UDC 547.833.6'284.3.07

76. Nobuo Itoh: Bischler-Napieralski Reaction in Phosphorus Pentoxide-Pyridine. IV.*1 Synthesis of 1-Acetonylisoquinoline Derivatives.

(*Tokyo Research Laboratory, Tanabe Seiyaku Co., Ltd.**2)

In the first paper[1] of this series it was reported without evidence that the cyclization product of N-(3,4-dimethoxyphenethyl)-3,3-ethylenedioxybutyramide (I) under the usual Bischler-Napieralski conditions was an isoxazoloisoquinoline derivative (II′) and not 1-(2,2-ethylenedioxypropyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (III), the normal product of cyclization.

In this paper will be described the synthesis of (III) and 1-acetonyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IV). A support is also provided for (II′) by its reversion to (II).

Since the amide (I) could not be prepared in a good yield, 3,4-dimethoxyphenethylammonium 3,3-ethylenedioxybutyrate (I′) was used in its stead in the present experiment. Thus, the salt (I′) was dissolved in purified pyridine and treated with phosphorus pentoxide-sea sand mixture under reflux to yield (III) in a fair yield. Mild acid hydrolysis converted (III) into 1-acetonyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IV) in a smooth reaction and (IV) was reduced by the Huang-Minlon process to the known 1-propylisoquinoline derivative (V), thus providing the structural support for the compound (IV). Alkaline potassium permanganate oxidation of the methyl methosulfate of (III) yielding *m*-hemipic acid also lent support to structure (III).

Contrary to expectation, (IV) was a fairly stable compound and refluxing with phosphoryl chloride was found necessary for its conversion into (II). The cyclized product was found to be identical with the specimen mentioned in the first paper, in which the formula (II′) was proposed. Location of the double bond was now revised as seen in (II) based on the ultraviolet spectral data.

In conformity with its structure (II) suffered a smooth ring-fission to yield (VI) after absorbing two molar equivalents of hydrogen activated over the Adams catalyst. The N-acetyl derivative of (VI), which was obtained by a partial hydrolysis of O,N-diacetylated (VI), was oxidized with chromium trioxide to yield (VII), from which 1-acetonyl-tetrahydroisoquinoline derivative (VIII) could be readily obtained by acid hydrolysis. The latter compound (VIII) may be more conveniently prepared directly from (III) through catalytic reduction followed by acid treatment and will serve as a starting material for the synthesis of various benzoquinolizine type of compounds. Results along this line of experiments will be the subject of the forthcoming paper.

Experimental

3,4-Dimethoxyphenethylammonium 3,3-Ethylenedioxybutyrate(I′)—3,3-Ethylenedioxybutyric acid[2] (4 g.) in 20 cc. of anhyd. Et_2O was added in small portions to an Et_2O solution of homoveratrylamine (4 g.), separating a crystalline solid, which was collected on a filter in a quantitative yield. Purified from anhyd. benzene this formed colorless plates, m.p. 115°. *Anal.* Calcd. for $C_{16}H_{25}O_6N$: C, 58.7; H, 7.7; N, 4.3. Found: C, 58.95; H, 7.6; N, 4.8.

1-(2,2-Ethylenedioxypropyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (III)—To a boiling solution

*1 This paper constitutes a part of a series entitled "Bischler-Napieralski Reaction in P_2O_5-Pyridine" by Shigehiko Sugasawa. Part III. S. Sugasawa, N. Itoh: J. Org. Chem., **24**, 2042(1959).

*2 Toda-machi, Kita-adachi-gun, Saitama-ken (伊藤信夫).

1) N. Itoh, S. Sugasawa: Tetrahedron, **1**, 45(1957).

2) L. William, H. Schinz: Helv. Chim. Acta, **32**, 2158(1949). This acid was also prepared by reductive hydrolysis of benzyl 3,3-ethylenedioxybutyrate with H_2 activated over Pd catalyst. Both acids gave one and the same benzylthiuronium salt with correct analysis, melting at 142～143° with decomposition.

of the forgoing salt (I) (5 g.) in pure pyridine (80 cc.) an intimate mixture of P_2O_5 (15 g.) and sea sand (80 g.) was added in 4 portions with stirring. The heating was continued for 6 hr. The reaction product was worked up as usual and the crude product obtained was dissolved in benzene and purified by filtering through an alumina column to yield a reddish brown syrup (3.2 g.), which was directly hydrolyzed.

1-Acetonyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IV)—The foregoing ketal (3 g.) was dissolved in 20 cc. of 10% HCl and the resultant solution was shaken with benzene for some time. The aqueous solution was filtered through a wet filter paper, the filtrate was basifed with K_2CO_3, and the liberated base was taken up in benzene. From the benzene solution there was recoverd a basic oil in a yield of 2.3 g., which was obtained in crystalline form after purification through an alumina column. Colorless needles, m.p. 65~67°, as purified from benzene. *Anal.* Calcd. for $C_{14}H_{17}O_3N \cdot \frac{1}{2}H_2O$: C, 65.6; H, 7.1; N, 5.5. Found (in subst. dried at 30° for 12 hr. *in vacuo*): C, 65.15; H, 7.2; N, 5.2.
Picrate: Yellow plates from EtOH, m.p. 206~207°(decomp.). *Anal.* Calcd. for $C_{20}H_{20}O_{10}N_4$: C, 50.4; H, 4.2; N, 11.8. Found: C, 50.5; H, 4.3; N, 11.6.
2,4-Dinitrophenylhydrazone: Reddish yellow needles from EtOH, m.p. 168°(decomp.). *Anal.* Calcd. for $C_{20}H_{21}O_6N_5 \cdot \frac{1}{2}H_2O$: C, 55.0; H, 5.1; N, 16.05. Found (in subst. dried at 100° for 12 hr. *in vacuo*): C, 54.75; H, 5.0; N, 15.55.

1-Propyl-6,7-dimethoxy-3,4-dihydroisoquinoline (V)—A mixture of the afore-mentioned ketone (0.2 g.), hydrazine hydrate (0.2 g.), ethylene glycol (0.2 g.), and KOH (0.2 g.) was heated in an oil bath maintained at 140~150° for 4 hr. and then the bath temp. was raised to 190~200° to remove an excess of hydrazine hydrate and ethylene glycol. When cool the residue was extracted with benzene, from which a colorless oil (0.1 g.) was recovered. The latter was characterized as yellow plate-shaped picrate, m.p. 174~175°(EtOH), and was identified with an authentic picrate of (V). *Anal.* Calcd. for $C_{20}H_{22}O_9N_4$: C, 51.95; H, 4.8; N, 12.1. Found: C, 51.4; H, 4.8; N, 12.5.

2-Methyl-8,9-dimethoxy-5,6-dihydro-2*H*-isoxazolo[3,2-*a*]isoquinoline (II)—i) The 1-acetonylisoquinoline derivative (IV) (0.5 g.) in benzene (3 cc.) was mixed with $POCl_3$ (1.5 g.) and the whole was refluxed on a steam bath for 20 min. to separate an oily substance. After cool petr. ether was added to the reaction mixture and the whole was allowed to stand, and the supernatant layer was discarded after some time. A reddish yellow substance thus obtained, after being washed with petr. ether, was dissolved in ice water and the resultant aqueous solution was basified with K_2CO_3. The free base was collected in benzene, from which solution a yellow syrup was recovered in a quantitative yield (0.5 g.), which solidified on standing. This was purified from hexane and formed faint yellow needles, m.p. 139°, in which the absence of a ketonic group was proved from its infrared data and also from its indifference towards ketonic reagents. UV λ_{max}^{EtOH} mμ (log ε): 280 (3.5), 320 (3.78).

ii)[3] 3,3-Ethylenedioxybutyric acid (5.7 g.) in anhyd. benzene (25 cc.) was mixed with a solution of $SOCl_2$ (6.3 g.) in anhyd. benzene (15 cc.). The whole was warmed at 40~45° until the gas evolution subsided (ca. 3 hr., evolution of CO_2 was also observed, probably due to decomposition of the starting acid by acid reagents). After cool, the resultant yellow solution was added to a solution of homoveratrylamine (6 g.) in benzene (20 cc.) and basified with 40 cc. of 5% NaOH solution with cooling and stirring. After 1 hr.'s stirring, the benzene layer was washed with dil. HCl and H_2O, dried, and the solvent removed to leave an orange-yellow syrup (6.5 g.), which was not induced to crystallize. A sample of this crude amide gave a negative color test with $FeCl_3$, but after being treated with acid it responded to this reagent giving a purple coloration.
2,4-Dinitrophenylhydrazone: Yellow crystals, m.p. 159~160°. *Anal.* Calcd. for $C_{20}H_{23}O_7N_5$: N, 15.7. Found: N, 15.4.

A mixture of the crude amide (I) (2.8 g.) thus obtained in anhyd. benzene (20 cc.) and $POCl_3$ (5 g.) was gently refluxed on a steam bath for 2 hr., giving a reddish solution. Benzene and an excess of $POCl_3$ were evaporated to leave a reddish syrup, which could not be induced to crystallize and was treated with 30 cc. of 5% HCl and a small amount of EtOH. After heating for 0.5 hr., the mixture was shaken once with benzene to remove some resinous material, the aqueous layer was basified with NH_4OH, and the base that liberated was extracted with Et_2O. A solid substance (ca. 1.5 g.) was recovered from the Et_2O solution and formed very faint yellow prisms (from EtOH), m.p. 140~141°, undepressed when admixed with a sample obtained as in i). *Anal.* Calcd. for $C_{14}H_{17}O_3N$: C, 68.0; H, 6.9; N, 5.7. Found: C, 67.9; H, 6.65; N, 5.6.
Picrate: Yellow needles (from EtOH), m.p. 156°. *Anal.* Calcd. for $C_{20}H_{20}O_{10}N_4$: C, 50.4; H, 4.2; N, 11.8. Found: C, 51.1; H, 4.5; N, 12.1.

1-(2-Hydroxypropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VI)—A solution of the compound (II) (1 g.) in 20 cc. of EtOH, acidified with 0.5 cc. of 10% HCl, was reduced catalytically over Adams' Pt-catalyst, 200 cc. of H_2 being absorbed in 0.5 hr. The residue obtained on evaporation

3) This experiment was carried out by Dr. K. Mizukami in 1952.

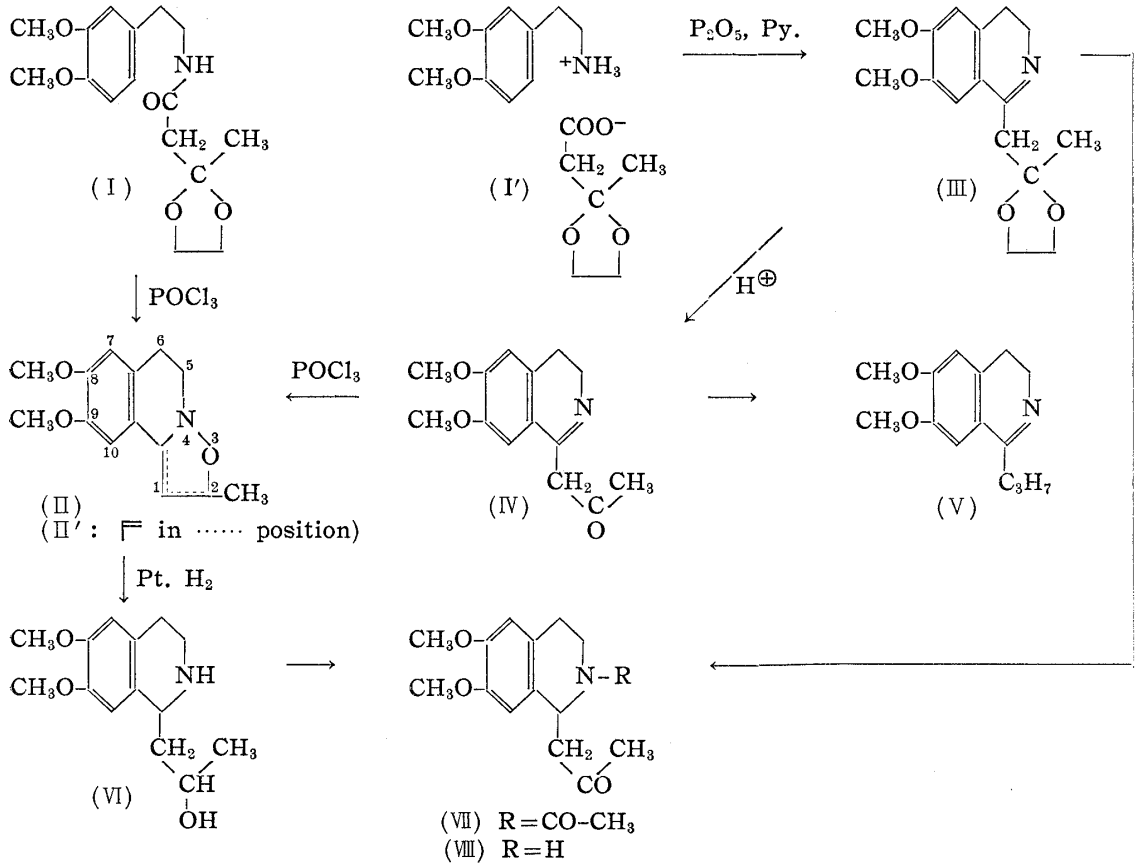
of EtOH from the filtrate was dissolved in H_2O and basified with K_2CO_3. The base thereby liberated was collected in benzene, dried, and the solvent was removed to leave a yellow syrup (1 g.). The latter was characterized as its picrate of yellow prisms from EtOH, m.p. 214°(decomp.). *Anal.* Calcd. for $C_{20}H_{24}O_{10}N_4$: C, 50.0; H, 5.0; N, 11.7. Found: C, 50.2; H, 4.9; N, 12.0.

1-Acetonyl-2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VII)—The O,N-diacetyl derivative of the foregoing compound (VI) was obtained as a yellow oil (1 g.) by treating (VI) (1 g.) with AcCl (1 g.) in the presence of 10 cc. of 10% Na_2CO_3 in the cold. Infrared spectrum of the crude product: $\nu_{-N-C=O}$ 1640 cm^{-1}, $\nu_{-O-CO-CH_3}$ 1735 cm^{-1}. The crude product (1 g.) was hydrolyzed by heating with MeOH solution of NaOH (1 g. in 15 cc. of MeOH) for 3 hr. MeOH was then evaporated and the residue was dissolved in benzene, thoroughly washed with H_2O, dried, and the solvent was removed to yield 0.8 g. of a yellew syrup, in whose infrared spectrum only $\nu_{-N-C=O}$ 1640 cm^{-1} was observed and the band at 1735 cm^{-1} corresponding to $-OCOCH_3$ disappeared.

This syrup (0.5 g.) in 5 cc. of pure pyridine was now treated with a solution of CrO_3 (0.2 g.) in pyridine (10 cc.). After 2 hr. of stirring the whole was allowed to stand overnight and then decomposed with ice water. The Et_2O extract of the above solution was washed thoroughly with H_2O and evaporated to leave 0.3 g. of a reddish yellow oily product, which was dissolved in benzene and purified through an alumina column to yield a yellow oil. IR cm^{-1}: $\nu_{C=O}$ 1715, $\nu_{-N-COCH_3}$ 1640. This was characterized as 2,4-dinitrophenylhydrazone, which came in reddish yellow prisms from EtOH, m.p. 139~140°. *Anal.* Calcd. for $C_{22}H_{25}O_7N_5$: C, 56.0; H, 5.35; N, 14.9. Found: C, 55.8; H, 5.0; N, 14.4.

1-Acetonyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIII)—i) The foregoing compound (0.2 g.) was deacetylated by heating with 5 cc. of 10% HCl on a steam bath until a clear solution resulted (ca. 3 hr.). When cooled, the reaction solution was basified with Na_2CO_3 and extracted with benzene, which was washed, dried, and the solvent was evaporated. Residual reddish brown syrup, dissolved in benzene, was purified through an alumina column. A yellow syrup (0.12 g.) thus obtained was characterized as a pictrate of yellow needles from EtOH, m.p. 203~204°(decomp.). *Anal.* Calcd. for $C_{20}H_{22}O_{10}N_4$: C, 50.2; H, 4.6; N, 11.7. Found: C, 49.7; H, 4.74; N, 11.9.

ii) To a solution of the crude (III) (0.5 g.) in EtOH (10 cc.), $NaBH_4$ (0.15 g.) was added and the mixture was allowed to stand overnight. EtOH was then removed, the residue was dissolved in 10% HCl, filtered from some undissolved material, and the filtrate was basified with K_2CO_3 with cooling. The base thereby liberated was taken up in benzene, dried, and solvent was evaporated to leave a yellow syrup, which was characterized as a picrate, which formed yellow needles from EtOH, m.p. 202~203°(decomp.), and was proved to be identical with the one obtained as above.



The writer wishes to express his hearty appreciation to Mr. M. Nakamura, Vice-President of Yawata Chemical Industries, for a generous donation of pure pyridine. He is also grateful to Dr. S. Sugasawa, Professor Emeritus of the University of Tokyo, and Dr. K. Abe, Director of this Laboratory, for their interest in this work. Thanks are also due to Mr. K. Tanikawa and Miss M. Ninomiya for infrared data and to members of the analysis room of the Faculty of Pharmaceutical Sciences, University of Tokyo, and of this Laboratory for microanalytical data.

Summary

Synthesis of 1-acetonyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IV) was described. On treatment with boiling phosphoryl chloride this underwent a smooth prototropic change to form isoxazole derivative (II) in almost theoretical yield, which had been described previously. Some chemical evidence in support of the structure of (II) was also provided.

(Received October 3, 1959)

UDC 615.771.7[547.233'222]-092 : 616.381-003.217-006.3

77. Morizo Ishidate, Yoshio Sakurai, Hiroshi Imamura, and Ayako Moriwaki : Studies on Carcinostatic Substances. XXVII.*1 Anti-tumor Activity of 2-Chloroethylamine Derivatives on the *in vitro*-Cultured Yoshida Sarcoma Cells.

(*Iatrochemical Institute of Pharmacological Research Foundation**2)

This paper deals with the result of anti-tumor screening of 2-chloroethylamine derivatives on the Yoshida sarcoma cells cultured *in vitro* by the procedure described in the preceding paper.[1] Attention was called to the fact that the effect was determined chiefly by the cytomorphological observation according to a similar standard as that adopted in animal experiments using rats bearing Yoshida sarcoma. For this reason, it would be a matter of particular interest to compare the results of the two experiments, *in vitro* and *in vivo*.

From these comparisons, two remarkable findings were observed. The one is a relationship between chemical and biological reactivities of the compounds and the other, the condition for biological reduction of the N-oxide derivatives of 2-chloroethylamine.

Experimental and Results

More than 200 derivatives of 2-chloroethylamine were tested for anti-tumor activity, some of which are listed in Table I with the results indicated by minimum effective concentration (MEC).

As seen in Table I, the test of the N-oxides ended in negative results except those having more than three 2-chloroethyl groups. In order to obtain an answer to the question of why the N-oxides themselves did not exhibit any activity on the cells *in vitro*, contrary to those *in vivo*, the following experiments with the Yoshida sarcoma were carried out.

Expt. 1 : Various doses of N-methyl-bis(2-chloroethyl)amine N-oxide (HN_2-O) were given intraperitoneally to each of the rats bearing 4-day-old Yoshida sarcoma. After every 30 and 120 min., the

---

*1 Part XXVI : This Bulletin, 8, 99(1960).

*2 26 Nishigahara 1-chome, Kita-ku, Tokyo (石舘守三, 桜井欽夫, 今村 博, 森脇絢子).

1) M. Ishidate, *et al.* : This Bulletin, 7, 873(1959).