CHEMICAL
&
PHARMACEUTICAL BULLETIN

Vol. 7 No. 5 July 1959

UDC 547.836.2

99. Tatsuo Ohta, Yo Mori, and Masuo Umeda : Furoquinolines. XVII.*1 On φ-Dictamnine of Asahina and Inubuse.

(*Tokyo College of Pharmacy**2)

Asahina and Inubuse[1] attempted the synthesis of dictamnine and reported that, contrary to their expectations, a compound, m.p. 225°, which they named φ-dictamnine, an isomer of isodictamnine with angular structure (I), was obtained. However, uncertainty of the structure of φ-dictamnine was pointed out by Grundon, *et al.*[2] by the fact that the compound (I) synthesized by a different route melted at 130°.[3] Later, the structure of (I) prepared by Grundon, *et al.* was confirmed by further syntheses[4~6] and also by rearrangement of dictamnine.[7]

The present paper deals with the reëxamination of φ-dictamnine synthesis from nordictamnal (II) according to the method of Asahina and Inubuse.[1] The condensation of (II) with cyanoacetic acid was performed elaborately at 30~35° and at 50~100°. The crude condensation product (A) was separated into $NaHCO_3$-soluble and -insoluble portions. The analytical data for nitrogen of the crude compounds obtained from both portions approximated that of (IIIc) or (IV), respectively, and not (IIIa) or (IIIb). Both compounds were purified by recrystallization to the crystals of m.p. 305~306°(decomp.), which were identical with (IV), and m.p. 307~308°, synthesized by condensation of (II) with diethyl malonate in pyridine and subsequent hydrolysis. (IIIa) reported by Asahina and Inubuse could not be isolated from the condensation product of (II) with cyanoacetic acid. This endorses its probability by the fact that the nitrile group in (IIIa) is easily hydrolyzed in alkaline medium even at low temperature. Moreover, there occurred no decomposition of the crude product (A) to each component when heated at 100° in alkaline solution, and by which (IV) was obtained by subsequent acidification and crystallization. Consequently, it is assumed that the main reaction proceeds to (IV) by lactonization of (IIIc) produced through (IIIa).

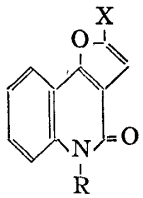
Decarboxylation of (IV) was accomplished by pyrolysis and the compound thus produced was identical with (V) prepared by condensation of 4-hydroxycarbostyril with malic acid.[8] Grundon[9] supported the structure of (V) from spectral evidence. Bromin-

---

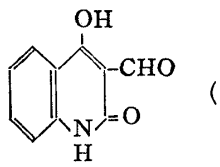
*1 Part XVI. T. Ohta : Ann. Rept. Tokyo Coll. Pharmacy, **8**, 149(1958).
*2 Kashiwagi 4-chome, Shinjuku-ku, Tokyo (太田達男, 森　陽, 梅田益雄).
1) Y. Asahina, M. Inubuse : Ber., **65**, 61(1932).
2) M.F. Grundon, N.J. McCorkindale, M.N. Rodger : J. Chem. Soc., **1955**, 4248.
3) m.p. 132~133° (T. Ohta, Y. Mori); m.p. 132~134° (H. Tuppy, F. Böhm).
4) T. Ohta, Y. Mori : This Bulletin, **4**, 415(1956).
5) *Idem.* : Proc. Japan Acad., **32**, 769(1956).
6) *Idem.* : This Bulletin, **5**, 80(1957).
7) H. Tuppy, F. Böhm : Monatsh., **87**, 735(1956).
8) R.F.C. Brown, G.K. Hughes, E. Ritchie : Australian J. Chem., **9**, 279(1956).
9) M.F. Grundon : Personal communication.

ation of (V) and subsequent Perkin rearrangement of 3-bromo compound (VI), m.p. 306~308°, furnished (VII), m.p. 313~315°(decomp.). Methylation of (VII) with dimethyl sulfate and potash by the procedure of Ohta and Mori[4] afforded the crystals of m.p. over 300°, which was identical with (VIII) synthesized previously by another route.[6] Parallelly, methylation of (VII) was carried out according to the procedure of Asahina and Inubuse, but the product obtained was fairly impure, and the presence of unchanged compound (VII) was proved by paper partition chromatography.

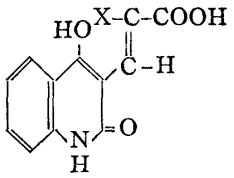
Further, (VIII) was methylated with diazomethane to yield (IX), m.p. 207~208°, which was quite identical with the sample obtained by another synthetic method.[6] From the foregoing and previous experiments,[4~6] it suggests that the so-called *φ*-dictamnine by Asahina and Inubuse was possibly an impure compound mixed with furo[3,2-*c*]quinolin-4(5*H*)-one (X) produced from (VII) by decarboxylation.



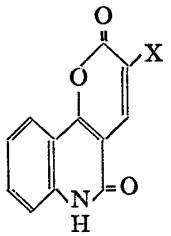
(I) R=CH_3, X=H
(VII) R=H, X=COOH
(VIIa) R=CH_3, X=COOH
(IX) R=CH_3, X=$COOCH_3$
(X) R=H, X=H



(II)



(IIIa) X=CN
(IIIc) X=COOH



(IIIb) X=CN
(IV) X=COOH
(V) X=H
(VI) X=Br

We would like to express our gratitude to Dr. Y. Asahina, Professor Emeritus of the University of Tokyo, for his courtesy in this work. Our thanks are also due to Mrs. Y. Baba and Miss T. Suzuki for the microanalytical data.

Experimental

All m.p.s are not corrected

Condensation of Nordictamnal with Cyanoacetic Acid—A mixture of finely powdered nordictamnal (5 g.), 10% KOH solution (250 cc.), and cyanoacetic acid (3 g.) was warmed at 30~35° until the aldehyde compound almost dissolved. When the temperature was raised over 40°, generation of NH_3 was evidently recognized and markedly at 50~70°. The mixture was acidified with HCl and the deposited yellowish crystals (6.1 g., 90.5%) were treated with $NaHCO_3$ solution. The $NaHCO_3$-soluble portion was acidified with HCl, and the crystals separated out were collected. Yield, 46~75%. The analysis of nitrogen of the crude crystals : Calcd. for (IIIa) : 10.93; (IIIb) : 11.76; (IIIc): 5.65; (IV) : 5.45. Found : N, 6.03. By one recrystallization of this compound from glacial AcOH, it showed the melting point of 289~291°(decomp.). Further, it was recrystallized four times from glacial AcOH to give yellow platelets, m.p. 305~306°(decomp.), whose m.p. was not lowered when mixed with the specimen of (IV) obtained by another synthetic route described below. The crude compound in AcOH showed scarcely yellowish green fluorescence, but it intensified gradually by recrystallization. This seems that the dicarboxylic acid (IIIc) converted to (IV) during crystallization. *Anal.* Calcd. for $C_{13}H_7O_5N$ (IV) : N, 5.45. Found : N, 5.46.

Repeated recrystallization of this crude $NaHCO_3$-insoluble compound (yield, 13~50%. Found: N, 5.87) from glacial AcOH gave yellow platelets, m.p. 305~306°(decomp.), which was identical with the crystals obtained from the $NaHCO_3$-soluble portion described above. It shows an intensive yellowish green fluorescence in AcOH solution. The analytical data of this compound agreed with (IV).

2,5-Dioxo-5,6-dihydro-2*H*-pyrano 3,2-*c*]quinoline-3-carboxylic Acid (IV)—a) The crude condensation product of (II) with cyanoacetic acid was heated with conc. H_2SO_4 on a water bath. This mixture was diluted with water and the compound deposited out was recrystallized from glacial AcOH to yellow platelets, m.p. 307~308°(decomp.) (reported m.p. 305~310°). It shows yellowish green fluorescence in AcOH solution. It is soluble in 0.5% K_2CO_3 solution and decomposes $NaHCO_3$,

but its Na salt is difficultly soluble in water. *Anal.* Calcd. for $C_{13}H_7O_5N$: C, 60.71; H, 2.74; N, 5.45. Found: C, 60.76; H, 2.98; N, 5.58.

b) A mixture of nordictamnal (2 g.), diethyl malonate (1.7 g.), pyridine (35 cc.), and piperidine (3 drops) was refluxed for 1⅔ hr., pyridine was distilled off, and water was added. The yellowish brown substance thereby deposited out was filtered off and the filtrate was acidified with HCl. The product thus obtained was hydrolyzed with 5% NaOH solution (60 cc.) by warming on a water bath for 50 min. The insoluble matter was filtered off and the filtrate was acidified with HCl. The yellowish precipitate was recrystallized from glacial AcOH to yellow platelets, m.p. 307~308° (decomp.), undepressed on admixture with respective specimen obtained by treatment of H_2SO_4 and by crystallization of the condensation product between (II) and cyanoacetic acid described above.

Decarboxylation of (IV)—0.1 g. of (IV) was sublimed by heating in a test tube. This was repeated, and the sublimate totalled 0.35 g. (29.2%) from 1.5 g. of (IV). Pale yellow prismatic needles (from glacial AcOH), m.p. 327~328° (reported, m.p. 335°). It shows a blue fluorescence under ultraviolet light in an AcOH solution. This compound was identified as 5,6-dihydro-2*H*-pyrano[3,2-*c*]-quinoline-2,5-dione (V), which was synthesized by condensation of 4-hydroxycarbostyril, malic acid, and conc. H_2SO_4 according to Brown, *et al.* (*loc. cit.*), by mixed fusion test and by comparison of the ultraviolet spectral curve.

3-Bromo-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinoline-2,5-dione (IV)—Prepared by standing for a week a mixture of 2 g. of (V), 10% bromine-glacial AcOH (24 cc.), and glacial AcOH (400 cc.). Yield, 1.4 g. m.p. 306~308° (reported, m.p. over 300°).

Perkin Rearrangement of (VI)—Achieved in accordance with the literature. Colorless needles from EtOH, m.p. 313~315°(decomp.)(reported, m.p. 310°). It shows a blue fluorescence in $NaHCO_3$ solution.

Methylation of (VII) with Dimethyl Sulfate and Potash—a) Authors' procedure : To 0.1 g. of (VII), Me_2SO_4 (0.2 cc.) and 50% KOH solution (0.25 cc.) were added alternately and mixed by kneading. Further, Me_2SO_4 (0.1 cc.) and 50% KOH solution (0.3 cc.) were added and mixed. After a while, it was diluted with water (5 cc.) and acidified with HCl. The precipitate was recrystallized from EtOH with charcoal to white needles, m.p. over 300°. It shows no fluorescence in $NaHCO_3$ solution in daylight, but shows a blue fluorescence under ultraviolet light in an EtOH solution.

b) Asahina-Inubuse's procedure : The methylation was performed faithfully according to the literature. The product thus obtained gave two spots of Rf 0.76 and Rf 0.71 on the paper partition chromatogram (control Rf of (VIII), 0.76; (VII), 0.71, ascending one-dimensional method : Toyo Roshi No. 50; flowing solvent : 50% AcOH). It stands to reason that there was obtained (I) mixed with (X), because Asahina and Inubuse carried out the decarboxylation of (VIII) without purification.

Methyl Ester of (VIII)—It was methylated with CH_2N_2. Colorless needles, m.p. 207~208°, undepressed on admixture with the sample of (IX) synthesized previously by another route.[6]

Summary

The reëxamination of the φ-dictamnine synthesis was carried out. The reaction of (II) with cyanoacetic acid in alkaline medium proceeded mainly to the dicarboxylic acid (IIIc). According to the present and previous experiments, it was concluded that φ-dictamnine obtained by Asahina and Inubuse was possibly an impure compound mixed with (X).

(Received December 3, 1958)