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STUDIES ON THE STRUCTURE OF RUBREMETINIUM CATION: A NEW SYNTHESIS OF C-BISNORRUBREMETINIUM SALT AND ITS MODEL COMPOUND

Yoshio Ban and Masanao Terashima

Faculty of Pharmaceutical Sciences, School of Medicine,
Hokkaido University, Sapporo, Hokkaido, Japan

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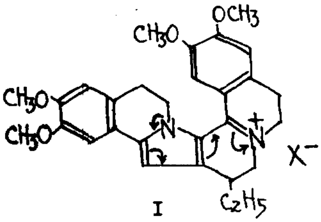
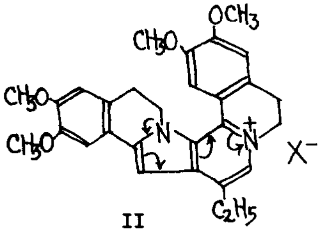
EMETINE is dehydrogenated with a variety of mild acidic oxidizing agents to afford so-called rubremetinium salt, which is the beautiful orange-red salt of a quaternary, monoacidic base. Although several structures had been suggested for the rubremetinium cation, the alternative structures, (I) and (II), have remained to be determined.[1]



I



II

The former formula $(C_{29}H_{33}O_4N_2X)$ was proposed by Battersby *et al.*[2] and the latter $(C_{29}H_{31}O_4N_2X)$ was preferred by Tietz and McEwen[3] who referred to it as Woodward's formulation. Thereafter, providing the further supporting data, Openshaw claimed the correctness of the formula (I).[1]

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[1] H.T. Openshaw, *Chemical Society Special Publication* No. 3, p.28. London (1955).

[2] A.R. Battersby, H.T. Openshaw and H.C.S. Wood, *Experientia* **5**, 114 (1949).

[3] R.F. Tietz and W.E. McEwen, *J.Amer.Chem.Soc.* **75**, 4945 (1953).

The total syntheses of this compound have already been achieved by several groups[4], but every known synthesis involved the oxidation process at the final step, which did not give the accurate number of hydrogen atoms eliminated from the penultimate product. This is the reason why none of these syntheses established its structure. In this paper, we wish to report a new synthesis of C-bisnorrubremetinium salt and its model compound of the same chromophore, without an oxidation process, which confirmatively supported the correctness of the formula (I) for rubremetinium cation.

A mixture of 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline (III) and ethyl α-chloroacetoacetate (IVa) was refluxed in ethanol to afford the ester (Va), colourless needles, m.p. 91-20°, in 94% yield, which gave the hydrazide (Vb), colourless prisms, m.p. 197-198°. The ester was hydrolysed with 10% ethanolic solution of potassium hydroxide to the free acid (Vc), pale blue amorphous solid, m.p. 160-162° (decomp.), in 97% yield, which was readily decarboxylated by heating in benzene to XI, colourless prisms, m.p. 110-110.5°, in quantitative yield. A mixture of the free acid (Vc), 3,4-dimethoxyphenethyl amine and dicyclohexylcarbodiimide in chloroform was allowed to stand at room temperature to yield Vd, colourless needles, m.p. 171-173°, in 23% yield, which was cyclized with phosphorus pentoxide to a free base (VIb), pale yellow prisms, m.p. 165-167°, in 46% yield. This base was converted with dimethyl sulphate to the quaternary base (VIIb), red prismatic needles, m.p. 176-178°, quantitatively. The absorption spectra of VIb in N/100 HCl and VIIb of the same chromophore as that of formula (I),

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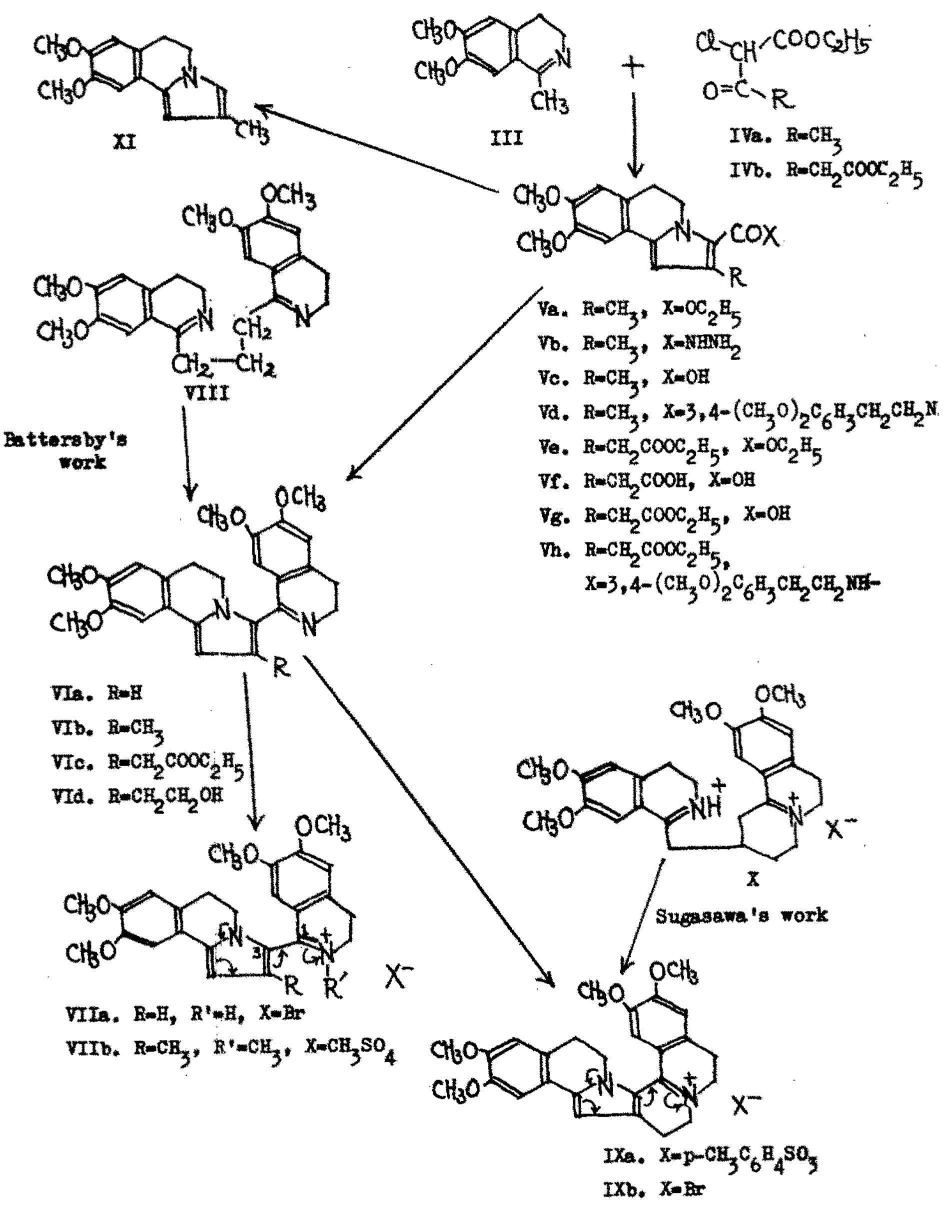
[4] [a] A.R. Battersby and H.T. Openshaw, *Experientia* **6**, 387 (1950); A.R. Battersby, H.T. Openshaw and H.C.S. Wood, *J.Chem.Soc*. 2463 (1953); [b] R.P.Evstigneeva, R.S. Livshits, L.I. Zakharkin, M.S. Bainova and N.A. Preobrazhenskii, *Dok.Akad.Nauk SSSR* **75**, 539 (1950) [*Chem.Abstr*. **45**, 7577 (1951)]; *Zh.Obshchei Khim*. (*J.Gen.Chem.U.S.S.R.*) **22**, 1467 (1952) [*Chem.Abstr*. **47**, 5949 (1953)]; [c] S. Sugasawa and Y. Ban, *Proc.Japan Acad*. **31**, 31 (1955); *Pharm.Bull.Japan* **3**, 53 (1955); T. Fujii, *Chem. & Pharm.Bull.Japan* **6**, 591 (1958); [d] M. Pailer and G. Beier, *Monatsh*. **88**, 830 (1957).



IVa. $R=CH_3$

IVb. $R=CH_2COOC_2H_5$

Va. $R=CH_3$, $X=OC_2H_5$

Vb. $R=CH_3$, $X=NHNH_2$

Vc. $R=CH_3$, $X=OH$

Vd. $R=CH_3$, $X=3,4-(CH_3O)_2C_6H_3CH_2CH_2N$

Ve. $R=CH_2COOC_2H_5$, $X=OC_2H_5$

Vf. $R=CH_2COOH$, $X=OH$

Vg. $R=CH_2COOC_2H_5$, $X=OH$

Vh. $R=CH_2COOC_2H_5$, $X=3,4-(CH_3O)_2C_6H_3CH_2CH_2NH-$

VIa. $R=H$

VIb. $R=CH_3$

VIc. $R=CH_2COOC_2H_5$

VId. $R=CH_2CH_2OH$

VIIa. $R=H$, $R'=H$, $X=Br$

VIIb. $R=CH_3$, $R'=CH_3$, $X=CH_3SO_4$

IXa. $X=p-CH_3C_6H_4SO_3$

IXb. $X=Br$

are shown as curves (1) and (2) of Fig. 1, respectively, either of which is similar but not identical with that (curve (3)) of rubremetinium cation. This type of compound (VIa) was already synthesized by mercuric acetate oxidation of VIII by Battersby, quoted by Openshaw who stated that the absorption spectrum of a solution of this salt (VIIa) was almost identical with that of rubremetinium bromide,[1] but the detail has not yet been published. Our experimental results described above are not enough for a decision between I and II, since the chromophoric system of these compounds (VIIb and VIb in HCl) can not be free from the effect induced by the inhibi-

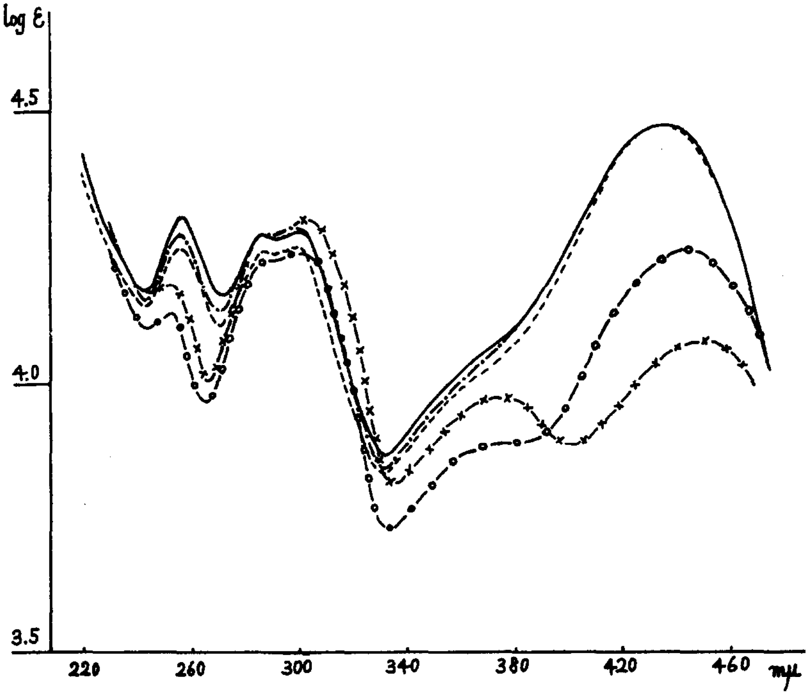


FIG. 1. Ultra-violet absorption spectra [in EtOH except (1)].

(1) —o—o— VIb in N/100 HCl
(2) —x—x— VIIb
(3) ———— (+)-Rubremetinium bromide (A.R. Battersby)[2]
(4) ---------- C-Bisnorrubremetinium bromide (M. Kirisawa)[5]
(5) — - — - C-Bisnorrubremetinium bromide (Present synthesis)

tion of free rotation of the axis C(3)-C(1').

Thus, a new synthesis of bisnorrubremetinium salt was attempted with success, substituting IVb for IVa in the above synthesis. A mixture of III and IVb was refluxed in ethanol to afford the diester (Ve), colourless prisms, m.p. 95-97°, in 54% yield. The ester was hydrolysed to dicarboxylic acid (Vf), pale blue solid, m.p. 160-161° (decomp.), in 86.5% yield, which was decarboxylated by heating in xylene to XI, m.p. 110°, although in a poor yield. The dicarboxylic acid (Vf) was refluxed with acetic anhydride in benzene for 20 min to yield the corresponding anhydride, pale yellow needles, m.p. 216° (decomp.), in 92.5% yield which in turn, was refluxed in a mixture of pyridine and ethanol to give the half ester (Vg), pale pink needles, m.p. 148° (decomp.) in 79% yield. A mixture of Vg, 3,4-dimethoxyphenethyl amine and dicyclohexylcarbodiimide in chloroform was kept at room temperature to yield the amide (Vh), colourless needles, m.p. 132°, in 66% yield, which was boiled with phosphorus pentoxide in toluene for 5 hr to give VIc, pale yellow prisms, m.p. 136°, in 47.2% yield. This ester was reduced with lithium aluminium hydride in a boiling mixture of ether and tetrahydrofuran for 3 hr to yield the alcohol (VId), pale yellow needles of a reasonable ultra-violet absorption spectrum identical with those of VIb and VIc, m.p. 163-164°, in 66% yield. Thus, a mixture of the alcohol (VId) and tosyl chloride in benzene was allowed to stand at room temperature, producing IXa, orange needles, m.p. 192-194°, quantitatively, which was readily converted to the corresponding bromide (IXb), orange red needles, m.p. 215° (lit. m.p. 236-237° as trihydrate,[5] and m.p. 215° [6]). The infrared spectrum of this bromide was identical with that of C-bisnorrubremetinium bromide kindly supplied by Professor Sugasawa and Dr. Kirisawa who obtained

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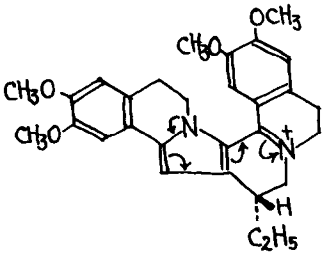
[5] M. Kirisawa, Chem. & Pharm.Bull.Japan 7, 38 (1959).

[6] M. Pailer and H. Strohmayer, Monatsh. 83, 1198 (1952).

their product by mercuric acetate oxidation of X.[5] The absorption spectra (curves (4) and (5) of Fig. 1) of the bromide (IXb) are in good agreement with that of rubremetinium cation, showing that both compounds have the same chromophore.

Since it could be generally accepted that dehydrogenation does not occur at the final step of the present synthesis of IXa and IXb, the formula (I) and accordingly the formula (XII) in terms of the absolute configuration[7] for rubremetinium cation are confirmatively supported. Good elemental analyses have been obtained on every recrystallized product.



XII

Acknowledgements - We are indebted to Professor Em.S. Sugasawa and Dr. M. Kirisawa for generous gifts of a sample and the infra-red spectrum of C-bisnorrubremetinium bromide.

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[7] E.E. van Tamelen and J.B. Hester, J.Amer.Chem.Soc. 81, 507 (1959); A.R. Battersby and S. Garratt, Proc.Chem.Soc. 86 (1959); Y. Ban, M. Terashima and O. Yonemitsu, Chem. & Ind. 569 (1959).