The author is deeply grateful for the kind encouragement of Prof. Emeritus Dr. H. Kondo and for valuable advices from Prof. E. Ochiai during the course of this work. Infrared measurements were by Mr. S. Tanaka, Faculty of Engineering, University of Tokyo, ultraviolet spectra and elemental analyses by Mr. K. Watanabe of this Laboratory, measurement of C-methyl group by Mr. M. Tobita, and Miss K. Kobayashi for pK measurement, all of whose kind cooperation is gratefully acknowledged. Expenses were defrayed by the Grant in Aid of Miscellaneous Scientific Researches from the Ministry of Education to which the author is greatly indebted.

Experimental

Isomerization of Isorhynchophylline into Rhynchophylline—A solution of 1 g. of isorhynchophylline dissolved in a dilute solution of AcOH, prepared from 1.6 g. of glacial AcOH and 20 cc. of water, was heated in a boiling water bath for 8 hrs., cooled, neutralized with Na_2CO_3, and extracted with ether. The extract was washed with water, dried over anhyd. Na_2SO_4, and ether evaporated. The residue was recrystallized from acetone to 0.4 g. of crystals melting at 216°, either alone or in admixture with rhynchophylline.

Summary

Reduction of rhynchophylline with lithium aluminum hydride afforded an indoline derivative, which indicated the 3-position of the oxindole ring in its molecule is a spiro type, and the formula (III) was forwarded for rhynchophylline in analogy with uncarine.

Rhynchophylline and isorhynchophylline are considered to be 4-epimers, similar to uncarine-A and -B, because their compositions are the same, their ultraviolet and infrared spectra are in close similarity, and the two easily undergo isomerization. From the measurement of pK, the formula (V) for rhynchophylline and (IV) for isorhynchophylline are proposed.

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56. **Kitaro Mizukami**: Synthesis in the Benzoquinolizine Group. XXIV.[1]

A Synthesis of *rac*-Dihydroisorotundine.

(*Faculty of Pharmaceutical Sciences, University of Tokyo**)

Many years ago, Kondo and Matsuno[2] isolated a new alkaloid, $C_{16}H_{21}O_3N$, from the rhizome of *Stephania rotunda* Loureio, indigenous to French Indo-China, which they named rotundine. Chiefly based on the results of degradation works thereof they proposed the structure (A), i.e. 2-methyl-3,9,10-trimethoxy-6,7-dihydro-11b*H*-benzo[*a*]-quinolizine, for rotundine. According to these authors the features of rotundine are the facts that it takes up only one mole of bromine in acetic acid to form dibromo-derivative and absorbs only one mole of hydrogen in the presence of Adams' platinum catalyst to yield dihydrorotundine, which still retains one double bond.

In the course of a projected synthesis of *rac*-dihydrorotundine (B)[3] it was found that the compound (C), one of the key intermediates for this synthesis, underwent the ketone fission reaction only with difficulty to yield the ketone (D), which was a rather unstable compound. Therefore it appeared to the present author worthwhile to syn-

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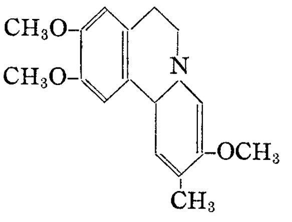
* Hongo, Tokyo (水上喜太郎).

[1] This paper constitutes part of a series entitled "Synthesis in the Quinolizine Group" by Shigehiko Sugasawa. Part XXIII: This Bulletin, **2**, 85(1954).

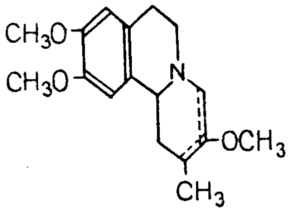
[2] H. Kondo, T. Matsuno: Yakugaku Zasshi, **64B**, 113, 274(1944).

[3] This will be the subject of the forthcoming paper.

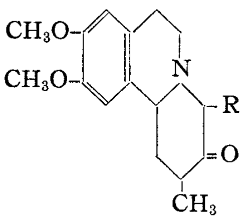
thesize the isomeric keto ester (E) and study its behavior toward ketone fission reaction, as a means of obtaining the compound (F), which may be named *rac*-dihydroisorotundine.



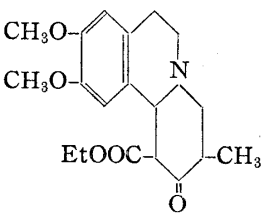
(A)



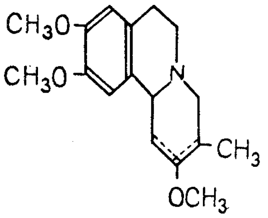
(B)



(C) R=COOEt
(D) R=H



(E)



(F)

As the first step, the synthesis of 2-oxo-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (IV) was undertaken. Thus 1-ethoxycarbonylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (I), prepared according to Osbond,[4] was condensed with ethyl acrylate in the presence of Triton B, to yield the compound (II). The latter underwent a smooth Dieckmann condensation by the agency of sodium hydride in toluene to form the keto ester (III), which was soluble in aqueous caustic soda solution and gave a distinct coloration with ferric chloride. When this was boiled with 10% hydrochloric acid the ketone fission proceeded smoothly and after the evolution of carbon dioxide ceased the ketone (IV) was isolated in over 80% yield. When this ketone was reduced by the Huang-Minlon method, there was obtained the hydrobenzoquinolizine (V), which gave crystalline picrate and this was identified with an authentic picrate of (V). Thus the structure of (IV) was supported.

The synthesis of 3-methyl derivative (XI) of (IV) was next undertaken. The corresponding 3-ethyl derivative of (IV) has already been recorded by Openshaw, *et al.*[5] as an intermediate for the synthesis of emetine. In the present work recourse was had to the method of Ban,[6] who condensed 3,4-dimethoxyphenethylamine, formaldehyde, and ethylmalonic acid to give 2-ethyl-2-(3,4-dimethoxyphenethylaminomethyl)malonic acid. When methylmalonic acid was used in place of ethylmalonic acid in the above work a good yield of the malonic acid (VI) was obtained, from which one of the carboxyl groups was readily removed on being heated with hydrous acetic acid. The resultant acid (VII) was esterified and the ester obtained was treated with ethoxycarbonylacetyl chloride to form the amide (VIII). The latter was then cyclized by heating with phosphoryl chloride in boiling benzene and the product was directly reduced catalytically over Adams' catalyst, followed by esterification to yield the tetrahydroisoquinoline derivative (IX). This was subjected to Dieckmann condensation, whereupon the keto ester (X) was obtained in a fair yield, which is soluble in aqueous caustic soda solution and gives a distinct ferric chloride color test. The ketone fission reaction of this compound proceeded just

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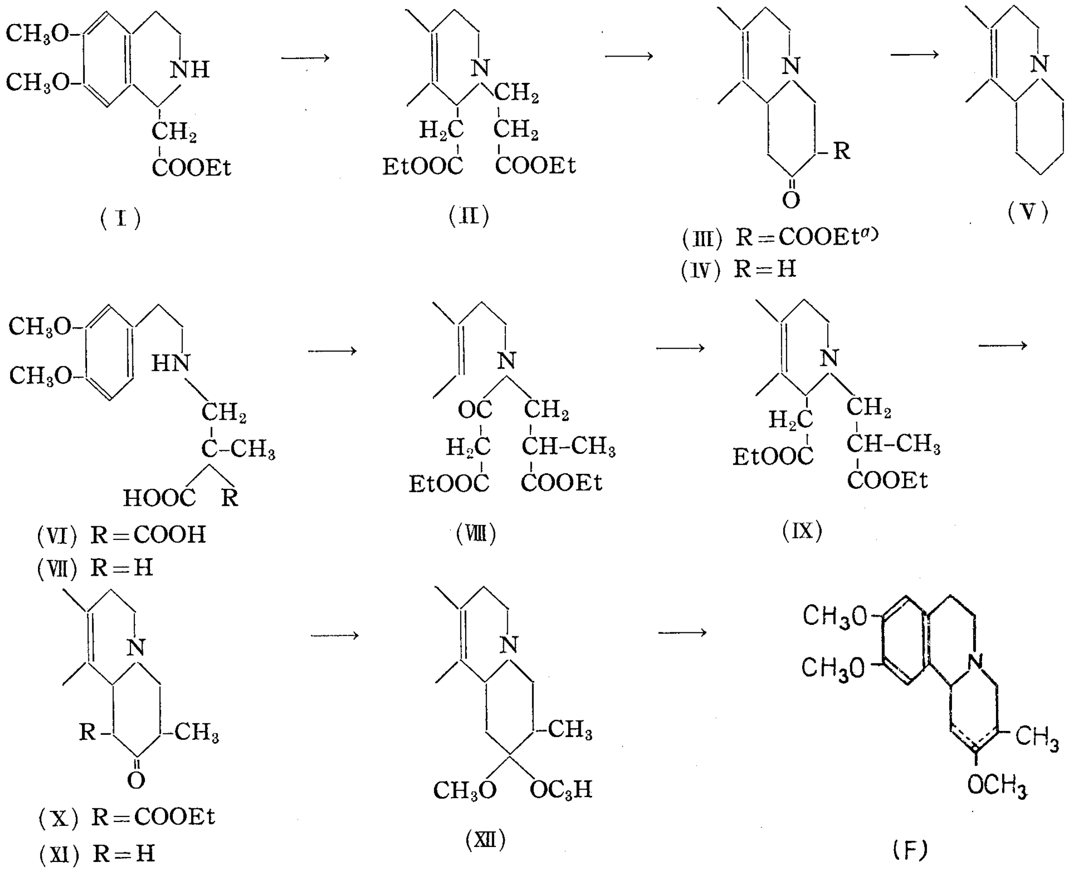
[4] J.M. Osbond : J. Chem. Soc., **1951**, 3464.
[5] A.R. Battersby, H.T. Openshaw, H.C.S. Wood : *Ibid.*, **1953**, 2463.
[6] Y. Ban : This Bulletin, **3**, 53(1955).

as smoothly as before to yield the ketone (XI) as a well-defined crystalline substance, showing infrared absorption maximum of a CO group in the normal region.

The ketone was now mixed with a small amount of anhydrous methanol and an excess of methyl orthoformate, the resultant solution was saturated with dry hydrogen chloride with cooling, and the whole was allowed to stand in a stoppered bottle overnight. From the reaction product some starting ketone was recovered and the dimethylketal (XII) was obtained as a colorless oil, in which the absence of ketonic contamination was proved by its infrared inspection. This compound (XII) was characterized as a crystalline methiodide.

Contrary to expectation (XII) was found to be stable to heat and it could be distilled *in vacuo* without losing a molecule of methanol. It also remained intact when heated with piperidine in a sealed tube, but suffered a loss of methanol molecule when heated with aluminum *tert*-butoxide at about 220° to form (XIII), *rac*-dihydroisorotundine, as a faint yellow viscous oil, which gave positive tetranitromethane and potassium permanganate tests. The results of analyses were also satisfactory.

This compound (F) was then treated with hydrogen activated over Adams' platinum catalyst, but no distinct uptake of hydrogen was observed and the product gave a positive tetranitromethane and potassium permanganate tests. The ketone (XI) was also recovered by dilute hydrochloric acid treatment. Thus the double bond in this compound was shown to be resistant to catalytic reduction.



a) The alternative structure with R (ethoxycarbonyl group) in 1-position is not excluded, but rather improbable due to steric reason.

A synthesis of *rac*-dihydrorotundine is now under way and the result will be published in due course.

The author is grateful to the Ministry of Education for a Grant in Aid for Scientific Research. Thanks are also due to Prof. S. Sugasawa for his interest in this work. He also wishes to express his appreciation to Mr. N. Ito for his skilled and unwearying technical assistance and to Messrs. S. Ushioda, G. Chihara, and K. Tanigawa for infrared spectral data.

Experimental

Ethyl 3-(1-Ethoxycarbonylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolino)propionate (II)—The compound (I : 5.3 g.) was mixed with ethyl acrylate (10 g.). Addition of 5 drops of Triton B caused a rise in temp. of this mixture from 22° to 38°. The whole was now heated on a steam bath for 10 hrs., cooled, and then was diluted with benzene. From the benzene layer the basic substance was extracted with dil. HCl, the acid solution was treated with decolorizing charcoal, filtered, and basified with K_2CO_3. The liberated base was taken up in benzene, washed, dried, and the solvent was evaporated, leaving 5.2 g. of an oily mixture of (I) and (II). The separation of these was effected by passing the benzene solution through an alumina column yielding 3.8 g.(52%) of (II)(Rf. 0.82) and recovering 1.5 g. of (I)(Rf. 0.67)[7]. (II) forms a faint yellow viscous oil and was characterized as its picrate.

Picrate : Yellow needles from EtOH, m.p. 117~118°. *Anal.* Calcd. for $C_{20}H_{29}O_6N \cdot C_6H_3O_7N_3$: C, 51.3; H, 5.3; N, 9.2. Found : C, 50.8; H, 5.2; N, 9.0.

Ethyl 2-Oxo-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine-3-carboxylate(III)—The foregoing ester (3.8 g.) in pure toluene (30 cc.) was mixed with NaH (0.6 g.) and the mixture was gently refluxed for 5 hrs. in N_2 atmosphere. On cooling Na compound of (III) separated out. Ice water was now added to decompose the unreacted NaH, the supernatant toluene layer was extracted with 10% NaOH solution, and the latter was combined with the original aq. layer and filtered through a wet filter. The clear filtrate was then saturated with CO_2, separating a crystalline solid. The separation was aided by addition of solid $NaHCO_3$. After some time the solid separated was collected on a filter. The filtrate was extracted with benzene, washed, dried, and the solvent was evaporated, leaving some solid, which was combined with the one obtained above. Yield, 1.8 g. or 55%. When purified from hexane-benzene (5:1) this formed faint yellow scales of m.p. 113~114°. It is soluble in dil. NaOH solution and gives purple $FeCl_3$-color test. I.R. : ν_{max}^{Nujol} 1684 cm^{-1}(-CO-CH_2-COOEt). *Anal.* Calcd. for $C_{18}H_{23}O_5N$: C, 64.7; H, 6.9; N, 4.2. Found : C, 64.5; H, 6.8; N, 4.2.

2-Oxo-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (IV)—The ketone fission of the foregoing compound was carried out smoothly by heating the foregoing keto ester (1.7 g.) with 10% HCl (10 cc.) at 110° for 2 hrs. The fission product was treated with decolorizing charcoal and the resultant yellow clear filtrate was strongly basified with K_2CO_3. The base liberated was collected in benzene and worked up as usual, yielding 1.28 g. of a crude crystalline substance. This was purified from EtOH, forming colorless pillars of m.p. 151~152°, which was obtained in a yield of 1.1 g, or 85% and gave a negative $FeCl_3$-color test. I.R. : ν_{max}^{Nujol} 1702 cm^{-1}(-CO-). *Anal.* Calcd. for $C_{15}H_{19}O_3N$: C, 68.9; H, 7.3; N, 5.4. Found : C, 68.5; H, 7.1; N, 5.3.

2,4-Dinitrophenylhydrazone sulfate : Orange yellow needles from EtOH, m.p. 177~178°(decomp.). *Anal.* Calcd. for $C_{21}H_{23}O_6N_5 \cdot H_2SO_4 \cdot H_2O$: C, 45.2; H, 4.85; N, 12.6. Found : C, 45.5; H, 5.1; N, 11.9.

2-Methyl-2-(3,4-dimethoxyphenethylaminomethyl)malonic Acid (VI)—Methylmalonic acid (18 g.) was dissolved in hydr. EtOH (EtOH 2 : H_2O 1) to make 150 cc. solution, to which 3,4-dimethoxyphenethylamine (17 g.) was added in portions with cooling and stirring, followed by an addition of formaldehyde solution (9.4 g. of ca. 30%). The resultant clear solution was allowed to stand in an ice-chest for 2 days, forming a thick slurry. This was filtered with suction and the crystalline solid was washed with a little cold water. Yield, 28.5 g. of colorless crystalline substance (m.p. 142°(decomp.)), which was pure enough for the next stage. The pure substance was obtained by dissolving the crude acid in $NaHCO_3$ soln., filtration, and acidifying with dil. AcOH. Colorless scales of m.p. 151°(decomp.). *Anal.* Calcd. for $C_{15}H_{21}O_6N$: C, 57.8; H, 6.8; N, 4.5. Found : C, 58.0; H, 6.5; N, 4.8.

Ethyl Ester of 2-Methyl-N-(3,4-dimethoxyphenethyl)-β-alanine (VII-ester)—The foregoing acid (I : 28 g.) suspended in hydr. AcOH (200 cc. of 60%) was heated in an oil bath to give a clear solution and the solution was refluxed until cessation of CO_2 evolution (ca. 3~4 hrs.). Water and AcOH were now removed *in vacuo* and the residue was dried in an evacuated desiccator over conc. H_2SO_4 overnight, giving 25 g. of a yellow vitreous substance (VII). This was dissolved in dehyd. EtOH (150 cc.) and heated on a steam bath for 4 hrs., during which time dry HCl-gas was introduced. On working up the product as usual there was obtained an oily ester, which distilled at 182~184°/0.4 mm. as a colorless viscous syrup. Yield, 17 g. The overall yield from 3,4-dimethoxyphenethylamine was 62% of the theoretical.

Picrate : Yellow prisms from EtOH, m.p. 148°. *Anal.* Calcd. for $C_{22}H_{28}O_{11}N_4$: C, 50.4; H, 5.4; N, 10.7. Found : C, 50.6; H, 5.0; N, 11.1.

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7) Each fraction of the eluate was treated by paper chromatography using BuOH·AcOH·H_2O (5:1:40). (I) Rf 0.67; (II) Rf 0.82.

Ethyl N-(3,4-Dimethoxyphenethyl)-N-(2-ethoxycarbonylpropyl)malonamate (VIII)—The foregoing compound gave a nearly theoretical yield of (VIII), when treated with ethoxycarbonylacetyl chloride in benzene solution in the presence of 10% Na_2CO_3 solution, with cooling and stirring. The product was a colorless viscous oil, which could not be induced to crystallize and was directly used in the next step.

Ethyl 2-Methyl-3-(1-ethoxycarbonylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolino)propionate (IX)—The above-mentioned ester (21 g.) in pure benzene (100 cc.) was mixed with freshly distilled $POCl_3$(60 g.) and the mixture was gently refluxed for 2 hrs., giving a dark reddish brown turbid solution. On cooling, petr. ether (250 cc.) was added and the whole was left in an ice-chest overnight. The supernatant layer was decanted, the residue was washed with petr. ether, and dissolved in dehyd. EtOH (150 cc.). The resultant solution was treated with decolorizing charcoal (ca. 1 g.) and the fluorescent orange red filtrate, after being acidified with AcOH (20 cc.), was shaken in H_2 atmosphere over Adams' Pt-catalyst (0.2 g.). 1050 cc. of H_2 was taken up smoothly, giving a yellow non-fluorescent solution. On evaporating the solvent *in vacuo* there was obtained a reddish syrup, which was dissolved in dehyd. EtOH (100 cc.) and refluxed on a steam bath for 2 hrs., introducing dry HCl-gas all the time. On working up the reaction product as usual there remained 12 g. of reddish syrup, which was dissolved in benzene and purified by filtering through an alumina column. 11.3 g.(65%) of yellowish crystalline substance was thus obtained, which formed faint yellow needles of m.p. 83~84°, when purified from hexane. *Anal.* Calcd. for $C_{21}H_{31}O_6N$: C, 64.1; H, 7.9; N, 3.6. Found : C, 64.3; H, 8.0; N, 3.7.

Ethyl 2-Oxo-3-methyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine-1-carboxylate (X)—The afore-mentioned ester (11 g.) in pure toluene (100 cc.) was mixed with NaH (2 g.) and the whole was refluxed in N_2 atmosphere. The condensation proceeded slowly, separating the Na compound of (X) on the wall of the flask. After 7 hrs.' heating the reaction product was worked up as before, yielding a yellow crystalline substance. Yield, 5.9 g. or 67%. When purified from hexane, this formed colorless scales of m.p. 98°, which gave a positive $FeCl_3$-color test in EtOH (purple) and was soluble in dil. NaOH solution. I.R. : $\nu_{\max}^{\text{Nujol}}$ 1696 cm^{-1}, 1729 cm^{-1}(-CO-CH_2-COOEt). *Anal.* Calcd. for $C_{19}H_{25}O_5N$: C, 65.7; H, 7.2; N, 4.0. Found : C, 65.3; H, 6.6; N, 4.2.

2-Oxo-3-methyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (XI)—The foregoing keto ester (5.5 g.) was refluxed with 10% HCl solution (30 cc.) with evolution of CO_2, which ceased after ca. 2 hrs. On working up the product as mentioned above there was obtained a crystalline substance which amounted to 4 g.(90%), coming in colorless needles (from hexane-MeOH), m.p. 139°. $FeCl_3$-color test was negative. I.R. : $\nu_{\max}^{\text{Nujol}}$ 1712 cm^{-1} (-CO-). *Anal.* Calcd. for $C_{16}H_{21}O_3N$: C, 69.8; H, 7.6; N, 5.1. Found : C, 69.6; H, 7.3; N, 5.25.

2,2,9,10-Tetramethoxy-3-methyl-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (XII)—The ketone (XI, 2 g.) in pure MeOH (10 cc.) was mixed with methyl orthoformate (4 g.) and to this mixture dry HCl-gas was introduced with cooling until saturation. The whole was now allowed to stand overnight in a stoppered bottle and then was warmed at 50~60° for 1 hr. The solvent was now removed, the residue was strongly basified with cold conc. K_2CO_3 solution. This was extracted thoroughly with ether, washed, dried, and the solvent was evaporated, leaving 2.2 g. of a syrupy substance. When hexane was added to the latter there separated the recovered ketone as a solid, which was filtered off, the filtrate was chromatographed through an alumina column (10 g.), and the column was eluted with hexane. The eluate left 1.2 g. of colorless syrup, whose methiodide formed well-defined yellow prisms of m.p. 179~180°(decomp.) when purified from benzene-MeOH, in which the absence of ketonic contamination was evidenced by I.R. inspection. The free ketal (XII) distilled at 190~195°(bath temp.) under 0.08 mm. From 0.1 g. of (XII) the original ketone (0.07 g. of m.p. 138~139°) was recovered on being treated with 5% HCl, and the presence of MeOH in the acid layer was proved by oxidizing to HCHO, which gave a distinct coloration with chromotropic acid. *Anal.* Calcd. for $C_{14}H_{15}N(OCH_3)_4$: CH_3O, 38.7. Found : CH_3O, 37.1.[8]

Methiodide : *Anal.* Calcd. for $C_{18}H_{30}O_4NI \cdot H_2O$: C, 47.4; H, 6.65; N, 2.9. Found : C, 47.5; H, 6.05; N, 3.1.

Picrate : Yellow prisms from EtOH, m.p. 160~161°(decomp.). *Anal.* Calcd. for $C_{24}H_{30}O_{11}N_4$: C, 52.4; H, 5.5; N, 10.2; CH_3O, 22.5. Found : C, 52.2; H, 5.2; N, 10.0; CH_3O, 22.2.

2,9,10-Trimethoxy-3-methyl-1,4,6,7(or 3,4,6,7)-tetrahydro-11b*H*-benzo[*a*]quinolizine (F)—A mixture of the foregoing compound (0.3 g.) and Al-*tert*-butoxide (0.1 g.) was heated in an oil bath (220°) for 20 mins., giving a reddish product. This was distilled at 210°(bath temp.) *in vacuo* (0.01 mm.), furnishing a faint yellow syrup, which gave a positive $C(NO_2)_4$ color test (orange red) and decolorized

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[8] The sample was sealed in a glass tube with 60% HI, heated in an oil bath at 130° for 1 hr., and then worked up as usual. cf. M. Furter : Helv. Chim. Acta, **21**, 1151(1938). The usual Zeisel method gave too low CH_3O value.

$KMnO_4$-soln. immediately. I.R.: $\nu_{\max}^{\text{Nujol}}$ 1642 cm^{-1}(–C=C–). *Anal.* Calcd. for $C_{14}H_{14}N(OCH_3)_3$: CH_3O, 32.1. Found: CH_3O, 32.2.

Methiodide: Faint yellow grains from MeOH–ether, m.p. 220~221°(decomp.). *Anal.* Calcd. for $C_{18}N_{26}O_3NI \cdot \frac{1}{2}H_2O$: C, 47.2; H, 6.55; N, 3.05. Found: C, 47.2; H, 6.25; N, 3.45.

Summary

A synthesis of *rac*-dihydroisorotundine (F) was described. Thus β-3,4-dimethoxyphenethylamine, formaldehyde, and methylmalonic acid were condensed to yield 2-methyl-2-(3,4-dimethoxyphenethylaminomethyl)malonic acid (VI) in an excellent yield, which suffered a smooth decarboxylation when boiled with hydrous acetic acid. The resultant monocarboxylic acid (VII) was esterified and then condensed with ethoxycarbonylacetyl chloride, furnishing a good yield of the amide (VIII), which was cyclized and reduced to form the isoquinoline derivative (IX). The latter underwent a smooth Dieckmann condensation, giving the β-keto ester (X) which, in conformity with its structure, was soluble in dilute sodium hydroxide solution and gave a positive ferric chloride color test. When boiled with 10% hydrochloric acid this underwent ketone fission and the resultant ketone (XI) was isolated in a fair yield, of which the corresponding dimethylketal (XII) was prepared by treating with methyl orthoformate in the presence of dry hydrogen chloride. The latter was found rather stable to heat and could be distilled without decomposition, but suffered a loss of a molecule of methanol when heated with aluminum *tert*-butoxide at 220°, thus furnishing *rac*-dihydroisorotundine (F) as a faint yellow syrup, which was characterized through its crystalline methiodide.

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