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103. Tetsuji Kametani,[*3] Keiichiro Fukumoto,[*3] and Toyoyuki Katagi : Studies on the Syntheses of Heterocyclic Compounds. LII.[*1] The Eschweiler-Clarke and Pictet-Spengler Reactions with β-Methoxysafrylamine.[*2]

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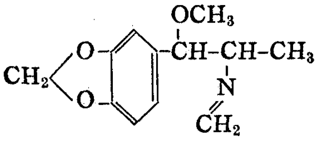
With regard to competition between the Eschweiler-Clarke and Pictet-Spengler reactions, Baltzly1) reported a few years ago that the attempt to produce dimethylhomoveratrylamine from homoveratrylamine[*4] or N-methylhomoveratrylamine by the Eschweiler-Clarke reaction2) gave mainly 2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. Recently it became necessary to compare N-methylated safrylamine[*5] with various isoquinoline derivatives synthesized later by the Pictet-Spengler reaction and examination was made for reaction between 1-methyl-2-methoxy-2-(3,4-methylenedioxyphenyl)ethylamine, namely, β-methoxysafrylamine (I), and formaldehyde by the Eschweiler-Clarke or Picter-Spengler reaction. In this case isoquinoline derivatives were not obtained by the Eschweiler-Clarke reaction as Baltzly1) had reported, and only N,N-dimethyl-β-methoxysafrylamine (II) was obtained and, in addition, 4-methoxyisoquinoline derivative was obtained by the Pictet-Spengler reaction, which was not obtained by the Bischler-Napieralski reaction. Accordingly, some results on both reactions with safrylamine (I) are herein described.

At first, a calculated amount of formaldehyde and formic acid was used in the Eschweiler-Clarke reaction in order to synthesize N-methyl-β-methoxysafrylamine (I), but a monomethylated compound was not obtained, although it was not expected, and only the expected N,N-dimethyl-β-methoxysafrylamine (II) was formed, it being recognized as a chloroplatinate complex. In this case, although there is an activating group in the parent phenethylamine *para* to the point of prospective ring closure, the expected isoquinoline3),4) was not obtained. Therefore, attempt was made to synthesize the isoquinoline derivatives (III) by the Pictet-Spengler reaction in order to determine the structure of the above-mentioned substance (II). In this case four kinds of different isoquinoline derivatives were formed via a Schiff base (Ia) as an intermediate compound in the Pictet-Spengler reaction, and this was thought to depend mainly upon the time and temperature,



(Ia)

and some other factors of this reaction. When the product (Ia) was heated for an additional several hours with 20% hydrochloric acid and evaporated on a water bath at atmospheric pressure, a small amount (28.8%) of 3-methyl-4-methoxy-6,7-methylenedioxy-

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[*1] Part LI. T. Kametani, K. Fukumoto : Yakugaku Kenkyu, **30**, 412(1958).

[*2] This study was reported at the Monthly Meeting of the Kinki Local Region held on December 20, 1958.

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[*4] homoveratryl= 3,4-dimethoxyphenethyl.

[*5] safryl= 1-methyl-2-methoxy-2-(3,4-methylenedioxyphenyl)ethyl.

1) R. Baltzly : J. Am. Chem. Soc., **75**, 6038(1953).

2) H.T. Clarke, H.B. Gillespie, S.Z. Weisshaus : *Ibid.*, 55, 4571(1933).

3) R. Baltzly, J.S. Buck : *Ibid.*, **62**, 161(1940).

4) J.C. Castrillon : *Ibid.*, **74**, 558(1952).

1,2,3,4-tetrahydroisoquinoline (III) and a considerable amount (64.7%) of 3-methyl-6,7-methylenedioxy-1,2-dihydroisoquinoline (IV) were obtained. Although the former product is easily soluble in ether, the latter does not dissolve in ether, but in benzene, and, therefore, the two compounds can be nearly separated. If the reaction mixture extracted with ether is distilled *in vacuo* for the sake of purification, only 4-demethoxy derivative (IV) is obtained owing to the demethanolation of (III) at a high temperature.

In the second place, when safrylamine and formaldehyde are heated continuously on a water bath for 7 hours and its reaction mixture is not treated with 20% hydrochloric acid, only 2,3-dimethyl-4-methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (VI) is formed quantitatively. In this case, even if the reaction mixture is not heated with hydrochloric acid, (V) is obtained and this is quite different from the case of heating for 30 minutes. As regards the purity of formaldehyde solution, the amount of formic acid contained in 37% formaldehyde solution was thought to be important and this was determined quantitatively. The result revealed that 3.22 mg. of formic acid is contained in 10 cc. of 37% formaldehyde solution. This amount is so little compared with the one of formaldehyde that it was thought to be negligible.

When the reaction mixture is heated with 20% hydrochloric acid after heating for 7 hours and extracted with an organic solvent, 4-demethoxy derivative (VII), i.e., 2,3-dimethyl-6,7-methylenedioxy-1,2-dihydroisoquinoline, is obtained in a yield of 51.4%. If it is distilled *in vacuo*, a colorless oil boiling at 165°/13 mm. Hg is obtained and its picrate agrees with that of (VII).

The Liebermann reaction of secondary amine is positive in (III) and (IV), but negative in (VI) and (VII). The melting point of the picrate of (VII) is quite similar to that of the picrate of (III), but the two were found to be different by mixed melting point test. (IV) and (VII) were very easily obtained by respectively heating (III) or (IV) with phosphoryl chloride in the presence of toluene. Demethanolation proceeds smoothly especially in the latter case of (VI). Synthesis of 4-methoxy derivative (VI) used as the starting material is so simple and quantitative in its yield that this procedure is thought to be the most convenient way to obtain 2,3-dimethyl-1,2-dihydroisoquinoline derivative (VII). There is, in addition, no need of treating with 20% hydrochloric acid in this reaction.

In order to dehydrogenate (IV) and (VII), palladium black or potassium permanganate was used. In the former case they were heated at 180∼200° and in the latter they were oxidized by one atom of oxygen per one mole of the starting material in sulfuric acid. The picrate of dehydrogenated substance obtained by the two methods was found to be identical, but the yield in the latter case was less than that from the former. In this case the properties of N-methylisoquinolinium compounds, which will be described later in experimental data, seemed to be rather surprising, but, according to studies[5] a quaternary isoquinolinium salt is thought to become a dehydrated substance of carbinol base, which was proved by chemical procedures, for instance, alkaline treatment such as 10% sodium hydroxide or by infrared spectrum. Therefore, when the free base of (IX) is obtained by its treatment with alkali, an intermediate carbinol base (XI) is thought to be formed and it can be extracted by ether or ethyl acetate.[*6] In order to determine the structure and relation of these compounds prepared from (I) by two different ways,

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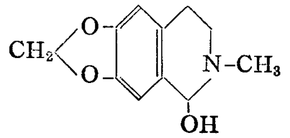
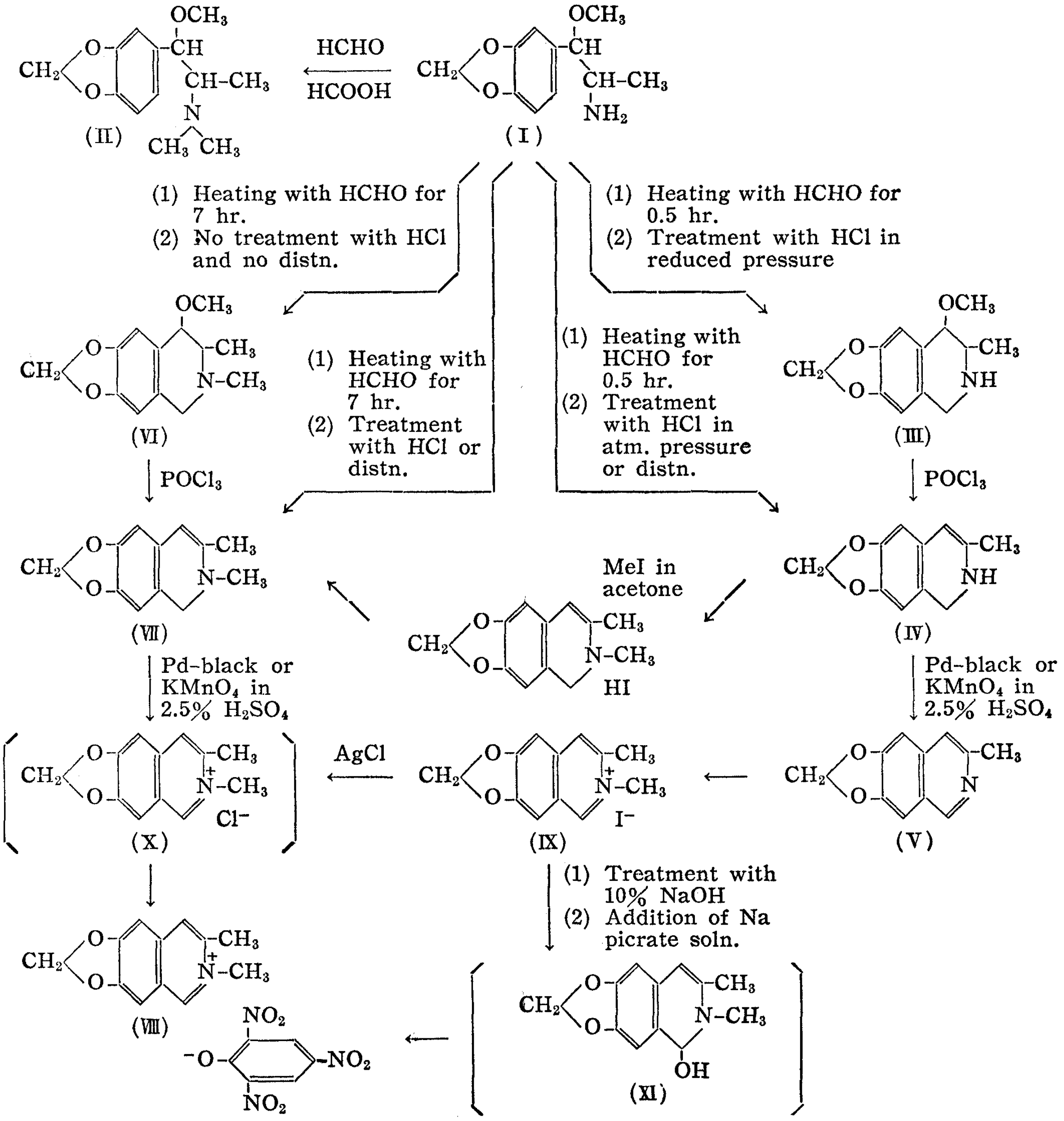
[5] T. Kametani, T. Katagi, Y. Nomura: Yakugaku Kenkyu, **30**, 188(1958).

[6] M. Freund, W. Will: Ber., **19**, 2797(1886).

[*6] According to M. Freund and W. Will,[6] the carbinol base such as the following compound easily dissolves in alcohol, ether, and chloroform.



attempt was made to introduce a methyl group into (IV) or (V) at the position of nitrogen. The picrate of (VII), which was prepared via the hydriodide from (IV) with methyl iodide and followed by alkali treatment, was found to be identical with the one prepared by way of (VI). The methiodide (IX) prepared from (V) was derivable to O-picrate (VIII) by way of chloride (X) or via chloride and the free base.



With regards the properties of 1,2-dihydroisoquinoline (IV) and (VII), they are thought to be very unstable. In fact, although the compound (IV) is comparatively stable, the substance (VII) is fairly unstable. Therefore, if it was allowed to stand overnight, it turned deep reddish, but it could be determined as a stable salt such as its picrate by treating it with picric acid solution after evaporation of extracted solvents. Further details on the properties of 1,2-dihydroisoquinoline derivatives will be described in the following paper.

Experimental[*7]

N,N,1-Trimethyl-2-methoxy-2-(3,4-methylenedioxyphenyl)ethylamine (II)—i) Attempted Monomethylation : A mixture of 5 g. of 1-methyl-2-methoxy-2-(3,4-methylenedioxyphenyl)ethylamine, 2 g. of 37% HCHO, and 1.3 g. of 85% HCOOH was heated on a steam bath for 10 hr. The reaction mixture was cooled, acidified with 10% HCl, and extracted with Et_2O. The acid solution was made alkaline with 10% NaOH and extracted with Et_2O. The ethereal extract was dried, evaporated, and distilled *in vacuo*, affording 4.1 g. of a colorless oil, b.p$_{14}$ 156°. This oil does not form a picrate and its HCl salt is very hygroscopic. The chloroplatinate showed m.p. 202°(decomp.) after recrystallization from EtOH. According to the following result of elementary analysis this compound was recognized as N,N-dimethyl derivative (II). *Anal.* Calcd. for $C_{13}H_{19}O_3N\cdot\frac{1}{2}(H_2PtCl_6)$: C, 35.30; H, 4.56. Found : C, 35.48; H, 4.46.

ii) Dimethylation : According to a similar procedure as i), 5 g. of the amine (I), 4 g. of 37% HCHO, and 10 g. of 85% HCOOH were used and worked up as described above, and 4.6 g. of colorless oil, b.p$_{19}$ 163~165°, was obtained. Its chloroplatinate agreed with the above sample by a mixed melting point test.

Reaction between β-Methoxysafrylamine (I) and Formaldehyde, heating for 30 min.—i) Treatment with HCl and Evaporation *in vacuo* after the Reaction : A mixture of 6 g. of β-methoxysafrylamine and 6 g. of 37% HCHO, which turned turbid on mixing, was heated for 30 min. on a water bath, and separated into 2 layers on cooling. The oily layer changed into a white gummy substance, which was extracted with benzene and 7 g. of viscous, yellowish residue was obtained on evaporating the benzene extract. This residue was mixed with 8 g. of 20% HCl, the mixture was heated on a water bath for 30 min., and evaporated to dryness *in vacuo*. This residue was dissolved in 10% HCl solution and this acid solution was made alkaline with 50% KOH, an oily substance being separated. This could not be extracted with Et_2O, but easily with benzene on warming. Thus 4 g. of reddish brown vitreous substance was obtained in 65.7% yield. After recrystallization from EtOH, yellowish prisms of m.p. 187~188° were obtained as a picrate. The free base dose not crystallize and its Liebermann reaction of secondary amine is positive (green-blue). *Anal.* Calcd. for $C_{12}H_{15}O_3N\cdot C_6H_3O_7N_3$: C, 48.00; H, 4.00; N, 12.44. Found : C, 48.19; H, 4.32; N, 12.72.

ii) Treatment with HCl for 2 hr. and Evaporation at Atmospheric Pressure : In a similar manner as above, a mixture of 5 g. of the amine (I) and 5 g. of 37% HCHO was heated on a water bath for 30 min. and extracted with benzene. 5.8 g. of yellow oil obtained by evaporation of benzene extract was mixed with 9 g. of 20% HCl and the mixture was evaporated to dryness on a water bath at atmospheric pressure. In this case more than 2 hr. was required for dryness. The residue was treated with alkali, extracted with Et_2O, dried, evaporated, and 1.3 g. of a yellowish, waxy solid was collected (28.8%). Its picrate was purified from EtOH as needles, m.p. 241~242°(decomp.). The Liebermann reaction of this free base is positive (deep blue). *Anal.* Calcd. for $C_{11}H_{11}O_2N\cdot C_6H_3O_7N_3$: C, 48.81; H, 3.37; N, 13.39. Found : C, 48.82; H, 2.93; N, 13.56.

A great deal of a reddish-brown oily substance, which was not soluble in Et_2O, was extracted with benzene. The extract was washed, dried, evaporated, and 3.3 g. (64.7%) of reddish viscous oil was obtained. Its picrate showed m.p. 187~188° after recrystallization from EtOH and agreed with the above-mentioned compound (III).

In this reaction 3.7 g. of resinous substance (Ia) was treated with 20% HCl, evaporated to dryness on a water bath during about 2.5 hr., and the residue was treated as usual. When the residue is distilled *in vacuo* for the sake of purification, 0.8 g. of colorless oil, b.p$_5$ 98~100°, is obtained, solidifying after a few days. Its picrate showed m.p. 241~242°(decomp.) after recrystallization from EtOH. Its free base was heated with $POCl_3$ in order to elucidate its structure and the picrate of this product treated as usual was found to be identical with that of the starting material. Therefore, the substance obtained by distillation is recognized to be a 4-demethoxyisoqninoline derivative (IV).

3-Methyl-6,7-methylenedioxyisoquinoline (V) (Dehydrogenation of IV)—i) Dehydrogenation with Pd-black : A mixture of 0.5 g (IV) with 50 mg. of Pd-black was heated at 195~200° for 1 hr. and 0.26 g. of a white solid was obtained by treating the reaction mixture as usual. Its picrate was obtained as plates or small needles of m.p. 243°(decomp.) after recrystallization. *Anal.* Calcd. for $C_{11}H_9O_2N\cdot C_6H_3O_7N_3$: C, 49.04; H, 2.91; N, 13.46. Found : C, 48.78; H, 2.78; N, 13.50.

ii) Oxidation with Potassium Permanganate : In 30 cc. of 2.5% H_2SO_4 solution, 0.5 g. of (IV) was dissolved and a saturated solution of 0.18 g. of $KMnO_4$ was added dropwise to the above-mentioned solution with constant shaking, the reddish purple color of $KMnO_4$ disappearing immediately. The brown MnO_2 that formed disappeared on warming at 50° in a water bath for 5 min. The mixture was neutralized with NH_4OH and extracted several times with AcOEt. The extract was dried, evaporated, and 0.2 g. (40.8%) of yellowish brown oil was obtained. It does not dissolve in 5% $NaHCO_3$

[*7] All m.p.s are not corrected.

and its Liebermann reaction is negative. Its picrate melted at 273°(decomp.) after recrystallization from EtOH-Me_2CO-Et_2O and was found to be identical with the one obtained by dehydrogenation of (IV) by a mixed melting point test.

Demethanolation of (III) with $POCl_3$—To a suspended solution of 0.45 g. of (III) in 13 cc. of dehyd. toluene, 4 g. of $POCl_3$ was added, and the mixture immediately turned into a white emulsion. This mixture was refluxed in an oil bath for 2 hr., the mixture turning clear and yellow 5 min. later. When the reaction was completed, a brown, oily precipitate formed in the bottom of the flask. A suitable amount of petr. ether was added to the cooled reaction mixture, the mixture was allowed to stand overnight, and the clear, upper solution was decanted. Afterwards, the residue was extracted with 20 cc. of 10% HCl, the acid solution was made alkaline, and was extracted with Et_2O. The extract was dried and evaporated, leaving 0.33 g. (89.7%) of a white substance. Its picrate was obtained as needles, m.p. 241~242°(decomp.), after recrystallization from EtOH, and was found to be identical with the picrate of (IV).

Reaction between β-Methoxysafrylamine (I) and Formaldehyde in Heating for 7 hr.—i) 2,3-Dimethyl-4-methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (VI) without Treatment with HCl: A mixture of 4.5 g. of the amine (I) and 4.5 g. of 37% HCHO was heated for 7 hr. on a water bath, two layers being separated and turning a yellow color. The cooled oily layer did not solidify, and it seemed the reaction mixture was not the same as in heating for 30 min. The oily layer was extracted with benzene, the extract was washed, dried, and evaporated, leaving 4.7 g. of yellowish brown, viscous substance. Its yield was quantitative. Its picrate was purified from EtOH, giving cubic crystals of m.p. 173~174°. The Liebermann reaction of this free base is negative. *Anal.* Calcd. for $C_{13}H_{17}O_3N \cdot C_6H_3O_7N_3$: C, 49.17; H, 4.34; N, 12.07. Found: C, 49.17; H, 4.78; N, 12.27.

ii) 2,3-Dimethyl-6,7-methylenedioxy-1,2-dihydroisoquinoline (VII) with Treatment with 20% HCl: In a similar manner as above, 10 g. of the amine (I) and 10 g. of 37% HCHO were heated for 7 hr. and 10.8 g. of yellowish brown substance was obtained. This substance was treated with 18 g. of 20% HCl and evaporated to dryness on a water bath during about 2.5 hr. The residue was dissolved in water and the acid solution was made alkaline with 50% NaOH after filtration. The precipitate was extracted repeatedly with benzene and ether. This extract was washed with water, dried, and evaporated, leaving 5.5 g. (51.4%) of a viscous oil. Recrystallization of the picrate from EtOH-Et_2O or Me_2CO-Et_2O gave yellow cubic crystals, m.p. 187°, which was similar to that of (III), but it was found to be different by mixed melting point test. Its admixture with the picrate of 4-methoxy derivative (VI) (m.p. 173~174°) melted over a range of 161~163°. Therefore, it was recognized to be different from the product (VI).

When 5 g. of the viscous substance (VI) obtained above was treated with 20% HCl in a like manner and then distilled *in vacuo*, 2 g. of an yellowish oil of b.p$_{13}$ 165° was obtained. *Anal.* Cacld. for $C_{12}H_{13}O_2N \cdot H_2O$: C, 65.14; H, 6.83. Found: C, 65.31; H, 7.36.

The picrate of this distilled oil melted at 184~186° after recrystallization from EtOH, this being recognized to be identical with the above-mentioned picrate of (VII). This picrate was dried at 60°, 10 mm. Hg for 3 days, but water of crystallization was not removed. According to the result of infrared spectrum, a band of hydroxyl group based on water of crystallization was recognized at 2.98 μ, as the band of water of crystallization of kainic acid is recogized at 3.0 μ. *Anal.* Calcd. for $C_{12}H_{13}O_2N \cdot C_6H_3O_7N_3 \cdot H_2O$: C, 48.00; H, 4.00; N, 12.44. Found: C, 48.18; H, 4.57; N, 12.34.

In case of distillation *in vacuo*, methanol is thought to be removed because of high temperature. In order to make certain, this substance was treated with $POCl_3$ but the original material was recovered.

Demethanolation of (VI) with $POCl_3$—A mixture of 0.5 g of 4-methoxy derivative (VI) and 4.5 g. of $POCl_3$, in the presence of 20 cc. of dehyd. toluene, was gently refluxed in an oil bath for 2.5 hr. The reaction mixture gradually turned brownish-black as the reaction proceeded and a black oil was separated after it was allowed to stand and cooled. This was slowly poured into a mixture of 10% HCl and ice, while cooling with ice and water. The acid layer was separated from toluene, made alkaline with 10% NaOH, and extracted with Et_2O. The extract was dried and evaporated, leaving 0.4 g. (94.1%) of a brownish, resinous substance. The Liebermann reaction of this base is negative. A cubic picrate of m.p. 185~187°(decomp.) was obtained after recrystallization from EtOH and it agreed to the one described above by mixed melting point test.

Methylation of (IV) with Methyl Iodide—A mixture of 1 g. of (IV), 0.9 g. of MeI, and 10 cc. of Me_2CO was gently refluxed on a water bath for 1.2 hr., and the mixture turned yellowish white and turbid gradually. After it was allowed to stand for several hours, 1 g. of white crystals of m.p. 268° (decomp.) was collected by filtration. By evaporation of its mother liquor, a black, viscous substance was obtained. Yield, 0.5 g.

The hydriodide of methylated product recrystallized from EtOH as white crystalline pillars of m.p. 288°(decomp.). *Anal.* Calcd. for $C_{12}H_{13}O_2N \cdot HI$: C, 43.50; H, 4.23; N, 4.23. Found: C, 43.39: H, 3.76; N, 4.25.

0.5 g. of this hydriodide was dissolved in water, neutralized with 10% NaOH, and this was extracted with benzene. The extract was dried and evaporated. The picrate of this brownish residue melted at 187°(decomp.) and agreed with an authentic sample (VII).

2,3-Dimethyl-6,7-methylenedioxyisoquinolinium Picrate (VIII)—i) Preparation by Way of Methiodide (IX) of (V): A mixture of 1.2 g. of (V), 1.1 g. of MeI, and 30 cc. of Me_2CO was gently refluxed for 2 hr. After allowing to stand, yellowish brown crystals were collected and washed with Me_2CO, giving 0.7 g. of needles (crude) of m.p. 282~284°(decomp.). Admixture of this substance (IX) with the hydriodide prepared from (IV) by methylation, melted over a range of 233~235°. This fact reveals that they are distinctly different.

To 0.2 g. of the methiodide (IX) suspended in 15 cc. of EtOH, 0.5 g. of AgCl was added and the mixture was refluxed on a water bath for 1.5 hr. The precipitate was filtered off and reddish brown filtrate was concentrated under a reduced pressure. This residue was dissolved in dil. EtOH and yellowish scaly crystals separated on adding sodium picrate solution to it. This picrate (VIII) came as yellow needles, m.p. 247~248°(decomp.) (sint. at 221~222°), after recrystallization from EtOH containing a small amount of Me_2CO. *Anal.* Calcd. for $(C_{12}H_{12}O_2N)^+(C_6H_2O_7N_3)^-$: C, 50.24; H, 3.28; N, 13.02. Found: C, 50.00, 50.07; H, 3.13, 3.27; N, 13.03.

From the methiodide, a brownish oil was obtained by basification with alkali and extraction with AcOEt. Its picrate agreed with an authentic sample.

ii) Dehydrogenation of (VII) over Pd-Black: A mixture of 0.8 g. of (VII) with 80 mg. of Pd-black was heated at 195~200° in an oil bath for 1 hr. and treated as usual. Yield, 0.4 g. The picrate of its product came as featherly yellow needles when recrystallized from EtOH, but yellowish prisms were obtained from EtOH and Et_2O. It sintered at 242° and melted at 248°.

iii) Oxidation of (VII) with $KMnO_4$: A solution of 0.5 g. of (VII) dissolved in 30 cc. of 2.5% H_2SO_4 solution was oxidized with a saturated solution of 0.18 g. of $KMnO_4$. In this case, there was a slight generation of heat. The mixture was made alkaline, extracted with AcOEt, dried, and evaporated, leaving 0.1 g. (18.6%) of deep brown, viscous oil. This substance does not dissolve in 5% Na_2CO_3 solution. Its picrate was obtained as needles by recrystallization from EtOH-Me_2CO-Et_2O and it was found to be identical with the one obtained by treatment with Pd-black.

Summary

The Eschweiler-Clarke and Pictet-Spengler reactions of β-methoxysafrylamine were examined. In the former reaction N,N-dimethyl-β-methoxysafrylamine was obtained in place of expected isoquinoline, but in the latter reaction four kinds of isoquinoline derivatives were formed according to reaction conditions of time and temperature. When heated for 30 minutes with formaldehyde solution, 3-methyl-1,2-dihydro- (IV) and 3-methyl-4-methoxy-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (III) were obtained, while 2,3-dimethyl-1,2-dihydro- (VII) and 2,3-dimethyl-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (VI) were obtained when heated for 7 hours. Especially in the latter case, it is interesting that 4-methoxy derivative is obtained only by heating with formaldehyde solution although it could not be synthesized by the Bischler-Napieralski reaction and that, in addition, the substance (VII) was obtained very easily by way of (VI).

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