UDC 547.94:582.751.9

125. Kazuko Narahashi: Alkaloids of the Root-bark of *Orixa japonica* THUNB. XI.*1 The Structures of Orixidine and Orixidinine.

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Orixine $C_{17}H_{21}O_6N$ was isolated in 1931 from *Orixa japonica* THUNB. by Terasaka,[1] who, in 1959, proposed structure (I) for this compound.[2] When orixine is treated with dry hydrogen chloride in ether, it loses one methoxyl group and is converted into nororixine (II), while when heated with 10~20% hydrochloric acid, it loses two methoxyl groups and two substances, orixidine $C_{15}H_{13}O_4N$ and orixidinine $C_{15}H_{15}O_5N$, are produced.

By the study of ultraviolet and infrared spectra, these substances are assumed to be 2(1*H*)-quinolone derivatives resulting from a ring closure between C-3 in the side chain and C-4 in the quinoline ring.[2]

The following discussions are based upon the experimental evidence which leads to structure elucidation of these compounds. When orixine (I) and nororixine (II) are heated with 10~20% hydrochloric acid and the resulting products are subjected to a careful chromatography, both orixidine, m.p. 191°, and orixidinine, m.p. 210°, are produced. Isoorixine (III) (N-methyl isomer of orixine) produces under a similar condition N-methylorixidine $C_{16}H_{15}O_4N$, m.p. 154~155°, and N-methylorixidinine $C_{16}H_{17}O_5N$, m.p. 212~213°.

Orixidine is optically inactive, and has one methylenedioxy group and one terminal methyl group by Kuhn-Roth oxidation method.

It resists periodic acid oxidation and catalytic hydrogenation at room temperature; it absorbs, however, one mole of hydrogen at 35~45° in the presence of palladium-carbon and is converted into dihydroorixidine, m.p. 226°.*3 It is noted that the ultraviolet spectrum of dihydroorixidine is very different from that of orixidine, but is very similar to orixidinine. The same relationship is observed in the case of their N-methyl derivatives. (Fig. 1)

On treatment with diazomethane in ether, orixidine produces N-methylorixidine, which is also obtained by heating isoorixine (III) with hydrochloric acid. The infrared spectra of orixidine and N-methylorixidine reveal the absence of the hydroxyl and methoxyl groups. On the basis of these results it seems that both dehydration and cyclization occur between hydroxyl group in the side chain and 2- or 4-position in the quinoline ring to form either angular or linear furoquinolone (IV), (VI) or pyranoquinolone type (VII), (VIII).

When orixidine is subjected to ozonolysis, neither formaldehyde, acetone nor 2-hydroxy-2-methylpropionic acid is formed, but isobutyric acid can be detected. This fact, coupled with the difference between the ultraviolet spectrum of orixidine and that of dihydroorixidine and also with the possible position of the double bond, suggests that pyranoquinolone structures (VII) and (VIII) as well as (IX) and (X) should be excluded for orixidine, and it seems reasonable to assume 2(1*H*)-quinolone structure (IV) for it.

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*1 Part X: This Bulletin, 8, 1142 (1960).

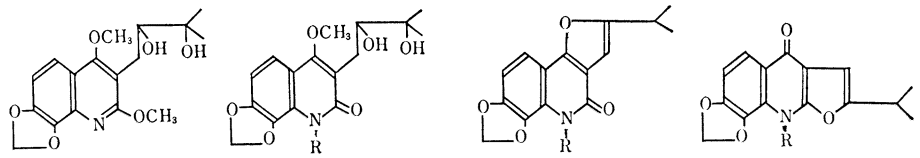
*2 Ueno, Tokyo (奈良橋和子).

*3 In the presence of Pd-C, furoquinoline alkaloids are reduced to dihydrofuroquinoline, while in the presence of Pt-O_2, they are reduced to tetrahydro compounds, i.e. 3-ethylcarbostyril compounds.

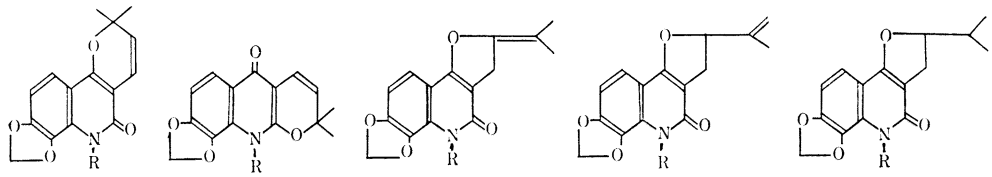
1) M. Terasaka: Yakugaku Zasshi, **51**, 707 (1931).

2) *Idem*: This Bulletin, **7**, 946 (1959); 8, 523 (1960).

This assumption is also comfirmed by infrared and ultraviolet spectral evidence as will be described later. The structures of orixidine and N-methylorixidine are, therefore, assumed to be (IV) and (V), and those of dihydroorixidine and dihydro-N-methylorixidine to be (XI) and (XII), respectively.



(I) (II) R=H (III) R=CH_3 (IV) R=H (V) R=CH_3 (VI)



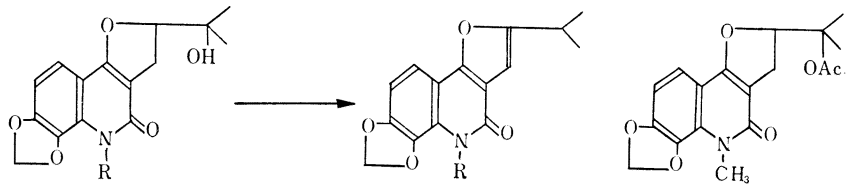
(VII) (VIII) (IX) (X) (XI) R=H (XII) R=CH_3

Orixidinine, produced together with orixidine from orixine, is optically active, $[\alpha]_D^{18.5°}$ −40.76°, has one methylenedioxy group and one terminal methyl group, and resists periodic acid oxidation and catalytic hydrogenation. When treated with diazomethane in ether it affords N-methylorixidinine, which is also produced by heating isoorixine (III) with hydrochloric acid. The ultraviolet spectra of these compounds suggest that they belong to 2(1*H*)-quinolone derivatives, which contain the OH function as exhibited by infrared absorption band at 3488 cm^{-1}. N-methylorixidinine is not acetylated with acetic anhydride and pyridine at room temperature, but under drastic conditions such as refluxing with acetic anhydride or with acetic anhydride and sodium acetate, it affords a monoacetate, m.p. 169~171° in good yield. The ultraviolet spectrum of the acetate is similar to that of N-methylorixidinine (Fig. 2).*4 Chromium trioxide oxidation of N-methylorixidinine and pyrolysis of its acetate results in recovering the original materials, but dehydration of orixidinine and N-methyl-orixidinine with conc. sulfuric acid gives rise to orixidine (IV) and N-methylorixidine (V), respectively, the identity of which was confirmed by admixture and ultraviolet and infrared spectra comparison. In view of these facts orixidinine and N-methylorixidinine are assumed to possess structures (XIII) and (XIV), respectively, and the acetate of the latter, structure (XV).

It is reported that angular furoquinolone is stable toward alkali, while linear furoquinolone is unstable and easily hydrolizable.[4,5]

*4 The fact that the ultraviolet spectrum remains unchanged suggests that expansion of ring C as in the case of balfourodine does not occur during the reaction. H. Rapoport, K.G. Holden: J. Am. Chem. Soc., **82**, 4395 (1960).

4) J.R. Price : Australian J. Chem., **12**, 458 (1959).
5) S. Goodwin, E.C. Horning : J. Am. Chem. Soc., **81**, 1908 (1959).



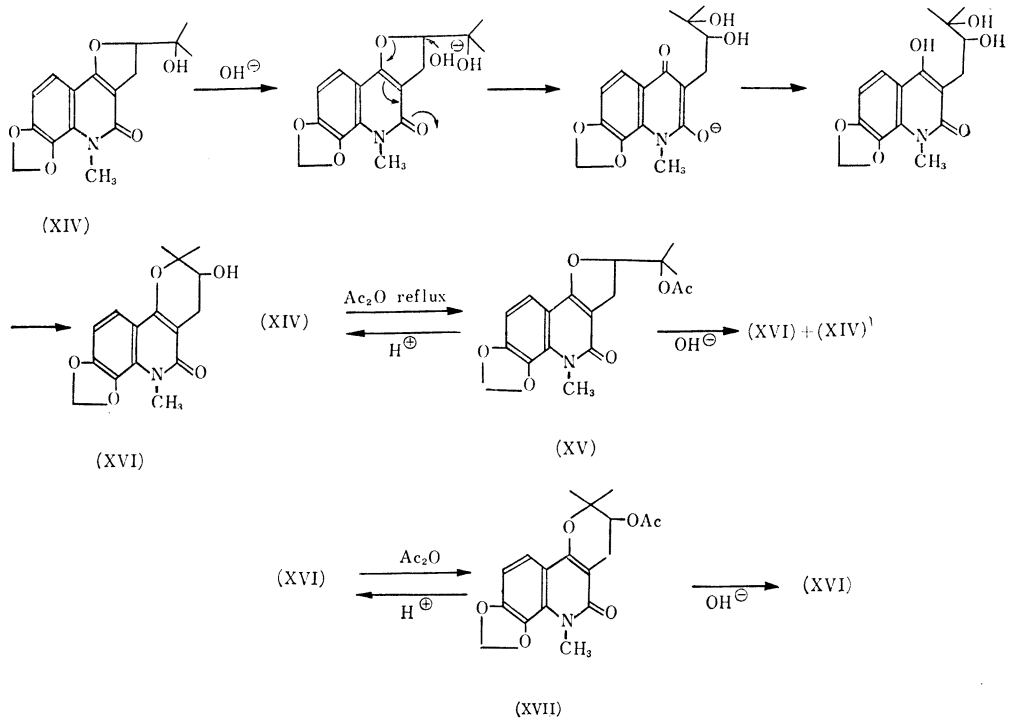
(XIII) R=H (IV) R=H (XV)

(XIV) R=CH_3 (V) R=CH_3

Although orixidine (IV) and N-methylorixidine (V) as well as dihydro compounds (XI) and (XII) are stable toward both acids and alkali, N-methylorixidinine (XIV) and its acetate (XV) having OH-groups in their side chain are stable toward acids but unstable toward alkali, causing an interesting transformation. When heated with ethanolic potassium hydroxide, (XIV) and (XV) afford an isomeric transformation compound (XVI) together with some of the starting material (XIV), the ratio of transformation being proportional to the concentration of alkali used.

Iso-N-methylorixidinine (XVI), $C_{16}H_{17}O_5N$, m.p. 233~234°, is optically active, $[\alpha]_D^{16.5°}$ −26.13°, has one methylenedioxy group and one terminal methyl group, and resists periodic acid oxidation. The presence of an OH group is clearly indicated by an absorption band at 3442 cm^{-1} in the infrared spectrum. Methylation of (XVI) with diazomethane in ether recovers the starting material, but when acetylated with acetic anhydride and pyridine at room temperature, (XVI) gives quantitatively the monoacetate (XVII), m.p. 151~152°, and with tosylchloride and pyridine a tosylate.

An attempt to pyrolize the acetate (XVII) or the tosylate results in recovering the starting materials, and so is the case in dehydration of (XVI) with concentrated sulfuric



(XIV)

(XVI) (XIV) (XV)

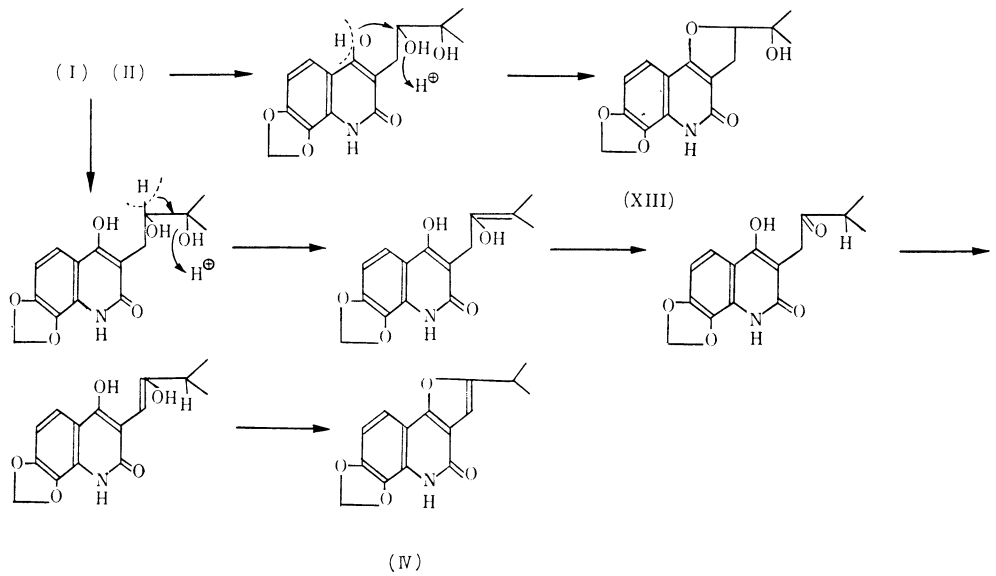
(XVI) (XVII) (XVI)

acid; under more drastic conditions, such as chromium trioxide oxidation, no recognizable substance is obtained. (XVI) is stable toward acids and alkali, whereas its acetate (XVII) is quantitatively saponified to iso-N-methylorixidinine (XVI). The relationship thus far established may be as follows.

The comparison of the ultraviolet spectra of iso-N-methylorixidinine (XVI) and N-methylorixidinine (XIV) shows no marked difference between them, although in (XVI) a series of maxima in the region of 314, 323 (shoulder) and 328 mμ exhibits some hypsochromic shift to 305 and 323 (shoulder) mμ presumably because of the stretching of ring C resulting from the difference between six and five rings.

When orixine (I) or nororixine (II) is treated with 20% hydrochloric acid, orixidine (IV) is mainly produced, whereas when treated with 10% hydrochloric acid, orixidinine (XIII) is the major product. There exists no equilibrium and once produced, orixidine (IV) and orixidinine (XIII) are stable toward acids.

It seems very probable that in orixidine (IV) dehydration of 1,2-glycol at first takes place, followed by ring closure, causing the disappearance of its optical activity, while in orixidinine (XIII) cyclization preceeds dehydration, thus maintaining its optical activity.



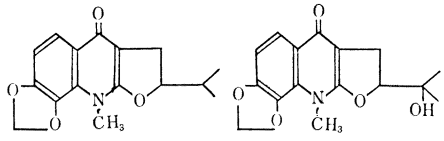
The problem as to whether orixidine and orixidinine have angular furoquinolone structure rather than linear one must be more fully discussed. Arndt[6] studied the reaction of diazomethane on 4-hydroxy-2(1*H*)-quinolone and 1-methyl-4-hydroxy-2(1*H*)-quinolone and proved that only 4-oxygen in their molecule is selectively methylated.

This generalization was further applied to various 4-hydroxy-2(1*H*)-quinolone derivatives[7,8] and contributed toward establishing the linearity of the structures of furoquinoline alkaloids.[9~11] The fact that treatments of orixidine and orixidinine with diazomethane produces N-methyl derivatives and does not generate a methoxyl group, suggests a 2(1*H*)-quinolone structure.

6) F. Arndt, L. Ergener, O. Kutlu : Ber., **86**, 951 (1953).
7) R. F. C. Brown, P. T. Gilham, G. K. Hughes, E. Ritchie : Australian J. Chem., **7**, 181 (1954).
8) R. G. Cooke, H. F. Haynes : *Ibid.*, **11**, 225 (1958).
9) M. F. Grundon, N. J. Mccorkindale : J. Chem. Soc., **1957**, 2177.
10) H. Tuppy, F. Böhm : Monatsh., **87**, 720 (1956).
11) R. F. C. Brown : Australian J. Chem., 8, 121 (1955).

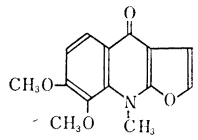
As seen in Tabel I and in Fig. 3, dihydro-N-methylorixidine and N-methylorixidinine are quite different from lunine (XVIII) and hydroxylunine (XIX).[12]

2(1*H*)-Quinolone structure is also supported from the infrared and ultraviolet spectral data. As criteria to angular and linear dihydrofuroquinolone derivatives, infrared absorptions in the 6μ region and ultraviolet absorptions of related substances are given in Table I and in Fig. 3, respectively. The substance listed are lunine (XVIII), hydroxylunine (XIX), recently synthesized 6,7-methylenedioxy-2,3-dihydrofuro[3,2-*c*]quinoline-4(5*H*)-one (XXIII), 5-methyl-6,7-methylenedioxy-2,3-dihydrofuro[3,2-*c*]-quinoline-4-one (XXIV), 9-methyl-7,8-methylenedioxy-2,3-dihydrofuro[2,3-*b*]-quinoline-4-one (XXV) from kokusagine,[13] 7,8-dimethoxy-9-methyl-2.3-dihydrofuro[2,3-*b*]-quinoline-4-one (XXVI) from skimmianine,[14] dihydroorixidines, and orixidinines.

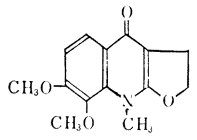


(XVIII)

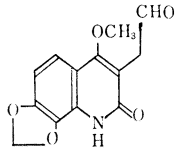
(XIX)



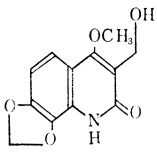
(XXVIII)



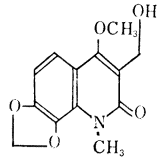
(XXVI)



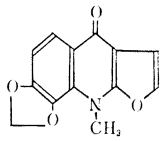
(XX)



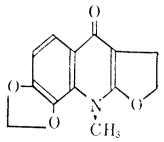
(XXI)



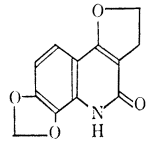
(XXII)



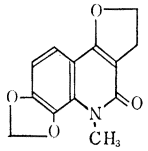
(XXVII)



(XXV)



(XXIII)



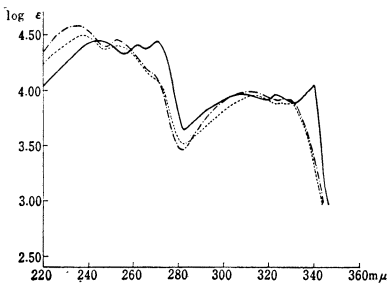
(XXIV)

It is reported[15,16] that 2(1*H*)-quinolones exhibit the first absorption maximum in the 6 μ region at a shorter wave length than 4(1*H*)-quinolones and have a minimum in the region between 6.34 μ (1570 cm^{-1}) and 6.65 μ (1504 cm^{-1}), while in 4(1*H*)-quinolones a characteristic maximum in this region is observed at about 6.43 μ (1553 cm^{-1}).

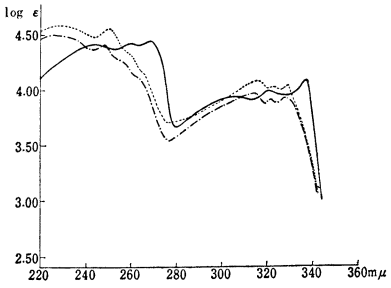
In the case of 2- and 4-pyridones,[17] the absorption of $\nu_{C=O}$ appears at 1666~1655 cm^{-1} in 2-series, and at 1577~1575 cm^{-1} in 4-series. That the first absorption maximum of dihydroorixidine and orixidinine derivatives in the 6 μ region occurs as a broad band at higher wave numbers, accompanied with a minimum in the region between 1515~1575 cm^{-1}, indicates the possibility of the 2(1*H*)-quinolone system for orixidine and orixidinine.

On the basis of pKa measurement Rapoport, *et al.* suggested that 2(1*H*)-quinolones show little change in the ultraviolet absorption when the spectra are measured in acids

12) S. Goodwin, A. F. Smith, A. A. Velasquez, E. C. Horning : J. Am. Chem. Soc., **81**, 6209 (1959).
13) M. Terasaka, T. Ohta, K. Narahashi : This Bulletin, **2**, 159 (1954).
14) Y. Asahina, M. Inubuse : Yakugaku Zasshi, **50**, 1133 (1930).
15) H. Rapoport, K. G. Holden : J. Am. Chem. Soc., **82**, 4395 (1960).
16) M. F. Grundon, N. J. McCorkindale, M. N. Rodger : J. Chem. Soc., 1955, 4284
17) A. R. Katritzky, R. A. Jones : *Ibid.*, 1960, 2947.

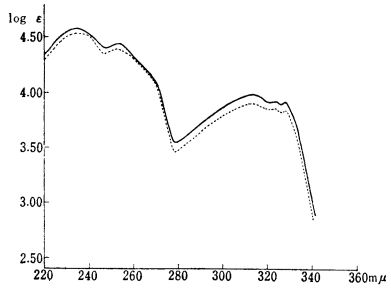


Ultraviolet Spectra (in EtOH)
——— Orixidine (IV)
····· Dihydroorixidine (XI)
—·—·— Orixidinine (XIII)

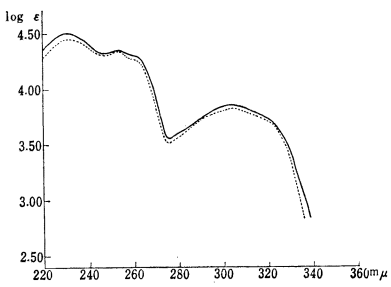


Ultraviolet Spectra (in EtOH)
——— N-methylorixidine (V)
····· Dihydro-N-methylorixidine (XII)
—·—·— N-methylorixidinine (XIV)

Fig. 1.



Ultraviolet Spectra (in EtOH)



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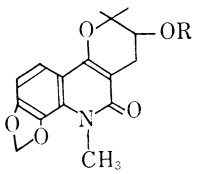
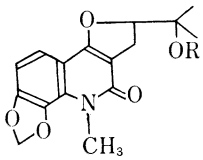
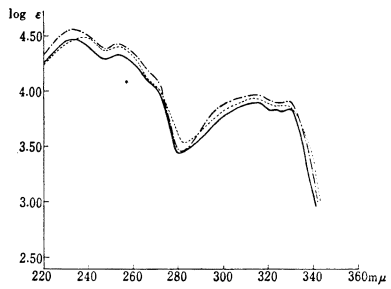


——— R = H (XIV)
····· R = CH_3CO (XV)

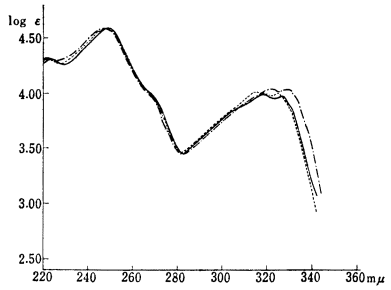


——— R = H (XVI)
····· R = CH_3CO (XVII)

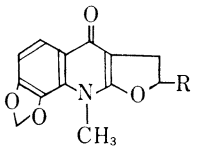
Fig. 2.



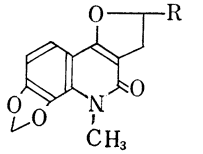
Ultraviolet Spectra (in EtOH)



Ultraviolet Spectra (in EtOH)



——— R = H (XXV)
—·—·— R = $C\langle^{CH_3}_{CH_3}$ (XIX)
OH
····· R = $C\langle^{CH_3}_{CH_3}$ (XVIII)
H



——— R = H (XXIV)
—·—·— R = $C\langle^{CH_3}_{CH_3}$ (XIV)
OH
····· R = $C\langle^{CH_3}_{CH_3}$ (XII)
H

Fig. 3.

Table 1. Infrared Absorptions of 4-Alkoxy-2(1*H*)-quinolones and 2-Alkoxy-4(1*H*)-quinolones

	$\lambda_{max}^{CHCl_3}$ in 6 μ region					
4-Alkoxy-2(1*H*)-quinolones						
II	1659	1640	1580		1499	1489
III	1642	1623	1595		1510	
XI	1670	1631				1486
XII	1658	1627	1605		1512	1465
XIII	1681	1645			1503	1481
XIV	1665	1635	1607		1510	1466
XV	1671	1642	1595		1515	1499
XVI	1644	1622	1598		1503	1470
XVII	1633	1599			1506	
XX	1666	1650	1592		1495	
XXI	1657	1631	1575		1485	
XXII	1633	1600			1500	1471
XXIII	1672	1640			1505	1480
XXIV	1662	1632	1608		1513	1470
2-Alkoxy-4(1*H*)-quinolones						
XVIII		1642	1587	1565	1517	
XIX		1652	1610	1553		1447
XXV		1641	1599	1575	1530 1505	1483
XXVI		1622	1591	1542	1520 1482	1470

or alkali, while 4-quinolones exhibit pronounced shifts in acids,[15] which are mostly, but not always, hypsochromic, or bathochromic[12] in accordance with the variety and position of substituents on the benzene ring.[5,18~20]

The ultraviolet spectra of orixidine (IV), orixidinine (XIII) and the isomeric transformation compound (XVI) do not vary to an appreciable extent in acid solution. It is of particular interest that linear furoquinolones (XVIII), (XIX), (XXV), and (XXVI), have absroption maxima and minima between 220~230 mμ, while all the angular furoquinolones including 2(1*H*)-quinolones exhibit no such bands. All these evidences appear to support the validity of the proposed structures for orixidine and orixidinine.

Experimental*5

Formation of orixidine (IV) and orixidinine (XIII) from (I) : 1. Reaction of (I) with 10% Hydrochloric Acid——A solution of 932 mg. of (I) in 25 cc. of 10% HCl was refluxed over a wire-gauze for 3 hr. and allowed to stand overnight to yield 195.5 mg. of colorless needles (Crystals No. 1), which were collected and washed with H_2O. The filtrate together with the washings was made alkaline with KOH and extracted with Et_2O. The aqueous solution was made ammonia alkaline with NH_4Cl, extracted with $CHCl_3$ and the extract, after washing, drying and removal of the solvent, yielded 589.4 mg. of a grey white powder, which gave on addition of MeOH 499 mg. of colorless prisms (Crystals No. 2). The crystals No. 1 were dissolved in $CHCl_3$, chromatographed over 15 g. of Al_2O_3 and eluted successively with $CHCl_3$ and $CHCl_3$ containing 1% and 2% of MeOH. A main fraction was eluted with $CHCl_3$ containing 2% of MeOH, and crystallized from MeOH to yield 175 mg. of (IV), colorless needles, m.p. 191°. *Anal.* Calcd. for $C_{15}H_{13}O_4N$: C, 66.41; H, 4.83; N, 5.16; O, 23.59; (C)-CH_3, 5.54. Found : C, 66.47; H, 4.84; N, 5.20; O, 23.31; (C)-CH_3, 3.17. (0.57*M*). UV λ_{max}^{EtOH} mμ (log ε) : 243 (4.40), 258.5 (4.42), 268 (4.46), 307 (3.95), 321 (4.01), 336 (4.12). λ_{min}^{EtOH} mμ (log ε) : 252 (4.35), 262.5 (4.39), 279 (3.65), 315 (3.91), 328 (3.94).

The crystals No. 2 were purified by chromatography on 40 g. of Al_2O_3 using a solvent systems of $CHCl_3$ containing 1%, 2%, 3% and 5% of MeOH, and main fraction, which was eluted with $CHCl_3$ containing 5% of MeOH, was crystallized from benzene to yield 395 mg. of (XIII), colorless prisms,

*5 All melting points are uncorrected. N. B. Each fraction from chromatography contains 20 cc. of solvent.

18) G. W. Ewing, E. A. Steck : J. Am. Chem. Soc., **68**, 2181 (1946).
19) E. A. Steck, G. W. Ewing, F. C. Nachod : *Ibid.*, **71**, 238 (1949).
20) R. D. Brown, F. N. Lahey : Australian J. Soc. Res. A, 3, 615 (1950).

m.p. 209~210°. *Anal.* Calcd. for $C_{15}H_{15}O_5N$: C, 62.28; H, 5.23; N, 4.84; O, 27.65; (C)-CH_3, 5.19. Found : C, 62.49; H, 5.02; N, 4.80; O, 27.90; (C)-CH_3, 3.06 (0.59*M*). UV λ_{max}^{EtOH} mμ (log ε) : 226.5 (4.49), 235 shoulder (4.46), 248 (4.41), 265 shoulder (4.01), 314 (3.97), 322 (3.91), 328 (3.95). λ_{min}^{EtOH} mμ (log ε) : 242.5 (4.35); 276 (3.54); 318 (3.89); 324 (3.88).

2. Reaction of (I) with 20% Hydrochloric Acid——A solution of 867 mg. of (I) in 20 cc. of 20% HCl was refluxed for 3 hr. and treated as above to yield 527.0 mg. of crystals No. 1 and 188.8 mg. of crystals No. 2. On purification by chromatography on Al_2O_3, (IV), m.p. 191°, 370 mg., and (XIII), m.p. 210°, 156.5 mg. were obtained.

Formation of orixidine (IV) and orixidinine (XIII) from (II) : 1. Reaction of (II) with 10% Hydrochloric Acid——A solution of 204 mg. of (II) in 5 cc. of 10% HCl was refluxed on an oil bath for 3 hr. and, after cooling, was diluted with 2 volumes of H_2O and extracted with $CHCl_3$. After the $CHCl_3$ extract was washed with H_2O, and dried, the solvent was evaporated. The residue was dissolved in $CHCl_3$ and chromatographed on 30 g. of Al_2O_3.

Fraction No.	Eluant	m.p. (°C)	Yield (mg.)
1~4	$CHCl_3$	187	1.5
5~7	$CHCl_3$ containing 2% of MeOH	181~185	12.2
8	〃 3% of MeOH	204~206	58.6
9~11	〃 5% of MeOH	206~207	18.8

Frs. 5~7 were recrystallized from MeOH to afford colorless needles, m.p. 188~189°, which were identified as (IV) by admixture and infrared and ultraviolet spectra comparison. Frs. 8~11, after recrystallization from a mixture of MeOH-benzene (1:10), afforded colorless prisms, m.p. 208~209°, which were identified as (XIII) by admixture and infrared and ultraviolet spectra comparison.

2. Reaction of (II) with 20% Hydrochloric Acid——A solution of 55 mg. of (II) in 2 cc. of 20% HCl was refluxed for 3 hr. and treated as described above. 39.6 mg. of the residue from the $CHCl_3$ extract was dissolved in $CHCl_3$ and chromatographed on 7 g. of Al_2O_3.

Fraction No.	Eluant	m.p. (°C)	Yield (mg.)
1~2	$CHCl_3$		0.6
3~4	$CHCl_3$ containing 2% of MeOH	181~184	16.8
5~7	〃 3% of MeOH	197~202	7.0
8~10	〃 5% of MeOH	206~207	3.6

Frs. 3~4, on recrystallization from MeOH, afforded colorless needles, m.p. 188~189°, which were identified as (IV) by admixture and infrared spectrum comparison. Frs. 8~10, on recrystallization from benzene, afforded colorless prisms, m.p. 208~209°, which were identified as (XIII) by admixture and infrared spectrum comparison.

Formation of N-methylorixidine (V) and N-methylorixidinine (XIV) from (III) : 1. Reaction of (III) with 10% Hydrochloric Acid——A solution of 30 mg. of (III) in 0.8 cc. of 10% HCl was refluxed for 2 hr. and treated as described above. The residue from the $CHCl_3$ extract was dissolved in $CHCl_3$ and chromatographed on 5 g. of Al_2O_3, eluted first with $CHCl_3$, then with $CHCl_3$ containing 1% of MeOH, and each fraction was crystallized from Me_2CO to yield 2.0 mg. of (V) and 11.0 mg. of (XIV), respectively. They were identified by admixture, infrared and ultraviolet spectra comparison with authentic samples.

2. Reaction of (III) with 20% Hydrochloric Acid——A solution of 30 mg. of (III) in 0.8 cc. of 20% HCl was refluxed for 2 hr. and treated as described above to yield 8.6 mg. of (V) and 2.4 mg. of (XIV). They were identified by admixture, infrared and ultraviolet spectra comparison with authentic samples.

N-Methylorixidine (V)——To a solution of 100 mg. of (IV) in 15 cc. of dehyd. EtOH was added with cooling at 0° in 3 portions 6 cc. of an Et_2O solution of CH_2N_2 and the solution was allowed to stand for 2 days in an ice-box. The solvent and excess CH_2N_2 were removed by distillation and the residue was dissolved in $CHCl_3$ and chromatographed on 15 g. of Al_2O_3. A main fraction eluted with $CHCl_3$ and crystallized from dehyd. EtOH to 69 mg. of colorless needles, m.p. 154~155°. *Anal.* Calcd. for $C_{16}H_{15}O_4N$: C, 67.36; H, 5.30; N, 4.91; N-CH_3, 5.27. Found : C, 67.64; H, 5.14; N, 5.37; N-CH_3, 7.73. UV λ_{max}^{EtOH} mμ (log ε) : 245 (4.69), 261 (4.40), 271 (4.45), 311 (3.99), 323 (3.98), 339 (4.05). λ_{min}^{EtOH} mμ (log ε) : 255 (4.35), 265 (4.38), 282 (3.65), 320 (3.93), 330 (3.89).

N-Methylorixidinine (XIV)——To a solution of 100 mg. of (X) in 30 cc. of dehyd. EtOH was added 6 cc. of an Et_2O solution of CH_2N_2 and the solution was treated as described above. The product obtained was chromatographed on 15 g. of Al_2O_3, eluted with $CHCl_3$ containing 1% of MeOH and crystallized from benzene to 70 mg. of colorless prisms, m.p. 212~213°. *Anal.* Calcd. for $C_{16}H_{17}O_5N$: C, 63.36; H, 5.65; N, 4.62; N-CH_3, 4.96. Found : C, 63.19; H, 5.29; N, 4.69; N-CH_3,

7.18. UV λ_{max}^{EtOH} mμ (log ε) : 233 (4.58), 253 (4.45), 268 shoulder (4.16), 314 (3.99), 323 shoulder (3.92), 328 (3.93). λ_{min}^{EtOH} mμ (log ε) : 246.5 (4.39), 278 (3.55), 326 (3.91), 320 (3.92).

Dihydroorixidine (XI)——A solution of 60 mg. of (IV) in 6 cc. of EtOH was hydrogenated over pd-C (freshly prepared from 3 cc. of 1% $pdCl_2$ and 30 mg. of activated C) at 40～45°, and ca. 2 cc. of H_2 uptake was observed. The hydrogenated product was dissolved in $CHCl_3$ and chromatographed on 10 g. of Al_2O_3. The fraction, on elution with $CHCl_3$ and crystallization from MeOH afforded 15 mg. of colorless needles, m.p. 225～227°. *Anal.* Calcd. for $C_{15}H_{15}O_4N$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.11; H, 5.86; N, 4.80. UV λ_{max}^{EtOH} mμ (log ε) : 226 (4.58), 234 shoulder (4.56), 249 (4.54), 266 shoulder (4.15), 309 shoulder (4.05), 315 (4.11), 323 (4.05), 329 (4.07). λ_{min}^{EtOH} mμ (log ε) : 243 (4.56), 277.5 (3.70), 320 (4.03), 325 (4.02).

Dihydro-N-methylorixidine (XII)——A solution of 100 mg. of (V) in 30 cc. of MeOH was hydrogenated over pd-C (freshly prepared from 10 cc. of 1% $pdCl_2$ and 100 mg. of activated C) at ca. 40～45°. The reduction was completed after 1 hr. The hydrogenated product was dissolved in $CHCl_3$ and chromatographed on 20 g. of Al_2O_3. A main fraction, which was eluted with $CHCl_3$, was rechromatographed on 20 g. of Al_2O_3 using a mixture of hexane-benzene (1:1) and crystallized from Et_2O to give 35 mg. of colorless prisms, m.p. 135～136°. *Anal.* Calcd. for $C_{16}H_{17}O_4N$: C, 66.88; H, 5.96; N, 4.88. Found : C, 66.68; H, 5.80; N, 5.00. UV λ_{max}^{EtOH} mμ (log ε) : 237 (4.51), 253.5 (4.41), 270 shoulder (4.16), 316 (3.93), 324 (3.88), 330 (3.88). λ_{min}^{EtOH} mμ (log ε) : 247 (4.38), 282 (3.52), 322 (3.88), 328 (3.87).

Ozonolysis of (IV)——1. To a solution of 131 mg. of (IV) in 30 cc. of AcOEt was introduced O_3 at −60° for 1 hr. until the solution colored brown, and subsequent catalytic hydrogenation was carried out over 130 mg. of 50% pd-C. After the catalyst was filtered off, the presence of H·CHO was tested with an aliquot of the filtrate with a cool, EtOH solution of Dimedone, but its attempt failed. The presence of Me_2CO was tested with 2,4-dinitrophenylhydrazine (HCl solution), but acetone-2,4-dinitrophenylhydrazone was not obtained. To the residue after evaporation was added 3 cc. of 5*N* NaOH, and the mixture was refluxed at 150° for 30 min. and, after cooling, the solution was made strongly acidic with H_2SO_4 and 10 g. of $MgSO_4$, and steam-distilled, while introducing O_2 into the solution. The distillate was titrated with *N*/50 NaOH, pKa 4.45, the titrate concentrated *in vacuo* and passed over Amberlite IR 120. The eluate was subjected to paper chromatography as ethyl amine salts.[21] Vivid spots of acids (Rf=0.18, 0.37.) were detected. The Rf values of standard AcOH, 2-hydraxy-2-methylpropionic acid*[6] and isobutyric acid are 0.18, 0.21 and 0.37, respectively. The presence of AcOH and isobutyric acid was, therefore, confirmed.

2. Into a solution of 511.2 mg. of (IV) in 65 cc. of $CHCl_3$ was introduced O_3 at −35～40° for 2.5 hr. After the $CHCl_3$ was removed *in vacuo*, the residue was dissolved in 50 cc. of MeOH and reductively decomposed over 500 mg. of 50% pd-C. The catalyst was filtered off, the filtrate was made alkaline with NaOH, the MeOH, was removed by distillation, and, after addition of 10 cc. of 5*N* NaOH to the residue, the solution was refluxed at 150° for 2.5 hr. The solution was made acidic with H_2SO_4 and steam-distilled at 150～170° introducing N_2 into it. The distillate was titrated with *N*/50 NaOH, pKa 4.12 (78.8 mg. of isobutyric acid was collected). The titrated solution was concentrated *in vacuo* and passed over Amberlite IR 120. The eluate was made slightly acidic with *N*/50 H_2SO_4, a solution of 115 mg. of *p*-bromophenacylbromide in 3.5 cc. of EtOH was added and the solution was refluxed on a steam bath for 1 hr. Upon cooling with ice-wathr, crystals (unchanged *p*-bromophenacylbromide) separated, which were filtered off, and the filtrate was evaporated, dissolved in benzene and chromatographed on 10 g. of Florisil.

Fraction No.	Eluant	m.p. (°C)	Yield (mg.)
1～2	benzene	110	4.5
3～4	〃	62～75	37.5
5～7	benzene-$CHCl_3$ (9:1)	138～140	9.8

Frs. 3～4, after rechromatographed over 10 g. of Florisil gave 21.4 mg. of colorless scaly crystals, m.p. 72～74°. The substance recrystallized from MeOH-petr. ether showed no depression of melting point on admixture with synthetic isobutyric acid *p*-bromophenacylester, m.p. 73～75°. Their infrared spectra were also identical. *Anal.* Calcd. for $C_{12}H_{13}O_3Br$: C, 50.54; H, 4.59. Found : C, 49.62; H, 4.91.

N-Methylorixidinine acetate (XV)——1. A solution of 100 mg. of (XIV) in 1.5 cc. of Ac_2O and 200 mg. of AcONa was refluxed in an oil bath at 150～160° for 1.5 hr. After cooling, most of the excess Ac_2O was removed *in vacuo*, the residue was made alkaline with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried, evaporated, and the residue was dissolved in $CHCl_3$

*[6] It was synthesized by hydrolysis of acetone cyanhydrine. R.F.B. Cox, R.T. Stormont; Org. Synthesis. II. 447; W.G. Young, R.T. Dillon, H.J. Lucas; J. Am. Chem. Soc., **51**, 2531 (1929).

21) B. Lindgvist, T. Storgards : Acta Chem. Scand., **7**, 87 (1953).

and chromatographed on 20 g. of Al_2O_3. The fraction on elution with $CHCl_3$ and by recrystallization from a mixture of MeOH-hexane (0.1:10) yielded 109 mg. of colorless needles or prisms, m.p. 169~171°. *Anal.* Calcd. for $C_{18}H_{19}O_6N$: C, 62.60; H, 5.55; N, 4.06. Found : C, 62.45; H, 5.81; N, 4.05. IR λ_{max}^{Nujol} cm^{-1} : $\nu_{C=O}$ 1741. UV λ_{max}^{EtOH} mμ (log ε) : 233 (4.52), 253 (4.38), 268 shoulder (4.13), 314 (3.90), 323 shoulder (3.85), 328 (3.84). λ_{min}^{EtOH} mμ (log ε) : 246.5 (4.34), 278 (3.46), 326 (3.83), 320 (3.85).

2. A solution of 150 mg. of (XIV) in 5 cc. of Ac_2O was refluxed on an oil bath for 3 hr. After cooling, most of the excess Ac_2O was distilled off *in vacuo*, the remaining Ac_2O was decomposed with H_2O and the separated crystalline precipitate was collected. 162.4 mg. of colorless needles were obtained on recrystallization from hexane, which were identical with (XV) with regard to the melting point and IR spectra.

Iso-N-methylorixidinine(XVI) : **1. Hydrolysis of (XVII) by 10% Methanolic Potassium Hydroxide**——A solution of 128.4 mg. of (XVII) in 10 cc. of MeOH and lg. of KOH was refluxed on a boiling water bath for 2 hr. After cooling, the MeOH was distilled off *in vacuo*, the residue was made ammonia alkaline with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried, and the $CHCl_3$ was distilled off, whereby 124.2 mg. of colorless needles, m.p. 186~189°, were obtained. Recrystallization from benzene yielded 38 mg. of colorless prisms, m.p. 212~213°, which were identified as (XIV) by mixed melting point determination. The residue (64.3 mg.) from the mother liquor was dissolved in $CHCl_3$ and chromatographed on 8 g. of Al_2O_3.

Fraction No.	Eluant	m.p. (°C)	Yield (mg.)
1~5	$CHCl_3$	212~213	18.9
6~7	〃	202~203	14.0
8~9	$CHCl_3$ containing 1% of MeOH	232~233	30.6
10	〃	233~234	

Frs. 8~10 on crystallization from benzene afforded 25 mg. of colorless needles, (XVI), m.p. 233~234°. *Anal.* Calcd. for $C_{16}H_{17}O_5N$: C, 63.36; H, 5.65; N, 4.62. Found : C, 62.78; H, 5.75; N, 4.62. UV λ_{max}^{EtOH} mμ (log ε) : 230 (4.45), 254 (4.36), 263 shoulder (4.24), 305 (3.82), 323 shoulder (3.68). λ_{min}^{EtOH} mμ (log ε) : 247 (4.31), 260 (4.25), 275 (3.52). Hydrolysis with 10% methanolic hydrochloric acid resulted in the formation of (XIV).

2. Reaction of (XIV) with 10% Methanolic Potassium Hydroxide——A solution of 112 mg. of (XIV) in 11 cc. of MeOH and 1.1 g. of KOH was refluxed on a boiling water bath for 4 hr. and treated as described above. 100.2 mg. of colorless needles, m.p. 182~186°, were chromatographed on 20 g. of Al_2O_3.

Fraction No.	Eluant	m.p. (°C)	Yield (mg.)
1~8	$CHCl_3$	212~213	33.8
9	$CHCl_3$ containing 0.5% of MeOH	202~209	68.0
10~12	〃	233~234	4.5

Frs. 9, after rechromatography, gave 23.8 mg. of (XIV) m.p. 212~213°, and 33.8 mg. of (XVI), m.p. 233~234°, overall yield : 57.6 mg. of (XIV) and 38.3 mg. of (XVI).

3. Reaction of (XIV) with 20% Methanolic Potassium Hydroxide——A solution of 265.8 mg. of (XIV) in 30 cc. of MeOH and 6 g. of KOH was refluxed on a boiling bath for 10 hr. and treated as described above. 257.0 mg. of colorless needles were chromatographed on 25 g. of Al_2O_3.

Fraction No.	Eluant	m.p. (°C)	Yield (mg.)
1~2	$CHCl_3$		0.9
3~4	$CHCl_3$ containing 1% of MeOH	186~189	54.7
5~9	〃	233~234	189.1

Frs. 3~4, after rechromatography, afforded 22 mg. of (XIV), m.p. 212~213°, and 28 mg. of (XVI), m.p. 233~234°, overall yield : 22 mg. of (XIV) and 217.1 mg. of (XVI).

Iso-N-methylorixidinine Acetate (XVII)——A solution of 36.8 mg. of (XVI) in 6 cc. of pyridine and 2 cc. of Ac_2O was allowed to stand overnight at room temperature, and, after the solvent was distilled off, the residue was made alkaline with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried and the $CHCl_3$ was distilled off, whereupon 35.8 mg. of colorless needles, m.p. 150~151°, were obtained. They were chromatographed on 6 g. of Al_2O_3 and eluted first with benzene, then $CHCl_3$, and $CHCl_3$ containing 1% of MeOH. A main fraction eluted with $CHCl_3$ and crystallized from benzene to 30.6 mg. of colorless needles, m.p. 151~152°. *Anal.* Calcd. $C_{18}H_{19}O_6N$: C, 62.60; H, 5.55; N, 4.06. Found : C, 62.51; H, 5.38; N, 4.06. IR λ_{max}^{Nujol} cm^{-1} : $\nu_{C=O}$ 1739. UV λ_{max}^{EtOH} mμ (log ε) : 229 (4.50) 254 (4.36), 262.5 shoulder (4.32), 305 (3.85), 323 shoulder (3.40). λ_{min}^{EtOH} mμ (log ε) : 248.5 (4.32), 259.5 (4.31), 275 (3.55).

Hydrolysis of (XVII)——A solution of 45 mg. of (XVII) in 5 cc. of MeOH and 2 cc. of 35% HCl was refluxed on a boiling water bath for 3.5 hr. After cooling, the MeOH was distilled off *in vacuo*, the residue was made alkaline with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ solution gave colorless needles, m.p. 231~232°. They were recrystallized from benzene to 25.2 mg. of (XVI), m.p. 232~233°. Hydrolysis of (XVII) with 10% methanolic KOH afforded (XVI), m.p. 232~233°.

Reactions of (V), (XII) and (XVI) with 10% Methanolic Potassium Hydroxide.

Reactions of (V), (XII) and (XVI) with 20% Hydrochloric Acid——All of the above reactions resulted in recovery of the original substances.

Dehydration of (XIV) by Means of Conc. Sulfuric Acid——100 mg. of (XIV) was added with cooling to 1.5 cc. of conc. H_2SO_4; after 20~30 sec. the solution colored violet and, by shaking, the solid largely went into solution. To make a complete solution 0.5 cc. of conc. H_2SO_4 was added, the solution was poured onto ice-water and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried and the $CHCl_3$ was removed by distillation. 90 mg. of the residue was dissolved in benzene and chromatographed on 7 g. of Al_2O_3.

Fraction No.	Eluant	m.p. (°C)	Yield (mg.)
1~5	benzene		2.2
6~7	$CHCl_3$	151~152	63.7
8~10	$CHCl_3$ containing 1% of MeOH	138~140	17.8

Frs. 6~7 yielded colorless needles, m.p. 153~154°, from MeOH, which were identical with (V) by melting point determination on admixture, infrared and ultraviolet spectra comparison. *Anal.* Calcd. for $C_{16}H_{15}O_4N$: C, 67.36; H, 5.30; N, 4.91. Found : C, 67,26; H, 4.95; N, 5.01.

Dehydration of (XIII) by Means of Conc. Sulfuric Acid——66 mg. of (XIII) was added, with cooling and shaking to 0.7 cc. of conc. H_2SO_4, and 0.3 cc. of conc. H_2SO_4 was further added in order to make a complete solution, whereby the solution colored from yellow to brown. The solution was poured onto ice-water and extracted with $CHCl_3$. The $CHCl_3$ solution, when treated as above, yielded 59.6 mg. of a residue, which was dissolved in $CHCl_3$ and chromatographed on 7 g. of Al_2O_3.

Fraction No.	Eluant	m.p. (°C)	Yield (mg.)
1~2	$CHCl_3$		0.4
3~4	$CHCl_3$ containing 2% of MeOH	178~184	38.8
5~8	〃 3% of MeOH	181~184	9.8

Frs. 3~8 were rechromatographed on 7 g. of Al_2O_3, eluted with $CHCl_3$ containing 2% of MeOH and crystallized from MeOH to give 26.7 mg. of colorless needles, m.p. 189° The substance was identical with (IV) by melting point determination on admixture, IR and UV spectra comparison. *Anal.* Calcd. for $C_{15}H_{13}O_4N$: C, 66.41; H, 4.83; N, 5.16. Found : C, 66.61; H, 4.75; N, 4.99.

Isokokusagine (XXVII)—208.8 mg. of kokusagine was heated at 120° with 5 cc. of CH_3I in a sealed tube for 4 hr. After cooling, the yellow brown product was dissolved in $CHCl_3$ and chromatographed on 15 g. of Al_2O_3. A fraction eluted with $CHCl_3$ and crystallized from dehyd. EtOH gave 187.5 mg. of colorless prisms, m.p. 247~248°. *Anal.* Calcd. for $C_{13}H_9O_4N$: C, 64.20; H, 3.73; N, 5.76. Found : C, 64.29; H, 3.52; N, 5.74. UV λ_{max}^{EtOH} mμ (log ε) : 243 shoulder (4.21), 254 (4.39), 273 shoulder (4.19), 304 shoulder (3.54), 339 (3.98), 345 shoulder (3.95). λ_{min}^{EtOH} mμ (log ε) : 292 (3.30).

Formation of (XXIV) and (XXV)— 1. Catalytic Reduction of (XXVII)——1) A solution of 90 mg. of (XXVII) in 40 cc. of dehyd. EtOH was hydrogenated over Pd-C (freshly prepared from 9 cc. of 1% $PdCl_2$ and 90 mg. of activated charcoal). The catalyst was filtered off and the filtrate, freed from EtOH by distillation, yielded 92 mg. of a residue, m.p. 163°, which was dissolved in $CHCl_3$ and chromatographed on 15 g. of Al_2O_3.

Fraction No.	Eluant	m.p. (°C)	Yield (mg.)
1~2	$CHCl_3$	199 (sint. at 160)	55
3	〃	202~203	5.8
4~5	〃	207	17

Frs. 1~2 were crystallized from Me_2CO to give 34.2 mg. of colorless needles, m.p. 202~203°. *Anal.* Calcd. for $C_{13}H_{11}O_4N$: C, 63.67; H, 4.52; N, 5.71. Found : C, 63.42; H, 4.20; N, 5.52. UV λ_{max}^{EtOH} mμ (log ε) : 232 (4.47), 253.5 (4.34), 268 shoulder (4.07), 316 (3.89), 330 (3.83). λ_{min}^{EtOH} mμ (log ε) : 246.5 (4.29), 279 (3.43), 327 (3.82).

Frs. 4~5 were crystallized from Me_2CO to give 10.4 mg. of colorless needles, m.p. 208~209° of (XXV). *Anal.* Calcd. for $C_{13}H_{11}O_4N$: C, 63.67; H, 4.52; N, 5.71. Found : C, 63.99; H, 4.48; N, 549. UV λ_{max}^{EtOH} mμ (log ε) : 223 (4.31), 248 (4.61), 268 shoulder (3.99), 317 (4.00), 327 (3.98). λ_{min}^{EtOH} mμ (log ε) : 228.5 (4.27), 282 (3.45), 323 (3.98).

The UV spectrum exhibited that the compound (XXV) was, in the course of reduction in H_2-atmosphere, gradually converted into (XXIV). It is of interest in this case that (XXIV) was resulted without any consumption of H_2.

Catalytic Reduction of (XXVII)——2) A hot solution of 60 mg. of (XXVII) in 50 cc. of benzene was hydrogenated over 80 mg. of 50% Pd-C for 1.5 hr. A product was chromatographed and crystallized from Me_2CO to give 44.2 mg. of colorless needles, m.p. 209°, which was found to be identical with (XXV) by melting point determination on admixture, IR and UV spectra comparison. No other substances were produced.

2. Reaction of (XXII) with 10% Hydrochloric Acid——A solution of 40 mg. of (XXII)[22] in 2 cc. of 10% HCl was refluxed on a wire gauze for 1.5 hr. After cooling, the solution was made alkaline with NH_4OH and extracted with warm $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried and the $CHCl_3$ was evaporated. The residue crystallized from MeOH to give 34 mg. of colorless needles, m.p. 202°, which were chromatographed on 7 g. of Al_2O_3. Of the five fraction eluted, Fr. 1. was crystallized from Me_2CO to afford colorless needles, m.p. 204°, which were identical with (XXIV) by melting point determination on admixture, IR and UV spectra comparison, *Anal.* Calcd. for $C_{13}H_{11}O_4N$: C, 63.67; H, 4.52; N, 5.71. Found : C, 63.56; H, 4.65; N, 5.80.

Fr. 4. on recrystallization from Me_2CO yielded 3.4 mg. of colorless needles, m.p. 209°, which were identical with (XXV) by melting point determination on admixture, IR and UV spectra comparison. *Anal.* Calcd. for $C_{13}H_{11}O_4N$: C, 63.67 : H, 4.52; N, 5.71. Found : C, 63.87; H, 4.70; N, 5.55.

Formation of (XXIII) : Reaction of (XXI) with 10% Hydrochloric Acid——A solution of 100 mg. of (XXI)[22] in 2.5 cc. of 10% HCl was refluxed for 1 hr. and treated as described above to yield 64 mg. of (XXIII), colorless needles, m.p. 272°. *Anal.* Calcd. for $C_{12}H_9O_4N$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.42; H, 3.83; N, 6.10. UV λ_{max}^{EtOH} mμ (log ε) : 226 (4.49), 234 shoulder (4.45), 249 (4.44), 266 shoulder (4.01), 304 shoulder (3.89), 310 shoulder (3.94), 315 (3.94), 330 (4.01). λ_{min}^{EtOH} mμ (log ε) : 243 (4.36), 277.5 (3.50), 320 (3.93), 326 (3.93).

Isoskimmianine (XXVIII)——500 mg. of skimmianine was heated with 5 cc. of CH_3I at 120° in a sealed tube for 4 hr. The reaction product was dissolved in $CHCl_3$ and chromatographed on 30 g. of Al_2O_3. A main fraction on elution with $CHCl_3$ and on recrystallization from Me_2CO yielded 477.5 mg. of (XXVIII), colorless needles, m.p. 188～189°. *Anal.* Calcd. for $C_{14}H_{13}O_5N$: C, 64.86; H, 5.01; N, 5.40. Found : C, 64.58; H, 5.30; N, 5.23. UV λ_{max}^{EtOH} mμ (log ε) : 236 (4.46), 259.5 (4.70), 294.5 (3.65), 335 (4.05), 342 shoulder (4.00). λ_{min}^{EtOH} mμ (log ε) : 243 (4.43), 284 (3.60), 302 (3.63).

Formation of (XXVI) : Catalytic Reduction of (XXVIII)——100 mg. of (XXVIII) was dissolved in 25 cc. of MeOH and hydrogenated over Pd-C (freshly prepared from 10 cc. of 1% $PdCl_2$ and 100 mg. of activated Charcoal). The catalyst was filtered off and the MeOH was evaporated to yield 91 mg. of colorless prisms, m.p. 164～166°, which was purified by chromatography on 15 g. of Al_2O_3.

Fraction No.	Eluant	m.p. (°C)	Yield (mg.)
1～3	$CHCl_3$		1.0
4	〃	168～178	20.0
5～6	〃	176～178	58.3
7～11	$CHCl_3$ containing 2% of MeOH		2.3

Frs. 4 and 5～6, on recrystallization from Me_2CO, yielded 62 mg. of (XXVI), colorless needles, m.p. 176～178°. *Anal.* Calcd. for $C_{14}H_{15}O_4N$: C, 64.36; H, 5.79; N, 5.36. Found : C, 64.80; H, 5.60; N, 5.25. UV λ_{max}^{EtOH} mμ (log ε) : 223 (4.00), 252 (4.39), 310 (4.11), 320 (4.08). λ_{min}^{EtOH} mμ (log ε) : 230 (3.86), 274 (3.07), 317 (4.07).

The author wishes to express her deep gratitude to Prof. T. Okamoto of the University of Tokyo for his kind and helpful guidance and to Prof. M. Terasaka of this College for his encouragement throughout the course of this work. She is also grateful to Dr. M. Natsume and Dr. S. Sakai of the University of Tokyo and to Prof S. Hara of this College for their valuable advices. She is indebted also to Miss Y. Tomikawa for her cooporation in this work and to the members of Analytical Center of the University of Tokyo for the measurment of infrared spectra and to Mrs. Y. Baba and Miss K. Okabe of this College for the elementary analysis.

Summary

The structures of orixidine and orixidinine, both demethylation products of orixine, were discussed and their 2(1*H*)-quinolone structures were established. It is assumed that orixidine and orixidinine should have structures (IV) and (XIII), respectively, while that of the isomeric transformation product of (XIV), iso-N-methylorixidinine, structure (XVI).

(Received May 2, 1961)

22) M. Terasaka : This Bulletin, 8, 529 (1960).