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89. Shigehiko Sugasawa and Kimihiko Kohno: Synthesis in the Azabenzoquinolizine Group. I. A Synthesis of 1, 2, 3, 6, 7, 12b-Hexahydro-4*H*-1, 3-dioxolo[*j*]pyridazo[3, 2-*a*]isoquinoline.

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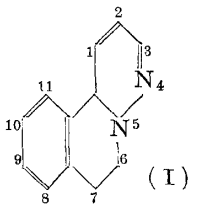
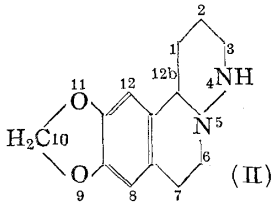
Azabenzoquinolizines, which possess an additional nitrogen atom in C-ring of benzoquinolizine, are hitherto unknown in literature. Being interested in their chemical, physical, and pharmacological properties we undertook the synthesis of the whole series of this type of compounds and the present paper is concerned with the synthesis of the compound (II) mentioned in the title, a derivative of 6, 7-dihydro-11b*H*-pyridazo[3, 2-*a*]-isoquinoline (I).

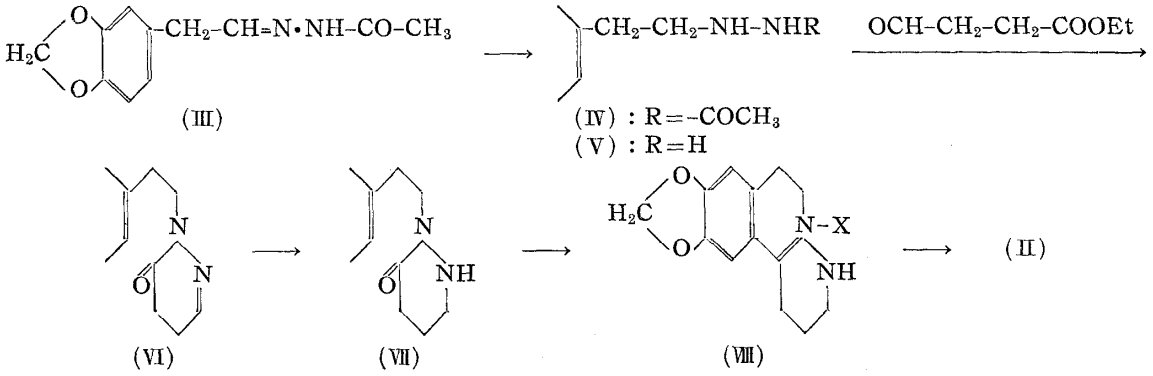

(I)


(II)

3, 4-Methylenedioxyphenethylhydrazine (V) appeared to be a suitable starting material for our purpose and its preparation was first attempted through reduction of homopiperonylic acid hydrazide by means of lithium aluminum hyride. Even under very mild working conditions the reduction proceeded with liberation of ammonia, yielding 3, 4-methylenedioxyphenethylamine as an only isolable product. An attempted reduction of 2-(3, 4-methylenedioxyphenethylidene)hydrazine was also unsuccessful, because homopiperonal azine was apparently the main product even when an excess of the hydrazine was reacted with homopiperonal. So acetohydrazide was used instead of the hydrazine.

Homopiperonal, conveniently prepared from safrole by the known method,[1] was condensed with acetohydrazide, giving 1-acetyl-2-(3, 4-methylenedioxyphenethylidene)-hydrazine (III) in good yield, which was reduced catalytically to the substituted acetohydrazide (IV). Acid hydrolysis of the latter furnished 3,4-methylenedioxyphenethylhydrazine (V) as a colorless viscous liquid of b.p_5 175° in a fair yield.

The hydrazine thus obtained was now condensed with ethyl 3-formylpropionate, yielding hydropyridazinone derivative (VI), which took up 1 mole of activated hydrogen over Adams' platinum catalyst to yield the hexahydro compound (VII). Cyclization of the latter was effected with phosphoryl chloride in boiling benzene, giving the tricyclic



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1) cf. Org. Syntheses, **28**, 35.

ammonium salt (VIII), showing that the presence of an additional nitrogen adjacent to the lactam nitrogen did not interfere with the isoquinoline type of cyclization. The ultimate compound (II) was obtained by treating (VIII) with sodium borohydride in methanolic solution.

Pharmacological property of (II) is now being examined.

Experimental

1-Acetyl-2-(3, 4-methylenedioxyphenethylidene)hydrazine (III)—Freshly prepared homopiperonal (3.2 g., 1 mole) in anhyd. EtOH (30 cc.) was mixed with acetohydrazide (1.5 g., 1 mole) with evolution of heat. The reaction was completed by warming on a steam bath for several mins. On cooling, the product separated as colorless needles in nearly theoretical yield, which was pure enough for the next step. Purified from hydrous EtOH (ca. 60%), forming colorless needles of m.p. 135°. Reduced Fehling solution when heated. *Anal.* Calcd. for $C_{11}H_{12}O_3N_2$: C, 60.0; H, 5.5; N, 12.7. Found: C, 60.4; H, 5.1; N, 12.5.

1-Acetyl-2-(3, 4-methylenedioxyphenethyl)hydrazine (IV)—The foregoing compound (III) (4 g.) in anhyd. EtOH (100 cc.) added with pure AcOH (2 g.) was reduced catalytically in the presence of PtO_2 (0.3 g.), absorbing ca. 1 mole of H_2. Worked up as usual, the reaction product yielded a colorless syrup, which was dissloved in H_2O, basified, and extracted repeatedly with ether. The ether extract was dried and evaporated, leaving colorless oil, which reduced Fehling solution in the cold. Hydrochloride: Colorless pillars (from anhyd. EtOH-acetone), m.p. 165°. *Anal.* Calcd. for $C_{11}H_{14}O_3N_2 \cdot HCl$: C, 51.0; H, 5.8; N, 10.8. Found: C, 50.6; H, 5.4; N, 11.1.

3, 4-Methylenedioxyphenethylhydrazine (V)—The foregoing base (IV) (5 g.) was heated with 20 cc. of ca. 20% HCl on a steam bath for about 40 mins. On cooling, the whole was basified with aq. NaOH and the free base was extracted repeatedly with ether, which was dried and evaporated. The hydrazine distilled at 175°/6 mm., forming colorless viscous liquid, which reduced Fehling solution instantaneously in the cold. Yield, 1.95 g. or 48%.
Hydrochloride: Colorless pillars (from EtOH), m.p. 145°. *Anal.* Calcd. for $C_9H_{12}O_2N_2 \cdot HCl$: C, 49.9; H, 6.05; N, 12.9. Found: C, 49.9; H, 6.4; N, 12.9.

4, 5-Dihydro-2-(3, 4-methylenedioxyphenethyl)-3(2*H*)-pyridazinone (VI)—Equimolar portions of the foregoing hydrazine (V) and ethyl β-formylpropionate[2] were mixed with evolution of heat. The whole was now heated on a steam bath for 2 hrs. to complete the reaction. From the reaction product H_2O and EtOH were removed *in vacuo*, and to the warm residue was added a little EtOH. This mixture was kept in an ice chest, separating colorless solid, which was purified first from 60% and then from 30% EtOH, forming colorless needles of m.p. 104°. Yield, 50% of the pure product. Reduced Fehling solution when warmed. *Anal.* Calcd. for $C_{13}H_{14}O_3N_2$: C, 63.4; H, 5.7; N, 11.4. Found: C, 63.45; H, 5.6; N, 11.4.

2-(3, 4-Methylenedioxyphenethyl)hexahydro-3-pyridazinone (VII)—Catalytic reduction of the compound (VI) was effected smoothly over PtO_2 in EtOH solution acidified with AcOH. From the reduction mixture EtOH and AcOH were removed *in vacuo*, leaving colorless syrup, which solidified on being triturated in the cold (m.p. 94~95°). Purified from a large amount of ligroine, it formed colorless elongated plates, m.p. 98.5°, which was proved to be a free base. Yield, 70% of the pure compound. *Anal.* Calcd. for $C_{13}H_{16}O_3N_2$: C, 62.9; H, 6.5; N, 11.3. Found: C, 63.3; H, 6.2; N, 10.9.
Hydrochloride: Colorless minute needles (from MeOH), m.p. 195°. *Anal.* Calcd. for $C_{13}H_{16}O_3N_2 \cdot HCl$: C, 54.8; H, 6.0; N, 9.85. Found: C, 55.0; H, 5.8; N, 9.6.

1, 2, 3, 4, 6, 7-Hexahydro-1, 3-dioxolo[*j*]pyridazo[3, 2-*a*]isoquinolinium Iodide (VIII)—The above-mentioned compound (VII) (2 g.), $POCl_3$, and pure benzene (20 cc.) were mixed together and the whole was refluxed gently on a steam bath for ca. 1.5 hrs., separating a yellowish red layer. On cooling, the supernatant benzene layer was decanted, the residue was washed with petroleum ether, and then was extacted with dil. aq. HCl (ca. 2%), giving a reddish solution. This was treated with activated charcoal and the resultant faint golden yellow filtrate was added with KI, separating reddish yellow layer, which was probably the iodide hydriodide, but was not induced to crystallize. This was therefore taken up in $CHCl_3$, dried, and evaporated, leaving a yellow caramel-like residue. Yield, 1 g., or 34%.

1, 2, 3, 6, 7, 12b-Hexahydro-4*H*-1, 3-dioxolo[*j*]pyridazo[3, 2-*a*]isoquinoline (II)—The afore-said crude salt (VIII) (1 g.) in 40 cc. of MeOH was reduced by adding 1 g. of $NaBH_4$ in small portions with cooling. The reaction was completed by warming on a water bath for ca. 1 hr. On cooling, the whole was acidified with dil. HCl (15 cc. of ca. 7%), filtered, and the filtrate was basified with aq. NaOH (20 cc. of 10%). The freed base was repeatedly extracted with ether, dried, and evaporated,

2) S. Sugasawa: J. Pharm. Soc. Japan, **46**, 640(1926).

leaving a faint reddish yellow liquid of a characteristic odor, which reduced Fehling Solution when warmed. Yield, 0.6 g. Characterized as the hydrochloride, which forms colorless needles of m.p. 253° from MeOH-acetone. Yield of the pure hydrochloride was 20% based on (Ⅶ). *Anal.* Calcd. for $C_{13}H_{16}O_2N_2 \cdot HCl$: C, 58.1; H, 6.4; N, 10.4. Found: C, 57.9; H, 6.7; N, 10.0.

Summary

1, 2, 3, 6, 7, 12b-Hexahydro-4*H*-1, 3-dioxolo[*j*]pyridazo[3, 2-*a*]isoquinoline (II) was synthesized by cyclizing 2-(3, 4-methylenedioxyphenethyl)hexahydro-3-pyridazinone followed by reduction with sodium borohyride. This is the first exmple of aza-benzoquinoline type of compound recorded in literature. Phrmacological property of the compound (II) is now being examined.

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90. Ikuo Suzuki: Rearrangement Reaction of Picolyl Ethers with Sodium Amide. II.

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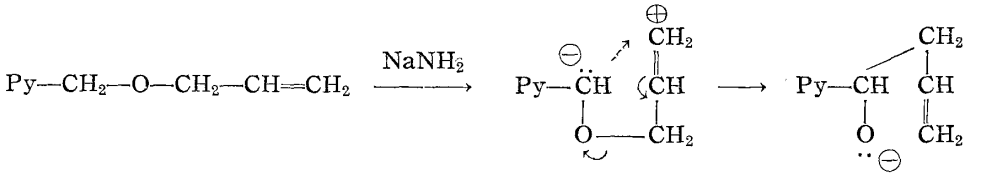
In the preceding paper,[1] it was shown that alkyl- or benzylpyridylcarbinols (α or γ) were obtained from alkyl or benzyl (α or γ)picolyl ethers by the application of sodium amide in decalin, xylene, or benzene.

In the present investigation, it has been found that allyl α-picolyl and γ-picolyl ethers underwent rearrangment to pyridylcarbinols with sodium amide in benzene or xylene, as in the foregoing cases, and further interesting reactions were observed, details of which are set in the present paper.

Reaction of allyl α-picolyl ether (I) or allyl γ-picolyl ether (I′) with equivalent amount of sodium amide in benzene, by boiling for 2～3 hours, respectively yields a viscous oil of $b.p_2$ 83～90°(picrate, m.p. 98～100°) and of $b.p_3$ 122～123°(picrate, m.p. 114～116°). These oily compounds were found to be respectively identical with allyl-α-pyridylcarbinol (II) and ally-γ-pyridylcarbinol (II′), obtained from α- and γ-pyridyl aldehydes by the application of allylmagnesium bromide in ether.



(Py = α or γ-substituted pyridine)

In the case of α-position the rearrangement occurs with good yield (84%) and the starting material is not recovered, but in the case of γ-substituent the rearrangement occurs with a poor yield (15%) and the starting material is recovered in a yield of 65%.

When the same reaction is carried out in xylene at an oil-bath temperature of 130～140°, the yield of rearrangement of the γ-compound increases to 60%, and that of the recovered starting material decreases (30%), while in the case of α-compound, a non-viscous oil of $b.p_5$ 75～81°(picrate, m.p. 91～92°) is obtained in a yield of 57.5%. The

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1) Part I: This Bulletin, **4**, 211(1956).