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.

(Received April 25, 1955)

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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.

(*Pharmaceutical Institute, Medical Faculty, University of Tokyo***)

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]

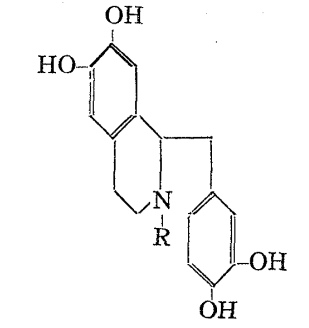
Recently, Harley-Mason[9,10] showed that this type of dehydrogenation could also be

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

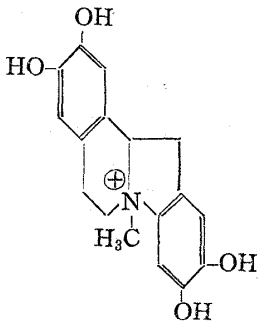
** Hongo, Tokyo (菅沢重彦, 金岡祐一).

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.
5) S. Sugasawa, K. Kakemi : Ber., **71**, 1860(1938).
6) S. Sugasawa, K. Kodama : Proc. Imp. Acad. (Tokyo), **17**, 102(1941).
7) S. Sugasawa, N. Sugimoto, T. Nakata : *Ibid.*, **18**, 655(1942).
8) S. Sugasawa, N. Sugimoto : *Ibid.*, **18**, 656(1942).
9) Harley-Mason : J. Chem. Soc., **1953**, 200.
10) Harley-Mason : *Ibid.*, **1953**, 1465.

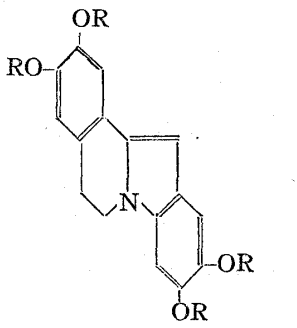
applied to suitably substituted secondary amines such as (IV) and (V) to yield the corresponding tertiary amines (VI) and (VII), respectively, using potassium ferricyanide as the oxidation agent. Adrenochrome could be prepared from adrenaline in a like manner.



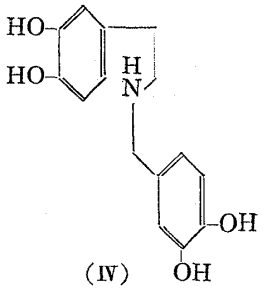
(I) R=CH_3, (V) R=H



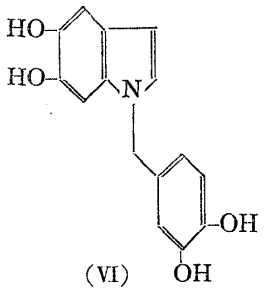
(II)



(III) R=CH_3, (VII) R=H



(IV)



(VI)

Since it appears that polynuclear-condensed nitrogen ring compounds, in which the nitrogen atom is common to two rings, can advantageously be prepared by this method, attempts are being made to examine the scope of this reaction and as the first example, the compound (XIV) mentioned in the title was prepared.

3-(3′,4′-Dimethoxybenzal)phthalide (VIII) was heated with N-methylformamide,[11] yielding two kinds of substances. The main and the less soluble one formed faint yellow prisms of m.p.178~182° and was proved to be the expected 3-(3′,4′-dimethoxybenzal)-N-methylphthalimidine (IXb) by analysis. The minor product, which was not obtained quite pure, was probably the N-nor compound (IXa), which owed its formation to the formamide contained in methylformamide as an impurity.

The stepwise reduction of (IXb), first to 3-veratryl-N-methylphthalimidine (Xb) catalytically, followed by electrolytic reduction, yielding 1-veratryl-N-methylisoindoline (XIb), was found preferable to the one-step reduction[11] for the preparation of (XIb) from (IXb) in a larger amount. Demethylation of (XIb) was effected by refluxing it with an excess of conc. hydrobromic acid.

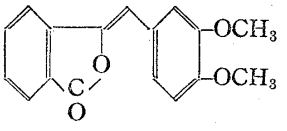
The resultant 1-(3′,4′-dihydroxybenzyl)-N-methylisoindoline (XIIb) salt was treated either with ferric salt or chloranil under a variety of conditions but the product was a dark blue-colored intractable tarry substance, from which nothing definite was isolated, even after methylation or acetylation.

Therefore, the dehydrogenation of 1-(3′,4′-dihydroxybenzyl)isoindoline (XIIa) salt was attempted, bearing the experiments of Harley-Mason[9,10] in mind. Thus the ethanolic solution of (XIIa) was treated with chloranil as is described in the experimental section. The product was methylated and then purified through an alumina column, yielding colorless scales of m.p. 202~203°. From the results of analyses and the positive Ehrlich's color test 2,3-dimethoxy-6*H*-indolo[2,1-*a*]isoindole (XIV) was attributed to this compound.

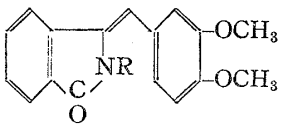
The tertiary phenolic base (XIIb) appeared to be far more sensitive toward dehydrogenation agents than is the correspoding secondary base (XIIa) and this seemed to be the

11) cf. S. Sugasawa, K. Kodama : Proc. Imp. Acad. (Tokyo), **18**, 565(1942).

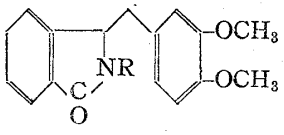
main reason for the unsuccessful experiments with the latter compound.



(Ⅷ)

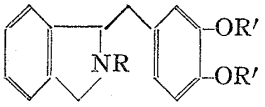


(Ⅸ) a, b

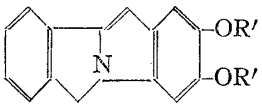


(Ⅹ) a, b

a-series R=H
b-series R=CH_3



(XI) ($R'=CH_3$) a, b.
(XII) ($R'=H$) a, b.



(XIII) $R'=H$
(XIV) $R'=CH_3$

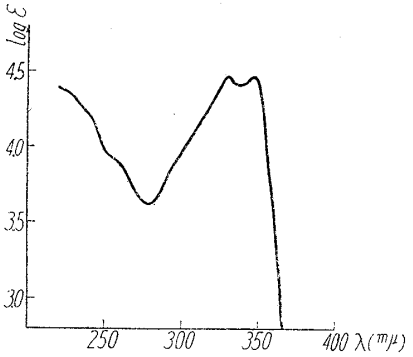


Fig. 1. Ultraviolet Absorption of (XIV) (in Ethanol)

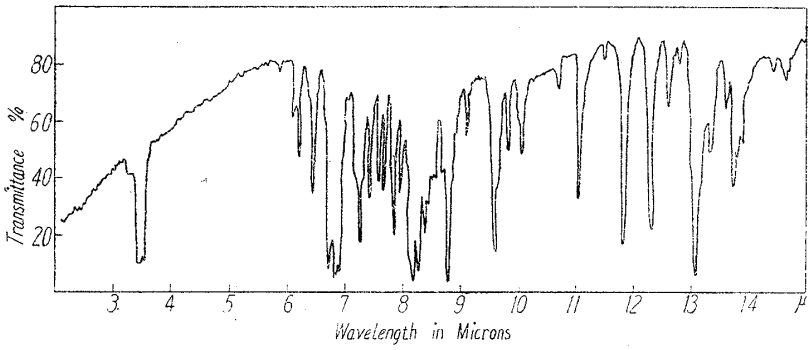


Fig. 2. Infrared Absorption of (XIV) (in Nujol)

The authors wish to thank the members of the Central Analysis Room of this Institute and also Mrs. Hisamichi and Mr. Yoda of Tokyo Research Laboratories of Gohei Tanabe & Co. for microanalytical data.

Experimental

N-Methyl-3-(3′,4′-dimethoxybenzal)phthalimidine (IXb)—3,4-Dimethoxybenzalphthalide (Ⅷ: 8 g.), prepared according to the method of Sugasawa and Kodama,[11] and methylformamide (8.3 g. of $b.p_{30}$ 90~95°) were heated in an oil bath at 180~185°(oil-bath temp.) for 10 hrs., and the reaction product was mixed with 40% EtOH while hot. On cooling, yellowish crystalline solid separated was collected on a filter, washed with 40% EtOH, and was purified repeatedly from acetone. The main and less soluble product formed faint yellow prisms of m.p. 178~182°, yield 5.7 g. For analysis this was further purified from EtOAc, separating in faint yellow prisms of m.p. 181~183°. *Anal.* Calcd. for $C_{18}H_{17}O_3N$ (IXb): C, 73.2; H, 5.8; N, 4.75. Found: C, 72.75; H, 6.0; N, 4.9.

From the acetone mother liquor was recovered ca. 1.5 g. of substance, which sintered at about 125°, almost melted at 135~145°, and became clear at 160°, and was probably a mixture of (IXb) and its N-nor compound (IXa). Its purification met with a great difficulty.

N-Methyl-3-veratrylphthalimidine (Xb)—The foregoing compound (8 g.) was dissolved in glacial AcOH and was reduced over Adams' Pt at 40~50°; 685 cc. of H_2 were absorbed in ca. 3 hrs., giving a colorless clear solution. The solvent was removed *in vacuo*, leaving faint yellow viscous syrup, which gradually solidified on standing. Purified from benzene-petr. ether, forming colorless needles of m.p. 106~108°; yield, 7.3 g. *Anal.* Calcd. for $C_{18}H_{19}O_3N$: C, 72.7; H, 6.45; N, 4.7. Found: C, 72.85; H, 6.35; N, 4.5.

3-Veratrylphthalimidine (Xa)—3-(3′,4′-Dimethoxybenzal)phthalimidine (Ⅸa: 17 g.), prepared according to the method of Sugasawa and Kodama,[11] was catalytically reduced in the same way, 1510 cc. of H_2 being absorbed in ca. 5 hrs. (Xa) was obtained as colorless pillars of m.p. 127~128° from benzene-ligroine. Yield, 15.8 g. *Anal.* Calcd. for $C_{17}H_{17}O_3N$: C, 72.05; H, 6.0; N, 4.9. Found: C, 71.9; H, 6.0; N, 4.95.

N-Methyl-1-veratrylisoindoline (XIb)—The compound (Xb: 4 g.) was dissolved in a mixture of H_2SO_4 (150 cc. of 40%) and EtOH (150 cc. of 95%) and reduced electrolytically according to Tafel (25~35°, 8 amp./100 cm^2 cathode) for 6 hrs. EtOH was evaporated *in vacuo* from the colorless clear catholyte and the residual liquid was extracted with benzene after being basified with Na_2CO_3. The benzene layer was repeatedly extracted with dil. HCl and the acid solution was evaporated

in vacuo, leaving reddish syrup, which solidified on being triturated with EtOH–ether and was purified from the same solvent, forming colorless needles of m.p. 187~189°; yield, 3.1 g. *Anal.* Calcd. for $C_{18}H_{21}O_2N \cdot HCl$: N, 4.4. Found: N, 4.15.

1-Veratrylisoindoline (XIa)—The compound (Xa) was reduced in a like manner, yielding the hydrochloride of (XIa) as colorless pillars of m.p. 234~236° from EtOH–ether. *Anal.* Calcd. for $C_{17}H_{19}O_2N \cdot HCl$: N, 4.6. Found: N, 4.75.

Attempted Dehydrogenation of N-Methyl-1-(3′, 4′-dihyroxybenzyl)isoindoline (XIIb)—The compound (XIb: 5.5 g.) was mixed with HBr (15 cc. of d=1.49) and the whole was heated at 130~140°(oil-bath temp.) for 3 hrs. Evaporation *in vacuo* left a reddish syrup which formed colorless prisms of m.p. 205~209° when purified from EtOH–ether; yield, 3.1 g. Gave yellowish green coloration with $FeCl_3$. *Anal.* Calcd. for $C_{16}H_{17}O_2N \cdot HBr$: C, 57.3; H, 5.4; N, 4.15. Found: C, 56.75; H, 6.0; N, 3.75. Besides, there was obtained uncrystallizable caramel-like substance, which was not investigated further.

(XIIb)·HBr thus obtained was mixed with an equivalent amount of AcOK and the mixture was dissolved in EtOH, to which solution was added ethanolic chloranil suspension in small portions, with shaking. The reddish orange coloration appeared on the addition of the oxidizing agent, but this soon disappeared, then the next portion was added. When about 1/4 of the required amount of chloranil was consumed, the mixture assumed a bluish green coloration, which became deeper as the oxidation proceeded. After all the chloranil was added, the solvent was removed *in vacuo*, leaving a bluish residue, from which nothing definite could be isolated in spite of much elaboration.

The dehyrogenation in AcOH proceeded more slowly than in the above case, giving a reddish orange solution as the end product. On evaporating the solvent *in vacuo* at about 40° the solution gradually turned blue and the residue was again a bluish resin, from which nothing definite was obtained either on methylation or acetylation.

The dehydrogenation by means of $K_3Fe(CN)_6$ in the presence of $NaHCO_3$ also failed to give any encouraging result.

1-(3′,4′-Dihydroxybenzyl)isoindoline (XIIa)—The compound (XIa)·HCl (2.5 g.) was heated with HBr (13 cc. of d=1.49) at 130~140°(oil-bath temp.) for 4 hrs. On cooling, colorless twig-shaped crystals separated from the solution, which were filtered and purified from EtOH–ether, forming colorless pillars of m.p. 211~215°; yield, 2 g. Gives green $FeCl_3$ coloration. *Anal.* Calcd. for $C_{15}H_{15}O_2N \cdot HBr$: C, 55.95; H, 5.0; N, 4.35. Found: C, 55.9; H, 5.55; N, 4.15.

2, 3-Dimethoxy-6*H*-indolo[2,1-a]isoindole (XIV)—The compound (XIIa)·HBr (4 g.) and AcOK (1.56 g.) were dissolved in EtOH (50 cc. of 95%). To this solution was added ethanolic suspension of chloranil[12] in small portions with stirring. Each addition caused reddish yellow coloration, which soon disappeared giving a faint brown solution. After ca. 1/5 of the oxidizing agent was added a portion of the solution was tested with Ehrlich's reagent, giving violet coloration. After all the oxidizing agent was added in 2.5 hrs., the reaction mixture was stirred for 1 hr. at room temp. and then evaporated *in vacuo* under 50°. The dark red muddy residue was repeatedly extracted with boiling ether to remove tetrachlorohydroquinone and then was suspended in H_2O (30 cc.), to which aq. KOH (25 g. of 30%) and Me_2SO_4 (6.6 g.) were added in small portions with stirring. After being agitated for 1 hr. the mixture was extracted with benzene, leaving much tarry substance undissolved. The benzene solution was washed with water, dried, concentrated, and was filtered through an alumina column, giving blue-black layer on the top, and faint red and yellow ones following. From the benzene eluate of the second layer crystalline solid was obtained on evaporation of the solvent, which was sparingly soluble in EtOH, and insoluble in dil. HCl. Purified from benzene-petr. ether it formed colorless scales of m.p. 202~203°, which gave purplish Ehrlich color test in conformity with its constitution (XIV). Yield, 0.7 g. *Anal.* Calcd. for $C_{17}H_{15}O_2N$: C, 77.0; H, 5.7; N, 5.3. Found: C, 76.6; H, 5.55; N, 5.2. Ultraviolet absorption (95% EtOH): λ_{max} 330 mμ (log ε 4.48), 347.5 (4.47). Ultraviolet and infrared absorption spectra of (XIV) are given in Figs. 1 and 2.

Summary

For the purpose of examining the scope of the Robinson dehydrogenation reaction as a tool for building up polynuclear condensed nitrogen-ring compounds, in which the nitrogen atom is common to two rings, 1-(3′,4′-dihydroxybenzyl)isoindoline and its N-methyl derivative were treated with chloranil in ethanolic solution. The former gave the expected 2,3-dihydroxy-6*H*-indolo[2,1-*a*]isoindole, characterized as its dimethyl

12) Chloranil (3.45 g.) was dissolved in boiling EtOH (500 cc. of 95%) and this solution was rapidly cooled with running water, while being swirled, so as to cause fine crystallization of chloranil.

derivative, but the latter failed to give any definite oxidation product under a variety of working conditions, yielding only intractable, dark blue tarry substance.

(Received April 26, 1955)

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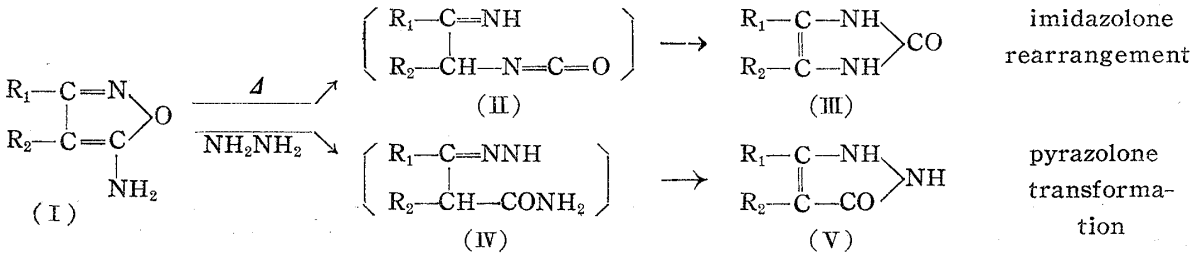
53. **Hideo Kanō and Yasuo Makisumi**: Studies on Isoxazole Derivatives. VIII.[1] Catalytic Hydrogenation of 5-Aminoisoxazoles.

(*Research Laboratory, Shionogi & Co., Ltd.**)

In part III[2] and V[3] of this series, one of the authors (Kanō) reported on the "imidazolone rearrangement" and "pyrazolone transformation" of 5-aminoisoxazoles (I). In both cases, it was considered that these transitions occurred with the ring cleavage of (I) at N—O bond, and each intermediate was assumed to be the isocyanate (II) and the amide (IV).



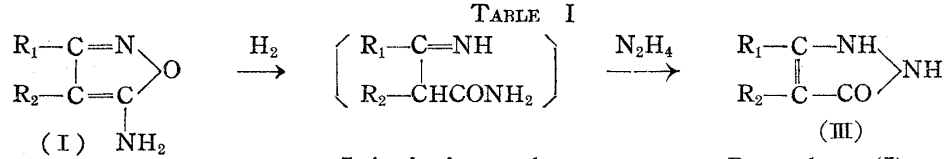
Recently, the catalytic hydrogenation of 3-pheyl-5-aminoisoxazole and its acyl derivatives was studied by Shaw and Sugowdz,[4] the former yielding β-aminocinnamide and the latter, a mixture of β-aminocinnamoyl acylamide and hydroxypyrimidine. These amides reacted with hydrazine or phenylhydrazine to give pyrazolones.

In the imidazolone rearrangement and pyrazolone transformation, the ring opening of (I) was affected by the substituents at 3- and 4-positions of 5-aminoisoxazoles. Such ring opening however did not occur with 3-phenyl-5-aminoisoxazole.

The present paper is a report on catalytic hydrogenation of 5-aminoisoxazoles (I) and its acyl derivatives (VI) which have substituents at 3- and 4-positions.

(I) readily absorbed 1 mole of hydrogen in the presence of Raney nickel in ethanol at room temperature, and after hydrogenation the basic products were treated with hydrazine. The pyrazolones (III) were obtained. The results of these reactions are shown in Table I. (VI) also easily absorbed 1 mole of hydrogen in the presence of

Table I



R_1	R_2	5-Aminoisoxazole No.	Pyrazolone-(5) No.	m.p. °C
CH_3	H	(I a)	(III a)[8]	218~219
CH_3	CH_3	(I b)	(III b)[9]	271~272
C_2H_5	CH_3	(I c)	(III c)	232~233

* Imafuku, Amagasaki, Hyogo-ken (加納日出夫, 牧角徳夫).

1) Part VII: J. Pharm. Soc. Japan, **74**, 138(1954).
2) Part III: *Ibid.*, **72**, 1118(1952).
3) Part V: *Ibid.*, **73**, 383(1953).
4) G. Shaw, G. Sugowdz: J. Chem. Soc., **1954**, 665.