[Chem. Pharm. Bull. 28(9)2831—2835(1980)]

The Synthesis of 1-Chloroxanthone and Related Dichloroxanthones

ICHIZO OKABAYASHI and NORIKO IWATA

Niigata College of Pharmacy[1]

(Received April 26, 1980)

1-Chloroxanthone (**2**) was obtained by cyclization of 2-chloro-6-phenoxybenzoic acid (**10**) prepared from 2-nitro-6-phenoxybenzoic acid (**8**) *via* 2-amino-6-phenoxybenzoic acid (**9**). Similarly, 1,5-dichloroxanthone (**14a**) and 1,7-dichloroxanthone (**14b**) were obtained from 2-(2-chlorophenoxy)-6-nitrobenzoic acid (**11a**) and 2-(4-chlorophenoxy)-6-nitrobenzoic acid (**11b**), respectively. Furthermore, 2,6-dichloroxanthone (**19**) was prepared by cyclization of 4-chloro-2-(4-chlorophenoxy)benzoic acid (**18**).

Dichloroxanthone **B**, obtained by cyclization of 5-chloro-2-(3-chlorophenoxy)benzoic acid (**16**) and reported by Nargund *et al.* as 1,7-dichloroxanthone, could not be separated into 1,7- (**14b**) and 2,6-dichloroxanthone (**19**) by recrystallization, column chromatography or thin-layer chromatography, but was proved here to be a mixture of **14b** and **19** by gas chromatography.

Keywords——2-substituted-6-phenoxybenzoic acids; 1-chloroxanthone; 1,5-dichloroxanthone; 1,7-dichloroxanthone; 2,6-dichloroxanthone; cyclization of 5-chloro-2-(3-chlorophenoxy)benzoic acid; Ullmann reaction

No report has yet appeared on the synthesis from 2-chloro-6-nitrobenzoic acid of 1-chloroxanthone and dichloroxanthones in which a chlorine is substituted at the 1 position of xanthone. In this paper we report the preparation of these chloroxanthones by means of the Ullmann reaction from 2-chloro-6-nitrobenzoic acid and phenols.

Dhar[2] cyclized 2-(3-chlorophenoxy)benzoic acid (**1**) with sulfuric acid and obtained chloroxanthone **A** (mp 100°), which was believed to be 1-chloroxanthone. Chloroxanthone **A**, reported by Dhar as 1-chloroxanthone, could not be separated into 1- and 3-chloroxanthone by recrystallization or column chromatography. However, it was reported to be a mixture of 1- and 3-chloroxanthone by Goldberg *et al.*,[3] who obtained 1-chloroxanthone (**2**) (mp 137°) by means of the Sandmeyer reaction from 1-aminoxanthone (**6**).

Compound **6**[4] was obtained by the reduction of 1-nitroxanthone (**4**) separated by recrystallization from the cyclization product of 2-(3-nitrophenoxy)benzoic acid (**3**) [this product was a mixture of **4** and 3-nitroxanthone (**5**)]. Compound **4**[5] is alternatively obtained by cyclization of 2-nitro-6-phenoxybenzoic acid (**8**).[6]

We prepared 2-nitro-6-phenoxybenzoic acid (**8**) by means of the Ullmann reaction from 2-chloro-6-nitrobenzoic acid (**7**) and phenol in 1-pentanol in the presence of sodium carbonate. Compound **8** was reduced with iron (II) sulfate and aqueous ammonia to 2-amino-6-phenoxybenzoic acid (**9**), which was converted to 2-chloro-6-phenoxybenzoic acid (**10**) by means of the Sandmeyer reaction. Cyclization of **10** with sulfuric acid gave 1-chloroxanthone (**2**) (mp 137°).

In a similar way, 2-(2-chlorophenoxy)-6-nitrobenzoic acid (**11a**) was obtained by condensing **7** with *o*-chlorophenol, and **11a** was reduced to 2-amino-6-(2-chlorophenoxy)benzoic acid

---

[1] Location: *5829 Kamishin'ei-cho, Niigata 950-21, Japan.*

[2] S.N. Dhar, *J. Chem. Soc.*, **117**, 1061 (1920).

[3] A.A. Goldberg and A.H. Wragg, *J. Chem. Soc.*, **1958**, 4234.

[4] C.F. Koelsch and F.J. Lucht, *J. Am. Chem. Soc.*, **71**, 3556 (1949).

[5] A.A. Goldberg and H.A. Walker, *J. Chem. Soc.*, **1953**, 1348.

[6] This compound was first used by Goldberg *et al.*,[5] but the method for preparing it and its physical data were not published.

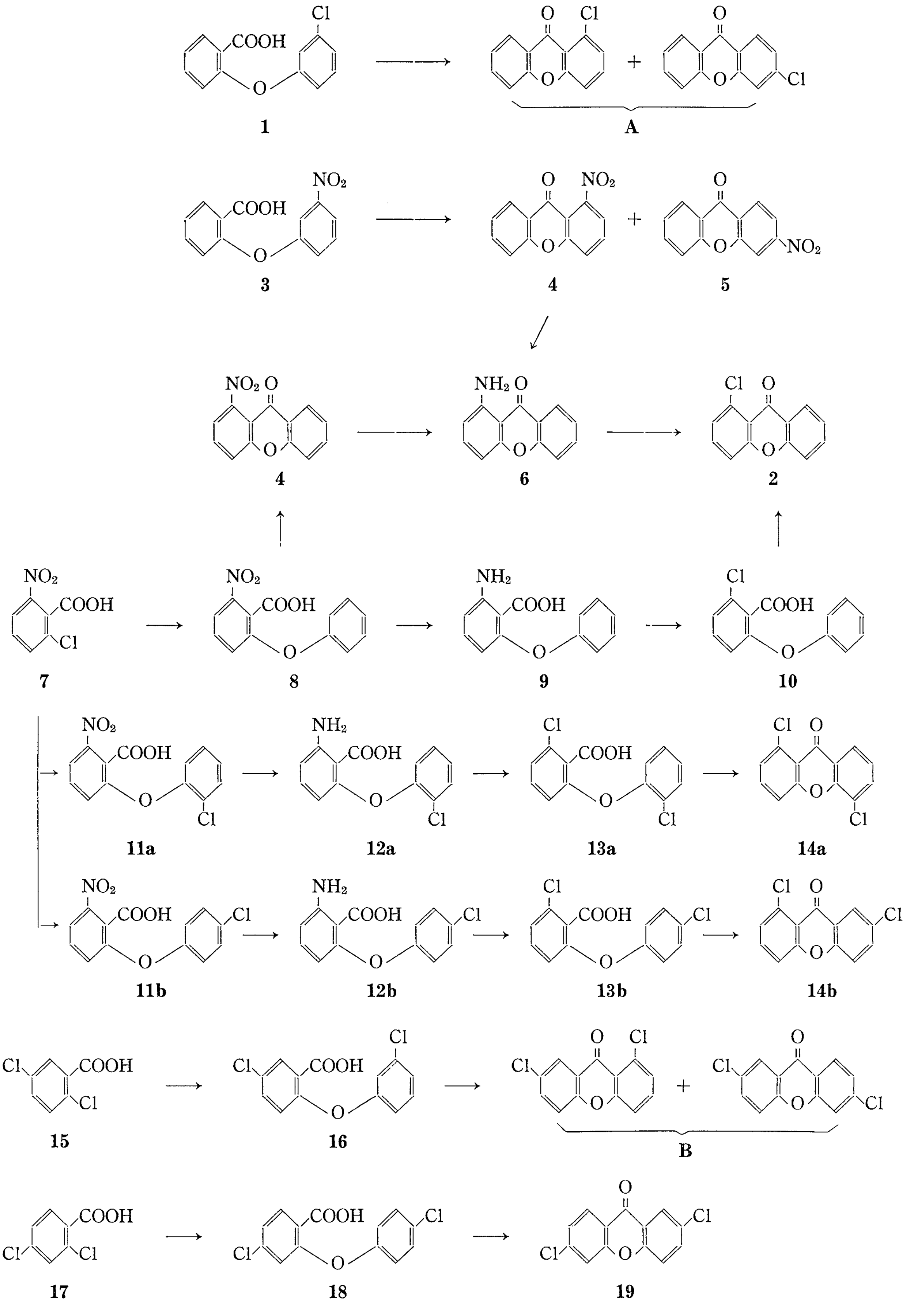
1
A
3
4
5
6
2
7
8
9
10
11a
12a
13a
14a
11b
12b
13b
14b
15
16
B
17
18
19
COOH
Cl
NO2
NH2
O

Chart 1

(**12a**), which was converted to 2-chloro-6-(2-chlorophenoxy)benzoic acid (**13a**). 1,5-Dichloroxanthone (**14a**) was obtained by cyclization of **13a**.

The product of cyclization of 5-chloro-2-(3-chlorophenoxy)benzoic acid (**16**) with sulfuric acid was reported to be 1,7-dichloroxanthone by Nargund *et al.*7) Since we expected the compound to be a mixture of 1,7- (**14b**) and 2,6-dichloroxanthone (**19**), we prepared **14b** from **7** *via* 2-(4-chlorophenoxy)-6-nitrobenzoic acid (**11b**), 2-amino-6-(4-chlorophenoxy)benzoic acid (**12b**) and 2-chloro-6-(4-chlorophenoxy)benzoic acid (**13b**).

The melting point of 1,7-dichloroxanthone (**14b**) (172—173.5°) prepared by cyclization of **13b** does not agree with that (187°) given by Nargund *et al.*, as expected. Repetition of Nargund's work gave a compound of mp 153—185°. Two recrystallizations of this product from ethanol gave two compounds of mp 170—210° and mp 142—146°. It is thus considered that Nargund's compound, dichloroxanthone **B**, is a mixture of **14b** and **19**. Therefore, **19** was prepared by cyclization of 4-chloro-2-(4-chlorophenoxy)benzoic acid (**18**) obtained by means of the Ullmann reaction from 2,4-dichlorobenzoic acid (**17**) and *p*-chlorophenol in the presence of sodium methoxide. 2,6-Dichloroxanthone (**19**) had a melting point of 219—220°.

The analysis of dichloroxanthone **B** obtained by cyclization of **16**, since it could not be resolved into **14b** and **19** by recrystallization, column chromatography or thin-layer chromatography, was carried out by means of gas chromatography. It was found that the crude dichloroxanthone **B** (mp 153—185°) was not a single compound, but a mixture of 48% 1,7-dichloroxanthone (**14b**) and 52% 2,6-dichloroxanthone (**19**). If recrystallization was repeated several times, the solid tended to separate into two parts, one having a higher melting point, being comparatively less soluble in ethanol and containing a large proportion of **19**, while the other had a lower melting point, was more soluble in ethanol and contained a large proportion of **14b**. It was found that the compound, mp 170—210°, obtained by two recrystallizations of the crude dichloroxanthone **B** described above contained 15% **14b** and 85% **19**, and the other compound, mp 142—146°, contained 70% **14b** and 30% **19**.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Infrared absorption spectra were recorded in potassium bromide discs with a Hitachi model 215 spectrometer. Mass spectra were measured with a Hitachi RMU-7M double focusing spectrometer. Gas chromatography was performed with a Hitachi model 163 machine.

2-Nitro-6-phenoxybenzoic Acid (**8**)——A mixture of **7** (4.03 g, 0.02 mol), phenol (2.16 g, 0.023 mol), Na_2CO_3 (2.12 g), 1-pentanol (9 ml), Cu powder (0.1 g) and CuI (0.1 g) was heated under reflux for 3 hr, then diluted with water. The solvent was removed by steam distillation. The residual aqueous solution was filtered and the filtrate was acidified with HCl. The resulting oily precipitate slowly solidified. The solid was collected and extracted with boiling water, and the insoluble product (2.52 g, 49%) was recrystallized from 30% MeOH to give colorless needles, mp 160—162°. *Anal.* Calcd for $C_{13}H_9NO_5$: C, 60.24; H, 3.50; N, 5.40. Found: C, 60.32; H, 3.54; N, 5.21. MS *m/e*: 259 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O).

2-Amino-6-phenoxybenzoic Acid (**9**)——A solution of **8** (2.59 g, 0.01 mol) in 14% aqueous NH_3 (30 ml) was slowly added to a solution of $FeSO_4 \cdot 7H_2O$ (18 g) in water (60 ml) with heating and stirring in a boiling water bath. Stirring and heating were continued for another 2 hr. After cooling, 25% NaOH solution (20 ml) was added. The mixture was filtered and the filtrate was acidified with AcOH. The precipitate (1.56 g, 68%) was recrystallized from 50% MeOH to give colorless needles, mp 108—109.5°. *Anal.* Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.28; H, 4.87; N, 6.01. IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O).

2-Chloro-6-phenoxybenzoic Acid (**10**)——A mixture of **9** (1.15 g, 0.005 mol) and 5 N HCl (32 ml) was cooled to 0—5° in an ice-salt bath. A solution of $NaNO_2$ (0.44 g) in water (3 ml) was added dropwise to the stirred mixture; the solid almost dissolved. CuCl was prepared by adding a solution of $NaHSO_3$ (1.4 g) and NaOH (0.7 g) in water (10 ml) at 60° to a stirred solution of $CuSO_4 \cdot 5H_2O$ (4.9 g) and NaCl (1.7 g) in water (20 ml) at the same temperature; the CuCl was washed by decantation and dissolved in 10 N HCl (14 ml). The diazonium salt solution was filtered and slowly added to the stirred CuCl solution at 40°. After 15 min, the mixture was heated in a boiling water bath with stirring for 1 hr, then allowed to stand overnight at

---

7) C.N. Deshpande, P.S. Sattur, and K.S. Nargund, *J. Karnatak Univ.*, 2, 33 (1957) [*Chem. Abstr.*, **53**, 14100*b* (1959)].

room temperature. The pale brown solid (0.84 g, 67%) was recrystallized from 45% MeOH to give colorless prisms, mp 167—168°. *Anal.* Calcd for $C_{13}H_9ClO_3$: C, 62.79; H, 3.65. Found: C, 62.81; H, 3.56. IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O).

1-Chloroxanthone (2)——A mixture of **10** (0.75 g, 0.003 mol) and H_2SO_4 (4 ml) was heated in a boiling water bath for 30 min, and poured into ice-water (100 ml). The precipitate was collected and extracted with hot Na_2CO_3 solution. The insoluble product (0.57 g, 82%) was recrystallized from 65% EtOH to give colorless needles, mp 136—137°, both alone and admixed with a sample$^{3)}$ obtained from **6** by means of the Sandmeyer reaction. The IR spectrum was identical with that of a sample$^{3)}$ obtained from **6**. IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O).

2-(2-Chlorophenoxy)-6-nitrobenzoic Acid (11a)——This compound was prepared from **7** (8.06 g, 0.04 mol) and *o*-chlorophenol (5.91 g, 0.046 mol) in a manner similar to that used for the preparation of **8**. The product (5.98 g, 51%) was recrystallized from 30% MeOH to give colorless needles, mp 163°. *Anal.* Calcd for $C_{13}H_8ClNO_5$: C, 53.17; H, 2.75; N, 4.77. Found: C, 53.14; H, 2.61; N, 4.90. MS *m/e*: 293 (M$^+$). IR ν_{max}^{KBr} cm^{-1}: 1715 (C=O).

2-Amino-6-(2-chlorophenoxy)benzoic Acid (12a)——This compound was prepared from **11a** (2.94 g, 0.01 mol) in a manner similar to that used for the preparation of **9**. The product (1.85 g, 70%) was recrystallized from 30% MeOH to give colorless needles, mp 91—92.5°. *Anal.* Calcd for $C_{13}H_{10}ClNO_3$: C, 59.22; H, 3.82; N, 5.31. Found: C, 58.97; H, 3.74; N, 5.18. IR ν_{max}^{KBr} cm^{-1}: 1655 (C=O).

2-Chloro-6-(2-chlorophenoxy)benzoic Acid (13a)——This compound was prepared from **12a** (2.64 g, 0.01 mol) in a manner similar to that described for the preparation of **10**. The product (1.76 g, 62%) was recrystallized from 30% MeOH to give colorless prisms, mp 138—139°. *Anal.* Calcd for $C_{13}H_8Cl_2O_3$: C, 55.15; H, 2.85. Found: C, 54.85; H, 3.12. IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O).

1,5-Dichloroxanthone (14a)——This compound was prepared from **13a** (0.85 g, 0.003 mol) in a manner similar to that used for the preparation of **2**. The product (0.56 g, 70%) was recrystallized from aqueous acetone and then EtOH to give colorless needles, mp 192°. *Anal.* Calcd for $C_{13}H_6Cl_2O_2$: C, 58.90; H, 2.28. Found: C, 58.79; H, 2.10. IR ν_{max}^{KBr} cm^{-1}: 1665 (C=O).

2-(4-Chlorophenoxy)-6-nitrobenzoic Acid (11b)——This compound was prepared from **7** (4.03 g, 0.02 mol) and *p*-chlorophenol (2.96 g, 0.023 mol) in a manner similar to that described for **8**. The product (3.50 g, 60%) was recrystallized from 40% MeOH to give colorless needles, mp 170.5—171.5°. *Anal.* Calcd for $C_{13}H_8ClNO_5$: C, 53.17; H, 2.75; N, 4.77. Found: C, 53.28; H, 2.79; N, 4.71. MS *m/e*: 293 (M$^+$). IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O).

2-Amino-6-(4-chlorophenoxy)benzoic Acid (12b)——This compound was prepared from **11b** (2.94 g, 0.01 mol) in a manner similar to that described for **9**. The product (1.98 g, 75%) was recrystallized from 35% MeOH to give colorless needles, mp 114—115°. *Anal.* Calcd for $C_{13}H_{10}ClNO_3$: C, 59.22; H, 3.82; N, 5.31. Found: C, 59.50; H, 3.98; N, 5.10. IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O).

2-Chloro-6-(4-chlorophenoxy)benzoic Acid (13b)——This compound was prepared from **12b** (2.64 g, 0.01 mol) in a manner similar to that used for the preparation of **10**. The product (1.84 g, 65%) was recrystallized from 50% EtOH to give colorless prisms, mp 130.5—132°. *Anal.* Calcd for $C_{13}H_8Cl_2O_3$: C, 55.15; H, 2.85. Found: C, 55.13; H, 2.81. IR ν_{max}^{KBr} cm^{-1}: 1695 (C=O).

1,7-Dichloroxanthone (14b)——This compound was prepared from **13b** (0.85 g, 0.003 mol) in a manner similar to that described for **2**. The product (0.69 g, 87%) was recrystallized from EtOH to give colorless needles, mp 172—173.5°. *Anal.* Calcd for $C_{13}H_6Cl_2O_2$: C, 58.90; H, 2.28. Found: C, 58.73; H, 2.27. IR ν_{max}^{KBr} cm^{-1}: 1665 (C=O).

5-Chloro-2-(3-chlorophenoxy)benzoic Acid (16)——2,5-Dichlorobenzoic acid (**15**) (0.96 g, 0.005 mol), *m*-chlorophenol (0.75 g, 0.006 mol), Cu powder (0.02 g) and CuI (0.02 g) were added to a solution of Na (0.23 g) in MeOH (25 ml). The MeOH was distilled off and the semi-solid residue was placed in an oil bath at 100°. The temperature was raised to 200° during a period of 20 min with occasional stirring and held there for 15 min. The mixture was cooled, then extracted with boiling water and filtered. The filtrate was acidified with HCl. The precipitate was collected and extracted with boiling water. The insoluble product (1.17 g, 82%) was recrystallized from 50% MeOH to give colorless needles, mp 122—123.5° (lit.,$^{7)}$ mp 131°). IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O).

4-Chloro-2-(4-chlorophenoxy)benzoic Acid (18)——This compound was prepared from 2,4-dichlorobenzoic acid (**17**) (1.34 g, 0.007 mol) and *p*-chlorophenol (1.04 g, 0.008 mol) in a manner similar to that described for the preparation of **16**. The product (1.55 g, 78%) was recrystallized from 50% MeOH and then absolute MeOH to give colorless needles, mp 186—188°. *Anal.* Calcd for $C_{13}H_8Cl_2O_3$: C, 55.15; H, 2.85. Found: C, 55.42; H, 2.96. IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O).

2,6-Dichloroxanthone (19)——This compound was prepared from **18** (1.13 g, 0.004 mol) in a manner similar to that used for **2**. The product (0.74 g, 70%) was recrystallized from EtOH to give colorless needles, mp 219—220° (lit.,$^{8)}$ mp 215.5—216.5°). *Anal.* Calcd for $C_{13}H_6Cl_2O_2$: C, 58.90; H, 2.28. Found: C, 58.96; H, 2.44. IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O).

---

8) E. McNelis, *J. Org. Chem.*, **28**, 3188 (1963).

Cyclization of 5-Chloro-2-(3-chlorophenoxy)benzoic Acid (16)——A mixture of **16** (0.85 g, 0.003 mol) and H_2SO_4 (5 ml) was heated in a boiling water bath for 30 min, and the solution was poured into ice-water (100 ml). The precipitate was collected and extracted with hot Na_2CO_3 solution, and the insoluble dichloroxanthone **B** (0.64 g, 80%) was collected. It had a melting point of 153—185°. The crude dichloroxanthone **B** and two compounds obtained by recrystallizations as described below were analyzed by gas chromatography using a glass column (2 m×3 mm) packed with 1.5% OV-1 on Chromosorb W (80—100 mesh). The conditions for gas chromatography were as follows: column temperature, 210°; injection temperature, 260°; carrier gas, N_2. Retention times: **14b**, 15.3 min; **19**, 11.8 min. The results indicated that the crude dichloroxanthone **B** was a mixture of **14b** (48%) and **19** (52%). Two compounds, mp 170—210° and mp 142—146°, obtained by two recrystallizations of the crude dichloroxanthone **B** from EtOH were mixtures of **14b** (15%) and **19** (85%), and **14b** (70%) and **19** (30%).

Acknowledgement The authors are grateful to the staff of the Analytical Center of Kyoto University for the elemental analyses, and to Assistant Professor Akira Kato of Niigata College of Pharmacy for mass spectral measurements.

Chem. Pharm. Bull.
28(9)2835—2838(1980)

Studies on Heterocyclic Compounds. XXXII.[1] Synthesis of 8-Substituted Theophyllines from 6-Amino-5-benzylideneamino-1,3-dimethyluracils with Nickel Peroxide

SATOSHI MINEO, HARUO OGURA,[2a] and KUNIO NAKAGAWA[2b]

School of Pharmaceutical Sciences, Kitasato University[2a] *and Faculty of Pharmaceutical Sciences, Tokushima University of Arts and Science*[2b]

(Received April 28, 1980)

Oxidation of 6-amino-5-benzylideneamino-1,3-dimethyluracils (Ia—e) with nickel peroxide (Ni–PO) in dimethylsulfoxide (DMSO) afforded 8-substituted theophyllines (IIa—e) and dimethylsulfone. Ni–PO oxidation of the Schiff base acetate (V) of 5,6-diamino-1,3-dimethyluracil with D-glucose did not give a nucleoside analog; in stead, 1,3,7,9-tetramethyl-2,4,6,8-(1H,3H,7H,9H)pyrimido[5,4-*g*]pteridinetetrone (VI) and penta-*O*-acetylgluconic acid were obtained. The reaction mechanisms of Ni–PO and the Schiff bases (Ia—e, V) are discussed.

Keywords——8-substituted theophyllines; 6-amino-5-benzylideneamino-1,3-dimethyluracils; Nickel peroxide; oxidative cyclization; 1,3,7,9-tetramethyl-2,4,6,8-(1H,3H,7H,-9H)-pyrimido[5,4-*g*]pteridinetetrone; penta-*O*-acetylgluconic acid

In our previous paper, it was shown that Schiff bases of *o*-aminophenols with benzaldehydes were oxidized by nickel peroxide (Ni–PO) in an organic solvent to give the corresponding 2-substituted phenylbenzoxazoles.[3] Schiff bases of 5,6-diamino-1,3-dimethyluracil with benzaldehyde or aldoses were treated with N-bromosuccinimide[4a] or $HgCl_2$[4b] to give theophylline nucleoside analogs. As an extension of work on the synthesis of 8-substituted theophyllines from 4,5-diaminopyrimidine by oxidative cyclization,[5] we now report the synthesis of 8-

---

[1] XXXI: H. Ogura, H. Takahashi, and O. Sato, *Nucleic Acid Research*, s **6**, 13 (1979).

[2] Location: *a) Shirokane, Minato-ku, Tokyo 108, Japan*; *b) Yamashiro-cho, Tokushima-shi, Tokushima 770, Japan.*

[3] K. Nakagawa, H. Onoue, and J. Sugita, *Chem. Pharm. Bull.*, **12**, 1135 (1964).

[4] *a)* H. Ogura, H. Takahashi, and M. Sakaguchi, *Heterocycles*, **3**, 93 (1975); *b)* M. Sakaguchi, Y. Miyata, H. Ogura, K. Gonda, S. Koga, and T. Okamoto, *Chem. Pharm. Bull.*, **27**, 1094 (1979).

[5] J.H. Lister, "Fused Pyrimidines, Part II, Purines," ed. by D.J. Brown, Wiley-Interscience, New York, 1971, pp. 69—71, and references cited therein.