SYNTHESES IN THE PURINE SERIES

XXXIV. TRANSFORMATIONS OF N,N'-DIMETHYLXANTHINES IN REACTION WITH PHOSPHORUS OXYCHLORIDE IN THE PRESENCE OF TERTIARY AMINES

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As is well known, in reaction with phosphorus oxychloride in the presence of phosphorus pentachloride, N,N'-dimethylxanthines are converted to 2,6-dichloromonomethylpurines [1-4]. Tertiary amines are sometimes used instead of phosphorus pentachloride. In particular, in the presence of N,N-dimethylaniline, theobromine (Ia) is converted to 2,6-dichloro-7-methylpurine (IIa) in 25% yield [5]. Without the dimethylaniline, the yield of IIa does not exceed 10-15%.

It may be suggested that the tertiary amine in part assists the occurrence of reaction because it hinders the evolution of hydrogen chloride from the reaction sphere: The HCl, just like phosphorus pentachloride, assists in converting the reaction product of Ia or 8-chlorotheobromine (Ib) with phosphorus oxychloride-the comparatively stable adduct (III)-into the amidochloride (VI), which further splits out methyl chloride to form II [6].



The rise in yield of IIa from 10-15% to 30% on heating Ia with POCl₃, not in an open system, but in a tube [7], which excludes loss of hydrogen chloride, can probably be explained from these same positions.

And actually the use of dimethylaniline hydrochloride instead of the base made it possible to raise the yield of IIa to 35-40%. None the less, it continued to fall short of the almost quantitative yields of II which are attained when PCl₅ is used [3, 4]. The suggestion arose that this could be explained by the ability of dimethylaniline to react with adduct III to form a para condensation product. The formation of a similar by-product - 2-chloro-6-p-dimethylaminophenyl-9-methylpurine (V) - has been observed in the conversion of 1,9-dimethylxanthine (VI) to 2,b-dichloro-9-methylpurine (VII) [8].

From the products of a reaction of Ia with POCl₃ which was carried out in the presence of dimethylaniline [5], together with 21-22% of IIa, it was possible to isolate a bright red substance, rather readily soluble in phosphorus oxychloride, whose elemental analysis corresponded to the empirical formula $C_{15}H_{17}Cl_3$ - N_5O_2 . After treatment with water and crystallization from alcohol, it is converted into a compound of the empirical formula $C_{15}H_{17}Cl_2N_5 \cdot C_2H_5OH$. The structure of this red substance as a para condensation product of dimethylaniline with a molecule of the purine was confirmed by its NMR spectrum (see Fig 1; the ethyl alcohol signals are omitted). Three signals (chemical shifts of 3.2, 4.3, and 4.4 ppm) indicate the presence of four N-methyl groups, of which the two equivalent ones should be assigned to the dimethylamino

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Fig. 1. NMR spectrum of compound VIIIB (IXB).

group methyls. The two doublets with centers at 6.87 and 7.86 ppm with equal spin-spin interaction constants indicate the presence of a para-disubstituted benzene ring. By analogy with the formation of compound V, and also on the basis of the greater electrophilicity of C_6 as compared with C_2 in the III adducts [4, 6, 9], the substance isolated directly from the reaction products should be considered the dichlorophosphate (VIIIA) or (IXA); and the compound obtained from it, the chloride (VIIIB) or (IXB).

Compound VIIIA (IXA) was also obtained in the reaction of dimethylaniline with adduct (IIIa). On prolonged boiling in phosphorus oxychloride or chlorobenzene it is not changed, but compound VIIIB (IXB) is capable of being converted to 2-chloro-6-

p-dimethylaminophenyl-7-methylpurine (X), which quite agrees with observations about the stability of the III adducts in distinction from the easily cleaved amidochlorides (IV).



To eliminate the possibility of the occurrence of a secondary para condensation process in the reaction of N,N'-dimethylxanthines with phosphorus oxychloride in the presence of a tertiary amine, in which a considerable amount of the adduct (III) is used up, triethylamine hydrochloride was used instead of dimethylaniline hydrochloride. This replacement led at once to a sharp rise in the yields of the corresponding chloropurines: from Ia, IIa [3] was obtained in 90-95% yield; from Ib, IIb [4] was obtained in 92-95% yield; and from VI, compound VII [1, 2] was obtained in 70-75% yield. It is not excluded that the stated results can be used in the future in converting keto derivatives of other N-heterocyclic compounds into the corresponding chlorides for use in the synthesis of biologically active substances.

EXPERIMENTAL

The NMR spectrum of VIIIB was taken on an INM 4H-100 instrument in $CDCl_3$ using a δ -scale relative to tetramethylsilane. The IR spectrum of VIIIA was taken on a UR-10 instrument in vaseline oil; designations of absorption band intensities are as follows: v.w. - very weak; w. - weak; m. - medium; s. - strong; and v.s. - very strong.*

Compound VIIIA (IXA). A. A mixture of 15 g of Ia, 90 ml of POCl₃, and 18 ml of dimethylaniline was boiled for 8 h. The solid which separated on cooling was washed with a small amount of POCl₃ and then with petroleum ether, and was dried in a vacuum disiccator over KOH. The weight of the precipitate was 6.5 g (about 18%), dec. point 160-175°C. IR frequencies, cm⁻¹: 510-517 (s.); 565 (v.w.); 605 (w.); 645 (v.w.); 708 (v.w.); 755 (v.w.); 780 (w₆); 790 (w₆); 853 (v.w.); 941 (w₆); 1012 (m₆); 1105 (s.); 1186 (m₆); 1240 (m₆); 1315 (s.); 1279 (v.s.); 1460 (v.s.); 1585 (v.s.).

The phosphorus oxychloride was distilled off, and ice was added to the residue; then the mixture was neutralized with a concentrated ammonia solution, it was filtered, and the precipitate was crystallized from water. Compound IIa was obtained (3.56 g, 21%), mp 194-195°C.

B. To a solution obtained by boiling 3 g of Ia in 20 ml of phosphorus oxychloride was added 1.8 ml of dimethylaniline, with stirring, at 20°C. The solution at once turned red, and a precipitate separated after

* The spectra were taken by co-workers of the physical chemistry laboratory (Yu. N. Sheinker, director).

2 or 3 days. Its weight was 1.5-1.7 g, dec. point 160-175°C. Its IR spectrum was identical to that of sample VIIIA (IXA) obtained by the preceding method.

Compound VIIIB (IXB). A suspension of 6 g of VIIIA in a small amount of water was neutralized to pH 8 with a 10% sodium hydroxide solution; the mixture was filtered, and the solid was washed with water, al-cohol, and ether. Its weight was 3.9 g, mp 140-147°C (dec). For analysis it was crystallized from absolute alcohol, mp 145-147°C (dec). Found, %: C 51.75; H 6.04; Cl 17.42; N 18.60. $C_{15}H_{17}Cl_2N_5 \cdot C_2H_5OH$. Calculated, %: C 53.12; H 5.99; Cl 18.49; N 18.23.

<u>2-Chloro-6-p-dimethylaminophenyl-7-methylpurine (X)</u>. Compound VIIIB (IXB) (1 g) in 30 ml of chlorobenzene was boiled for 20-25 h, and the solution was evaporated. The residue was washed with water, and 0.4 g of X was obtained. For analysis it was crystallized from benzene, mp 210-215°C. Found, %: C 57.42; H 5.38; Cl 12.21; N 23.29. $C_{14}H_{14}CIN_5$. Calculated, %: C 58.43; H 4.87; Cl 12.35; N 24.35.

2,6-Dichloro-7-methylpurine (IIa) [3]. A mixture of 50 g of Ia, 60 g of triethylamine hydrochloride, and 400 ml of phosphorus oxychloride was boiled for 25-30 h. The solid which separated on cooling was removed, added to ice, and neutralized with a concentrated ammonia solution. Compound IIa (33-34 g, mp 192-194°C) was obtained. The residue after stripping off the POCl₃ was decomposed with ice, neutralized with concentrated ammonia solution, and the solid was crystallized from water. There was obtained 15-18 g of IIa, mp 193-195°C. Total yield of IIa, 90-95%.

2.6.8-Trichloro-7-methylpurine (IIb). A mixture of 10 g of Ib, 12 g of triethylamine hydrochloride, and 50 ml of POCl₃ was boiled for 20 h. The precipitate which fell was added to ice and neutralized with concentrated ammonia solution; 5 g of IIb was isolated, mp 158-160°C. The phosphorus oxychloride was distilled off and the residue was treated similarly; 5.4-5.6 g of IIb was obtained, mp 158-160°C. Total yield, 92-95%.

2,6-Dichloro-9-methylpurine (VII) [1, 2]. Compound VI (20 g) and 30 g of triethylamine hydrochloride in 200 ml of POCl₃ were boiled for 25-30 h. The excess POCl₃ was distilled off, ice was added to the residue, and the mixture was brought to pH 2-3 with concentrated ammonia solution. The solid was washed with water to a neutral reaction, and it was crystallized from water. There was obtained 16-17 g (70-75%) of VII, mp 154-155°C. The substance was identical with a known sample of VII [1, 2] in mp and R_f .

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