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Synthesis of 6-(β-Bromoethyl)-10,11-methylenedioxy-5,6,7,8-tetrahydrodibenz-[c,e]azocine (DA-VIII-MBr) as a New Specific α-Adrenergic Blocking Agent

6-(β-Bromoethyl)-10,11-methylenedioxy-5,6,7,8-tetrahydrodibenz[c,e]azocine (DA-VIII-MBr) as a new specific α-adrenergic blocking agent was synthesized.

Ishida, *et al.*[1] reported that a new compound with a β-halogenoethylamino group, 6-(β-bromoethyl)-10,11-methylenedioxy-5,6,7,8-tetrahydrodibenz[c,e]azocine (I) abbreviated as DA-VIII-MBr, had a more specific α-adrenergic blocking action than dibenamine or phenoxybenzamine. It showed a more specific blocking action on the responses of isolated strips of rat aorta and the blood pressure in pithed rats to adrenaline than on the responses to 5-hydroxytryptamine.

The structure of I, in which the nitrogen bearing the β-halogenoalkyl group is part of an eight-membered ring system, is very interesting, since it shows that I is an apogalanthamine analog[2] and Belleau[3] reported that a 2-benzazocine derivative was a potent adrenergic blocking agent.

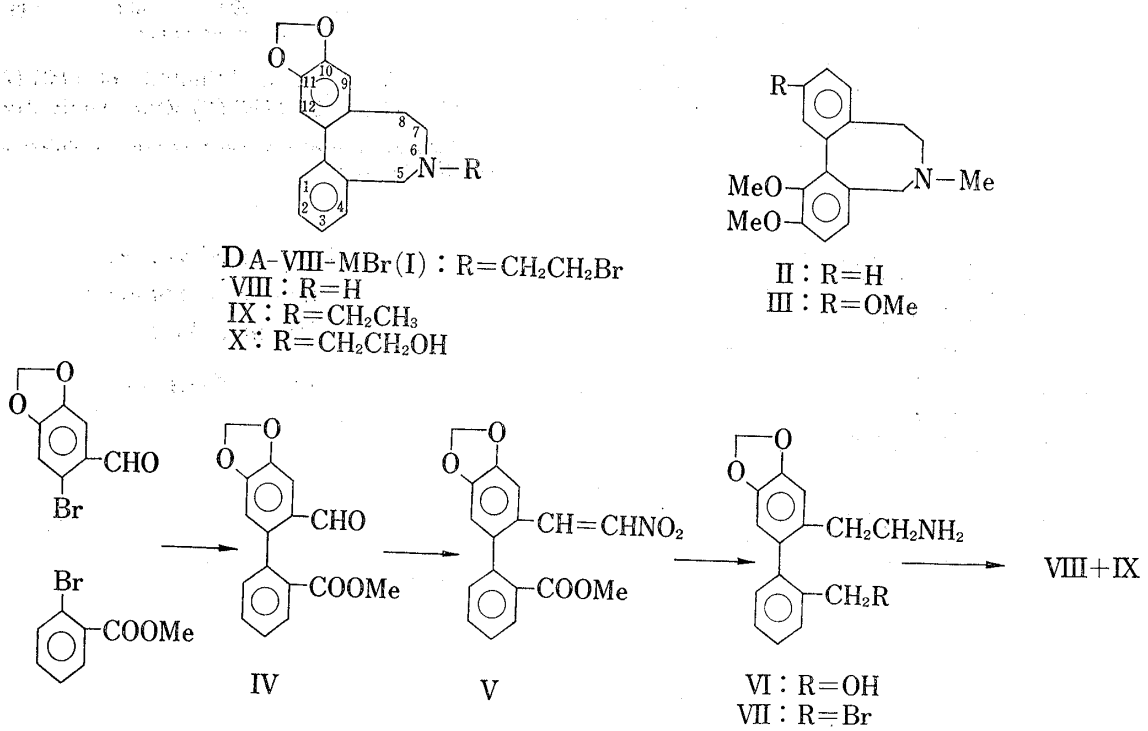

Chart 1

This paper briefly reports the synthesis of DA-VIII-MBr (I). Previously we reported[4,5] the syntheses of the apogalanthamine derivatives, II and III. The striking characteristic of

1) Y. Ishida, K. Watanabe, S. Kobayashi, and M. Kihara, presented at the Kinki Regional Meeting of the Japanese Pharmacological Society, June 14, 1975 (Nagoya): *Mel. Pharmacol.*, submitted.
2) K. Kotera, M. Motomura, S. Miyasaki, T. Okada, Y. Hamada, R. Kido, K. Hirose, M. Eigyo, H. Jyoyama, and H. Sato, *Shionogi Kenkyusho Nempo*, **17**, 88 (1967).
3) B. Belleau, *Can. J. Biochem. Physiol.*, **36**, 731 (1958).
4) S. Kobayashi and S. Uyeo, *J. Chem. Soc.*, **1957**, 638.
5) J. Koizumi, S. Kobayashi, and S. Uyeo, *Chem. Pharm. Bull.* (Tokyo), **12**, 696 (1964).

the synthesis of I was the quantitative conversion (92.7%) of methyl 2'-formyl-4',5'-methylenedioxy-2-biphenylcarboxylate (IV) to methyl 4',5'-methylenedioxy-2'-(2-nitrovinyl)-2-biphenylcarboxylate (V) *via* the Schiff's base of IV. The ester (IV) (mp 102—103°, lit.[6] mp 103—104°) was obtained by Ullmann condensation of 6-bromopiperonal with methyl 2-bromobenzoate in 21% yield (from 6-bromopiperonal). Then IV was heated with *n*-butylamine and the resulting Schiff's base was treated with nitromethane and acetic acid to afford V, $C_{17}H_{13}O_6N$, mp 167—170°. IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O), 1680 (C=C), 1480, 1330 (NO_2). This compound was found to be in the *trans* form on the basis of its nuclear magnetic resonance (NMR) spectrum: ($CDCl_3$) τ: 2.33 (1H, d, J=14 Hz, C<u>H</u>=CH-NO_2), 2.63 (1H, d, J=14 Hz, CH=C<u>H</u>-NO_2). The nitrostyrene (V) was reduced with lithium aluminum hydride to an aminoalcohol (VI) and then treated with phosphorus tribromide to yield a bromide (VII). Cyclization to form an eight-membered heterocyclic ring was accomplished by heating VII with ethanolic potassium hydroxide. 10,11-Methylenedioxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]-azocine (VIII), $C_{16}H_{15}O_2N$, was thus obtained in 32.3% yield (from V) and melted at 98.5—100°. Its structure was supported by its NMR and Mass spectra: ($CDCl_3$) τ: 8.51 (1H, s, NH), 7.84—6.60 (4H, m, 2×-CH_2-), 6.83 and 6.12 (each 1H, d, J=14 Hz, AB type of C-5 H_2), 4.05 (2H, s, OCH_2O), 3.32 (1H, s, C-9-H), 3.26 (1H, s, C-12-H), 2.73—2.64 (4H, m, aromatic H), and *m/e* 253 (M^+). An unexpected by-product formed during cyclization was found to be N-ethylated VIII (IX), $C_{18}H_{19}O_2N$, mp 78.5—81.5°, NMR spectrum ($CDCl_3$) τ: 8.81 (3H, t, J=7 Hz, N-CH_2-C<u>H</u>$_3$), 7.72—6.70 (6H, m, 3×-CH_2-), 7.09 and 6.38 (each 1H, d, J=13.5 Hz, AB type of C-5 H_2), 4.05 (2H, s, OCH_2O), 3.31 (1H, s, C-9-H), 3.24 (1H, s, C-12-H), 2.80—2.68 (4H, m, aromatic H). Mass Spectrum *m/e* 281 (M^+). IX seemed to be formed by ethylation of VIII with ethyl bromide, which may have been formed by the action of phosphorus tribromide on ethanol. Treatment of VIII with ethylene chlorohydrin in the presence of triethylamine caused its quantitative conversion to aminoethanol (X), $C_{18}H_{19}O_3N$, mp 101—103°, IR ν_{max}^{KBr} cm^{-1}: 3450 (OH). Bromination of X with phosphorus tribromide gave I, mp 227—230°, the structure of which was supported by elemental analysis and NMR spectral data as follows. *Anal.* Calcd. for $C_{18}H_{18}O_2NBr \cdot H_2O$: C, 57.15; H, 5.33; N, 3.70. Found: C, 57.51; H, 5.68; N, 3.30. NMR ($CDCl_3$) τ: 7.84—6.28 (10H, m, 5×-CH_2-), 4.05 (2H, s, OCH_2O), 3.33 (1H, s, C-9-H), 3.27 (1H, s, C-12-H), 2.86—2.64 (1H, m, aromatic H).

Faculty of Pharmaceutical Sciences,
Tokushima University,
Shomachi-1-chome, Tokushima, 770,
Japan

Shigeru Kobayashi
Masaru Kihara
Kayo Yamasaki
Yukio Ishida
Koozo Watanabe

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6) T. Ikeda, W.I. Taylor, Y. Tsuda, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, **1956**, 4749.