TRANSFORMATION FROM APORPHINE N-OXIDES TO 1-(N-METHYL-N-HYDROXYLAMINOETHYL)PHENANTHRENE DERIVATIVES[1,§]

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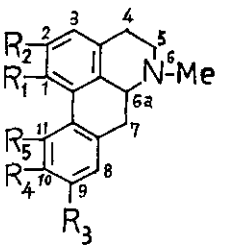
Abstract— Heat treatment of aporphine N-oxides prepared by the m-chloroperbenzoic acid (m-CPBA) oxidation of aporphines afforded 1-(N-methyl-N-hydroxylaminoethyl)phenanthrene derivatives which were characterized by the physical and chemical evidences. The biogenetic pathway from aporphines to phenanthrenes is also discussed.

Beforetime, as an execution of the structural elucidation of the alkaloids, the Hofmann elimination has been investigated extensively. In the case of aporphine alkaloids, the C_6-C_{6a} bond cleavage in ring B takes place and forms phenanthrenes, methine bases[2]. The ring B cleavage in aporphines can also be achieved by reflux with an acid chloride or with an acid anhydride[3] or by reaction with cyanogen bromide in chloroform[4]. On the other hand, it is well known that the tertiary amine N-oxides undergo Cope elimination by heating, and recently Shamma[5] and Takao[6] have reported the same elimination by the pyrolysis of protopine N-oxides. Because of the similarity of both Hofmann and Cope eliminations, the possibility of the transformation from the aporphine N-oxides to the phenanthrenes was presumed. In this paper we wish to report the preparation of aporphine N-oxides and transformation to phenanthrenes.

Though there are several kinds of oxidizing agents used for preparation of tertiary amine N-oxides, m-chloroperbenzoic acid (m-CPBA) was used as an oxidizing agent[7] because of the consideration of facility of treatment, stability of reagents, and good yields of product. Ten aporphine alkaloids (1a-j), as shown in Scheme I, were treated with m-CPBA by the method described in Experimental section, respectively. The aporphine N-oxides (2a-j) were obtained and characterized



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a.	R-(-)-N-methylxylopine	$R_1 + R_2 = OCH_2O$, R_3 = OMe, $R_4 = R_5$ = H.
b.	R-(-)-dicentrine	$R_1 + R_2 = OCH_2O$, $R_3 = R_4$ = OMe, R_5 = H.
c.	R-(-)-nuciferine	$R_1 = R_2$ = OMe, $R_3 = R_4 = R_5$ = H.
d.	S-(+)-N-methylactinodaphnine	$R_1 + R_2 = OCH_2O$, R_3 = OH, R_4 = OMe, R_5 = H.
e.	S-(+)-N-methylnandigerine	$R_1 + R_2 = OCH_2O$, R_3 = H, R_4 = OH, R_5 = OMe.
f.	S-(+)-O-methylbulbocapnine	$R_1 + R_2 = OCH_2O$, R_3 = H, $R_4 = R_5$ = OMe.
g.	S-(+)-N-methyllaurotetanine	$R_1 = R_2 = R_4$ = OMe, R_3 = OH, R_5 = H.
h.	S-(+)-boldine	$R_1 = R_4$ = OMe, $R_2 = R_3$ = OH, R_5 = H.
i.	S-(+)-isocorydine	$R_1 = R_2 = R_4$ = OMe, R_3 = H, R_5 = OH.
j.	S-(+)-glaucine	$R_1 = R_2 = R_3 = R_4$ = OMe, R_5 = H.

Scheme I

by the physical and spectral data[8], as shown in Table I.

Transformation from aporphine N-oxides to 1-(N-methyl-N-hydroxylaminoethyl)phenanthrenes was established by refluxing the N-oxides in suitable solvents, respectively. All products were optically inactive and showed the same uv absorption maxima at ca 220, 260, 340 and 360 nm and mass fragments [$M^+ - \cdot CH_2N<^{CH_3}_{OH}$] as phenanthrene alkaloids[9a], respectively. All of these products also gave a deep pink colour by triphenyltetrazolium chloride[10,11]. Therefore, it was presumed that these products are corresponding to 1-(N-methyl-N-hydroxylaminoethyl)phenanthrenes (3a-j). In order to prove the structures of these phenanthrenes, the

Table I. The physical and spectral data of aporphines and their N-oxides

aporphines					N-oxides					
compds.	mp(°C)	tlc* (Rf)	^{1}Hnmr N-Me(δ)	M.W.	compds.	mp(°C)	tlc* (Rf)	^{1}Hnmr N-Me(δ)	ms(M^+)	yields (%)
1a	108-110	0.73	2.52	309	2a**	195-198 (·HCl)	0.23	3.32	325	50
1b	162-163	0.75	2.54	339	2b**	95-97	0.24	3.02	355	34
1c	165	0.70	2.54	284	2c**	202-205 (·HCl)	0.21	3.38	310	32
1d	210-212	0.70	2.57	325	2d	170-172	0.22	4.02	341	36
1e	169-170	0.71	2.53	325	2e	233-235	0.23	3.88	341	50
1f	129-130	0.72	2.54	339	2f	105-108	0.21	3.54	355	36
1g	237-238	0.73	2.52	341	2g	125-127	0.22	3.90	357	50
1h	161	0.74	2.58	327	2h	155-157	0.25	3.78	343	20
1i	180-181	0.74	2.51	341	2i	228-230 (·HCl)	0.26	3.50	357	65
1j	120-121	0.72	2.50	355	2j	95-97	0.23	3.92	371	20

*Solvent system for tlc, chloroform : methanol = 6 : 1.

**In the preparation of aporphine N-oxides (see experimental section), the chloroform solution should not be warmed and the methanol eluent must be concentrated under reduced pressure at room temperature. If not, it will be transfered into phenanthrenes.

converted products (3a-j) were treated with zinc powder and sulphuric acid, and then the reduction products, 1-(N-methylaminoethyl)phenanthrenes (4a-j), were treated with formalin and sodium borohydride, respectively. The N-methylation products, 1-(N,N-dimethylaminoethyl)phenanthrenes (5a-j), were identified by comparisons (mp, tlc, ^{1}Hnmr, uv and ir) with authentic samples which were derived by the Hofmann elimination of the parent aporphine alkaloid methiodides (6a-j). These results were shown in Table II.

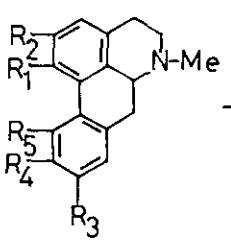
The ring B cleavage of aporphine N-oxides carries out without distinction of R- or S- configuration at C_{6a} (8 and 9). But it seems R- configuration aporphine *N-oxides more easily transfer to phenanthrenes than S- configuration.* Moreover, the reactivity of Hofmann elimination of quaternary ammonium hydroxides were compared with that of Cope elimination of tertiary amine N-oxides. In the case of dicentrine (1b), N-methyldicentrinium hydroxide (7b) easily affords dicentrine

Table II. The physical and spectral data of 1-(N-methyl-N-hydroxylaminoethyl)-phenanthrenes and 1-(N,N-dimethylaminoethyl)phenanthrenes (methine bases)

1-(N-methyl-N-hydroxylaminoethyl)-phenanthrenes							1-(N,N-dimethylaminoethyl)phenanthrenes (methine bases)				
compds.	mp(°C)	tlc* (Rf)	^{1}Hnmr N-Me(δ)	ms(M^+)	[$M^+ - \cdot CH_2N\langle^{CH_3}_{OH}$]	yields (%)	compds.	mp(°C)	tlc* (Rf)	^{1}Hnmr N-Me(δ)	yields (%)
3a[1]	185-187	0.59	2.50	325	265	41	5a	84-85	0.63	2.51	48
3b[1]	195-198	0.60	2.52	355	295	48	5b	156-158	0.64	2.56	50
3c[1]	oil	0.57	2.53	310	250	38	5c	204-206 (·$HClO_4$)	0.61	2.37	47
3d[2]	oil	0.58	2.45	341	281	40	5d	203-205	0.63	2.25	45
3e[3]	oil	0.59	2.51	341	281	42	5e	oil	0.64	2.45	2
3f[3]	oil	0.57	2.54	355	295	35	5f	oil	0.61	2.38	49
3g[2]	oil	0.59	2.50	357	297	50	5g	250-252 (·HBr)	0.64	2.50	42
3h[2]	oil	0.61	2.54	343	283	48	5h	273-276 (·HBr)	0.64	2.40	40
3i[3]	oil	0.63	2.50	357	297	46	5i	oil	0.67	2.44	44
3j[2]	oil	0.59	2.48	371	311	40	5j	118-120	0.63	2.58	46

1. chloroform, 2. methanol and 3. toluene were used as solvent for reflux.

* Solvent system for tlc, chloroform : methanol = 6 : 1.



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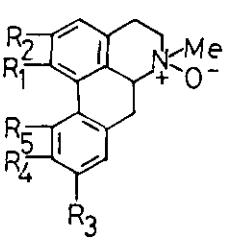

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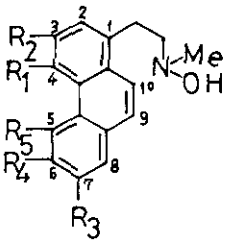

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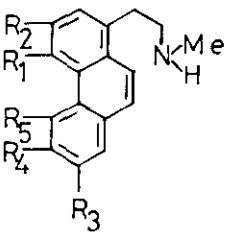

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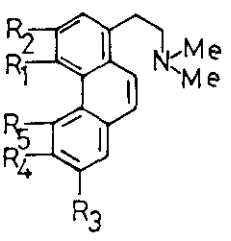

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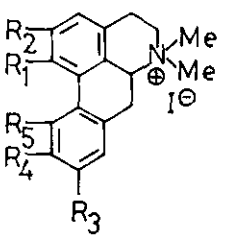

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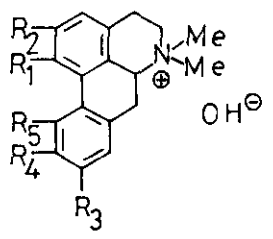

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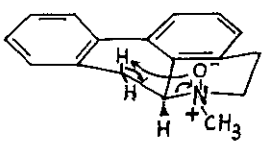

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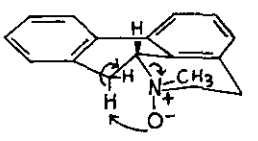

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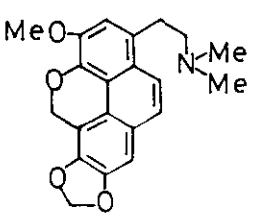

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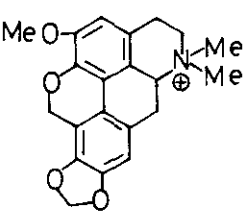

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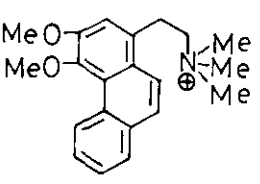

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methine, 1-(N,N-dimethylaminoethyl)-3,4-methylenedioxy-6,7-dimethoxyphenanthrene (5b) by reflux in methanol. The transformation from dicentrine N-oxide (2b) to 1-(N-methyl-N-hydroxylaminoethyl)-3,4-methylenedioxy-6,7-dimethoxyphenanthrene (3b) is also carried out with facility by reflux in chloroform or in methanol. In the case of N-methylnandigerine (1e), both N,N-dimethylnandigerinium (7e) and N-methylnandigerine N-oxide (2e) do not change by reflux in methanol or in ethanol for about 20 h , respectively. But when a water solution of the former was heated in the boiling water for 3 h , a small amount of 1-(N,N-dimethylaminoethyl) -3,4-methylenedioxy-5-methoxy-6-hydroxyphenanthrene (5e) was afforded. On the other hand, the latter easily gave 1-(N-methyl-N-hydroxylaminoethyl)-3,4-methylenedioxy-5-methoxy-6-hydroxyphenanthrene (3e) with good yields by reflux in toluene for 3 h .

Owing to the fact that the phenanthrene alkaloid, thaliglucine (thalphenine methine) (10), and the quaternary aporphine alkaloid, thalphenine (11), have been isolated from the same plant, Thalictrum polygamum[12], it is presumed that phenanthrene alkaloids probably are derived biogenetically from the Hofmann elimination of quaternary aporphine salts[9b]. In general, Hofmann elimination of quaternary aporphine alkaloids always affords tertiary phenanthrene alkaloids as methine bases. On the other hand, both aporphine N-oxides and phenanthrene alkaloids have occurred in natural sources[13], and the secondary phenanthrene alkaloid, N-noratherosperminine (4c), has been also isolated together with the tertiary and quaternary phenanthrene alkaloids, atherosperminine (5c) and N-methylatherosperminium (12)[14].

From these facts it also may be able to presume that phenanthrene alkaloids are formed biogenetically by the pathway of aporphines ⟶ aporphine N-oxides ⟶ 1-(N-methyl-N-hydroxylaminoethyl)phenanthrenes ⟶ secondary ⟶ tertiary ⟶ quaternary phenanthrene alkaloids.

EXPERIMENTAL

All mps were taken on a Yanaco micro-melting point apparatus and are uncorrected. $[\alpha]_D$ were measured on a Jasco model Dip-181 Digital Polarimeter. Uv absorption spectra were obtained on a Beckman model 34 Spectrophotometer. Ir spectra were taken on a Hitachi model 260-30 infrared Spectrophotometer. The ^{1}Hnmr spectra were taken on a Varian EM 360 L 60 MHz Spectrometer with tetramethylsilane as internal standard and chemical shifts were recorded in δ units. Mass spectra were

measured with a Jeol JMS-D-100 mass Spectrometer at 12 eV and the relative intensities are reported in the parentheses. E.M. Merck 7734 silica gel 60 was used for column chromatography and silica gel GF-254 was used for thin layer chromatography. All aporphine alkaloids are available in our laboratory except (-)-nuciferine and (+)-boldine. m-Chloroperbenzoic acid (m-CPBA) was purchased from Wako Pure Chemical Industries, Ltd., Japan.

General Procedure for the m-CPBA Oxidation of Aporphine Alkaloids (1a-j) — The chloroform solution of m-CPBA (0.75 gm, ca 0.45 mol.) was gradually added to the chloroform solution of the aporphine alkaloid (0.50 gm, ca 0.15 mol.) (1a-j) with stirring at room temperature, respectively. The stirring was continued for 1 h , and then the mixture was heated to do reflux on the water bath for 1-2 h . The conversion of the starting materials into N-oxides (2a-j) was revealed by tlc. After cooling the reaction mixture was passed through a silica gel column and eluted with chloroform in order to remove the unchanged base and m-CPBA and m-chlorobenzoic acid. The methanol was used as further eluent, the methanol eluent was concentrated to expel solvent under reduced pressure. The yields of the aporphine N-oxides (2a-j) were in the range of 20- 65%. The physical and the spectroscopic data of the aporphine N-oxides are shown in Table I.

General Procedure for the Transformation from Aporphine N-Oxides (2a-j) to 1-N-Methyl-N-hydroxylaminoethylphenanthrenes (3a-j) — Each of the aporphine N-oxides (2a-j) (15 mg) was dissolved in a suitable solvent and heated to reflux on a water bath or mantle heater for 2-3 h and concentrated, respectively. The conversion from the starting materials into products were revealed by tlc. The concentrated solution was put on a silica gel column and chromatographed with chloroform-methanol (7:1, v/v) as eluent. The eluent was concentrated to leave 1-(N-methyl-N-hydroxylaminoethyl)phenanthrenes (3a-j) which were in the range of 35- 50%, and all of them were optically inactive. Their physical and spectroscopic data are shown in Table II.

Reactions of 1-(N-Methyl-N-hydroxylaminoethyl)phenanthrenes (3a-j) with Triphenyltetrazolium Chloride — Triphenyltetrazolium chloride (ca 1.0 mg) was dissolved in one drop of an ethanol solution of the samples (3a-j) which was put on a watch glass, and one drop of 2N-sodium hydroxide was added, respectively. A deep pink

colour immediately developed.

General Procedure for the Reduction of 1-(N-Methyl-N-hydroxylaminoethyl)phenanthrenes (3a-j) and N-Methylation of the Reduction Products (4a-j) — (i) Reduction of 1-(N-methyl-N-hydroxylaminoethyl)phenanthrenes (3a-j): 1-(N-methyl-N-hydroxylaminoethyl)phenanthrenes (6.0 mg) were dissolved in 20% sulphuric acid (10 ml). The excess of zinc powder (1.0 gm) was added in the solution with stirring. The stirring was continued for 3-4 h, respectively. The mixture was filtered, and the filtrate was basified with ammonia and extracted with chloroform. The chloroform solution was dried (K_2CO_3) and concentrated to leave a light yellowish brown viscous residue (4a-j) under reduced pressure. (ii) N-methylation of the reduction products: The residues (ca 6.0 mg) (4a-j) obtained from (i) were treated with formalin (1-2 drops) and excess sodium borohydride (200 mg) by ordinary method, respectively. The N-methylation products (5a-j) were characterized by the physical and spectroscopic data, as shown in Table II, and identified directly by comparisons (uv, tlc, mp, ir and ^{1}Hnmr) with the authentic samples, methine bases, which were derived from the Hofmann elimination of the parent aporphine alkaloid methiodides (6a-j).

General Procedure for the Hofmann Elimination of the Aporphine Alkaloid Methiodides (6a-j) — A solution of aporphine methiodides (6a-j) (each 1.0 gm), potassium hydroxide (10 gm) and water (50 ml) was heated in a boiling water for 3 h, respectively. After cooling, the mixture was extracted with ether (100 ml x 3). The ether solution was combined and shaken with 2% sulphuric acid. The acidic solution was basified with ammonia and extracted with chloroform. The chloroform solution was dried (K_2CO_3) and evaporated to give a light yellowish residue. The reaction products, methine bases were optically inactive, [yields: 40-50% (except 6e)], and characterized by the physical and spectroscopic data which were shown in Table II.

Hofmann Elimination of N-Methyldicentrinium Hydroxide (7b) — Excess silver oxide [prepared from silver nitrate (2.0 gm) and 10% sodium hydroxide] was added to the solution of dicentrine methiodide (6b) (600 mg) in methanol with stirring at room temperature. The stirring was continued for 2 h, and then the mixture was filtered. The filtrate was heated to reflux on the water bath for 1 h. The methanol solution

was concentrated and chromatographed on a silica gel with chloroform-methanol (7:1, v/v) as eluent. The eluent was concentrated under reduced pressure to deposit the crystals, dicentrine methine (5b) (200 mg), mp 155-158°C.

Hofmann Elimination of N,N-Dimethylnandigerinium Hydroxide (7e) — A solution of N,N-dimethylnandigerinium hydroxide (7e) in methanol or ethanol was prepared by treating N-methylnandigerine methiodide (6e) (1.0 gm) and silver oxide . Each solution was heated to do reflux on a water bath for 20 h, respectively. Though the conversion from 7e into methine was checked by tlc, there was no spot corresponding to methine. On the other hand, the water solution of 7e was prepared and heated in boiling water for 3 h. After cooling, the solution was extracted with ether (100 ml x 4). The ether solution was combined and shaken with 2% sulphuric acid. The acidic solution was basified with ammonia and extracted with chloroform. The chloroform solution was dried (K_2CO_3), concentrated and chromatographed on a silica gel column with chloroform-methanol (7:1, v/v) as eluent. The eluent was concentrated to give a light greenish brown residue (20 mg).

ACKNOWLEDGEMENT

We gratefully thank Prof. C. M. Chen, Tsing Hua University, for the mass measurements, and Prof. T. H. Yang, Taipei Medical College, for the sample of (-)-nuciferine. Prof. J. P. Rosazza, University of Iowa, for the sample of (+)-boldine.

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Received, 5th August, 1985