5-Benzylideneamino-1,3-dimethyl-6-phenethyluracil (VI)——A solution of IIa (0.43 g, 0.0015 mol) in EtOH (300 ml) containing 10% palladium-carbon (0.2 g) was hydrogenated at room temperature and atmospheric pressure. After the consumption of hydrogen (135 ml) had stopped, the solution was filtered. Benzaldehyde (0.16 g, 0.0015 mol) was added to the filtrate and the mixture was refluxed for 2 hr. After cooling, the precipitates were filtered off and recrystallized from EtOH to give VI (0.21 g, 40%[9]), mp 121—122°, *Anal.* Calcd for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.09; N, 12.10. Found: C, 72.34; H, 6.01; N, 11.99. IR cm^{-1}: 1685, 1643 (CO). NMR (DMSO-d_6): δ 2.60—3.43 (m, 4H, $-CH_2-CH_2-$), 3,27 (s, 3H, N–Me), 3.50 (s, 3H, N–Me), 7.25 (s, 5H, Ph), 7.37—8.00 (m, 5H, Ph), 9.33 (s, 1H, =CH–). MS *m/e*: 347.

6-Chloro-6-deoxy-8-phenyl-9-deazatheophylline (XIII)——A mixture of IVa (0.51 g, 0.002 mol), phosphorus oxychloride (10 ml), and sulfolane (1 ml) was refluxed for 5 hr at 250°. The reaction mixture was concentrated *in vacuo* and the residue was triturated with chilled 5% NH_3. The insoluble material was filtered off, washed with chilled H_2O, and dried in a desiccator (P_2O_5) *in vacuo* to give XIII (0.54 g, 100%). IR cm^{-1}: 1675 (CO). MS *m/e*: 273, 275.

6-Arylamino-6-deoxy-8-phenyl-9-deazatheophyllines (XIV—XVI) (Table III)——A mixture of IVa (0.255 g, 0.001 mol), phosphorus oxychloride (3 ml), sulfolane (1 ml), and an appropriate arylamine (0.003 mol) was refluxed for 3 hr at 250°. The reaction mixture was concentrated *in vacuo* and the residue was triturated with chilled 5% NH_3. The insoluble material was filtered off, washed with H_2O, dried, and recrystallized to give the corresponding XIV—XVI.

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9) Calculated on the basis of IIa.

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Direct Fractionation Procedure for Hydrogen Peroxide-Acetic Acid Oxidation Products from Aromatic Amines by Reversed-Phase Liquid Chromatography

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In order to eliminate the tedious, multi-step isolation process commonly used in the synthesis of aromatic amine oxides employing hydrogen peroxide and acetic acid, a direct chromatographic fractionation procedure was developed. The polar reagents were found to be flushed out, while the N-oxide was retained by a reversed-phase column packed with styrene-divinylbenzene copolymer gel or octadecylsilanized silica gel as the stationary phase, and using methanol-water as the mobile phase. By stepwise elution, clean-up of the reagents and direct fractionation of the N-oxide from the crude reaction mixture were simultaneously accomplished.

Keywords——hydrogen peroxide-acetic acid N-oxidation; aromatic amine oxide; pyridine 1-oxide and homologs; pyrazine 1-oxide and homologs; pyrazine 1,4-dioxide and homologs; reversed-phase liquid chromatography

Ochiai and his co-workers developed a new procedure for the N-oxidation of heteroaromatic compounds such as pyridine, quinoline and their homologs by heating with hydrogen

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peroxide and acetic acid.[2-4] This method has been widely applied in the field of heterocyclic chemistry, for many reasons, particularly the simplicity of the reagents and the reaction procedure, and the high yield it usually produces. However, after completion of the reaction, a tedious and time-consuming process is usually required to isolate the product.

First, it is necessary to decompose excess hydrogen peroxide with a reducing agent or to remove the peroxide by repeated evaporation and dilution to prevent the hydrogen peroxide from exploding upon concentration. Consequently, direct fractionation of the product by distillation is not possible. Further, due to the hydrophilic properties of N-oxides, fractionation of the product from a reaction mixture containing water and hydrophilic reagents by organic solvent extraction is inefficient. Acid often has to be added to separate the basic product from the crude extract as a salt. In this case, an alkali is then added to neutralize and to isolate the free base, followed by the addition of a saturated salt solution to liberate the product, which is commonly extracted several times using chloroform. The crude extract is finally purified by distillation or recrystallization. However, there is still a possibility of explosive decomposition during distillation.

One of the authors (Hara) is developing a generalized procedure for the direct fractionation of synthetic products from crude reaction mixtures by high performance liquid chromatography (HPLC),[5-7] which appeared to be very suitable as an improved isolation procedure for use in the synthesis of N-oxidation products from heteroaromatics.

A reversed-phase column packed with styrene-divinylbenzene copolymer (PS) gel or octadecylsilanized silica gel (ODS) was selected in order to examine the separation of the components associated with hydrogen peroxide-acetic acid N-oxidation, because excess reagents which should be eliminated from the reaction mixture are substantially hydrophilic and are not as strongly retained by a reversed-phase column as the organic products. The capacity ratio of solutes in reversed-phase liquid chromatography depends on the polarity of the mobile phase, which is usually adjusted by altering its composition. As an example, when using a methanol-water mixture as the mobile phase, the retention of the solute increases as the content of water in the system increases. This principle was applied in our present examination of retention behavior in HPLC.

In accordance with our reasoning, hydrogen peroxide and acetic acid were found to be least strongly retained; they were flushed out even when pure water was used as the mobile phase, which normally affords maximum retention for reversed-phase columns. On the other hand, N-oxides were more strongly retained in a methanol-water system than the polar reagents. The capacity ratio for N-oxides increases as their lipophilicity increases or as the water content in the mobile phase is increased. Though less lipophilic N-oxides such as pyridine 1-oxide, pyrazine 1,4-dioxide and its methyl derivative were not sufficiently retained on PS gel columns, they were retained to some extent by ODS columns when pure water was used as the mobile phase. In general, the retention of N-oxides in ODS columns was stronger than in PS gel columns. More lipophilic compounds such as the N-oxides of alkylpyridine, quinoline and higher homologs were well retained by either of the reversed-phase columns. Isomeric N-monoxides and N,N-dioxides were produced from the pyrazine derivatives. Separation of these compounds was achieved, together with clean-up of the polar reagents.

It was observed that the heteroaromatic compounds used as starting materials in this study were retained by either reversed-phase column more strongly than the corresponding N-oxides. Consequently, the less strongly retained polar reagents, more strongly retained

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Table I. Liquid Chromatographic Retentions of Hydrogen Peroxide-Acetic Acid N-Oxidation Products

Substrate	*n*-Hexane/ethyl acetate (v/v)[a]	k'[b]	Methanol/ water(v/v)[c]	k'	Methanol/ water (v/v)[d]	k'
Pyridine	1 : 1	4.0	7 : 3	0.9		
α-Picoline	1 : 1	4.2	7 : 3	1.7		
2,6-Lutidine	1 : 1	2.7	4 : 1	2.0		
Quinoline	1 : 1	2.4	9 : 1	1.7		
Pyrazine	1 : 1	4.7	1 : 1	0.9	1 : 1	1.8
2-Me-pyrazine	1 : 1	4.8	1 : 1	1.4	1 : 1	2.4
2,6-Di-Me-pyrazine	1 : 1	5.1	1 : 1	2.5	1 : 1	3.6

Product	Methanol/ water (v/v)[c]	k'	Methanol/ water (v/v)[d]	k'	Ref
Pyridine 1-oxide	0 : 1	0.9	1 : 1	2.2	4
α-Picoline 1-oxide	1 : 4	0.9	1 : 1	2.6	8
2,6-Lutidine 1-oxide	2 : 3	1.3	1 : 1	3.2	9
Quinoline 1-oxide	3 : 2	1.7	1 : 1	3.8	10
Pyrazine 1-oxide	1 : 9	0.7	3 : 7	1.5	11
Pyrazine 1,4-dioxide	1 : 9	0.3	3 : 7	0.9	11
2-Me-pyrazine 1-oxide	1 : 4	1.2	3 : 7	2.0	11
2-Me-pyrazine 4-oxide	1 : 4	1.6	3 : 7	2.4	11
2-Me-pyrazine 1,4-dioxide	1 : 9	0.3	3 : 7	1.1	11
2,6-Di-Me-pyrazine 1-oxide	3 : 7	2.5	3 : 7	3.8	12
2,6-Di-Me-pyrazine 4-oxide	3 : 7	1.5	3 : 7	3.6	12
2,6-Di-Me-pyrazine 1,4-dioxide	1 : 9	0.7	3 : 7	1.4	12

a) Solvent system for silica gel LC.
b) Capacity ratio was calculated as $k'=(V_R-V_0)/V_0$ where V_R is the retention volume at the chromatographic peak and V_0 is the column void volume, which was meaeured with *p*-toluenesulfonic acid in water.
c) Solvent system for PS gel LC.
d) Solvent system for ODS LC.

N-oxides and lipophilic aromatic amines were all separated by stepwise elution using methanol-water as the mobile phase in HPLC. The retention data for several heteroaromatics and their N-oxides related to the hydrogen peroxide-acetic acid N-oxidation reaction are listed in Table I.

Based on the results obtained above, a direct preparative fractionation of N-oxides was examined. The crude reaction mixture obtained by the hydrogen peroxide-acetic acid oxidation of quinoline was injected directly into a PS gel column. Elution employing methanol-water as the mobile phase allowed complete clean-up of the polar reagents and simultaneous quantitative fractionation of the organic product. The purity of the product was high; it showed a single peak in analytical HPLC using either normal or reversed-phase columns with any of several suitable solvent systems. Crude reaction mixtures obtained by the N-oxidation of pyridine, pyrazine and their homologs shown in Table I were also separated in a similar manner. Quantitative recovery of the products described in the literature[4,8–12] was achived. No deterioration of the columns was observed, even though the crude reaction mixtures were injected repeatedly and columns were used for a long time.

The specific features of the reversed-phase liquid chromatography procedure described in this article are the simplicity of the process, quantitative recovery and high purity of the products. The chromatographic system selected here is not only useful for the preparation of

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N-oxides but also for following the progress of the reaction and for optimization of the reaction conditions in aromatic amine oxide synthesis.

Experimental

General——Packing materials were TSK-gel 110 (Toyo Soda Mfg. Co., Tokyo), a spherical porous styrene-divinylbenzene copolymer gel 10 μ in diameter, Wakogel LCK–ODS 10 (Wako Pure Chemicals Co., Osaka), a spherical octadecylsilanized silica gel 10 μ in diameter, and Wakogel LCH 10 (Wako Pure Chemicals Co.), an irregularly shaped silica gel, about 10 μ in diameter, with a pore size of 70 Å. The glass column system, chromatographic equipment and chromatographic procedure were the same as reported earlier.[5,7] Solvents and chemicals used were products of Wako Pure Chemicals Co.

Isolation of Quinoline 1-Oxide——The purity of quinoline purchased was checked by analytical HPLC employing the silica gel-*n*-hexane/ethyl acetate system prior to its use as a starting material. Two minor peaks due to impurities emerged in front of and to the rear of the main peak. These fractions were saved and the pure substance corresponding to the main peak was collected. The crude reaction mixture[9] obtained from 1.3 g (10 mmol) of quinoline was directly injected into the top of a PS gel column, 30 cm × 15 mm I.D. The flow rate of methanol–water (3: 2 v/v) was 3 ml/min under a pressure of 12 kg/cm². The peaks of acetic acid and N-oxide were monitored with a UV detector at 254 nm. Hydrogen peroxide in the eluent was detected off-line by post column chemical reaction with potassium iodide solution. The product ($k'=1.7$) was fractionated and removal of the solvent afforded 1.3 g (0.9 mmol) of quinoline 1-oxide which was identical with a standard sample on the basis of spectroscopic measurements. Stepwise elution was continued, with increasing methanol content, but no further peak appeared. When unreacted quinoline was present, a peak emerged at $k'=3.6$ with methanol/water (4: 1 v/v).

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Dibenzotetracyclic Derivatives. III.[1] Synthesis of 9-γ-Methylaminopropyl-9,10-dihydro-9,10-propanoanthracene

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Studies on the structure-activity relationship of 9-γ-methylaminopropyl-9,10-dihydro-9,10-bridged anthracene antidepressants led us to synthesize 9-γ-methylaminopropyl-9,10-dihydro-9,10-propanoanthracene (**3**). The key intermediates, 9-β-propenyl-9,10-dihydro-9,10-propanoanthracene derivatives (**8** and **9**), were successfully synthesized by nitrous acid deamination of the ethanoanthracene derivative (**7**).

Keywords——antidepressant; 9-substituted-9,10-dihydro-9,10-propanoanthracene; 9,10-dihydro-9,10-ethanoantracene; nitrous acid deamination; ring enlargement

9-γ-Methylaminopropyl-9,10-dihydro-9,10-ethanoanthracene (maprotiline, **2**) was synthesized[3] and developed into a clinically useful antidepressant by the Ciba–Geigy research group.

In the previous paper we reported the synthesis of 9-γ-methylaminopropyl-9,10-dihydro-9,10-methanoanthracene (ID-9206, **1**),[1] which shows more potent antidepressive activity

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