Summary

Synthesis of some steroidal hormones having 6-alkoxy-4,6-dien-3-one structure was carried out. 17β-Acetoxyandrost-4-ene-3,6-dione (V), prepared by oxidation with chromium trioxide of 6β-hydroxy-17β-acetoxyandrost-4-en-3-one (VI), was treated with ethanol and *p*-toluenesulfonic acid monohydrate to give 6-ethoxy-17β-acetoxyandrosta-4,6-dien-3-one (VI). The treatment of 17α-acetoxypregn-4-ene-3,6,20-trione (X) with ethanol (or methanol) and *p*-toluenesulfonic acid monohydrate gave 6-ethoxy-(or methoxy)-17α-acetoxypregna-4,6-diene-3,20-dione (XIa or XIb). (X) was synthesized from 17α-acetoxypregn-4-ene-3,20-dione (VII) by the modified method of Romo.

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Tatsuo Ohta and Susumu Mihashi: Furoquinolines. XXI.[*1] Synthesis and Alkoxyl Interchange of 4-Ethoxyfuro[2,3-*b*]quinoline and its 2,3-Dihydro Analogs.

(*Tokyo College of Pharmacy*[*2])

Berinzaghi, Deulofeu, Labriola, and Muruzabal[1] showed that, by the influence of alcoholic alkali, an interchange occurs between the methoxyl group at the 4-position of furoquinoline alkaloid and alkoxyl group of the particular alcohol used. By this means, the ethoxyl and propoxyl analogs of skimmianine (Ia) and ethoxyl analog of γ-fagarine (IIa) were obtained.

The present paper deals with the synthesis of the title compounds and their alkoxyl interchange reaction. Respective refluxing of 4-chloro-3-(2-chloroethyl)carbostyril (I) and its 7-methoxy derivative (II) with ethanolic potassium hydroxide solution gave 4-ethoxy-2,3-dihydrofuro[2,3-*b*]quinoline (III) and its 7-methoxy derivative (IV). Dehydrogenation of (III) with N-bromosuccinimide in the presence of benzoyl peroxide, followed by heating of the product with collidine, yielded 4-ethoxyfuro[2,3-*b*]quinoline (V), identical with the ethoxyl analog[2] of dictamnine obtained previously by alkoxyl interchange of dictamnine.

Reconversion of (V) to dictamnine (VI) with 10% methanolic potassium hydroxide solution was concluded easily but 2,3-dihydrodictamnine (VII), 2,3-dihydroevolitrine (VIII), and 2,3-dihydroskimmianine (IX) did not undergo transformation, except (VII) into (III), into the corresponding ethoxyl analogs with 10% ethanolic potassium hydroxide solution. Further, an attempt was made to obtain (VII) and (VIII) respectively from (III) and (IV) with 10% methanolic potassium hydroxide solution, but it failed in spite of prolonged heating or the reaction in sealed tube.

From these experimental results, it may be concluded that the carbon atom in the 4-position of the furo[2,3-*b*]quinoline ring has small electron density due to the overlapping of the resonance effect of the furan and pyridine ring. Therefore, the alkoxyl group in the 4-position of the furoquinoline alkaloids is quite easily substituted with other alkoxide ions.

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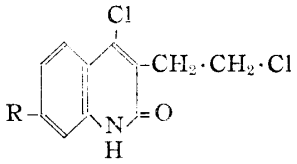
*1 Part XX. T. Ohta, *et al.*: This Bulletin, **8**, 377 (1960).

*2 Kashiwagi 4-chome, Shinjuku-ku, Tokyo (太田達男, 三橋 進).

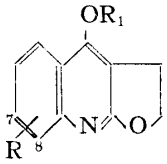
1) B. Berinzaghi, V. Deulofeu, R. Labriola, A. Muruzabal: J. Am. Chem. Soc., **65**, 1357 (1943).

2) T. Ohta, *et al.*: Tokyo Yakka Daigaku Kenkyû Nempô, **4**, 255 (1954).

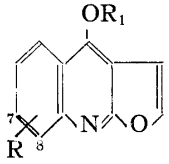
On the other hand, the resonance of the furan ring is lost by hydrogenation and further the oxygen atom in the furan ring contributes *-E* effect to the quinoline ring. Accordingly, 2,3-dihydrofuro[2,3-*b*]quinolines are less reactive to anionoid reagents. These considerations are supported by Buchmann and Hamilton,[3] who demonstrated that the 2-alkoxyl group in quinoline decreases the activity of the 4-chlorine radical towards nucleophilic substitution.



(I) R=H
(II) R=MeO



(III) R=7,8-H, R_1=Et
(IV) R=7-MeO, R=8-H, R_1=Et
(VII) R=7,8-H, R_1=Me
(VIII) R=7-MeO, R=8-H, R_1=Me
(IX) R=7,8-MeO, R_1=Me



(Ia) R=7,8-MeO, R_1=Me
(IIa) R=7-H, R=8-MeO, R_1=Me
(V) R=7,8-H, R_1=Et
(VI) R=7,8-H, R_1=Me

Experimental

4-Ethoxy-2,3-dihydrofuro[2,3-*b*]quinoline (III)——4-Chloro-3-(2-chloroethyl)carbostyril (I) (1.0 g.) was refluxed with 10% EtOH-KOH solution (50 cc.) for 2 hr., the solvent was evaporated, and water (100 cc.) was added to the residue. The reddish brown oily substance thereby obtained was dissolved in $CHCl_3$, washed with water, dried, and the solvent was distilled off. The dehyd. benzene solution of the residue obtained was passed through an Al_2O_3 column (1.2×10 cm.). The effluent liquor showing a violet fluorescence under ultraviolet ray was discarded and the following effluent of benzene solution exhibiting faint blue fluorescence under ultraviolet ray was evaporated. The residue (0.38 g., m.p. 111~118°) was crystallized from 50% MeOH to white needles, m.p. 122.5~123°. *Anal.* Calcd. for $C_{13}H_{13}O_2N$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.94; H, 6.13; N, 6.51.

4-Ethoxy-7-methoxy-2,3-dihydrofuro[2,3-*b*]quinoline (IV)——4-Chloro-7-methoxy-3-(2-chloroethyl)carbostyril (II) (350 mg.) was heated under reflux with 15% EtOH-KOH solution (18 cc.) for 3.5 hr. and treated as described above. The anticipated (IV) was obtained from the eluate of a chromatogram of Al_2O_2 as white needles, m.p. 191~192.3°(from EtOH). *Anal.* Calcd. for $C_{14}H_{15}O_3N$: N, 5.71. Found: N, 5.46.

4-Chloro-7-methoxy-2,3-dihydrofuro[2,3-*b*]quinoline,[4] m.p. 129~133°, was separated from the lower chromatogram in yield of 108 mg.

4-Ethoxyfuro[2,3-*b*]quinoline (V)——A mixture of 65 mg. of (III), N-bromosuccinimide (54 mg.), benzoyl peroxide (2 mg.), anhyd. AcONa(400 mg.), CCl_4 (20 cc.), and glacial AcOH (1 cc.) was refluxed for 4 hr. on a water bath. After cool, the whole was poured into 2% NaOH solution, the CCl_4 layer was washed with water, dried, and the solvent was evaporated *in vacuo*. The residue was heated with collidine (b.p. 159~162°) for 7 hr. on an asbestos wire gauze and the solvent was distilled off *in vacuo*, by which a brown oily matter was obtained. This was chromatographed on Al_2O_3 (1.5×10 cm.) in hexane solution and the chromatogram exhibiting faint blue fluorescence under ultraviolet ray was eluted with $CHCl_3$, from which needle crystals were obtained. Its picrate crystallized from MeOH to pillars, m.p. 188~189°, and was identified with that prepared from (V) obtained by alkoxyl interchange of dictamnine.

Dictamnine from (V)——To 25 mg. of (V), 10% MeOH-KOH solution (1 cc.) was added and refluxed for 2 hr. After removal of the solvent, water was added to the residue, and the insoluble matter was taken up in $CHCl_3$. The crystallization of the $CHCl_3$ residue from hexane gave crystals of m.p. 132°, which showed no depression of m.p. when mixed with authentic dictamnine, m.p. 133°.

Conversion of (VII) to (III)——It was carried out by refluxing a mixture of 20 mg. of (VII) and 10% EtOH-KOH solution (1 cc.) for 3 hr. Yield, 8.6 mg. The crystals purified from hydr. EtOH were identified with the specimen of (III) described above.

Attempted Conversion of (VIII) and (IX) to the Ethoxyl Analogs——Dihydroevolitrine (60 mg.) and dihydroskimmianine (100 mg.) were respectively heated to boil with 10% EtOH-KOH solution for 3.5 hr. The original compounds were recovered in both cases.

3) F. J. Buchmann, C. S. Hamilton: J. Am. Chem. Soc., **64**, 1357 (1942).
4) T. Ohta, Y. Mori: Proc. Japan Acad., **33**, 346 (1957).

Attempted Conversion of (III) and (IV) to (VII) and (VIII)——Refluxing of (III) with 10% MeOH-KOH solution for 5 hr. or heating in a sealed tube for 3 hr. in boiling water resulted in recovery of the original material. The same treatment of (IV) failed to produce (VIII).

The authors are indebted to Mrs. Baba and Miss Okabe for the microanalyses.

Summary

The ethoxyl analogs of 2,3-dihydrodictamnine (III) and 2,3-dihydroevolitrine (IV) were prepared from the corresponding 4-chloro-3-(2-chloroethyl)carbostyrils (I and II) by heating with ethanolic alkali. Dehydrogenation of (III) gave the ethoxyl analog of dictamnine (V), whose alkoxyl interchange with methanolic potassium hydroxide furnished dictamnine (VI). 2,3-Dihydrodictamnine (VII), 2,3-dihydroevolitrine (VIII), and 2,3-dihydroskimmianine (IX) did not undergo conversion, except (VII), to the corresponding ethoxyl analogs with ethanolic alkali. An attempted conversion of (III) and (IV) to the respective (VII) and (VIII) failed.

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Toshiro Murata: Metabolic Fate of 1-Ethynylcyclohexyl Carbamate. IV.[*1] Supplementary Studies on the Glucuronide excreted from the Urine of Man receiving 1-Ethynylcyclohexyl Carbamate.

(*Faculty of Pharmacy, University of Kumamoto*[*2])

In the previous paper[2] of this series, isolation of a glucuronide from the urine of man who received 1-ethynylcyclohexyl carbamate (ECC) orally was reported. The glucuronide thus obtained was paper chromatographically proved to be a glucuronide of 1-ethynyl-4-hydroxycyclohexyl carbamate (OH-ECC) which has been isolated as a metabolite of ECC by the present author[2] and by McMahon,[3] and whose chemical structure was established by McMahon.[4]

In the present work, attempt was made to obtain crystalline derivative of the glucuronide. The purified glucuronide was successively methylated and acetylated with diazomethane and acetic anhydride. The derivative obtained was identified as methyl [(4-ethynyl-4-carbamyloxycyclohexyl) tri-O-acetyl-β-D-glucopyranosid]uronate from its elemental analysis and infrared absorption spectrum.

Experimental

Isolation of Urinary Glucuronide of OH-ECC——Isolation of the glucuronide was carried out by the method described in a previous paper.[2]

Preparation of Derivative of the Glucuronide——An Et_2O solution of CH_2N_2, freshly prepared

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*1 Part III. This Bulletin, **9**, 167 (1961).
*2 Kuhonji, Ōe-machi, Kumamoto (村田敏郎).
1) Part II. T. Murata: This Bulletin, **9**, 146 (1961).
2) T. Murata: *Ibid.*, 8, 629 (1960).
3) R. E. McMahon: J. Am. Chem. Soc., **80**, 411 (1958).
4) *Idem*: J. Org. Chem., **24**, 1834 (1959).