HETEROCYCLES. XVI.[1] METHYLATION OF THE CYCLIC ENAMINO KETONES

Masayuki Onda,* Yasumasa Sugama, and Reiko Yabuki
School of Pharmaceutical Sciences, Kitasato University
Minato-ku, Tokyo 108, Japan

Abstract —— Methylation of the tetrahydrobenzo(a)quinolizinone 2 and the dihydrobenzo(a)quinolizinone 3 has been examined. The regioselectivity at the nitrogen and oxygen atoms is tremendously affected by the solvents.

Enamino ketones are ambident nucleophiles with three potentially attacking atoms (N, C_β and O), and the regioselectivity is affected by the nature of enamino ketones, electrophilic reagents and solvents. For cyclic enamino ketones O-alkylation generally occurs and C-alkylation is exceptionally observed.[2] In the course of our studies on the benzo(c)phenanthridine alkaloids, we had an opportunity to examine methylation of the cyclic enamino ketones and found that the regioselectivity is tremendously influenced by the solvents.

The tetrahydrobenzo(a)quinolizinone 2 and the dihydrobenzo(a)quinolizinone 3 were prepared in 88 and 92% yields, respectively, by mercuric acetate oxidation of 9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-3-methyl-2-oxobenzo(a)quinolizine 1.[3]

Methylation of 2 with dimethyl sulfate in benzene gave the tetrahydrobenzo(a)-quinolizinium methyl sulfate 4 (93%), which was converted into 2 (95%) on heating in 10% hydrochloric acid at 60°C for 1.5 h. On sodium borohydride reduction in methanol and treatment with 10% hydrochloric acid, 4 afforded 1 (90%).

On methylation in methanol, 2 provided the tetrahydrobenzo(a)quinolizinone metho-sulfate 5 (70%), which was converted into 2 (92%) on heating in Claisen's alkali at 60°C for 6 h.

The structures of 4 and 5 were ascertained by the above chemical correlation. In addition, the ^{1}H nmr spectra supported these structures and excluded the C-methylated compound (4: δ 6.18 s, 1-H and δ 4.10 s, 2-OMe; 5: δ 6.38 s, 1-H and δ 4.04 s or 4.02 s or 3.94 s, 5-Me).

Methylation of 3 with dimethyl sulfate in benzene furnished the dihydrobenzo(a)-quinolizinium methyl sulfate 6 (89%), which gave 1 (95%) on sodium borohydride reduction in methanol and treatment with 10% hydrochloric acid (δ 7.55 s, 1-H and δ 4.29 s, 2-OMe). On methylation in chloroform, 3 afforded the dihydrobenzo(a)-quinolizinone methosulfate 7 (74%) (δ 7.70 s, 1-H and δ 4.09 s or 4.00 s, 5-Me). In conclusion, for 2 and 3 O-methylation occurred in the aprotic solvent and N-methylation in the protic solvent. No example of N-alkylation of cyclic enamino ketones appeared in the literatures as far as we know.

EXPERIMENTAL SECTION

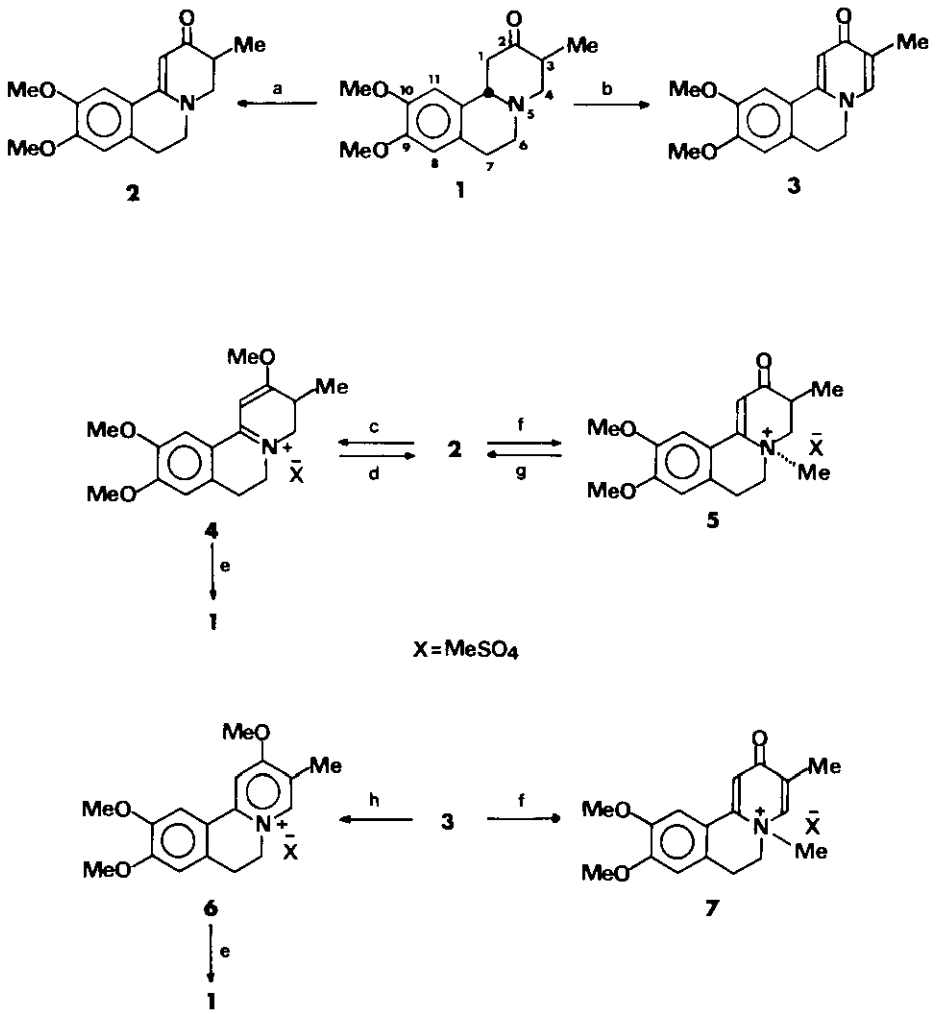
Melting points are uncorrected. Spectral data were recorded on the following spectrometers: IR — Hitachi 260-30; ^{1}H nmr — JEOL JNM PS-100 (100 MHz) (reference, tetramethylsilane);[4] mass — JEOL JMS DX-300.

9,10-Dimethoxy-3-methyl-2-oxo-3,4,6,7-tetrahydro-2H-benzo(a)quinolizine 2

A mixture of mercuric acetate (2.4 g) and disodium ethylenediaminetetraacetate-2 water (3.7 g) in 1% acetic acid (50 ml) was added to a solution of 1 (1.0 g) in 1% acetic acid (80 ml), and the whole was stirred at 55°C in a stream of nitrogen for 5.5 h. The reaction mixture was filtered and concentrated in vacuo. The residue was made alkaline with 10% aqueous NaOH and extracted with chloroform. After being dried over Na_2SO_4, the organic phase was concentrated in vacuo, and the residue was recrystallized from benzene to yield 2 (880 mg, 88%) as yellow needles of mp 182—183°C. IR ($CHCl_3$): 1613 cm^{-1} (C=O). ^{1}H nmr ($CDCl_3$) δ: 7.10 (1H, s, 11-H), 6.60 (1H, s, 8-H), 5.56 (1H, s, 1-H) (exchangeable with D_2O), 3.91, 3.87 (3H each, s, 9-, 10-OMe's), 1.17 (3H, d, J 6 Hz, 3-Me). Mass m/z: M^+, 273.137 (273.137 for $C_{16}H_{19}NO_3$). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.30; H, 7.01; N, 5.12. Found: C, 70.20; H, 7.04; N, 5.05.

6,7-Dihydro-2H-9,10-dimethoxy-3-methyl-2-oxobenzo(a)quinolizine 3

A solution of mercuric acetate (2.7 g) in 5% acetic acid (50 ml) was added to a solution of 1 (1.0 g) in 5% acetic acid (30 ml), and the whole was stirred at 90°C for 4 h. Work-up of the reaction mixture, followed by recrystallization of the crystalline solid from chloroform/ethyl acetate, gave 3 (912 mg, 92%) as colorless needles of mp 259—260°C. IR ($CHCl_3$): 1640 cm^{-1} (C=O). ^{1}H nmr ($CDCl_3$) δ: 7.25



a) $Hg(OAc)_2$/EDTA-2Na/1% AcOH; b) $Hg(OAc)_2$/5% AcOH;

c) Me_2SO_4/benzene; d) 10% HCl; e) $NaBH_4$/MeOH, 10% HCl;

f) Me_2SO_4/MeOH; g) Claisen's alkali; h) Me_2SO_4/chloroform

Chart 1

(1H, s, 4-H), 7.16 (1H, s, 11-H), 6.77, 6.68 (1H each, s, 1-, 8-H's), 3.98 (2H, t, J 6 Hz, 6-H_2), 3.91 (6H, s, 8-, 9-OMe's), 2.99 (2H, t, J 6 Hz, 7-H_2), 2.03 (3H, s, 3-Me). Mass m/z: M^+, 271.121 (271.121 for $C_{16}H_{17}NO_3$). Anal. Calcd for $C_{16}H_{17}NO_3$-1/3H_2O: C, 69.25; H, 6.42; N, 5.05. Found: C, 69.35; H, 6.30; N, 5.11.

3-Methyl-3,4,6,7-tetrahydro-2,9,10-trimethoxybenzo(a)quinolizinium Methyl Sulfate 4

A mixture of 2 (379 mg) and dimethyl sulfate (590 mg) in anhydrous benzene (10 ml) was stirred at room temperature overnight. The precipitate was collected and recrystallized from methanol/ether to yield 4 (516 mg, 93%) as greenish yellow needles of mp 153–154°C. IR ($CHCl_3$): 1630 cm^{-1} (C=N). ^1H nmr ($CDCl_3$) δ: 7.36 (1H, s, 11-H), 6.82 (1H, s, 8-H), 6.18 (1H, s, 1-H), 4.38–3.69 (4H, m, 4-, 6-H_2's), 4.10 (3H, s, 2-OMe), 3.99, 3.94 (3H each, s, 9-, 10-OMe's), 3.62 (3H, s, $MeSO_4^-$), 3.23–2.80 (3H, m, 3-H, 7-H_2), 1.22 (3H, d, J 7 Hz, 3-Me). Anal. Calcd for $C_{18}H_{25}NO_7S$: C, 54.11; H, 6.30; N, 3.50. Found: C, 53.97; H, 6.22; N, 3.40.

Conversion of 4 into 1 and 2

a) A mixture of 4 (90 mg) and $NaBH_4$ (60 mg) in methanol (4 ml) was stirred at room temperature for 1.5 h, and then acidified with 10% HCl. The reaction mixture was concentrated in vacuo, and the residue was extracted with chloroform. After being dried over Na_2SO_4, the organic phase was concentrated in vacuo, and the residue was recrystallized from methanol to yield 1 (56 mg, 90%) as colorless needles of mp 142–143°C. This compound was identified with an authentic sample[3] of 1 by direct comparison.

b) A solution of 4 (99 mg) in 10% HCl (1 ml) was stirred at 60°C for 1.5 h. The reaction mixture was made alkaline with 10% aqueous Na_2CO_3 and extracted with chloroform. Work-up afforded 2 (64 mg, 95%) as yellow needles of mp 182–183°C (from benzene). This compound was shown to be identical with 2 prepared from 1 by direct comparison.

9,10-Dimethoxy-3-methyl-2-oxo-3,4,6,7-tetrahydro-2H-benzo(a)quinolizine Methosulfate 5

A mixture of 2 (194 mg) and dimethyl sulfate (283 mg) in anhydrous methanol (6 ml) was stirred at room temperature for 17 h. The precipitate was collected and recrystallized from methanol to yield 5 (200 mg, 70%) as light greenish yellow

plates of mp 169—170°C. IR ($CHCl_3$): 1615 cm^{-1} (C=O). ^1H nmr (CF_3COOH) δ: 7.35 (1H, s, 11-H), 6.96 (1H, s, 8-H), 6.38 (1H, s, 1-H), 4.40—3.64 (4H, m, 4-, 6-H_2's), 4.04 (6H), 4.02 (3H), 3.94 (3H) (s each, 5-Me, 9-, 10-OMe's, $MeS\bar{O}_4$), 3.40—2.86 (3H, m, 3-H, 7-H_2), 1.20 (3H, d, J 8 Hz, 3-Me). Anal. Calcd for $C_{18}H_{25}NO_7S$-1/2H_2O: C, 52.92; H, 6.41; N, 3.42. Found: C, 52.81; H, 6.38; N, 3.42.

Conversion of 5 into 2

A solution of 5 (74 mg) in Claisen's alkali (1 ml) was stirred at 60°C for 6 h. The reaction mixture was extracted with chloroform. After being dried over Na_2SO_4, the organic phase was concentrated in vacuo, and the residue was recrystallized from benzene to yield 2 (44 mg, 92%) as yellow needles of mp 182—183°C. This compound was shown to be identical with 2 prepared from 1 by direct comparison.

6,7-Dihydro-3-methyl-2,9,10-trimethoxybenzo(a)quinolizinium Methyl Sulfate 6

A mixture of 3 (275 mg) and dimethyl sulfate (210 mg) in anhydrous chloroform (3 ml) was stirred at room temperature for 4 h. The precipitate was collected and recrystallized from ethanol/ether to yield 6 (370 mg, 89%) as light yellow plates of mp 207—208°C. IR (KBr): 1640 cm^{-1} (C=N). ^1H nmr (CF_3COOH) δ: 8.18 (1H, s, 4-H), 7.55 (2H, s, 1-, 11-H's), 7.07 (1H, s, 8-H), 4.58 (2H, t, J 6 Hz, 6-H_2), 4.29 (3H, s, 2-OMe), 4.09 (6H), 3.98 (3H) (s each, 9-, 10-OMe's, $MeS\bar{O}_4$), 3.28 (2H, t, J 6 Hz, 7-H_2), 2.38 (3H, s, 3-Me). Anal. Calcd for $C_{18}H_{23}NO_7S$·3/4H_2O: C, 52.60; H, 6.00; N, 3.41; S, 7.80. Found: C, 52.56; H, 6.00; N, 3.32; S, 7.90.

Conversion of 6 into 1

A mixture of 6 (338 mg) and $NaBH_4$ (330 mg) in methanol (20 ml) wa stirred at 60°C for 1 h, and then acidified with 10% HCl. The reaction mixture was concentrated in vacuo and extracted with chloroform. After being dried over Na_2SO_4, the organic phase was concentrated in vacuo, and the residue was recrystallized from methanol to yield 1 (215 mg, 95%) as colorless needles of mp 142—143°C. This compound was identified with an authentic sample[3] of 1 by direct comparison.

6,7-Dihydro-2H-9,10-dimethoxy-3-methyl-2-oxobenzo(a)quinolizine Methosulate 7

A mixture of 3 (207 mg) and dimethyl sulfate (244 mg) in anhydrous methanol

(8 ml) was stirred at room temperature for 3 h. The precipitate was collected and recrystallized from methanol/ether to yield 7 (230 mg, 74%) as colorless plates of mp 242—244°C. IR (KBr): 1640 cm^{-1} (C=O). ^1H nmr (CF_3COOH) δ: 8.14 (1H, s, 4-H), 7.70 (1H, s, 1-H), 7.50 (1H, s, 11-H), 7.03 (1H, s, 8-H), 4.54 (2H, t, J 6 Hz, 6-H_2), 4.09 (9H), 4.00 (3H) (s each, 5-Me, 9-, 10-OMe's, $MeS\bar{O}_4$), 3.26 (2H, t, J 6 Hz, 7-H_2), 2.40 (3H, s, 3-Me). Anal. Calcd for $C_{18}H_{23}NO_7S$-1/2H_2O: C, 53.19; H, 5.95; N, 3.44; S, 7.89. Found: C, 53.04; H, 5.82; N, 3.50; S, 7.85.

REFERENCES AND NOTES

1. Part XV: H. Takahashi, Y. Kubota, H. Yamaguchi, and M. Onda, Chem. Pharm. Bull., 1984, 32, in press.
2. A. I. Meyers, A. H. Reine, and R. Gault, J. Org. Chem., 1969, 34, 698.
3. M. Onda, R. Matsui, and Y. Sugama, Chem. Pharm. Bull., 1977, 25, 2359.
4. Assignments were made on the basis of the proton chemical shifts of the related compounds.[3]

Received, 10th September, 1984