51. Tetsuji Kametani, Kazuo Ohtsuki, and Miyoshi Fukui: Studies on the Syntheses of Isoquinoline Derivatives and their Analogs. XXXVII. A New Method for the Preparation of 1-Substituted 3-Methyl-3,4-dihydroisoquinoline Derivatives by the Reaction of Allylbenzene and Heterocyclic Acid Amide or Oxime.

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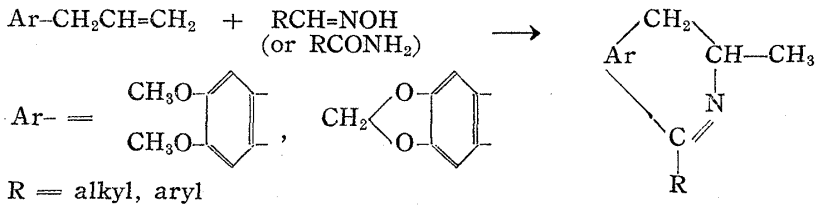
As described in earlier reports,[1~5] 1-substituted 3-methyl-3,4-dihydroisoquinoline derivatives are formed on reacting safrole or methyleugenol with acid amide or aldoxime in a suitable solvent in the presence of phosporyl chloride. It was found that 1-substituted 3-methyl-6,7-methylenedioxy(or dimethoxy)-3,4-dihydroisoquinoline is obtained by heating a mixture of 1 mole each of safrole or methyleugenol and acid amide in benzene or toluene with an excess of phosphoryl chloride.[1,2] The same results were obtained in the case of aldoxime in place of acid amide. A mixture of 1 mole each of allylbenzene and aldoxime was allowed to react first in an ice bath, then for some time at room temperature, and finally boiled gently in a water or an oil bath. The reaction mixture was then decomposed with ice water, impurities such as safrole or methyleugenol removed, and the basic substance collected. Thus, 3,4-dihydroisoquinolines were obtained in ca. 30% yield in a single process.[3]



In our previous experiments only aliphatic and aromatic acid amides and oximes were used. It appeared for us not without interest to apply this new method to heterocyclic aldoximes or acid amides in synthesizing various isoquinoline derivatives having a heterocyclic substituent in 1-position for pharmacological evaluation since it is known that 1-(2′-thienyl)-3-methyl-6,7-methylenedioxy-3,4-dihydroisoquinoline shows approximately 1/5 the analgesic action of 3-dimethylamino-1,1-di(2′-thienyl)butene-1.[6]

1-(2′-Thienyl)-3-methyl-6,7-dimethoxy(or methylenedioxy)-3,4-dihydroisoquinoline (I or II) was obtained by reacting safrole or methyleugenol with thiophene-2-carboxylic amide by the agency of phosphoryl chloride in a suitable solvent in the usual manner, their yield being 35.5% or 16.3%, respectively. The latter was proved to be identical with an authentic sample, prepared by the Bischler-Napieralski reaction by the mixed melting point test. The former (I) was obtained as white crystals, m.p. 113~113.5°.

By reacting methyleugenol on furan-2-carboxylic amide or 2-furfuraldoxime, the objective 1-(2′-furyl)-3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (III), m.p. 128~130°, was obtained in 16% and 20% yield, respectively. From safrole, oily 1-(2′-furyl)-3-methyl-6,7-methylenedioxy-3,4-dihydroisoquinoline (IV) was obtained in 14.5% or 11.5% yield, respectively, as the amide or oxime was used. This compound was charac-

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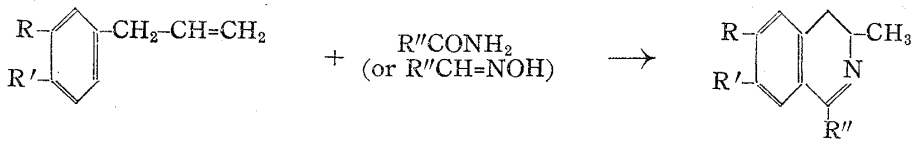
1) Kametani: J. Pharm. Soc. Japan, **72**, 1090(1952).
2) Kametani: *Ibid.*, **72**, 1537(1952).
3) Kametani, Ninomia: *Ibid.*, **72**, 1539(1952).
4) Kametani: *Ibid.*, **73**, 12(1953).
5) Kametani, Ohtsuki: *Ibid.*, **73**, 685(1953).
6) Kametani, Inagaki: *Idid.*, **74**, 417(1954).

terized as a picrate of m.p. 184~184.5°. The use of oxime generally gave better yield than the amide.

In previous paper, we reported that the reaction between nicotinamide and methyleugenol by $POCl_3$ did not give the isoquinoline derivative, but 3-cyanopyridine instead. We now found that isonicotinamide behaved in a similar manner, giving 4-cyanopyridine. Ritter and Murphy procedure[7] was, however, found successful and thus the objective (V) was obtained by reacting the above-obtained 4-cyanopyridine with methyleugenol, using conc. sulfuric acid as a condensation agent.

Contrary to the foregoing, Kametani's method was successfully applied to methyleugenol and 4-methylthiazole-5-carboxylic amide,[8] giving 1-[5'-(4'-methyl)thiazolyl]-3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (VI).

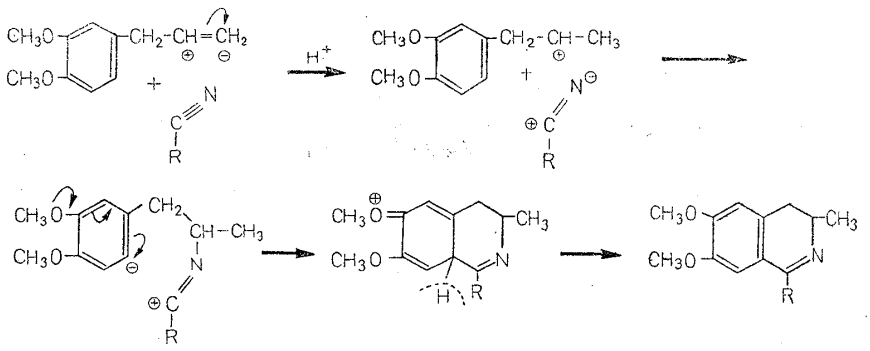


(I) R=R'=-OCH_3, R''=2-thienyl-
(II) R=R'=-OCH_2O-, R''=2-thienyl-
(III) R=R'=-OCH_3, R''=2-furyl-
(IV) R=R'=-OCH_2O-, R''=2-furyl-
(V) R=R'=-OCH_3, R''=4-pyridyl-
(VI) R=R'=-OCH_3, R''=5-(4-methyl)-thiazolyl-

As was shown in the foregoing results, 3-methyl-3,4-dihydroisoquinoline having heterocyclic substituent in 1-position could be prepared from heterocyclic acid amide or oxime and allylbenzene derivative according to Kametani's method, with the exception of pyridyl derivative. Ritter-Murphy method worked successfully, however, though the reaction condition did not allow the use of safrole as one of the starting materials. Though our method is attended with poor yield (30% at best), it is so simple in manipulation, that it will offer a promising tool for the synthesis of 3-methyl-3,4-dihydroisoquinoline derivatives, in case this drawback can be surmounted.

The mechanism of this reaction has not yet been revealed, but it is thought that an amide or oxime is dehydrated by $POCl_3$ and the 1/3 proton formed by the reaction between 1 mole of water formed and $POCl_3$ reacts with charged allylbenzene and then the nitrile in nascent state reacts with the positively charged allylbenzene, forming isoquinoline derivatives. Accordingly it is supposed that the yield of this reaction cannot exceed 30%.

$$RCONE_2 \longrightarrow RCN + H_2O$$
$$RCH{=}NOH \longrightarrow RCN + H_2O$$
$$H_2O + \tfrac{1}{3}\,POCl_3 \longrightarrow HCl + \tfrac{1}{3}\,H_3PO_4$$
$$\tfrac{1}{3}\,H_3PO_4 \longrightarrow \tfrac{1}{3}\,H^+ + \tfrac{1}{3}\,H_2PO_4^-$$



7) Ritter, Murphy: J. Am. Chem. Soc., **74**, 763(1952).
8) Harington, Maggridge: J. Chem. Soc., **1939**, 444.

Judging from the above ideas, the additional 2/3 of proton seems to be necessary for completing the reaction, so a few drops of conc. H_2SO_4 was added to the reaction mixture, but the objective isoquinoline was not obtained due to the formation of much resin.

The authors are grateful to Prof. Sugasawa of Tokyo University and Prof. Horii of Osaka University for their helpful advices and encouragements during the cource of this work. Thanks are also due to Mr. Fukuda of the Central Analysis Room of this Institute for microanalytical data.

Experimental

1-(2′-Thienyl)-3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (I)—Methyleugenol (2.8 g.), thiophene-2-carboxylic amide (2 g.), dried benzene (10 cc.), and $POCl_3$ (10 cc.) were heated gradually on a steam bath. The reaction mixture, changing to brown after a few minutes, began to boil after about 7~8 mins., and the crystals of the amide disappeared, giving a homogeneous liquid. After being heated for a total of 1 hr., the mixture was poured into crushed ice and water (ca. 50 g.), and the solvent and aqueous layers were separated. Then the aqueous layer was basified with 10% NH_4OH and the white precipitate separated was collected in ether, washed, dried, and evaporated. The residue was obtained as a yellowish oily substance, yield 1.6 g. (35.5%), which gradually solidified after standing at room temperature. The residue was triturated with a little EtOH and was collected on a filter. This crude crystal was purified several times from ligroine added with a little benzene, forming colorless crystals of m.p. 113~113.5°. The picrate was purified from EtOH, forming yellowish plates of m.p. 188.5~189°. *Anal.* Calcd. for $C_{16}H_{17}O_2NS$ (Free base) : C, 66.87; H, 5.96. Found : C, 67.14; H, 5.85. *Anal.* Calcd. for $C_{16}H_{17}O_2NS \cdot C_6H_3O_7N_3$ (Picrate) : C, 51.16; H, 3.80. Found : C, 51.40; H, 3.86.

1-(2′-Thienyl)-3-methyl-6,7-methylenedioxy-3,4-dihydroisoquinoline (II)—After gradually adding $POCl_3$ (10 cc.) drop by drop into a mixture of safrole (2.6 g.), thiophene-2-carboxylic amide (2 g.), and dried benzene (10 cc.), the mixture was heated on a steam bath for about 1 hr. The reaction mixture was decomposed with crushed ice and treated as usual, giving 0.7 g. (16.3%) of yellowish brown oily substance. After a few days, it solidified completely. It was triturated with a little EtOH, collected on a filter, and purified from EtOH, forming colorless crystals of m.p. 139~139.5°. This was proved to be identical with the melting point reported in the literature.[6]

1-(2′-Furyl)-3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (III)—(a) Reaction between Amide and Methyleugenol : After adding an excess of $POCl_3$ (10 cc.) into a mixture of methyleugenol (1.6 g.), furan-2-carboxylic amide (1.0 g.), and dried benzene (10 cc.), the mixture was heated on a steam bath by which the crystalline amide dissolved in a hot reaction mixture after a few minutes. In this case no evolution of heat occured on mixing but the reaction mixture turned dark brown after refluxing gently. After being heated for 2 hrs., a brownish basic substance (0.4 g., 16%) was obtained on treating by the usual procedure. This product was purified from ligroine repeatedly, giving granular crystals of m.p. 128~130°. The picrate was purified from EtOH, giving yellowish silky crystals of m.p. 184~184.5°. *Anal.* Calcd. for $C_{16}H_{17}O_3N$ (Free base) : C, 70.83; H, 6.32. Found : C, 71.34; H, 6.10. *Anal.* Calcd. for $C_{16}H_{17}O_3N \cdot C_6H_3O_7N_3$ (Picrate) : C, 52.80; H, 4.03. Found : C, 53.04; H, 4.07.

(b) Reaction between Oxime and Methyleugenol : Safrole (2.2 g.), *sin*-furfuralaldoxime (1.5g.), and dried benzene (10 cc.) were mixed and an excess of $POCl_3$ (10 cc.) was added to the foregoing mixture drop by drop. After being gently refluxed for ca. 1.5 hrs. on a steam bath, the mixture was treated as usual, and reddish brown viscous syrup was obtained. Yield, 0.4 g. (11.5%). The purified picrate was identical with a specimen prepared from the amide by the foregoing method.

1-Isonicotinyl-3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (V)—(a) Cyclization Reaction by $POCl_3$: After a mixture of isonicotinamide (1.0 g.), methyleugenol (1.5 g.), abs. xylene (40 cc.), and abs. chloroform (10 cc.) was refluxed in an oil bath for 2.5 hrs., 0.7 g. of a basic substance was obtained by treating as usual. This crude product was purified from ligroine, giving colorless needles of m.p. 83°. This agreed with the melting point of 4-cyanopyridine reported in the literature (*loc. cit.*).

(b) Cyclization Reaction by conc. H_2SO_4 : 4-Cyanopyridine (0.7 g.) obtained in the above experiment was added with conc. H_2SO_4 (2 cc.) and dissolved with stirring and cooling (0~3°). Then methyleugenol (1.0 g.) was added during ca. 2 mins. and the temperature of the reaction mixture was raised to 35°. After stirring at a room temperature for 3 days, the mixture was decomposed with ice water, separating a solid substance. After this was filtered, the aqueous acid layer was basified with 10% Na_2CO_3 solution and the separated base was collected in ether, washed, dried, and the ether evaporated, leaving a viscous oil (1 g.), which solidified on standing for a few days. The picrate was purified from dil. acetone, forming yellowish crystals of m.p. 122~124°. This

picrate was dried under 35° *in vacuo* for a few days, giving yellowish red crystals. *Anal.* Calcd. for $C_{17}H_{18}O_2N_2 \cdot 2C_6H_3O_7N_3$ (Dipicrate) : C, 47.02; H, 3.27. Found : C, 46.97; H, 3.34.

1-[5'-(4'-Methyl)thiazolyl]-3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (VI)—A mixture of 4-methylthiazole-5-carboxylic amide (0.5 g.), methyleugenol (0.7 g.), dried toluene (35 cc.), and $POCl_3$ was refluxed for 3 hrs. Then the reaction mixture was decomposed with ice water and treated as usual. A basic substance (0.3 g.) was obtained by extraction with ether. The hydrochloride was purified from abs. EtOH-ether, giving colorless crystals of m.p. 153~155°(decomp.). The picrate was recrystallized from dil. EtOH, forming yellow needles of m.p. 203~205°(decomp.) (sint. at 93~103°). *Anal.* Calcd. for $C_{16}H_{18}O_2N_2S \cdot C_6H_3O_7N_3 \cdot 4H_2O$(Picrate) : C, 43.5; H, 4.18. Found: C, 43.8; H, 4.32.

Summary

Reactions of various heterocyclic aldoximes and acid amides with methyleugenol or safrole, by utilization of the new isoquinoline synthesis (Kametani procedure[1~5]) gave the objective 1-substituted 3-methyl-6,7-dimethoxy (or 6,7-methylenedioxy)-3,4-dihydroisoquinoline, but the yield was generally less than 30%. The acid amides used were furan- and thiophene-2-carboxylic amides, and 4-methylthiazole-5-carboxylic amide. As the oxime, 2-furfuraldoxime was used, but the use of pyridine-carboxylic amide did not give the objective and unexpectedly cyanopyridine was obtained.

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52. Shigehiko Sugasawa and Yuichi Kanaoka : Application of the Robinson Dehydrogenation Reaction. I.* A Synthesis of 2,3-Dimethoxy-6*H*-indolo[2,1-a]isoindole.

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Treating laudanosoline (I) salt with chloranil in ethanolic solution, Robinson and Sugasawa[1] obtained dehydrolaudanosolinium salt(II), the then unknown dibenzoindolizinium type of compound, in a good yield and they elucidated its structure chiefly by submitting the product to the Hofmann and Emde degradation reactions. The mechanism of this Robinson dehydrogenation reaction was also postulated. The discovery of (II)-type of cryptocaria alkaloid by Ewig, *et al.*[2] and the synthesis of the compound(III),[3] through which the structure of (II) was substantially supported, are probably worth mentioning in this connection.

Later, this dehydrogenation reaction was applied to homolaudanosoline salt under somewhat different working conditions and the corresponding dehydrohomolaudanosolinium salt was obtained,[4] the constititution of which was proved synthetically.[5] Further applications of this reaction were recorded by Sugasawa and his co-workers.[6~8]

Recently, Harley-Mason[9,10] showed that this type of dehydrogenation could also be

* Presented before the Meeting of the Pharmaceutical Society of Japan, Tokyo, May 14, 1955.

** Hongo, Tokyo (菅沢重彦, 金岡祐一).

1) R. Robinson, S. Sugasawa : J. Chem. Soc., **1932**, 789.
2) Ewig, *et al.* : Nature, **169**, 618(1952).
3) S. Sugasawa, K. Mizukami : This Bulletin, **3**, 42(1955).
4) S. Sugasawa, H. Yoshikawa : J. Chem. Soc., **1934**, 1538.
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8) S. Sugasawa, N. Sugimoto : *Ibid.*, **18**, 656(1942).
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10) Harley-Mason : *Ibid.*, **1953**, 1465.