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/cm^2. 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).

Acknowledgment We thank Mr. Toshimoto Ishii and Mr. Toshikazu Ohkuma of this College for their cooperation.

Chem. Pharm. Bull.
28(5)1644—1647(1980)

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

Makoto Sunagawa, Hiromi Sato, and Junki Katsube

Institute For Biological Science, Pharmaceuticals Division, Sumitomo Chemical Co., Ltd[2]

(Received December 17, 1979)

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

---

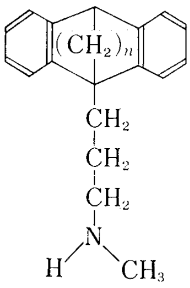
[1] Part II: M. Sunagawa, H. Sato, J. Katsube, and H. Yamamoto, *Chem. Pharm. Bull.*, 27, 1806 (1976).

[2] Location: *2-1, Takatsukasa 4-chome, Takarazuka-shi, Hyogo.*

[3] von M. Wilhelm and P. Schmidt, *Helv. Chem. Acta*, 52, 1385 (1969).

than the corresponding ethano compound (2) in experimental animals.[4] In an attempt to investigate the structure-activity relationship of the bridged anthracene antidepressants in more detail, our studies were extended to the synthesis of 9-γ-methylaminopropyl-9,10-dihydro-9,10-propanoanthracene (3). The present paper deals with the synthesis of the derivative **3**.

Compared with 9,10-methano and 9,10-ethanoanthracene derivatives, the next higher homolog, the 9,10-propanoanthracene derivative, has received limited attention in the literature,[5-7] and no efficient synthetic route to the 9-alkyl-substituted-9,10-propanoanthracene skeleton has hitherto been described.



1: $n=1$
2: $n=2$
3: $n=3$

Chart 1

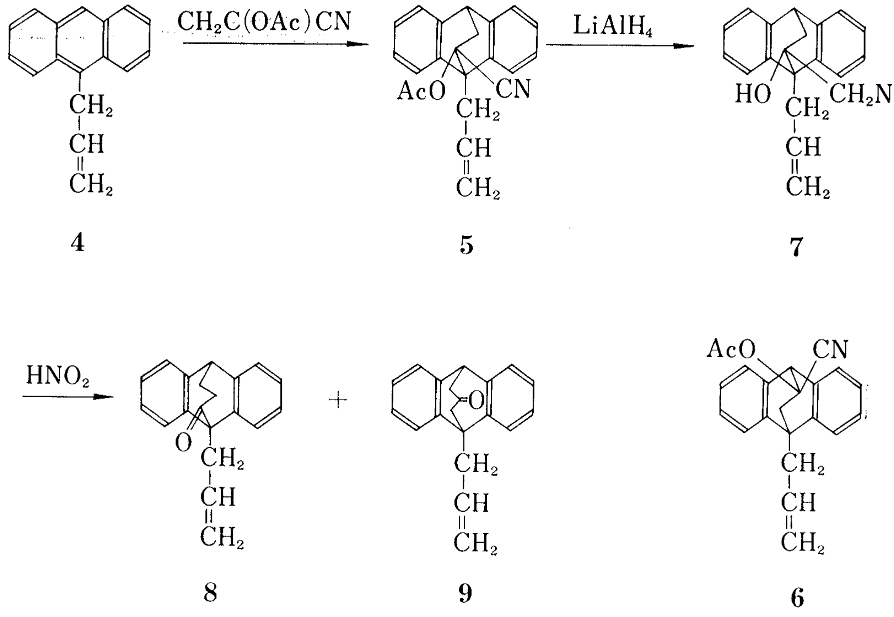


Chart 2

We have synthesized the 9-β-propenyl-9,10-dihydro-9,10-propanoanthracene skeleton, which can easily be converted to the target compound (**3**), by ring enlargement of an ethanoanthracene derivative using nitrous acid deamination.

That is, as shown in Chart 2, the aminoalcohol (**7**) was treated with aqueous sodium nitrite in glacial acetic acid to afford 13-oxo-9,10-dihydro-9,10-propanoanthracene (**8**) and the 12-oxo derivative (**9**) in a ratio of 6: 1.[8]

The starting aminoalcohol (**7**) was easily synthesized in two steps starting from 9-β-propenylanthracene (**4**). The Diels–Alder reaction between **4** and α-acetoxyacrylonitrile in toluene afforded two adducts (**5** and **6**; **5** was the main product), of which **5** was reduced with lithium aluminum hydride in ether to give the aminoalcohol (**7**) in good yield.[9]

The desired compound **3** was synthesized from **8** and **9** as follows: Clemmensen reduction of **8** and **9** afforded 9-β-propenyl-9,10-dihydro-9,10-propanoanthracene (**10**) in moderate yield. **10** was converted to the primary alcohol (**11**) by hydroboration. Oxidation of **11** with chro-

---

[4] H. Fukushima, N. Nakamura, and H. Yamamoto, *Arch. Int. Pharmacodyn.*, **227**, 161 (1977).

[5] E. Cioranescu, M. Banciu, R. Jelescu, M. Rentzea, M. Elian, and C.D. Nevitzescu, *Tetrahedron Lett.*, **1969**, 1871.

[6] S.J. Cristol and A.L. Noreen, *J. Org. Chem.*, **41**, 4017 (1976).

[7] R.J. Giguere, D.I. Rawson, and H.M.R. Hoffmann, *Synthesis*, **1978**, 902.

[8] The predominance of the 13-oxo derivative (**8**) upon deamination is consistent with the result in the case of a rigid system such as 6-aminomethylbicyclo[3,2,0]-2-hepten-6-ol. J.D. Roberts and W.F. Gorham, *J. Am. Chem. Soc.*, **74**, 2278 (1952).

[9] When the LiAlH$_4$ reduction of **5** was carried out in dioxane at 60—70°, 9-β-propenyl-12-hydroxy-9,10-dihydro-9,10-ethanoanthracene was obtained as a by-product.

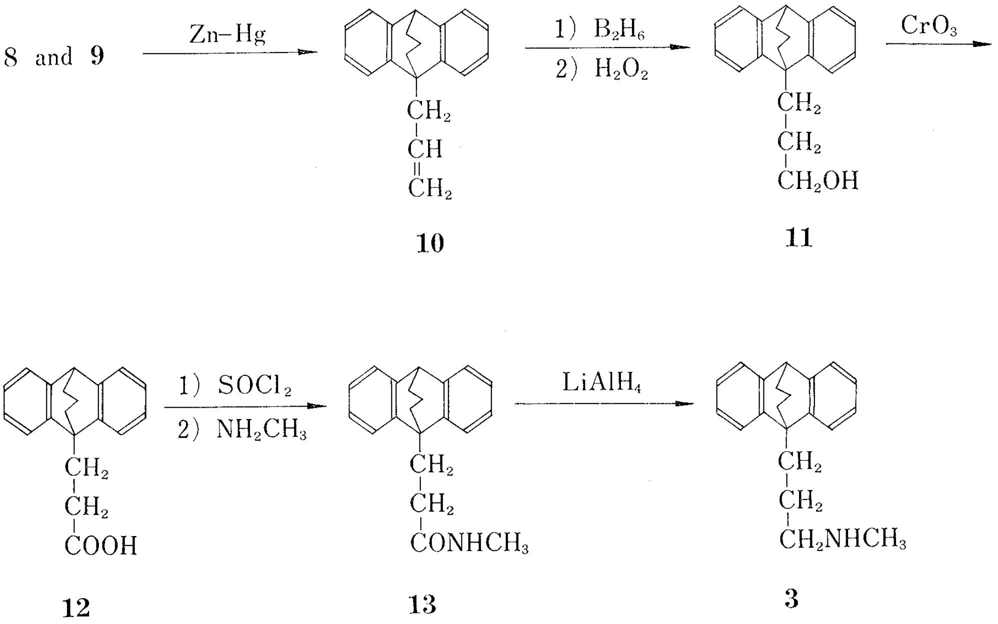


Chart 3

mium trioxide afforded the corresponding carboxylic acid (**12**), which was converted to the N-methyl amide derivative (**13**) by treatment with thionyl chloride and then methylamine. **13** was converted to the target compound **3** by reduction with lithium aluminum hydride.[10]

Experimental

All melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. NMR spectra were taken in $CDCl_3$ on a Varian T-60 spectrometer using tetramethylsilane as an internal standard. IR spectra were obtained on a Hitachi type 285 grating spectrophotometer.

Diels–Alder Reaction between 9-β-Propenylanthracene and α-Acetoxy Acrylonitrile——A mixture of 9-β-propenylanthracene (3.4 g) and α-acetoxyacrylonitrile (5.0 g) in toluene (5.0 g) was heated at 180—185° in an autoclave for 20 hr. The reaction mixture was evaporated to dryness *in vacuo* and the residue was purified on a short SiO_2 column to give 12-acetoxy-12-cyano-9-propenyl-9,10-dihydro-9,10-ethanoanthracene (**5**, 3.28 g), mp 153—154°. *Anal.* Calcd for $C_{22}H_{19}NO_2$: C, 80.22; N, 5.81; N, 4.25. Found: C, 80.14; H, 5.62; N, 4.07. and 11-acetoxy-11-cyano-9-β-propenyl-9,10-dihydro-9,10-ethanoanthracene (**6**, 0.82 g), mp 172—173°. *Anal.* Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.12; H. 5.77; N, 4.45.

12-Aminomethyl-12-hydroxy-9-β-propenyl-9,10-dihydro-9,10-ethanoanthracene (**7**)——A mixture of **5** (6.0 g) and LiAlH$_4$ (2.0 g) in dry diethyl ether (300 ml) was refluxed for 1.5 hr. Water was added to the reaction mixture to decompose excess LiAlH$_4$, AcOEt and Na_2SO_4 were added, and inorganic materials were removed by filtration.

The filtrate was evaporated to dryness to give an oily residue, which was crystallized from benzene–isopropylether to give colorless crystals [5.15 g (97.0%)] of **7**, mp 109—110°. *Anal.* Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.45; H, 7.59; N, 4.82.

Deamination of 12-Aminomethyl-12-hydroxy-9-β-propenyl-9,10-dihydro-9,10-ethanoanthracene (**7**)——A solution of $NaNO_2$ (2.0 g) in water (10 ml) was added dropwise to a solution of **7** (1.35 g) in AcOH (100 ml) at 15° over a period of 2 hr, and the whole was stirred at room temperature for 1 hr then at 90° for 30 min.

The reaction mixture was concentrated *in vacuo*, diluted with water and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4 and evaporated to dryness to give a crude oil, which was purified on an SiO_2 column to give 9-β-propenyl-13-oxo-9,10-dihydro-9,10-propanoanthracene **8** (0.728 g) [mp 123°. *Anal.* Calcd for $C_{20}H_{18}O$: C, 87.56; H, 6.61. Found: C, 87.76; H, 6.48. IR $\nu_{\max}^{\text{Nujol}}$ (cm^{-1}): 1705. NMR ($CDCl_3$) δ: 2.21 (4H, m), 3.52 (2H, m), 4.17 (1H, bt, $J=3.6$ Hz)] and 9-β-propenyl-12-oxo-9,10-dihydro-9,10-propanoanthracene **9** (0.122 g) [mp 134.5—136°. *Anal.* Calcd for $C_{20}H_{18}O$: C, 87.56; H, 6.61. Found: C, 87.24; H, 6.46. IR $\nu_{\max}^{\text{Nujol}}$ (cm^{-1}): 1690. NMR ($CDCl_3$) δ: 2.59 (2H, s), 2.72 (2H, d, $J=3.6$ Hz), 3.24 (2H, m), 4.25 (1H, t, $J=3.6$ Hz)].

---

[10] The pharmacological activity of **3** will be reported elsewhere.

9-β-Propenyl-9,10-dihydro-9,10-propanoanthracene (10)——A mixture of **8** (0.5 g), conc. HCl (1 ml) and toluene (1 ml) in the presence of zinc amalgam, which was prepared from Zn metal (1.0 g) and conc. HCl in H_2O (1 ml), was refluxed for 24 hr during which time a 0.5 ml portion of conc. HCl was added every 6 hr. Toluene was then added and the organic layer was washed with water, dried over Na_2SO_4, and evaporated to dryness to give an oily residue, which was purified on an SiO_2 column to give pure **10** as a colorless oil (228 mg). *Anal.* Calcd for $C_{20}H_{20}$: C, 92.26; H, 7.74. Found: C, 92.10; H, 7.74. IR $\nu_{\max}^{\text{film}}$ (cm^{-1}): 996, 912. NMR ($CDCl_3$) δ: 3.17 (2H, m), 3.98 (1H, t, $J=3.6$ Hz).

Compound **10** was also prepared from **9** in a manner analogous to the preparation of **10** from **8**.

9-γ-Hydroxypropyl-9,10-dihydro-9,10-propanoanthracene (11)——A solution of $BF_3\cdot OEt_2$ (0.85 g) in dry THF (1 ml) was added to a mixture of powdered $NaBH_4$ (170 mg) and **10** (250 mg) in dry THF (7.5 ml) at room temperature.

After stirring at the same temperature for 2.5 hr, excess B_2H_6 was decomposed by addition of water and then 3 N NaOH aq. (1.6 ml) and 30% H_2O_2 aq. (1.6 ml) were added. The reaction mixture was stirred at 40—45° for 4 hr. Water was added to the reaction mixture and the whole was extracted with AcOEt. The organic layer was washed with water, dried over Na_2SO_4 and evaporated to dryness to give a crude oil, which was purified on an SiO_2 column to give **11** as a colorless oil (219 mg). IR $\nu_{\max}^{\text{film}}$ (cm^{-1}): 3350. NMR ($CDCl_3$) δ: 3.73 (2H, t, $J=6$ Hz), 3.93 (1H, t, $J=3.6$ Hz).

β-(9,10-Dihydro-9,10-propano-9-anthryl)propionic Acid (12)——Jones' reagent (1.0 ml)[11] was added dropwise to a solution of **11** (210 mg) in acetone (4 ml) at room temperature. The reaction mixture was stirred for 30 min. Water was added to the reaction mixture, and the whole was extracted with AcOEt. The organic layer was washed with water, dried over Na_2SO_4 and evaporated to dryness to afford crude **12**, which was crystallized from isopropyl ether-benzene to give colorless crystals (189 mg) mp 173.5—176.5°. *Anal.* Calcd for $C_{20}H_{20}O_2$: C, 82,15; H, 6.89. Found: C, 81.94; H, 6.83.

β-(9,10-Dihydro-9,10-propano-9-anthryl)propionic Acid Methyl Amide (13)——A solution of **12** (180 mg) and $SOCl_2$ (0.3 ml) in benzene (3 ml) was refluxed for 4 hr and evaporated to dryness to give the corresponding acid chloride. A solution of the acid chloride in dry THF (4 ml) was added dropwise to 40% NH_2CH_3 aq. (3 ml) at 0—5°. The reaction mixture was stirred at the same temperature for 1 hr, diluted with water and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4 and evaporated down to give crude **13**, which was crystallized from EtOH to afford colorless crystals (154 mg) mp 161—163°. *Anal.* Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.71; H, 7.63; N, 4.53. IR $\nu_{\max}^{\text{Nujol}}$ (cm^{-1}): 1640.

9-γ-Methylaminopropyl-9,10-dihydro-9,10-propanoanthracene (3)——The amide (**12**, 150 mg) was added to $LiAlH_4$ (40 mg) in dry ether (8 ml) and the reaction mixture was refluxed for 2 hr.

Water was added to the reaction mixture to decompose excess $LiAlH_4$, then AcOEt and Na_2SO_4 were added, and inorganic materials were removed by filtration. The filtrate was evaporated to dryness to give **3** (146 mg), which was converted to the hydrochloride by treatment with HCl in isopropyl alcohol. An analytical sample was prepared by recrystallization from isopropyl alchol–isopropyl ether. mp 231—233°. *Anal.* Calcd for $C_{21}H_{25}N\cdot HCl$; C, 76.92; H, 7.99; N, 4.27; Cl, 10.81. Found: C, 76.75; H, 8.00; N, 4.23; Cl, 10.53.

---

11) C. Djerassi, R.R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).