14.4.

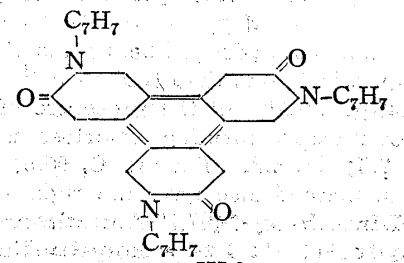
Bimolecular condensation product (VII ?): Colorless pillars of m.p. 162~164° from acetone-alcohol. Forms neither phenylhydrazone nor semicarbazone. *Anal.* Calcd. for $C_{24}H_{24}O_3N_2$ (2(VI) $-H_2O$): C, 74.2; H, 6.2; N, 7.2; Mol. Wt., 388. Found: C, 73.95; H, 6.0; N, 7.3. Mol. Wt. (micro-Rast), 379.

Trimolecular condensation product (VIII ?): Colorless plates of m.p. 196~198.5° from acetone. *Anal.* Calcd. for $C_{36}H_{33}O_3N_3$ (3VI $-3H_2O$): C, 77.8; H, 6.0; N, 7.6; Mol. Wt., 555. Found: C, 77.3; H, 6.3; N, 7.6; Mol. Wt. (micro-Rast), 547.

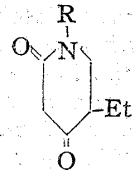


(VI)

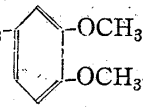
(VII ?)



(VIII ?)



(IX): R= $-CH_2C_6H_5$

(X): R= $-CH_2CH_2-$ 

Summary

A synthesis of *rac*-C-bisnoremetine was described starting from N-β-3',4'-dimethoxyphenethylpyrid-2-one-4-carboxylic acid, whose preparation had already been mentioned in the preceeding paper of this series. One of the four possible racemates was identified as a crystalline dipicrolonate and dipicrate.

N-Benzyl-2,4-dioxopiperidine was also prepared as a model substance. The characteristic property of which is that it easily suffers intermolecular self-condensation, giving bi- and tri-molecular condensation products at ordinary and elevated temperatures, respectively, both as well-defined crystalline compounds.

(Received January 11, 1954)

3) Sugasawa, Fujii: Unpublished.
4) Sugasawa, Ban: Unpublished.