Notes

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Synthesis of Quinolizine Derivatives. XIII.[*4] On the Relationship between Chemical Structure and Uterus Contracting Action of Quinolizidine Derivatives, and Synthesis of Some of these Derivatives.

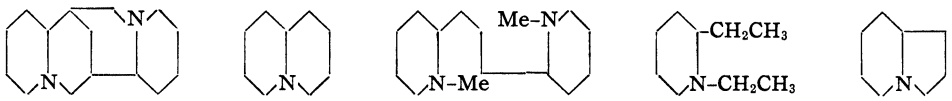
Sadao Ohki,[*1] Yoshiya Noike,[*2] Ichiro Matsuo,[*3] Fumiko Hamaguchi,[*1] and Tokuko Yanagi[*1]

*(Women's Department, Tokyo College of Pharmacy,[*1] Faculty of Pharmaceutical Sciences, University of Tokyo,[*2] and Medical Department, Self Defense Force[*3])*

Sparteine, the alkaloid of *Cytisus scoparius* and *Spartium scoparium*, has been used from olden times as a cardiotonic diuretic but since its effect is not reliable, it is hardly used in the present day for this purpose. Later, this alkaloid was found to have an uterus contracting action[1] and has been used widely for this objective since the second World War.

Sparteine preparation is mild and has a good uterus contracting action, and is devoid of various side effects that are usual in ergot and posterior pituitary preparations, such as convulsion, slackening of the uterus after use, sickness, and vomiting. Such a fact indicates that the mode of action of this alkaloid is different from that of other preparations. However, the action of this alkaloid is fairly weak and it was desirable to find substances with sparteine-like action. In order to attain this end, several attempts had been made in the past.[2~5]

Since sparteine (I) can be considered as two quinolizidine (II) rings fused at 1-, 2-, and 3-positions, the action of (II) was first examined. (II) shows an effect about 2.5 times that of (I). On the other hand, 1,1'-dimethyl-2,2'-trimethylenedipiperidine (III) and 1,2-diethylpiperidine (IV), formed by cyclization of the quinolizidine ring in (I) and (II), have almost no effect, while indolizidine (V), having a bridge-head nitrogen in the bond connecting the two rings, has only a weak effect.



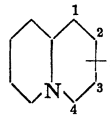
(I) (II) (III) (IV) (V)

It was assumed from the foregoing facts that at least one quinolizidine ring was necessary for a compound to show uterus contracting action like sparteine.

Therefore, tests were made with comparatively simple quinolizidine derivatives and the results obtained are listed in Table I. Comparatively strong effect was found in

*1 Ueno Sakuragi-cho, Taito-ku, Tokyo (大木貞雄, 浜口文子, 柳 徳子).
*2 Present address: Tokyo Research Laboratory, Tanabe Seiyaku Co., Ltd. Shimo-toda, Toda-machi, Kita-adachi-gun, Saitama-ken (野池美哉).
*3 Ikejiri, Setagaya-ku, Tokyo (松尾市郎).
*4 Part XII: Yakugaku Zasshi, **81**, 1083 (1961).

1) S. Okamoto: Kinki Sanfujinka Gakkai Kaiho, **3**, 151 (1917); H.O. Kleine: Klin. Wochschr., **1**, 360 (1939); F. Hisanaga: Fukuoka Igaku Zasshi, **40**, (2), 89 (1949); B. Nuki, F. Hisanaga: Folia Pharmacologica Japonica, **44**, (3), 11 (1949).
2) S. Ohki, Y. Noike: Yakugaku Zasshi, **72**, 490 (1952).
3) S. Ohki, Y. Noike K. Yamakawa: This Bulletin, **1**, 114 (1953).
4) S. Ohki, K. Yamakawa: *Ibid.*, **1**, 260 (1953).
5) S. Ohki, *et al.*: Yakugaku Zasshi, **79**, 1522 (1959).

TABLE I.  hydrochloride

Compd. No.	R	Activity[a] (Sparteine sulfate as 1)
(II)	H[6]	2.5
(VI)	3-*n*-C_3H_7[7]	0.25
(VII)	3-*n*-C_4H_9[7]	5.0
(VIII)	3-*n*-C_5H_{11}[7]	4.5
(IX)	3-iso-C_5H_{11}[7]	5.0
(X)	3-CH_2-CH=CH_2[8]	1.2
(XI)	4-CH_3[9,10]	0.25
(XII)	4-C_2H_5	0.2
(XIII)	3-CH_2OH[4]	0.17
(XIV)	3-C_6H_5[3]	1.6
(XV)	3-CH_2-C_6H_5[7]	3.0
(XVI)	4-CH_2-C_6H_5[9]	1.0
(XVII)	3-CH_2CH_2-C_6H_5[7]	4.0
(XVIII)	3-CH_2CH_2-OC_6H_5[7]	2.3
(XIX)	3-$(CH_2)_4$-OC_6H_5[11]	2.5
(XX)	3-$(CH_2)_5$-OC_6H_5[7]	0.33
(XXI)	3-CH_2-N$(CH_3)_2$[4]	0.33
(XXII)	3-$CH_2CH_2N(C_2H_5)_2$[2]	0.2
(XXIII)	3-CH_2-N⟨O⟩[7]	0.15
(XXIV)	3-CH_2NH-C_6H_{11}[7]	2.0
(XXV)	3-CH_2NH-C_6H_5[7]	1.0
(XXVI)	3-CH_2NH-C_6H_4-CH_3(*P*)[7]	0.5
(XXVII)	3-CH_2NH-C_6H_4-OCH_3(*P*)[7]	0.65
(XXVIII)	3-CH_2NH-CH_2CH_2-C_6H_5[7]	0.33
(XXIX)	3-CH_2NH-CH_2CH_2-C_6H_5[7]	1.0
(XXX)	3-CH_2NH-$C_{10}H_7$(*α*)[7]	0.60

a) All pharmacological tests were made with the hydrochloride of samples or the sample solution neutralized with hydrochloric acid, by the Magnus method using excised uterus of a guinea pig. Strength of the action was represented by the approximate ratio of effect to sparteine sulfate. Pharmacological tests were chiefly carried out by Mr. Saburo Tamura of the Fujisawa Pharmaceutical Industries, Ltd.

TABLE II.

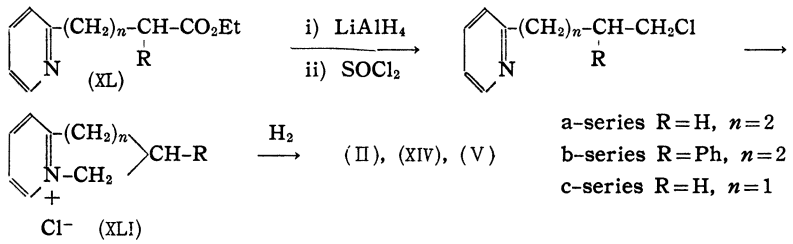
Compd. No.	Hydrochloride of	Activity[a] (Sparteine sulfate as 1)
(XXXI)	3-Methylindolizidine[12]	0.2
(XXXII)	3-Phenylindolizidine[12]	1.0
(XXXIII)	3-Phenylpyrrolizidine[12]	2.0
(XXXIV)	3,3′-Tetramethylenediquinolizidine[11]	1.0
(XXXV)	3,3′-Spirodiquinolizidine[5]	0.2
(XXXVI)	Dipiperido[1,2-*a*:1′,2′-*d*]piperazine[13]	1.25
(XXXVII)	Matrine	0
(XXXVIII)	Deoxynupharidine	0.5
(XXXIX)	*α*-Isosparteine[14]	1.0

a) Same as in Table I

6) *a*) G.R. Clemo, G.R. Ramage: J. Chem. Soc., **1931**, 437, 3190. *b*) V. Boekelheide, S. Rothchild: J. Am. Chem. Soc., **71**, 879 (1949). *c*) S. Ohki, Y. Noike: Paper presented at the 73rd General Meeting of the Pharmaceutical Society of Japan (1953). *d*) C. Tani, K. Ishibashi: Yakugaku Zasshi; **77**, 324 (1957).
7) I. Matsuo: Yakugakn Zasshi, **81**, 1083. (1961)
8) I. Matsuo, S. Ohki: *Ibid.*, **81**, 1075 (1961).
9) I. Murakoshi: *Ibid.*, **78**, 594 (1958).
10) N.J. Leonard, *et al.*: J. Am. Chem. Soc., **78**, 3456 (1956).
11) S. Ohki, I. Matsuo: This Bulletin, **7**, 892 (1959).
12) I. Murakoshi: Yakugaku Zasshi, **78**, 598 (1958).
13) T. Kato: *Ibid.*, **75**, 1239 (1955); K. Winterfeld, E. Will: Naturwiss., **42**, 178 (1955); F. Šorm: C.A., **43**, 2996 (1949).
14) F. Galinovsky, P. Knoth, W. Fischer: Monatsh., **86**, 1014 (1955).

3-butyl- (Ⅶ), 3-pentyl- (Ⅷ), 3-isopentyl- (Ⅸ), and 3-phenethyl-quinolizidine (XVII), and these compounds were found to have less side effects than (I).*5 Tests were also made with natural lupinus alkaloid, indolizidine derivatives, and analogous compounds but none of the compounds had any marked activity (Table Ⅱ).

Synthetic procedures for the compounds listed in the tables and not reported in the past literature and some of the known compounds by a different route were as follows: 4-Ethylquinolizidine (Ⅻ) was obtained by the Grignard reaction of 4-quinolizidinone[15] and ethylmagnesium bromide, hydrolysis of its product and dehydration, followed by catalytic reduction. Quinolizidine[6] (Ⅱ), 3-phenylquinolizidine (XIV), and indolizidine (Ⅴ)[16] were obtained by reduction of pyridinecarboxylic acid ester (XLa, b, c[17]) with lithium aluminum hydride, chlorination of the alcohol so formed, and intramolecular cyclization of its product to tetrahydroquinolizinium chloride (XLIa, b) and dihydroindolizinium chloride (XLIc), followed by their catalytic reduction.



1,2-Diethylpiperidine (Ⅳ) and 1,1′-dimethyl-2,2′-trimethylenedipiperidine (Ⅲ) were obtained by catalytic reduction of the methohalide of 2-ethylpyridine[18] and bis(2-picolyl)-methane.[19]

Experimental

4-Ethylquinolizidine*6 (XII)——4-Quinolizidinone[15] : A solution of 10.0 g. of ethyl 4-oxo-3-quinolizidine carboxylate and 3.1 g. of KOH in 60 cc. of EtOH was refluxed on a water bath for 5 hr. to effect saponification, EtOH was evaporated in a reduced pressure, and the residue was dissolved in water. This solution was acidified with AcOH, boiled for a few minutes to effect decarboxylation, and the solution was neutralized with Na_2CO_3. The solution was salted out with K_2CO_3, the separated oily substance was taken up in Et_2O, and Et_2O was evaporated in a reduced pressure after drying over Na_2SO_4. Low-pressure distillation of the residue afforded a fraction of b.$p_{4.5}$ 113～114°. Yield, 2.20 g.

4-Ethyl-Δ^3-dehydroquinolizidine : A solution of 2.0 g. of 4-quinolizidinone dissolved in dehyd. Et_2O was added dropwise into a Grignard reagent prepared from 2.8 g. of EtI, 0.63 g. of Mg, and 20 cc. of dehyd. Et_2O and the mixture was refluxed with stirring for 1 hr. Et_2O was then evaporated, the solid residue was heated for 1 hr. on a water bath, satd. NH_4Cl solution was added, and the mixture was allowed to stand over night. Saturated NaF solution was added, the mixture was filtered, and 40% NaOH was added to the filtrate. This alkaline mixture was extracted several times with Et_2O, Et_2O extract was dried over K_2CO_3, and evaporated. The residue was distilled in a reduced pressure and a pale yellow oil, b.p_4 70～86°, was obtained. This oil underwent decomposition on contact with air. Yield, 1.08 g.

(Ⅻ) from the Dehydro Compound : EtOH solution of 1.08 g. of the dehydro compound was submitted to catalytic reduction over PtO_2. The catalyst was filtered off, EtOH was evaporated from the filtrate,

*5 Detailed animal experiments were made by Messrs. S. Tomizawa and K. Kondo, results of which will be reported by them elsewhere.

*6 cf. The synthesis of 4-methylquinolizidine.[10]

15) W. E. Doering, R. A. N. Weil : J. Am. Chem. Soc., **69**, 2461 (1947).
16) cf. K. Winterfeld, E. Muller : Arch. Pharm., **284**, 269 (1951).
17) R. E. Counsell, T. O. Soine : J. Am. Pharm. Assoc., **49**, 289 (1960).
18) E. C. Gregg, Jr., D. Craig : J. Am. Chem. Soc., **70**, 3138 (1948).
19) N. J. Leonard, J. H. Boyer : *Ibid.*, **72**, 4818 (1950).

and the residue was distilled in a reduced pressure. Colorless oil, b.p_{20} 136°. Yield, 0.68 g.
Picrate : Yellow needles (from EtOH), m.p. 140~142°. *Anal.* Calcd. for $C_{11}H_{21}N \cdot C_6H_3O_7N_3$: C, 51.51; H, 6.06. Found : C, 51.28; H, 5.67.

3-Phenylquinolizidine (XIV)——β-Phenyl-2-pyridinebutanol : A solution of 2.7 g. of ethyl α-phenyl-2-pyridinebutyrate[3] (XLb) in 20 cc. of dehyd. Et_2O was added dropwise into a dehyd. Et_2O solution of 0.3 g. of $LiAlH_4$, with stirring and cooling in ice, and the mixture was stirred for 4 hr. at room temperature. The yellowish green solution was diluted with 2 cc. of AcOEt and 5 cc. of H_2O to decompose excess $LiAlH_4$ and the double salt, and the mixture was filtered. The Et_2O layer was dried over Na_2SO_4 and evaporated. The residue was distilled in a reduced pressure to furnish a yellow oil, b.$p_{0.08}$ 140~145°. Yield, 2.0 g. (87%).
3-Phenyl-1,2,3,4-tetrahydroquinolizinium Chloride (XLIb) : A dehyd. $CHCl_3$ solution of 1.2 g. of $SOCl_2$ was added dropwise into a solution of 1.8 g. of the above alcohol compound dissolved in dehyd. $CHCl_3$, with ice cooling. The mixture was warmed for 1 hr. on a water bath, and $CHCl_3$ and excess $SOCl_2$ were evaporated in a reduced pressure. The residue was dissolved in H_2O, basified with Na_2CO_3, salted out with K_2CO_3, and extracted with benzene. After drying over Na_2SO_4, the benzene solution was refluxed for 5 hr., by which crystals gradually precipitated out. The crystals were collected by filtration and furnished 0.47 g. of the chloride (XLIb) as deliquescent colorless needles. The filtrate was evaporated in a reduced pressure and the oily residue crystallized to furnish 0.47 g. of the same chloride. Total yield, 0.94 g. (48%).

This chloride was converted by the usual procedure into the iodide of colorless needles (from H_2O), m.p. 151°. *Anal.* Calcd. for $C_{15}H_{16}NI$: C, 53.41; H, 4.14; N, 4.15. Found : C, 53.37; H, 4.36; N, 4.57.
(XIV) from (XLIb) : EtOH solution of 0.5 g. of the chloride (XLIb) was submitted to catalytic reduction over PtO_2, the catalyst was filtered off, and EtOH was evaporated from the filtrate. The residue was dissolved in water, the solution was basified, and extracted with Et_2O. After drying over K_2CO_3, Et_2O was evaporated and the residue was distilled in a reduced pressure to furnish a colorless oil, b.p_3 101~106°. Yield, 0.24 g. (55%).
Picrate : Yellow needles (from EtOH), m.p. 153~154° (softening from ca. 148°).*7 *Anal.* Calcd. for $C_{15}H_{21}N \cdot C_6H_3O_7N_3$: N, 12.61. Found : N, 12.49.

This picrate showed no depression of the melting point on admixture with the picrate (m.p. 152~153°, after sintering) of 3-phenylquinolizidine.

Quinolizidine[6] (II)——Prepared according to the procedure for (XIV). δ-(2-Pyridyl)butanol[20] : Obtained from ethyl 2-pyridine butyrate[6b,15] (XLa) in 97% yield as colorless oil, b.p_6 145°.
Phenylurethan : Colorless prisms, m.p. 90°.
1,2,3,4-Tetrahydroquinolizinium Chloride (XLIa) : Obtained from 2-(4-chlorobutyl)pyridine, formed by chlorination of the alcohol compound. Deliquescent colorless crystals.
Gold salt : Yellow plates, m.p. 190~192°. *Anal.* Calcd. for $C_9H_{12}NAuCl_4$: C, 22.83; H, 2.53; Au, 42.77. Found : C, 23.33; H, 2.82; Au, 41.63.
(II) was finally obtained by reduction of (XLIa). Colorless oil b.p_{15} 70°.
Picrate : Yellow crystals, m.p. 198°.

Indolizidine[16] (V)——Obtained from ethyl 2-pyridinepropionate[17,20] by the same procedure as above. Colorless oil, b.p_{20} 50°.
Picrate : Yellow crystals, m.p. 230°.

1,2-Diethylpiperidine (IV) Hydrochloride——2-Ethylpyridine[18] : EtOH solution of 5.65 g. of 2-vinylpyridine, in AcOH acidity, was submitted to catalytic reduction over PtO_2 until absorption of 1300 cc. of H_2. The solution was treated in a conventional manner and 2-ethylpyridine was obtained as a colorless oil, b.p_{16} 140~142°. Yield, 3.20 g. (55%).
Picrate : Yellow needles, m.p. 107~108°.
Ethiodide : A mixture of 1.90 g. of 2-ethylpyridine and 8.42 g. of EtI was warmed on a water bath for 3 hr. Pale yellow needles (from dehyd. EtOH-Et_2O mixture), m.p. 115~118°. Yield, 2.76 g. (57%). *Anal.* Calcd. for $C_9H_{14}NI$: C, 41.08; H, 5.33; N, 5.33. Found : C, 40.66; H, 4.99; N, 5.16.
Hydrochloride of (IV) from the Ethiodide : The ethiodide was converted to the chloride by the usual procedure and its EtOH solution was submitted to catalytic reduction over PtO_2. The catalyst was filtered off, EtOH was evaporated from the filtrate, and the pale yellow oil that remained gradually solidified to colorless needles, (from AcOEt), m.p. 191~192°. Yield, 0.39 g. (18.3%). *Anal.* Calcd. for $C_9H_{20}NCl$: C, 60.85; H, 11.27; N, 7.89. Found : C, 60.35; H, 11.07; N, 8.20.

1,1'-Dimethyl-2,2'-trimethylenedipiperidine (III)——A mixture of 1.5 g. of 2,2'-trimethylenedipyri-

*7 The picrate of (XIV) was obtained as crystals of m.p. 152~153° and of m.p. 180~181°.[3] The former is considered to be a mixture of two kinds of diastereomers, on account of insufficient separation. Attempted separation of this picrate was not effected.

20) T. Morikawa : Yakugaku Zasshi, **75**, 593 (1955).

dine[19] and 10.0 g. of MeI was warmed in MeOH on a water bath for 3 hr., allowed to stand at room temperature over night, and filtered to collect the methiodide as pale yellow crystals (from MeOH), m.p. 242° (decomp.). Yield, 0.93 g.

The methiodide was converted to the chloride by the usual procedure and its EtOH solution was submitted to catalytic reduction over PtO_2. The catalyst was filtered off, EtOH was evaporated from the filtrate, and the residue was dissolved in H_2O. This solution was basified with Na_2CO_3, salted out with K_2CO_3, and extracted with Et_2O. After drying over K_2CO_3, Et_2O extract was evaporated and the residue was distilled in a reduced pressure to furnish colorless oil, $b.p_{10}$ 135°. Yield, 0.53 g. (54%).

Dipicrate: Yellow crystals, m.p. 208~209° (from EtOH). *Anal.* Calcd. for $C_{15}H_{30}N_2 \cdot 2C_6H_3N_3O_7$: C, 46.55; H, 5.17; N, 16.09. Found: C, 46.20; H, 5.26; N, 15.73. Au-salt: Yellow crystals, m.p. 210° (decomp.). *Anal.* Calcd. for $C_{15}H_{30}N_2 \cdot 2HAuCl_4$: C, 19.65; H, 3.49; Au, 42.85. Found: C, 19.58; H, 3.37; Au, 42.49.

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Summary

3-Butyl-, 3-pentyl-, 3-isopentyl-, and 3-phenethylquinolizidines were found to have a comparatively strong uterus-contracting action like that of sparteine.

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Sumiyuki Akihama and Shigeshi Toyoshima: Antiviral Effect of Zinc Complexes on Japanese B Encephalitis Virus.*[1]

(*Pharmaceutical Institute, Keio-Gijuku University.*[2])

Ueda and Toyoshima[1] reported that *erythro*-1-(*p*-tolyl)-2-aminopropanol methansulfonate named "Methodrine" exerted a therapeutic effect on Japanese B encephalitis in mice. Totani[2] also found that a curative effect on patients suffering from Japanese B encephalitis (90% of patients were completly cured) was obtained by the simultaneous administration of this drug and ACTH-Zn, and asserted that such a synergistic action was not observed with other adrenocortical steroid drugs and ACTH preparation containing no zinc. These findings suggested that zinc itself might possess an antiviral effect or potentiate the effect of other drugs on the virus. This paper describes a survey of the antiviral effect of zinc complexes of several amino acids and organic reagents on Japanese B encephalitis virus in mice.

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*2 Shinjuku-ku, Tokyo (秋浜澄行, 豊島 滋).

1) T. Ueda, S. Toyoshima, K. Takahashi, M. Muraoka: Keio J. Medicine, 8, 199 (1959).
2) T. Totani: Read before the committee for the treatment of Japanese B encephalitis in Tokyo. October, 1959.