substituents. By contrast, any considerable amount of the conformer bearing 5-nitro and one N-ethyl diaxial conformation is not detected in I. There might exist considerable differences between tetrahydro-1,3-oxazines and hexahydropyrimidines in the magnitudes of effects, such as the lone pair-lone pair repulsion,[9] 1,3-diaxial alkyl-nitro interaction, and so on. Conformational study on antimicrobial 5-amino-5-methylhexahydropyrimidines[5] are now undertaken.

Experimental

NMR Measurements——A JEOL JNM-C-60H spectrometer equipped with a JES-VT-3 variable temperature probe was used. Spectra were taken at 60 MHz for 10% CS_2 solutions using TMS as an internal standard, and recorded every 3—10 degree over the range between +22° and −63°.

Dipole Moment Measurements——The Dipolemeter FAM-3A (2 MHz) manufactured by Yamato Scientific Instruments Co. was used for the measurements. The dipole moments were measured in CCl_4 solution at 20°. Densities were measured with a pycnometer of *ca.* 5 ml capacity. The electronic polarization of 1,3-diethyl-5-methyl-5-nitrohexahydropyrimidine (I) was obtained by measuring the refractive index of I (n_D^{20} 1.4728). The moments were calculated essentially by the method of Halverstadt and Kumler.[10]

9) R.A.Y. Jones, A.R. Katritzky, and M. Snarey, *J. Chem. Soc.* (*B*), **1970**, 131; E.P. Chen and R.G. Jesaitis, *Chem. Commun.*, **1970**, 1533.
10) I.F. Halverstadt and W.D. Kumler, *J. Am. Chem. Soc.*, **64**, 1982, 2988 (1942).

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Synthesis of Norepinephrine-O-sulfates

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In the studies of the metabolism of norepinephrine (NE), norepinephrine-O-sulfates *i.e.* NE-3-sulfate and NE-4-sulfate, were required and the chemical synthesis was undertaken. The synthetic route of the desired NE-O-sulfates from catechol diacetate is outlined in Chart 1.

3,4-Dihydroxyacetophenone (II), 4-benzyloxy-3-hydroxyacetophenone (IIIa), 3-benzyloxy-4-hydroxyacetophenone (IIIb), 4-benzyloxy-α-bromo-3-hydroxyacetophenone (IV) and 4-acetoxy-3-benzyloxy-α-bromoacetophenone (VIII) were prepared by the methods similar to those described by Imai and Tamura[2] and identical with specimens given in literatures.[2,3]

In order to protect the resulting amino groups, amination of IV or VIII was carried out with dibenzylamine on refluxing in anhydrous benzene to give the aminoaryl ketone, 4-benzyloxy-α-N,N-dibenzylamino-3-hydroxyacetophenone (V) or 4-acetoxy-3-benzyloxy-α-N,N-dibenzylamino-acetophenone (IXa).

Because of the less reactivity of hydroxy group of V, N,N-dimethylaniline-sulfur trioxide, a mild sulfating agent, was able to sulfate V only to a small extent. Therefore, sulfation of V was attained with pyridine-sulfur trioxide.[4] IXa was deacetylated by hydrolysis with

1) Location: *Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
2) K. Imai and Z. Tamura, *Chem. Pharm. Bull.* (Tokyo), **16**, 1854 (1968).
3) J. Hukki and E. Honkanen, *Acta Chem. Scand.*, **13**, 329 (1959).
4) E.E. Gilbert, *Chem. Rev.*, **62**, 552 (1962).

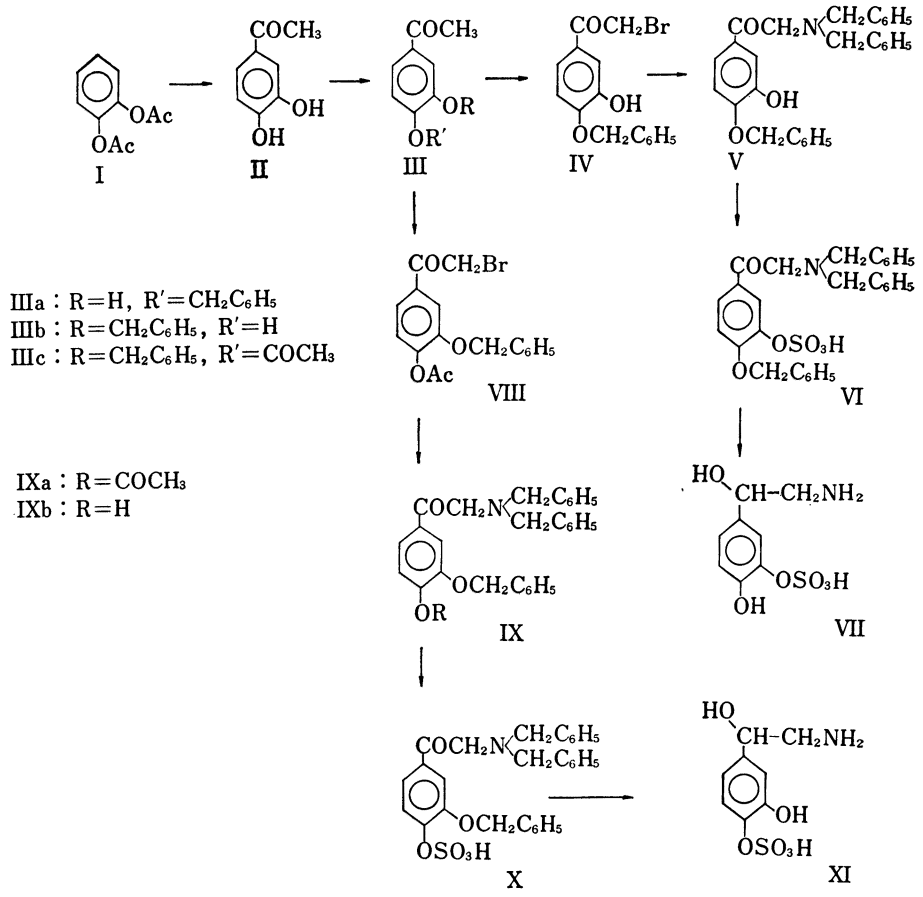

Chart 1

alkali prior to sulfation. In this case, the product (IXb) was treated with N,N-dimethylaniline-sulfur trioxide to afford 3-benzyloxy-α-N,N-dibenzylamino acetophenon-4-yl sulfate (X). Reduction of the amino ketones (VI and X) and concomitant removal of the protective N- and O-benzyl groups by catalytic hydrogenolysis over Pd-C gave norepinephrine-3-sulfate (VII) and norepinephrine-4-sulfate (XI) respectively. The treatment was carried out in an acidic medium to prevent the further decomposition of the resulting primary amine.

Data obtained from elemental analysis, infrared (IR) measurement and acid hydrolysis supported the structures of the final products VII and XI. The separation of VII and XI was achieved on a thin-layer of silica gel with a mixture of ethyl acetate, ethanol and acetic acid (15: 10: 2), the *Rf* values were 0.38 and 0.28 respectively.

Experimental[5]

3,4-Dihydroxyacetophenone (II), 4-Benzyloxy-3-hydroxyacetophenone (IIIa), 3-Benzyloxy-4-hydroxyacetophenone (IIIb), 4-Benzyloxy-α-bromo-3-hydroxyacetophenone (IV) and 4-Acetoxy-3-benzyloxy-α-bromoacetophenone (VIII)——These compounds were synthesized by methods given in literatures.[2,3]

4-Benzyloxy-α-N,N-dibenzylamino-3-hydroxyacetophenone (V)——N,N-Dibenzylamine (3.12 g, 0.021 mol) was added to a solution of IV (2.24 g, 0.007 mol) in anhydrous benzene at room temperature and

5) All melting points were taken on a micro hot-stage apparatus and uncorrected.

gently heated under reflux for 3 hr. The mixture was cooled and filtered. The filtrate was evaporated to dryness under reduced pressure. The residue was crystallized from ethanol as pale yellow needles (2.25 g, 74%), mp 108—110°. *Anal.* Calcd. for $C_{29}H_{24}O_3N$: C, 79.61; H, 6.22; N, 3.20. Found: C, 79.34; H, 6.12; N, 3.69. IR ν_{max}^{KBr} cm^{-1}: 1665 (C=O).

4-Benzyloxy-α-N,N-dibenzylamino-3-hydroxy Acetophenone (IXb)——VIII was condensed with dibenzylamine under reflux and treated as described above. As the reaction product (IXa) failed to crystallize, it was dissolved in ethanol and refluxed for 2.5 hr with 1N NaOH solution to cleave the acetyl group. The reaction mixture was cooled, neutralized with acetic acid in ethanol and concentrated. The oily residue was crystallized from methanol as white crystals, mp 104—106°. *Anal.* Calcd. for $C_{29}H_{27}O_3N$: C, 79.63; H, 6.17; N, 3.20. Found: C, 79.94; H, 6.29; N, 3.29. IR ν_{max}^{KBr} cm^{-1}: 1665 (C=O).

Pyridine Sulfur Trioxide Complex——Excess pyridine in carbon tetrachloride was cooled with dry ice-MeOH. Sulfur trioxide was added dropwise to the cooled mixture with constant stirring for 1 hr. The reaction vessel was removed from the cooling bath and allowed to stand at room temperature. The white precipitate of the complex was collected by suction, washed with carbon tetrachloride and then triturated with ice water. The product washed with acetone and ether was dried over P_2O_5 under reduced pressure at 70°, mp 101—103° (reported mp 97—100°; 121°; 137°; 155° and 175°).

4-Benzyloxy-α-N,N-dibenzylaminoacetophenon-3-yl Sulfate (VI)——Va (0.59 g, 1.4 mmol) in pyridine (2 ml) was added to a suspension of pyridine–sulfur trioxide complex (0.64 g, 4 mmol) in pyridine (4 ml). Under an anhydrous condition, the mixture was stirred for 5 hr and allowed to stand overnight at room temperature. Ice water was added to the reaction mixture to give white precipitate which was collected and washed with water until free of SO_4^{2-}, followed by ethanol and ether. The product was dried over $CaCl_2$ in a vacuum desiccator to obtain an amorphous solid. Yield *ca.* 50%, mp 149—151°. *Anal.* Calcd. for $C_{29}H_{27}O_6NS \cdot H_2O$: C, 65.05; H, 5.41; N, 2.61; S, 5.98. Found: C, 65.10; H, 5.54; N, 2.89; S, 6.05. IR ν_{max}^{KBr} cm^{-1}: 1045 (S=O), 1680 (C=O).

3-Benzyloxy-α-N,N-dibenzylaminoacetophenon-4-yl Sulfate (X)——Carbon disulfide (2.0 ml) and N,N-dimethylaniline (1.5 ml) were mixed and cooled with dry ice-MeOH. Chlorosulfonic acid (0.5 ml) was added dropwise to the cooled mixture with stirring. The reaction vessel was then removed from the cooling bath after removal of the carbon disulfide layer, and about one third of the jelly-like residue was taken and mixed with IXb (*ca.* 300 mg) in pyridine (0.5 ml). The mixture was stirred continuously for 30 min and then kept at room temperature overnight. The reaction mixture was treated as mentioned above. The resultant white amorphous solid was dried *in vacuo* over P_2O_5 at room temperature. Yield *ca.* 55%, mp 154°. *Anal.* Calcd. for $C_{29}H_{27}O_6NS \cdot 2/3H_2O$: C, 65.78; H, 5.10; N, 2.65; S, 6.05. Found: C, 65.58; H, 5.21; N, 2.91; S, 6.06. IR ν_{max}^{KBr} cm^{-1}: 1043 (S=O), 1685 (C=O).

Norepinephrine-3-sulfate (VII)——VI suspensed in 0.01N AcOH–EtOH was hydrogenated over 5% Pd-C for 18 hr at room temperature and atmospheric pressure. After removal of the catalyst, the filtrate was concentrated *in vacuo*, and then triturated with absolute ethanol to give white amorphous solid, mp 164.5—166.5° (decomp.). *Anal.* Calcd. for $C_8H_{11}O_6NS$: C, 38.55; H, 4.42; N, 5.62. Found: C, 38.19; H, 4.66; N, 5.25. IR ν_{max}^{KBr} cm^{-1}: 1045 (S=O). UV $\lambda_{max}^{H_2O}$ mμ (log ε): 221 (3.88), 275 (3.27).

Norepinephrine-4-sulfate (XI)——Catalytic hydrogenation of X was carried out over 5% Pd-C and treated as described above. The amorphous solid yielded *ca.* 62%, decomposed above 154°. *Anal.* Calcd. for $C_8H_{11}O_6NS \cdot \frac{1}{2}H_2O$: C, 37.20; H, 4.26; N, 5.42. Found: C, 36.94; H, 4.44; N, 5.18. IR ν_{max}^{KBr} cm^{-1}: 1045 S=O). UV $\lambda_{max}^{H_2O}$ mμ (log ε): 215 (3.85), 275 (3.31).

Acid Hydrolysis of NE-3-Sulfate and 4-Sulfate——VII or XI was acidified to pH 1 with 6N HCl and heated on a boiling water bath for 20 min. The hydrolysate was treated by the method similar to that described by Kawai.[6] Gas chromatogram showed the same retention time as the authentic NE derivative. The hydrolysate was also shown to be identical with the authentic NE on silica gel TLC with *n*-BuOH: AcOH: H_2O (4: 1: 5).

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6) S. Kawai and Z. Tamura, *Chem. Pharm. Bull.* (Tokyo), **16**, 1091 (1968).