SYNTHESES OF 5,7-ETHANO-4,5,5a,6,7,11b-HEXAHYDRO-2,6,7-TRIMETHYL-1H-BENZO[g]-HOMOQUINOLIN-9-OL AND 4,6-ETHANO-3,4,4a,5,6,10b-HEXAHYDRO-2,5,6-TRIMETHYL-BENZO[f]QUINOLIN-8-OL

Mikio Hori*, Tadashi Kataoka, Hiroshi Shimizu, Eiji Imai, Yoshinari Suzuki, and Norihiro Kawamura
Gifu College of Pharmacy, 6-1 Mitahora-higashi 5-chome, Gifu 502, Japan

Abstract ——— Novel 1,3-bridged 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine derivatives (3,9,13, and 16) were synthesized stereospecifically by acid-catalyzed cyclization in PPA starting from 6,11-dimethyl-8-methoxy-3,4,5,6-tetrahydro-2,6-methano-3-benzazocin-1(2H)-one.

Recently Snyder et al.[1] and Kolb[2] independently reported the new analgesic receptor models and explained agonistic or antagonistic properties on the basis of interaction between receptor sites and functional groups of analgesics. But their models completely disaccorded concerning the N-lone electron pair directions which, according to Kolb's report, determine agonistic properties of analgesics.

In order to solve the problem we report here the syntheses of tetracyclic benzomorphan derivatives[3] (3 and 9), of which N-lone electron pair directions are fixed in the same configuration as that of pentazocine. Furthermore reduction of 3 and 9 was tried with the intention of clarifying the effects of unsaturated nitrogen substituents on antagonistic characters.[4]

On treatment of the 6,11-dimethyl-2,6-methano-3-benzazocine-1(2H)-one[5] (4) with alkyl halides-NaH or with alkyl tosylates-K_2CO_3, N-alkylated products 5a-e were obtained in good yields.[6] When 4 was treated with diketene, amide derivative 5f was also obtained as an oil.[6] Several attempts to construct new 1,3-bridged ring from 5e or 5f by aldol type cyclization with NaH or n-BuLi were fruitless.

Therefore acid-catalyzed cyclization was investigated as another route. Reduction of 5a-d with $LiAlH_4$ gave alcohols 6a-d.[7] The stereochemistry of hydroxy groups in 6a-d were determined as β configuration by the NMR spectra in comparison with the reported data.[3,5] As preliminary experiment cyclization conditions of 6a were investigated. When 6a was allowed to react with 80% H_2SO_4, cyclization of 6a occurred together with sulfonation at C-9 position to give 7. Desulfonation of

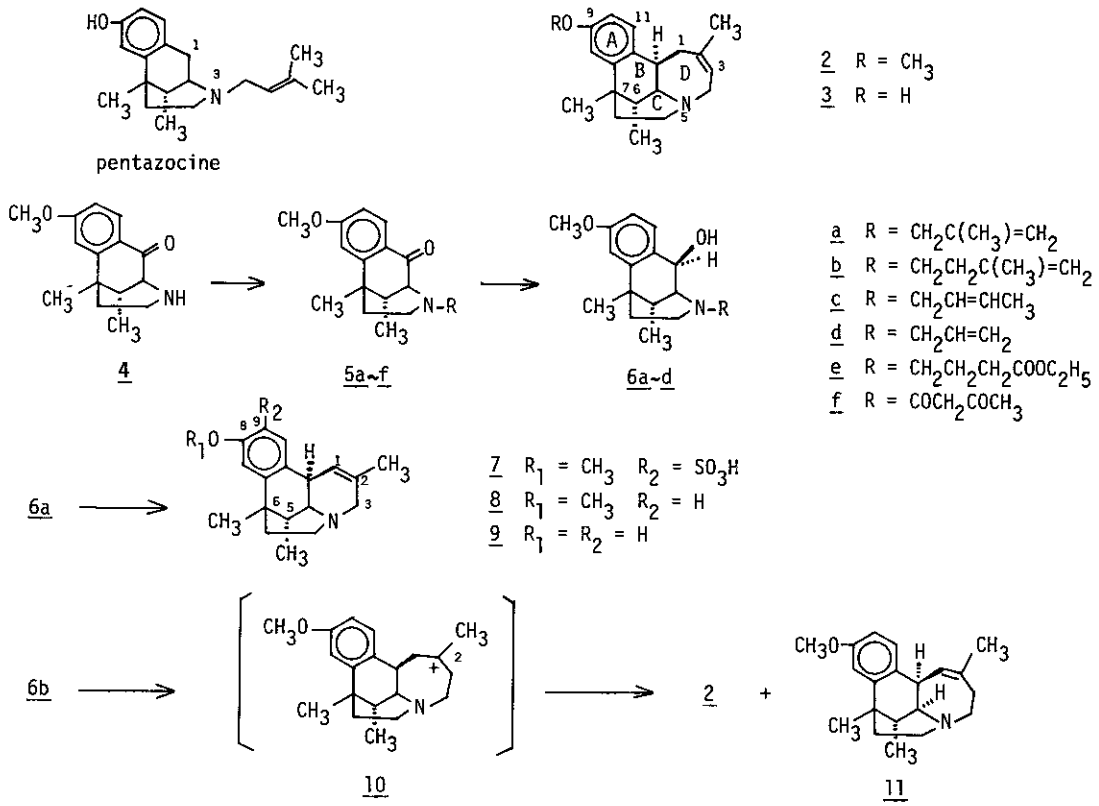

Fig. 1

7 was achieved in refluxing dil. H_2SO_4 to afford desired product 8 in 21.3% yield from 6a. Cyclization of 6a with polyphospholic acid (PPA) proceeded smoothly at 90°C to give 8 in improved yield (63.8%) as a single product.

8 : ^{1}H-NMR ($CDCl_3$) δ 0.84 (3H, d, C_5-CH_3, J = 7.0 Hz), 1.36 (3H, s, C_6-CH_3), 1.65 (3H, broad s, C_2-CH_3), 3.79 (3H, s, OCH_3), 6.00 (1H, broad d, C_1-H, J = 5.0 Hz), 6.60-7.32 (3H, m, arom H), mass m/e 283 (M^+), mp 255-260°C(dec) as hydrochloride.

However, N-2-butenyl (6c) and N-allyl derivatives (6d)[5] did not afford any cyclized product under the same conditions. These results showed that cyclization is very susceptible to steric hindrance and moreover needs some groups such as alkyl moiety on the C-3 of allyl substituents, which might stabilize a cation of intermediate 10. Though cyclization of 6b was also attempted under the above conditions, any cyclized product could not be detected. However, at room temperature the cyclized products were successfully obtained as a mixture of positional isomers, 2 (18.8%) and 11 (5.8%) as an oil.

2 : ^{1}H-NMR ($CDCl_3$) δ 0.86 (3H, d, C_6-CH_3, J = 7.0 Hz), 1.35 (3H, s, C_7-CH_3), 1.91 (3H, broad s, C_2-CH_3), 3.37 (2H, d, C_4-H, J = 7.0 Hz), 3.80 (3H, s, OCH_3), 5.48 (1H, broad t, C_3-H, J =

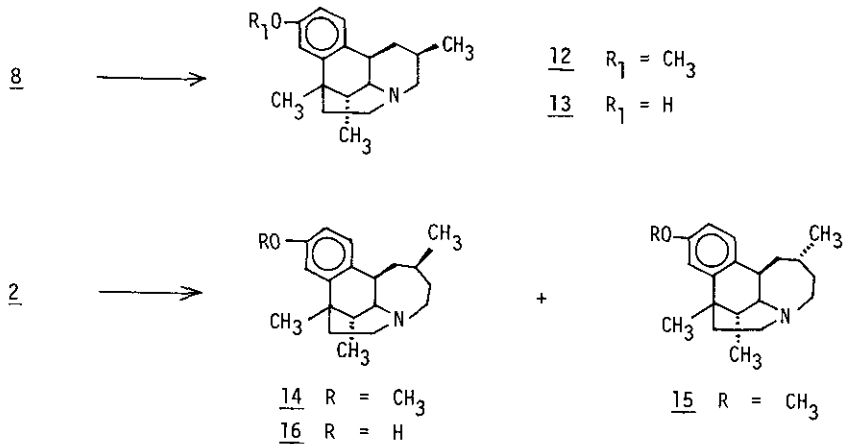

Fig. 2

7.0 Hz), 6.60-7.40 (3H, m, arom H), mass m/e 297 (M^+), mp 198°C as oxalate.

11 : ^{1}H-NMR ($CDCl_3$) δ 0.90 (3H, d, C_6-CH_3, J = 7.0 Hz), 1.36 (3H, s, C_7-CH_3), 1.87 (3H, broad s, C_2-CH_3), 3.52 (1H, dd, C_{11d}-H, J = 8.0, 3.5 Hz), 3.79 (3H, s, OCH_3), 6.03 (1H, broad d, C_1-H, J = 8.0 Hz), 6.55-7.30 (3H, m, arom H), mass m/e 297 (M^+), mp 93-95°C as oxalate hemihydrate. Vinyl proton of 2 was observed as broad triplet spin-coupled with C-4 methylene in NMR spectrum. On the other hand vinyl proton of 11 coupled with C_{11b} methine as broad doublet and closely resembled that of 8 with respect to chemical shifts and coupling constants. From these data positions of double bonds of 2 and 11 were determined as shown in Fig. 1.

Catalytic hydrogenation of 8 over Pt gave 12 in 78% yield as a sole product. Under the same conditions 2 was reduced into two diastereomers 14 (28%) and 15 (34%), whereas 11 yielded 14 (68%) exclusively. As reduction of sterically crowded double bonds of 8 and 11 proceeded stereospecifically, 12 and 14 might be formed by the catalytic approach from less hindered side. Therefore, the stereochemistry of 12 was determined to be $2R^{\bullet}$, $4aR^*$ and that of 14 was $2R^*$, $5aR^*$. On the other hand, the configuration of 15 was reverse to those of 12 and 14, and determined to be $2R^*$ and $5aS^*$.

12 : ^{1}H-NMR ($CDCl_3$) δ 0.81 (3H, d, C_5-CH_3, J = 7.0 Hz), 0.92 (3H, d, C_2-CH_3, J = 4.6 Hz), 1.35 (3H, s, C_6-CH_3), 3.79 (3H, s, OCH_3), 6.50-7.18 (3H, m, arom H), mass m/e 285 (M^+), mp 74-77°C as free base.

14 : ^{1}H-NMR ($CDCl_3$) δ 0.79 (3H, d, C_6-CH_3, J = 7.0 Hz), 1.03 (3H, d, C_2-CH_3, J = 6.0 Hz), 1.32 (3H, s, C_7-CH_3), 3.79 (3H, s, OCH_3), 6.58-7.30 (3H, m, arom H), mass m/e 299 (M^+), mp 89-90°C as oxalate hemihydrate·MeEtCO.

15 : ^{1}H-NMR ($CDCl_3$) δ 0.86 (3H, d, C_6-CH_3, J = 7.0 Hz), 0.97 (3H, d, C_2-CH_3, J = 6.0 Hz), 1.35 (3H, s, C_7-CH_3), 3.80 (3H, s, OCH_3), 6.60-7.30 (3H, m, arom H), mass m/e 299 (M^+),

mp 125-127°C as oxalate·2/3 H_2O.

Demethylation of the methoxy group of 8 was performed with EtSH-$AlCl_3$ to give 9 (90%, mp 181°C as hydrobromide hemihydrate). In the case of 2, 12 and 14, treatment with BBr_3 gave phenols 3 (73%, mp 220-225°C as free base), 13 (68%, mp 287-289°C(dec) as hydrochloride), and 16 (76.6%, mp 280-283°C(dec) as hydrochloride), respectively.

Relative configurations of ring B and D of these tetracyclic benzomorphans were assigned to be cis from the estimation of vicinal dihedral angle,[8] for example 50° for 11 ($J_{5a,11b}$ =3.5 Hz). Conformation of piperizine rings would be chair form judging from no chemical shift change between C_{11}-Me of α-metazocine[9] and C_5-Me of 8 and C_6-Me of 2, 11. This observation was confirmed from study with Dreiding models, and the N-lone electron pairs of piperidine rings are fixed in axial direction.

These tetracyclic benzomorphans showed interesting pharmacological activities. Compounds 3 and 16 showed agonistic activities, on the contrary 6-membered derivatives 8 and 13 showed antagonistic activities against morphine analgesia. These results will be reported in a separate paper[10] and further synthetic approaches for modified benzomorphans are in progress.

ACKNOWLEDGEMENT This work was supported in part by a Grant-in Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

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7. 6a (97.6%, mp 162.5-164°C as hemioxalate), 6b (66%, mp 121-123°C as oxalate), 6c (85.1%, mp 183-184°C as hemioxalate).
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Received, 29th June, 1983