At present only I has been identified as a product, and the yield of I at pH 7.4 was larger than that expected for reaction 3 alone (50%). This suggests that products of the decomposition of II can reduce II to I, as a large concentration of II was used for the product determination. Further studies are necessary on this.

Experimental

Materials——4-Diethylaminoantipyrine was prepared as described previously.[2] The buffers used in this study were prepared from: $HClO_4$, HOAc–NaOAc (pH 5.5), NaH_2PO_4–Na_2HPO_4 (pH 7.4), and $Na_2B_4O_7$ (pH 10.4). The pH values of the aqueous acetonitrile solutions were determined with a Hitachi-Horiba M-7 pH meter after kinetic measurements. The ionic strength of the solutions was adjusted by addition of $NaClO_4$. Acetonitrile and sodium perchlorate were purified as described previously.[8]

Apparatus——A Hokuto Denko HA-101 potentiostat, HF-102 coulometer, and a Riken Denshi SP-J5V recorder were used for controlled potential electrolysis. Electrolysis was carried out as described previously.[8] A Hitachi 101 spectrophotometer equipped with a thermostatically controlled cell compartment was used for spectrophotometric measurements.

Kinetic Measurements——All reactions were carried out at $25 \pm 0.1°$. I (10 mg) was subjected to electrolysis in acetonitrile (20 ml) containing 0.1 M $NaClO_4$ at 0.45 V for 2 min. Dissolved oxygen was removed by passing nitrogen through the solution. From the electricity consumed (0.891 coulombs) the concentration of II generated was calculated to be 0.463 mM. An aliquot of the resulting blue-violet solution (1—4 ml) was mixed with an appropriate amount of buffer (4—1 ml) in a standard spectrophotometric cell of 1.0 cm light path. The change of absorbance with time was measured at 590 nm.

8) H. Sayo and M. Masui, *J. Chem. Soc. Perkin II*, 1973, 1640.

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Studies on Psychotropic Agents. IV.[1] Alkylation of 2-Substituted 2,3,4,5-Tetrahydro-1H-pyrido[4,3-*b*]indole Derivatives

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The alkylation of 2-substituted 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles (**1**) with sodium amide and alkyl halide in non-polar solvents proceeded most smoothly when the substituent in the 2 position was a benzyl group, and gave 5-alkyl-1,2,3,4-tetrahydropyrimido[1,6-*a*]indoles (**2**) and 5-alkyl-tetrahydropyrido[4,3-*b*]indoles (**3**). The ratio of **2** to **3** depended on the halide employed. The tetrahydropyrimido[1,6-*a*]indole derivatives (**5**) with a 3-(*p*-fluorobenzoyl)propyl group in the 2 position were also prepared.

Keywords——2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole derivative; 1,2,3,4-tetrahydropyrimido[1,6-*a*]indole derivative; alkylation; rearrangement; butyrophenone derivative

It has been reported that the alkylation of 2-substituted 2,3,4,5-tetrahydro-1*H*-pyrido-[4,3-*b*]indole derivatives (I) with sodium amide and dialkylaminoalkyl halide gives 5-(dialkylaminoalkyl) derivatives (II)[3,4] but that the reaction of the 2-methyl derivative (Ia) with

1) Part III: Y. Nagai, H. Uno, and S. Umemoto, *Chem. Pharm. Bull.* (Tokyo), **27**, 1159 (1979).
2) Location: *33–94, Enokicho, Suita, Osaka.*
3) U. Hörlein, *Chem. Ber.*, **87**, 463 (1954).
4) R.G.W. Spickett, *J. Med. Chem.*, **9**, 436 (1966).

benzyl chloride under the same conditions does not proceed smoothly.[3] Ebnöther *et al.*[5] reported that the treatment of Ia with butyllithium and diphenyliodonium chloride gave the 1,2,3,4-tetrahydropyrimido[1,6-*a*]indole derivative (III) by a rearrangement involving Mannich fragmentation, as shown in Chart 1. On the other hand, Nakazaki[6] reported that the alkylation of tetrahydrocarbazole (IV) afforded 4a-alkyltetrahydrocarbazolenines (V) and 9-alkyltetrahydrocarbazoles (VI). The present paper describes an extension of the above rearrangement to the preparation of various 2,5-disubstituted 1,2,3,4-tetrahydropyrimido[1,6-*a*]indoles (**2**, **5**), which are interesting as potential central nervous system agents, because 5,7-dimethyl-1,2,3,4-tetrahydropyrimido[1,6-*a*]indole (VII) has been reported to possess neuroleptic-like activities in animal tests.[7]

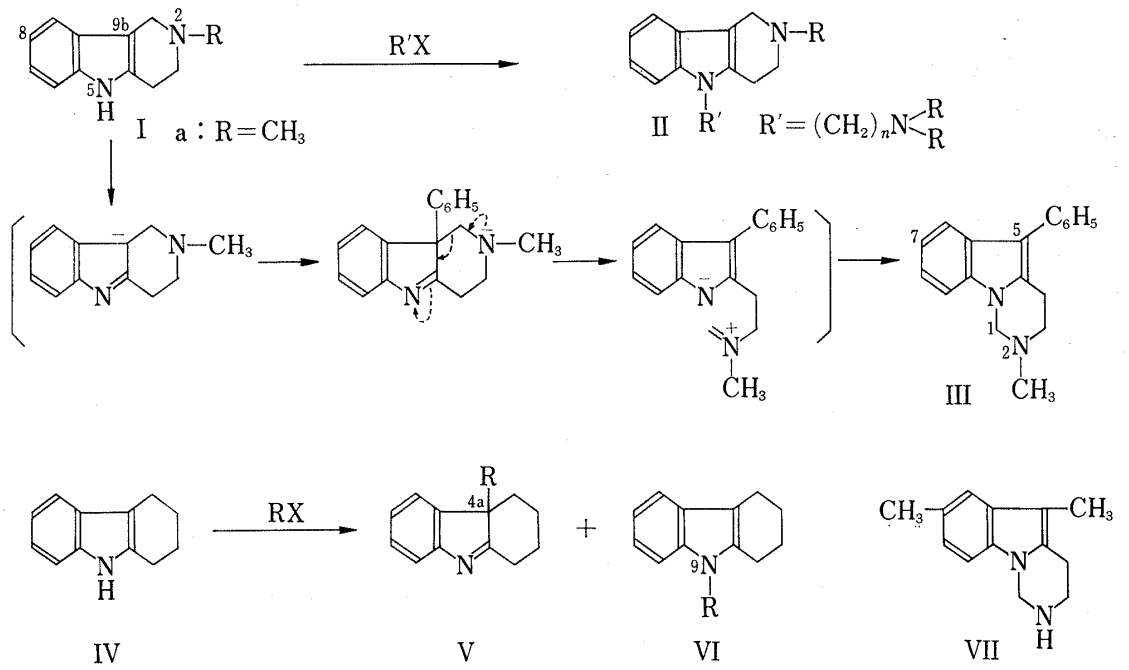

Chart 1

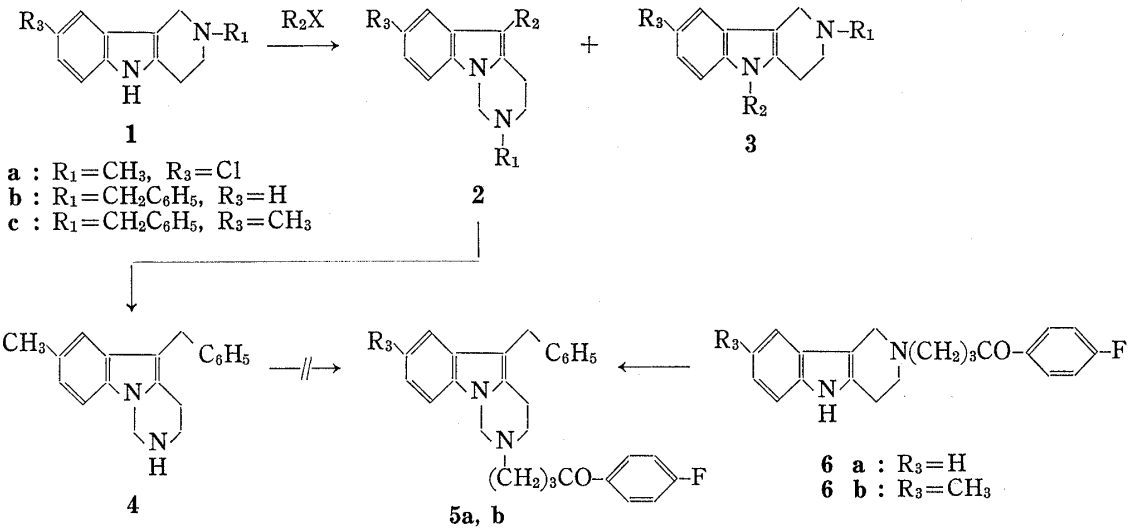

Chart 2

5) A. Ebnöther, P. Niklaus, and S. Süess, *Helv. Chim. Acta*, **52**, 629 (1969).
6) M. Nakazaki, *Bull. Chem. Soc. Jpn.*, **34**, 334 (1961).
7) G.N. Artemenko, Yu. I. Viklyaev, N.F. Kucherova, and L.N. Borisova, *Farmacol. Toksikol.*, **39**, 651 (1976).

The benzylation of 8-chloro-2-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**1a**) with sodium amide and benzyl chloride in toluene under conditions similar to those reported for the benzylation of Ia[3] gave the 5-benzyl-pyrimido[1,6-*a*]indole (**2a**) in 5% yield as well as many unknown products, as determined by thin-layer chromatography. Alkylation of the 2-benzyl-pyrido[4,3-*b*]indoles (**1b**, **c**) with alkyl halides under similar conditions, however, gave a mixture of two products, 5-alkyl-pyrimido[1,6-*a*]indoles (**2b**—**f**) and 5-alkyl-pyrido[4,3-*b*]indoles (**3b**—**f**). The nuclear magnetic resonance (NMR) spectra of **2** showed a methylene signal of the NCH_2N group at δ 4.66—4.83 as a singlet, which is characteristic of 1,2,3,4-tetrahydropyrimido[1,6-*a*]indoles.[5,8] The yield ratio of **2** to **3** was affected by the halides employed. Benzyl chloride gave the highest ratio, followed by allyl bromide, *n*-propyl bromide and *n*-butyl chloride. In this alkylation of **1**, like that[6,9] of IV, halides, which tend to react by the S_N1 mechanism, may attack predominantly the sterically hindered 9b position, since they are less affected by steric hindrance than halides which tend to react by the S_N2 mechanism.

We also attempted to introduce the 3-(*p*-fluorobenzoyl)propyl group, which is an important constituent of neuroleptic butyrophenone derivatives, into the 2 position of 1,2,3,4-tetrahydropyrimido[1,6-*a*]indole derivatives. The catalytic hydrogenation of **2f** on palladium carbon gave the 2-debenzylated derivative (**4**), which was treated with 3-(*p*-fluorobenzoyl)-propyl chloride or bromide; however, this reaction did not proceed owing to the low reactivity of the amino group at the 2 position. Treatment of 2-[3-(*p*-fluorobenzoyl)propyl]-pyrido[4,3-*b*]indoles (**6**)[10] with sodium amide and benzyl chloride, however, gave the desired compounds (**5**) in low yields.

The compounds (**2**, **5**) synthesized were examined pharmacologically by the usual methods for neuroleptic and thymoleptic activities, but did not show significant activities.

Experimental

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. NMR spectra were taken in $CDCl_3$ solution with a Varian 100 spectrometer using TMS as an internal standard, and MS spectra were taken with a Hitachi RMU-6L mass spectrometer.

Alkylation of 2-Benzyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles (1)——A mixture of **1** (0.02 mol) and sodium amide (0.026 mol) in toluene (benzene or xylene) (40 ml) was refluxed for 2 hr with stirring. After cooling, alkyl halide (0.022 mol) was added to the reaction mixture and the resulting mixture was refluxed for 3 hr. H_2O was added, and the organic layer was separated and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel with toluene–$CHCl_3$ (1: 1) for **2a**, with

Table I. Results of the Reactions of 2-Substituted 2,3,4,5-Tetrahydro-1*H*-pyrido-[4,3-*b*]indoles (**1**, **6**) with Several Halides

Halide	Products				Solvent
	Compd. No.	Yield (%)	Compd. No.	Yield (%)	
$ClCH_2C_6H_5$	**2a**	5			Toluene
$ClCH_2C_6H_5$	**2b**	42	**3b**	10	Toluene
$BrCH_2CH{=}CH_2$	**2c**	32	**3c**	15	Toluene
$Br(CH_2)_2CH_3$	**2d**	6	**3d**	31	Toluene
$Cl(CH_2)_3CH_3$	**2e**	3	**3e**	21	Xylene
$ClCH_2C_6H_5$	**2f**	55	**3f**	12	Benzene
$ClCH_2C_6H_5$	**5a**	3			Xylene
$ClCH_2C_6H_5$	**5b**	4			Xylene

8) C.J. Cattanach, A. Cohen, and B. Heath-Brown, *J. Chem. Soc.* (*C*), **1971**, 359.
9) M. Nakazaki and S. Isoe, *Nippon Kagaku Zasshi*, **76**, 1159 (1955).
10) R.P. Johnson and J.P. Oswald, U.S. Patent 3382250 (1968) [*C.A.*, **69**, 67356 (1968)]; R.P. Johnson and J.P. Oswald, U.S. Patent 3466293 (1969).

TABLE II. 1,2,3,4-Tetrahydropyrimido[1,6-*a*]indoles (**2**,**4**,**5**) and 2,3,4,5-Tetrahydro-1*H*-pyrido[4,3-*b*]indoles (**3**)

Compd. No.	R_1	R_2	R_3	mp (°C) (solvent)	Formula (salt)	Analysis (%) Calcd. (Found) C	H	Cl	F	N	MS(M^+)	NMR (ppm) NCH_2N
2a[a]	CH_3	$CH_2C_6H_5$	Cl	80— 81 (EtOH)								4.66
2b	$CH_2C_6H_5$	$CH_2C_6H_5$	H	100—102 (EtOH)	$C_{25}H_{24}N_2$	85.19 (85.10	6.86 6.77			7.95 8.12)		4.83
2c	$CH_2C_6H_5$	$CH_2CH{=}CH_2$	H	118—120 (AcOEt)	$C_{21}H_{22}N_2 \cdot C_4H_4O_4$[b]	71.75 (71.81	6.26 6.28			6.70 6.62)		4.74
2d	$CH_2C_6H_5$	$(CH_2)_2CH_3$	H	118—119 (AcOEt)	$C_{21}H_{24}N_2 \cdot 1.5C_4H_4O_4$	67.76 (67.89	6.32 6.47			5.85 5.89)	304	4.75
2e	$CH_2C_6H_5$	$(CH_2)_3CH_3$	H	133—135 (AcOEt)	$C_{22}H_{26}N_2 \cdot C_4H_4O_4$	71.86 (71.73	6.96 7.06			6.45 6.31)		4.75
2f	$CH_2C_6H_5$	$CH_2C_6H_5$	CH_3	121—123 (EtOH–benzene)	$C_{26}H_{26}N_2$	85.20 (85.15	7.15 7.40			7.65 7.35)		4.76
4	H	$CH_2C_6H_5$	CH_3	187—190 (dil. EtOH)	$C_{19}H_{20}N_2 \cdot HCl$	72.94 (72.94	6.77 6.90	11.33 11.43		8.96 8.89)		4.80
5a	$(CH_2)_3COC_6H_4$-*p*-F	$CH_2C_6H_5$	H	Oil	$C_{28}H_{27}FN_2O$	78.84 (78.71	6.38 6.39		4.45 4.27	6.57 6.44)	426	4.79
5b	$(CH_2)_3COC_6H_4$-*p*-F	$CH_2C_6H_5$	CH_3	Oil	$C_{29}H_{29}FN_2O$	79.06 (78.89	6.64 6.74		4.31 4.22	6.36 6.21)	440	4.74
3b[c]	$CH_2C_6H_5$	$CH_2C_6H_5$	H	154—155 (benzene–petr.ether)								
3c	$CH_2C_6H_5$	$CH_2CH{=}CH_2$	H	171—172 (EtOH)	$C_{21}H_{22}N_2 \cdot C_4H_4O_4$	71.75 (71.97	6.26 6.34			6.70 6.41)		
3d	$CH_2C_6H_5$	$(CH_2)_2CH_3$	H	217—220 (EtOH)	$C_{21}H_{24}N_2 \cdot HCl$	73.99 (73.70	7.39 7.45	10.40 10.60		8.22 8.14)		
3e	$CH_2C_6H_5$	$(CH_2)_3CH_3$	H	210—215 (EOtH)	$C_{22}H_{26}N_2 \cdot HCl$	74.44 (74.13	7.67 7.67	9.99 10.07		7.89 7.71)		
3f	$CH_2C_6H_5$	$CH_2C_6H_5$	CH_3	210—212 (dil. EtOH)	$C_{26}H_{26}N_2 \cdot C_4H_4O_4$	74.66 (74.79	6.27 6.39			5.81 5.80)		

a) Ref. 8. *b*) Maleate. *c*) Ref. 4.

toluene for **2b**—**f** and with $CHCl_3$ for **3**. The product, if an oil, was converted into the maleate or hydrochloride; if solid, it was purified by recrystallization. The results are summarized in Tables I and II.

5-Benzyl-7-methyl-1,2,3,4-tetrahydropyrimido[1,6-*a*]indole (4)——A mixture of **2e** (15 g) and 5% Pd-C (3 g) in 70% EtOH (370 ml) was subjected to catalytic hydrogenation at 60° under normal pressure. After the theoretical amount of H_2 had been absorbed, the catalyst was removed and 70% of the solvent was removed *in vacuo*. The precipitated crystals were collected and recrystallized from dil. EtOH to give 6.6 g (51.6%) of **4**.

5-Benzyl-2-[3-(*p*-fluorobenzoyl)propyl]-1,2,3,4-tetrahydropyrimido[1,6-*a*]indoles (5)——The benzylation of **6** with benzyl chloride was carried out by the procedure described for the alkylation of **1** using xylene as a solvent. The crude product was chromatographed on silica gel, and elution with toluene–$CHCl_3$ (20 : 1) gave **5** as an oily product.

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Synthesis of Conjugated Cholesterol and Cholestanols[1]

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The glucuronides, sulfates, glucosides and N-acetylglucosaminides of cholesterol and epimeric 5α-cholestan-3-ols have been synthesized. The formation of a β-glucoside linkage was readily achieved by means of the Koenigs-Knorr reaction with the corresponding α-acetohalosugar, employing cadmium carbonate as a catalyst. The preparation of 6,7α,7β-d_3-cholesterol glucuronide is also described.

Keywords——cholesterol; 5α-cholestan-3β-ol; 5α-cholestan-3α-ol; Koenigs-Knorr reaction; cadmium carbonate; glucuronide; glucoside; N-acetylglucosaminide; sulfate; d_3-cholesterol glucuronide

It is reasonably well substantiated that cholesterol sulfate is an activated precursor in the biosynthesis of steroid hormones.[3,4] In 1970, Wade reported the occurrence of cholesterol glucuronide in human blood,[5] but the metabolic and physiological significance of this conjugate still remains unclear. Conjugation of cholesterol appears to be an important biotransformation in living animals in connection with the biosynthesis of bile acids as well as steroid hormones. In recent years, considerable attention has been focused on the marked elevation of the plasma level of 5α-cholestan-3β-ol in patients with cerebrotendinous xanthomatosis.[6–8] On the other hand novel conjugated forms other than the common glucuronide

1) Part CXXXXV of "Studies on Steroids" by T. Nambara; Part CXXXXIV: J. Goto, H. Kato, F. Hasegawa, and T. Nambara, *Chem. Pharm. Bull.* (Tokyo), **27**, 1402 (1979).
2) Location: *Aobayama, Sendai, 980, Japan*; *a*) To whom inquiries should be addressed.
3) K.D. Roberts, L. Bandi, H.I. Calvin, W.D. Drucker, and S. Lieberman, *J. Am. Chem. Soc.*, **86**, 958 (1964).
4) R.B. Hochberg, S. Ladany, M. Welch, and S. Lieberman, *Biochemistry*, **13**, 1938 (1974).
5) A.P. Wade, *Clin. Chim. Acta*, **27**, 109 (1970).
6) G. Salen, *Ann. Intern. Med.*, **75**, 843 (1971).
7) Y. Seyama, K. Ichikawa, and T. Yamakawa, *J. Biochem.*, **80**, 223 (1976).
8) G. Salen and E.H. Mosbach, "The Bile Acids. Chemistry, Physiology, and Metabolism," Vol. 3, ed. by P.P. Nair and D. Kritchevsky, Plenum Press, New York, 1976, p. 115.