

BASE-INDUCED REACTIONS OF N-METHYL QUATERNARY SALTS OF 1-AZA-DIBENZO[c,f]BICYCLO[3.3.1]NONA-3,6-DIENE AND RELATED COMPOUNDS

Hiroaki Takayama,* Takashi Nomoto, and Takayoshi Suzuki
Faculty of Pharmaceutical Sciences, Teikyo University, Suarashi,
Sagamiko-machi, Tsukui-gun, Kanagawa-ken 199-01, Japan

Masayuki Takamoto and Toshihiko Okamoto
Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo,
Tokyo 113, Japan

Reactions of N-methyl quaternary salt (2) of 1-azadibenzo[c,f]-bicyclo[3.3.1]nona-3,6-diene (1) with various bases were examined, and consequently, 6-aza-6-methyldibenzo[b,i]bicyclo[3.2.2]nona-2,8-diene (4) was selectively obtained by the reaction of 2 with potassium t-butoxide in dioxane, in contrast 1-aza-1-methyl-5-methylene-dibenzo[c,f]octa-3,6-diene (3) was provided as a sole product by the reaction with potassium hydroxide in water, respectively. Isopavine alkaloids, (\pm)-amurensinine and (\pm)-reframine were also derived.

Previously, we reported¹ that N-methyl quaternary salts (2, X=OH) of 1-azadibenzo[c,f]bicyclo[3.3.1]nona-3,6-diene (1), which was facilely synthesized in high yield by the double-cyclization reaction of N,N-dibenzylaminoacetaldehyde diethylacetal, was derived to pharmacologically active 1-azadibenzo[c,f]octa-3,6-diene derivative (3) by thermal degradation. In the course of our studies

on the ring transformation of 1, we here wish to describe that 2 was converted into a basic skeleton of the isopavine alkaloids², namely, 6-aza-6-methyldibenzo[b,i]bicyclo[3.2.2]nona-2,8-diene (4)³ in high isolated yield, by employing strong bases such as n-BuLi, t-BuOK, and NaH in rather aprotic solvents, whereas 3 was provided as a sole product by the reaction of 2 (X=CH₃SO₄) with a large excess of KOH in water at refluxing temperature (Scheme 1, Table I).

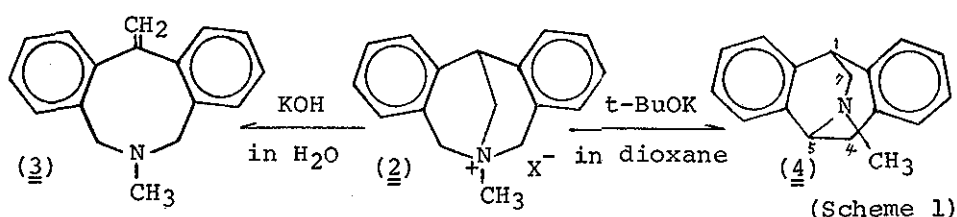


Table I Reactions of N-Methyl Quaternary Salts (2) with Bases

<u>2</u> : X	Base ^{*b}	Solvent	Temp (°C)	Time (hr)	Yield (%) ^{*d}	
					<u>3</u>	<u>4</u>
OH ^{*a}	none	none	180	1/4	28	38
CH ₃ SO ₄	KOH ^{*c}	water	100	14	55	0
CH ₃ SO ₄	KOH ^{*c}	water/diglyme (1:2.5)	150	3	1	50
I	n-BuLi	ether	-78~r.t.	16	0	66
I	t-BuOK	dioxane	r.t.	42	3	64
I	t-BuOK	diglyme	180	2/3	2	76
I	t-BuOK	dioxane	80	4	1	85
I	NaH	diglyme	180	1	0	81

^{*a}) See references 1).

^{*b}) 1.5 equiv. to 2.

^{*c}) 50 equiv. to 2.

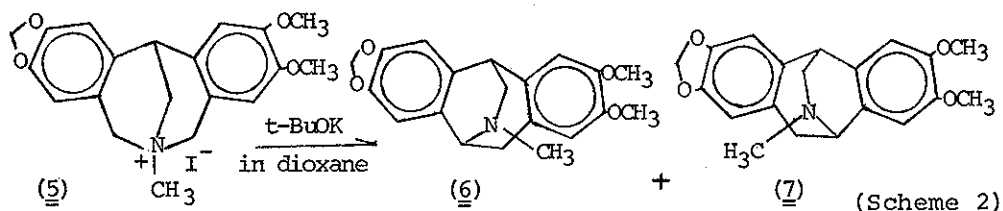
^{*d}) The isolated yield shown was unoptimized.

In a typical experiment, compound 2 (X=I) (1 mmol) in a solution of dioxane containing 1.5 equiv. of t-BuOK, was heated with stirring at 80°C for 4 hr under an argon atmosphere. After dilution

with water, the reaction mixture was extracted with dichloromethane and the resulting solution was evaporated under a reduced pressure, the residue was chromatographed on a silica gel column affording 4, mp 60-62°C, in 85% yield. 4: Mass m/e 235(M⁺), 192 (M-(CH₃-N=CH₂)), 144 (N-methylisoquinolinium ion)⁴, ¹H-NMR(δ in CDCl₃) 2.44(3H,s), 2.86(1H,dd,J=10.6, 5.0Hz), 2.94(1H,dd,J=17.5, 1.25Hz), 3.54(1H,dd,J=10.6, 1.25Hz), 3.58(1H,dd,J=17.5, 3.75Hz), 3.79(1H,dd,J=5.0, 1.25Hz), 3.89(1H,t,J=3.75Hz), ¹³C-NMR(δ in CDCl₃) 38.5(C₄,t), 45.3(N-CH₃,q), 46.9(C₁,d), 59.6(C₇,t), 62.6(C₅,d).

In an application of this modified Stevens rearrangement⁵, 5, prepared by the double-cyclization reaction of N-(3,4-dimethoxybenzyl)-N-(3,4-methylenedioxybenzyl)aminoacetaldehyde diethyl-acetal, in a dioxane solution containing 1.5 equiv. of t-BuOK was heated at 80°C for 4 hr and chromatographic separation gave (±)-amurensinine (6) and (±)-reframine (7) in 85% yield(1.8:1). 6:⁶ mp 192-194°C, Mass m/e 339(M⁺), 296(M-(CH₃-N=CH₂)), 188(N-methyl-6,7-methylenedioxyisoquinolinium ion)⁴, NMR(δ in CDCl₃) 2.48(3H,s), 2.70-3.04(2H,m), 3.36-3.70(4H,m), 3.77(3H,s), 3.86(3H,s), 5.85(2H,ABq,J=4.0, 1.5Hz), 6.48(1H,s), 6.58(1H,s), 6.65(2H,s). 7:⁷ oil(methiodide, mp 262-263°C), Mass m/e 339(M⁺), 296(M-(CH₃-N=CH₂)), 204(N-methyl-6,7-dimethoxyisoquinolinium ion)⁴, NMR(δ in CDCl₃) 2.47(3H,s), 2.8-3.04(2H,m), 3.44-3.80(4H,m), 3.86(6H,s), 5.85(2H,ABq,J=2.5, 1.0Hz), 6.45(1H,s), 6.59(1H,s), 6.68(1H,s), 6.71(1H,s). The spectroscopic data of the available natural products were identical with those of 6 and 7 respectively (Scheme 2).

In conclusion, the presented results suggest clearly that pharmacologically active type-3 and type-4 compounds can be selec-



tively synthesized from type-1 compounds.

Further studies along this line and the investigation on the reaction mechanism are in progress.

References and Notes

- 1) H. Takayama, M. Takamoto, and T. Okamoto, *Tetrahedron Lett.*, 1978, 1307. The crystalline 2 ($X=\text{CH}_3\text{SO}_4$) was dissolved in H_2O and passed through OH^- -treated IRA-401 ion exchange column and the resultant aq. solution was concentrated to dryness under a reduced pressure at below 30°C , followed by a vacuum distillation (oil bath temp. $180^\circ\text{C}/0.005$ Torr) affording a mixture of 3 (28%) and 4 (38%). The yields were sensitive to the reaction procedure.
- 2) S. F. Dyke and A. C. Ellis, *Tetrahedron*, 1971, 27, 3803 and the references cited therein.
- 3) 4 displayed various interesting pharmacological activities (unpublished result).
- 4) L. Dolejš and V. Hanuš, *Coll. Czech. Chem. Commun.*, 1968, 33, 600 ; L. Dolejš and J. Slavík, *ibid.*, 1968, 33, 3917.
- 5) S. H. Pine, *J. Chem. Educ.*, 1971, 48, 99 ; W. D. Ollis, M. Rey, O. S. Sutherland, and G. L. Closs, *J. Chem. Soc. Chem. Commun.*, 1975, 543 and the references cited therein.
- 6) F. Šantavý, L. Hruban, and M. Maturová, *Coll. Czech. Chem. Commun.*, 1966, 31, 4286 ; *Idem*, *J. Chem. Soc. Chem. Commun.*, 1966, 36.
- 7) J. Slavík, L. Slavíková, and L. Dolejš, *Coll. Czech. Chem. Commun.*, 1968, 33, 4066.
- 8) Compounds 3, 4, 6, and 7 (methiodide) gave correct elemental analyses.

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