an ethereal solution of 1.53 g. of (VI) was added dropwise with stirring. After additional 2 hours of stirring, the mixture was treated in a usual manner giving 1.40 g. of a crude product. Distillation gave a colorless oil, b.$p_{0.1}$ 116°. *Anal.* Calcd. for $C_{15}H_{23}O$: C, 80.36; H, 12.12. Found: C, 80.37; C, 12.08. $[\alpha]_D^{14}$: +14.6° (26.027 mg./cc. in EtOH).

Oxidation of (VII)—To a solution of 0.19 g. of (VII) in 4 cc. of glacial AcOH was added dropwise a solution of 0.09 g. of sodium dichromate in 2 cc. of the same solvent. The reaction mixture was poured into 30 cc. of water and extracted with ether. The ethereal solution was shaken with 5% Na_2CO_3 solution and the aqueous layer was acidified to give 0.12 g. of an acidic compound. After recrystallization from aq. MeOH the product was found to be identical with the monocarboxylic acid (IV).

Amide of (IV)—0.64 g. of (IV) was warmed with 1.5 cc. of $SOCl_2$ on a steam bath at 40° for an hour. The excess of the reagent was removed by distillation, and the residue was poured into aq. ammonia. The solidified acid amide, 0.60 g., was successively recrystallized from petroleum benzine and aq. MeOH to yield colorless needles, m.p. 138~140°. On admixture of this amide with the preparation[3] obtained from the oxidation of tetrahydrosesquibenihiol no depression of the melting point was observed. *Anal.* Calcd. for $C_{15}H_{27}ON$: C, 75.95; H, 11.39; N, 5.91. Found: C, 76.36; H, 11.41; N, 5.81. $[\alpha]_D^{17}$: +31.7° (23.619 mg./cc. in EtOH).

Summary

A saturated monocarboxylic acid, $C_{15}H_{26}O_2$, was isolated from the reaction mixture of catalytic hydrogenation of dihydroalantolactone, and the structure of this compound was confirmed to be 1,10-dimethyl-7-(2'-carboxyethyl)-decaline by comparison with the oxidation product of tetrahydrosesquibenihiol.

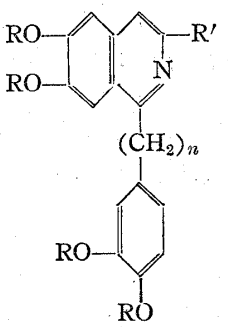
(Received June 14, 1954)

---

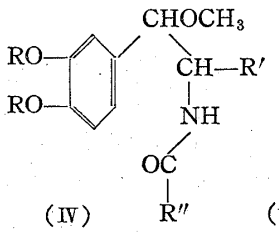
54. Shigehiko Sugasawa and Tohru Hino: Synthesis of 1-(3,4-Methylenedioxyphenyl)-3,5-dimethyl-7,8-methylenedioxyisoquinoline.

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

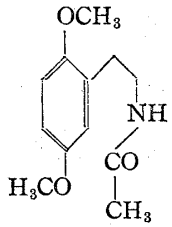
The well-known isoquinoline type of spasmolytics such as papaverine (I), eupaverine (II), and neupaverine (III) bases are all 1-substituted 6,7-dihydroxyisoquinoline derivatives which can be synthesized by cyclizing appropriately substituted β-(3,4-dihydroxyphenethyl)-amides (IV) with phosphoryl chloride. In these cases the cyclization takes place only at 6-position, i.e. *para* to the 3-hydroxyl group. That the isoquinoline ring-closure



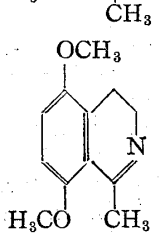
I : R=CH_3, R'=H, n=1
II : R-R=-CH_2-, R'=CH_3, n=1
III : R-R=-CH_2-, R'=CH_3, n=0



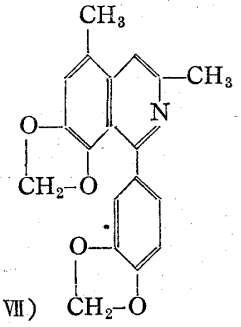
(IV)



(V)



(VI)



(VII)

* Hongo, Tokyo (菅沢重彦, 日野 亨).

can also be effected at the *ortho*-position of a hydroxyl group in case *para*-position is not available, was shown by Sugasawa and Shigehara[1], who prepared 1-methyl-5,8-dimethoxy-3,4-dihydroisoquinoline (VI) in a good yield by treating β-2,5-dimethoxyphenethylacetamide (V) with phosphoryl chloride.

It seemed for us not without interest to examine pharmacological properties of the compound (VII) mentioned in the title, because through this neupaverine isolog we can learn the influence of the site of methylenedioxy group upon spasmolytic effect, since an additional methyl group in 5-position can hardly affect the pharmacological properties of the compound.

6-Chloromethylsafrole (VIII), prepared according to Ichikawa[2], was reduced by means of zinc dust and aqueous alkali, furnishing 6-methylsafrole (IX). When this reduction was carried out in alcoholic solution 6-ethoxymethylsafrole, a colorless oil, was produced, from which the corresponding isosafrole was obtained as a colorless crystalline solid.

6-Methylisosafrole (X), prepared from (IX) by the agency of alkali, was converted to pseudonitrosite (XI) which on being treated with methanolic sodium methoxide gave the methoxy compound (XII). The latter compound was then reduced electrolytically according to Ban[3] to the saturated amine (XIV), which was acylated with piperonyloyl chloride to give the amide (XV) in a good yield.

The isoquinoline cyclization of this amide (XV), however, met with difficulty. When this was treated with phosphoryl chloride under a variety of conditions there was always produced a greenish tar, from which only a small amount of a crystalline basic substance was isolated, having the properties of the expected isoquinoline (VII) and which also analyzed correctly for this compound. Under milder conditions using carbon tetrachloride as a solvent, weaker basic, colorless crystalline substance was obtained in a fair yield, but this compound was found to be an oxazoline derivative (XVI), which type of compound was recently found by Yoshida[4] to form the usual intermediate in the Mannich synthesis of isoquinolines. The latter (XVI) gave (VII) on being boiled with phosphoryl chloride in boiling solvents, but again in a poor yield with much greenish resinous substance.

The alternate and better method to synthesize (VII) is to prepare 3,4-dihydroisoquinoline (XX) first, which is then dehydrogenated to the ultimate compound (VII). For this purpose the pseudonitrosite (XI) was treated with aqueous caustic soda solution and the nitrostyrene (XVII) thus obtained was then reduced electrolytically, giving the isopropylamine (XVIII). The piperonyloylamide (XIX) of the latter was cyclized by refluxing with phosphoryl chloride in benzene, yielding 3,4-dihydroisoquinoline (XX) in a fair yield.

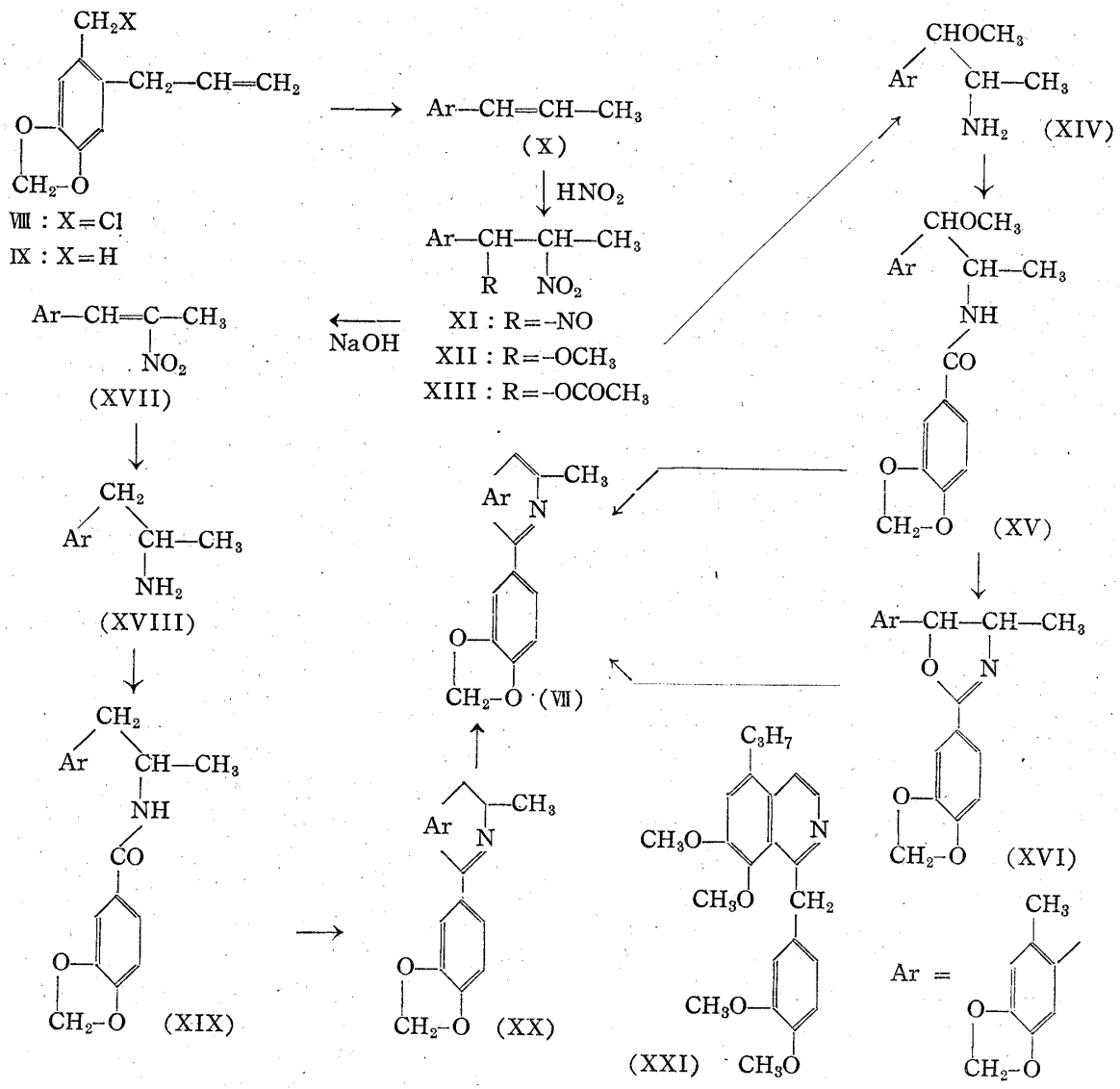
The dehydrogenation of (XX) to (VII) was best effected by treating the former with palladium on carbon in boiling *p*-cymene in the presence of cinnamic acid as a hydrogen acceptor, dry carbon dioxide being bubbled through all the time. The dehydro compound thus formed was proved to be identical with the one prepared by the first method through direct comparison.

During our work Clemo, *et al.*[5] described the synthesis of a similar compound (XXI) starting from eugenol.

The pharmacological assessments of (VII) and (XX)[6] are now under progress.

The authors are indebted to Messrs. Saito, Watanabe, Kaneko, and Nakazato for microanalytical data.

1) Sugasawa, Shigehara : Ber., **74**, 459(1941).
2) Ichikawa : J. Chem. Soc. Japan, **71**, 67(1950).
3) Ban : J. Pharm. Soc. Japan, **74**, 212(1954).
4) Yoshida : *Ibid.*, **74**, 633 (1954).
5) Clemo, *et al.* : J. Chem. Soc., **1953**, 678.
6) 3,4-Dihydroneupaverine, though less active than neupaverine, was found to be devoid of loathsome side-effect inherent in the latter (unpublished data by Misawa and Sugasawa).



Experimental

6-Methylsafrole (IX)—This was prepared from 6-chloromethylsafrole by applying Fuson's method[7]. Zn–Cu couple (prepared from 55 g. of Zn dust and 5 g. of crystalline $CuSO_4$) was mixed with aq. NaOH solution (220 cc. of 10%) and to this mixture was added 6-chloromethylsafrole (43 g.) in benzene during 2 hrs. with stirring at room temperature (about 10°); the temperature of the solution rose gradually to about 20°. The whole was stirred for 15 hrs., filtered, and Zn residue was washed with benzene. All benzene solutions were combined, washed with water, dried, and evaporated. The residue distilled at 110~114° under 7 mm. Hg as colorless oil; yield of (IX), 30.7 g. or 85%.

In case heat was applied in the above dehalogenation reaction there was obtained a small amount of colorless needles of m.p. 93~95° (from alcohol) together with (IX), which is probably 2,2′-diallyl-4,5,4′,5′-bis(methylenedioxy)-dibenzyl from its analytical data. *Anal.* Calcd for $C_{22}H_{22}O_4$: C, 75.4; H, 6.3. Found: C, 75.0; H, 6.5.

When the dechlorination reaction was effected in boiling aq. alcoholic NaOH solution, a colorless oil of $b.p_8$ 130~150° was obtained in 70% yield, which gave the corresponding iso-compound on being treated with amyl alcoholic NaOH. The latter was obtained as a crystalline solid, which forms colorless needles of m.p. 36~37° from alcohol. From the analytical data this was proved to be 6-ethoxymethylisosafrole. *Anal.* Calcd. for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3. Found: C, 71.0; H, 7.35.

6-Methylisosafrole (X)—Quick method by Hirao[8] for the isomerization of safrole was proved to be successful in this case. 6-Methylsafrole (40 g.) was mixed with KOH (0.4 g.) in 18 cc. of absolute

7) Fuson, *et al.*: J. Am. Chem. Soc., **63**, 2652 (1941).
8) Hirao: J. Ind. Chem. Soc. Japan, **29**, 242 (1926).

EtOH, and the mixture was then heated on an open flame to give an orange red clear solution, from which EtOH was distilled off, the residue was heated rapidly up to 250~260°, and kept at this temperature for 5~10 mins. On cooling, this was extracted with ether, washed, dried, and evaporated. Colorless liquid of $b.p_6$ 112~117° was obtained; yield, 30.7 g. or 77%. This solidified on being kept in an ice chest and formed colorless plates of m.p. 45~47° when purified from aqueous EtOH. *Anal.* Calcd. for $C_{11}H_{12}O_2$: C, 75.0; H, 6.9. Found: C, 74.5; H, 7.0.

6-Methylisosafrole Pseudonitrosite (XI)—6-Methylisosafrole (25 g.) in 150 cc. of ether was mixed with aq. $NaNO_2$ solution (50 g. nitrite in 100 cc. of water) and the mixture was vigorously stirred at −5° to 3°, while 180 cc. of 20% H_2SO_4 was added dropwise during 2 hrs. After being stirred for additional 1 hr. white solid separated was collected on a filter, washed thoroughly with water, EtOH, and ether. Colorless solid of m.p. 127°(decomp.) was obtained in the yield of 29.5 g or 82%. When treated with Ac_2O added with a few drops of conc. H_2SO_4 there was obtained 2-(α-acetoxy-β-nitropropyl)-4,5-methylenedioxytoluene (XIII), which forms colorless pillars of m.p. 102° from MeOH. *Anal.* Calcd. for $C_{13}H_{15}O_6N$: N, 5.0. Found: N, 5.0.

2-(α-Methoxy-β-nitropropyl)-4,5-methylenedioxytoluene (XII)—The pseudonitrosite (13 g.) was suspended in 100 cc. of absolute MeOH and to this mixture was added methanolic MeONa (prepared from 4.8 g. of Na) dropwise with agitation and cooling at 0°, furnishing reddish brown clear solution. The mixture was neutralized with glacial AcOH and MeOH was then evaporated *in vacuo*. To the residue was now added water and extracted with benzene, dried and evaporated, giving 9.3 g. of crude (XII) which forms colorless pillars of m.p. 104~105° from ligroine. *Anal.* Calcd. for $C_{12}H_{15}O_5N$: C, 56.9; H, 5.9; N, 5.5. Found: C, 56.4; H, 5.9; N, 6.0.

β-Methoxy-β-(3,4-methylenedioxy-6-methylphenyl)-isopropylamine (XIV)—The foregoing nitro compound (15 g.) was reduced electrolytically according to Ban[3] (6~7 A./100 cm^2 cathode, 25°) and worked up as usual. Colorless oil of $b.p_4$ 135~139° was obtained in the yield of 4.7 g. or 36%. Gives a picrate of yellow granules, m.p. 214~215° (decomp.), from MeOH. *Anal.* Calcd. for $C_{18}H_{20}O_{10}N_4$: C, 47.8; H, 4.4; N, 12.4. Found: C, 47.9; H, 4.55; N, 12.0.

N-(3,4-Methylenedioxybenzoyl)-β-methoxy-β-(3,4-methylenedioxy-6-methylphenyl)-isopropylamide (XV)—From the above-mentioned amine (1.5 g.) and piperonyloyl chloride (from 1.6 g. of the acid by means of $SOCl_2$) by the Schotten-Baumann method. Yield of the crude amide, 2.4 g. Purified from benzene-petroleum ether, forming colorless minute plates of m.p. 199~200°. Yield, 1 g. *Anal.* Calcd. for $C_{20}H_{21}O_6N$: C, 64.7; H, 5.7; N, 3.8. Found: C, 64.5; H, 5.8; N, 4.0.

1-(3,4-Methylenedioxyphenyl)-3,5-dimethyl-7,8-methylenedioxyisoquinoline (VII)—The aforementioned amide (0.7 g.) in toluene (10 cc.) was mixed with 3 cc. of $POCl_3$ and the mixture was refluxed for 2 hrs., deep green solution being obtained, from which 0.1 g. of brown syrup was isolated on being worked up as usual. This was dissolved in dry benzene and the solution was purified through an alumina column. The residue, remaining after the solvent was removed from the filtrate, was purified from benzene-petroleum ether, forming yellow pillars of m.p. 174~175°. *Anal.* Calcd. for $C_{19}H_{15}O_4N$: C, 71.0; H, 4.7; N, 4.4. Found: C, 70.3; H, 4.5; N, 4.4.

Picrate: Yellow plates from acetone, m.p. 230° (decomp.). *Anal.* Calcd. for $C_{25}H_{18}O_{11}N_4$: C, 54.5; H, 3.3; N, 10.2. Found: C, 54.9; H, 3.0; N, 10.3.

Hydrochloride: Orange yellow minute pillars, m.p. 254~255°(decomp.), from alcohol-ether. *Anal.* Calcd. for $C_{19}H_{15}O_4N \cdot HCl \cdot \frac{1}{2}H_2O$: C, 62.2; H, 4.6; N, 3.8. Found: C, 62.65; H, 4.9; N, 3.6.

2-(3,4-Methylenedioxyphenyl)-4-methyl-5-(3,4-methylenedioxy-6-methylphenyl)-oxazoline (XVI)—A mixture of the foregoing amide (1.5 g.), CCl_4 (15 cc.), and $POCl_3$ (5 cc.) was refluxed for 1.5 hrs., giving a deep green solution. The solvent and the excess of $POCl_3$ were removed *in vacuo*, leaving 0.8 g. of brown viscous syrup, which was dissolved in pure benzene and purified through an alumina column. The residue of the filtrate was purified from benzene-petroleum ether, forming colorless granules of m.p. 131~132°, which analysed correctly as the oxazoline (XVI). *Anal.* Calcd. for $C_{19}H_{17}O_5N$: C, 67.25; H, 5.0; N, 4.1. Found: C, 66.9; H, 5.2; N, 4.5.

Picrate: Yellow rosettes from acetone, m.p. 190~192°(decomp.). *Anal.* Calcd. for $C_{25}H_{20}O_{12}N_4$: C, 52.8; H, 3.5; N, 9.9. Found: C, 53.3; H, 3.8; N, 10.2.

On being treated with $POCl_3$ in boiling toluene, the oxazoline (0.5 g.) gave about 0.05 g. of the isoquinoline (VII).

β-Nitro-6-methylisosafrole (XVII)—The powdered pseudonitrosite (5 g.) was suspended in 40 cc. of benzene and this mixture was shaken with 25 cc. of 10% aq. KOH solution for 10~15 hrs., during which time the pseudonitrosite disappeared and yellow solution resulted. The supernatant benzene layer was washed with water, dried, and evaporated, leaving about 3 g. of yellow cystalline solid, which formed brilliant yellow minute plates of m.p. 122~123° from EtOH. *Anal.* Calcd. for $C_{11}H_{11}O_4N$: C, 59.7; H, 5.0; N, 6.3. Found: C, 60.2; H, 4.8; N, 6.4.

β-(3,4-Methylenedioxy-6-methylphenyl)-isopropylamine (XVIII)—The above-mentioned nitro compound was electrolytically reduced according to Ban[3]. Colorless viscous syrup of $b.p_5$ 124~125°. Yield, 60%.

Picrate : Orange yellow pillars from MeOH, m.p. 172°. *Anal.* Calcd. for $C_{17}H_{18}O_9N_4$: C, 48.3 ; H, 4.3; N, 13.3. Found : C, 48.6; H, 4.2; N, 13.3.

3,4-Methylenedioxybenzoyl-β-(3,4-methylenedioxy-6-methylphenyl)-isopropylamide (XIX)—From the foregoing amine and piperonyloyl chloride by the Schotten-Baumann method. Colorless scales of m.p. 131~133° from benzene containing a little benzine. *Anal.* Calcd. for $C_{19}H_{19}O_5N$: C, 66.9; H, 5.6; N, 4.1. Found : C, 66.6; H, 5.2; N, 4.1.

1-(3,4-Methylenedioxyphenyl)-3,5-dimethyl-7,8-methylenedioxy-3,4-dihydroisoquinoline (XX)—The foregoing amide (1.8 g.) was mixed with 20 cc. of toluene and 5 cc. of $POCl_3$ and the whole was refluxed for 2 hrs., giving greenish brown solution, which was added with petroleum ether, separating a brown syrup. After standing some time, the supernatant layer was discarded and the viscous residue was triturated with about 10 cc. of water, forming a yellow solid, which was filtered off with suction, washed, and then basified with Na_2CO_3 solution. The free base separated was now taken up in benzene, washed, dried, and evaporated. About 1 g. of the crude (XX) was obtained as colorless grains of m.p. 180~181° from ligroine. *Anal.* Calcd. for $C_{19}H_{17}O_4N$: C, 70.6; H, 5.3; N, 4.3. Found : C, 70.7; H, 5.5; N, 4.45.

Picrate : Yellow grains from acetone, m.p. 225°(decomp.). *Anal.* Calcd. for $C_{25}H_{20}O_{11}N_4$: C, 54.35; H, 3.6; N, 10.1. Found : C, 54.1; H, 3.7; N, 10.2.

Hydrochloride : Yellow minute plates of m.p. 196~198°(decomp.) from alcohol-ether. *Anal.* Calcd. for $C_{19}H_{17}O_4N \cdot HCl \cdot H_2O$: C, 60.4; H, 5.3; N, 3.7. Found : C, 60.3; H, 5.4; N, 4.0.

Dehydrogenation of (XX)—The afore-mentioned dihydro base (0.7 g.) and cinnamic acid (0.7 g.) were dissolved in 20 cc. of *p*-cymene and the mixture was boiled with 0.5 g. of 30% palladised carbon for 3~4 hrs., during which time dry CO_2 was passed through. On cooling, the catalyst was filtered off, washed with benzene, and the benzene filtrate was combined with *p*-cymene solution. The combined solution was thoroughly shaken with saturated $NaHCO_3$ solution to remove cinnamic acid and then the base was taken up in HCl. The aqueous acid solution, after once shaken with ether, was basified with Na_2CO_3. The base separated was collected in benzene, washed, dried, and evaporated, leaving about 0.5 g. of a brownish solid. The benzene solution of the latter was purified through an alumina column and the filtrate left about 0.4 g. of a solid substance of m.p. 167~169°, which was raised to 174~175° when purified from benzene-petroleum ether. This was identified as (VII) by direct comparison with an authentic specimen prepared by the alternate method.

Summary

For the purpose of pharmacological evaluation, 1-(3,4-methylenedioxyphenyl)-7,8-methylenedioxy-3,5-dimethylisoquinoline (VII) was prepared. Against our expectation, the ring-closure of piperonyloyl β-methoxy-β-(3,4-methylenedioxy-6-methylphenyl)-isopropylamide met with difficulty, giving mainly intractable resinous substance and only a small amount of the desired isoquinoline. 3,4-Dihydro derivative of (VII) was, however, obtained by the usual method in a fair yield, which was dehydrogenated smoothly to (VII) on being treated with palladium-charcoal in boiling *p*-cymene, in the atmosphere of carbon dioxide.

(Received June 15, 1954)