THE CHLORINATION OF CERTAIN PURINONES WITH PHOSPHORUS OXYCHLORIDE IN THE PRESENCE OF TERTIARY AMINES

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THE CHLORINATION OF CERTAIN PURINONES WITH PHOSPHORUS OXYCHLORIDE IN THE PRESENCE OF TERTIARY AMINES

Since Baddiley and Topham (2, p.678) first reported using dimethylaniline in the chlorination of barbituric acid with phosphorus oxychloride, the use of a mixture of this tertiary amine and phosphorus oxychloride has found extensive application in the preparation of numerous chloropyrimidines.

Because of the close chemical relationship of pyrimidine and purine derivatives, it seemed quite logical that this reaction could well be extended to the preparation of the rather inaccessible chloropurines. These chloropurines could then serve as valuable intermediates in the preparation of synthetic nucleosides (7, pp.833-838). It was for this reason that a study of the behavior of the reaction mixture of dimethylaniline, phosphorus oxychloride, and uric acid was undertaken. It was hoped that the main reaction product would be 2,6,8-trichloropurine.

Preliminary experiments were not very promising. Short periods of reaction time commonly employed in the preparation of chloropyrimidines were found to have little effect in chlorinating the purine ring. Most of the uric acid was recovered unchanged. Longer periods of reaction time resulted in yielding a phosphorylated

product insoluble in dilute hydrochloric acid and a product containing phosphorus which was soluble in dilute mineral acids. The acid insoluble material proved to be a complex phosphorylated, partially chlorinated purine derivative which defied all attempts of further purification and thus could not be further identified. The other phosphorus containing compound was readily purified and gave a sharp melting point (m.p. 209-211°). Since the nature of this latter product was not immediately apparent, the compound was subjected to further investigation.

Chemical analysis showed the empirical formula to be $C_{16}H_{21}N_2O_2P$. This data suggested that reaction had probably occurred between dimethylaniline and phosphorus oxychloride. Repeated experiments of long reaction time in the absence of uric acid gave the same product, although it was noted that the yield was much greater even in the presence of only catalytic amounts of uric acid.

Because of the fact that this compound could well shed considerable light on the direction that the reaction was taking, a systematic study of the structure of this compound was undertaken.

According to the literature Bourneuf (5, pp.1808-1823) phosphorylated dimethylaniline under pressure with

phosphorus oxychloride and obtained an alkali-soluble product, $C_{16}H_{21}N_2O_2P$, melting point 199° (capillary), 249° (block). Bourneuf (5, pp.1808-1823) also obtained from the same reaction mixture, three alkali-insoluble side products, tetramethyldiaminodiphenylmethane (m.p. 90°), the oxide of hexamethyltriaminotriphenylphosphine (m.p. 262°), and its hydrate (m.p. 318°). The analytical data given for the side products were very questionable, suggesting impure samples, while the position of phosphorylation in no case had been determined.

Dimethylaniline has likewise been phosphorylated with phosphorus trichloride by a number of investigators (5, pp.1808-1815; 15, p.20; 17, pp.745-748) who isolated dimethylaminophenylphosphinous acid from the reaction mixture, but in no instance established the position of phosphorylation.

Judging by the properties and the analytical data it seemed apparent that the product obtained in this laboratory ($C_{16}H_{21}N_2O_2P$) and that reported by Bourneuf (5, pp.1808-1823) with the same empirical formula were identical. However, in view of the uncertainty regarding the position of phosphorylation and the discrepancies in the melting point in what appeared to be the same product, this problem was subjected to further investigation.

Bis(p-chlorophenyl)phosphinic acid was prepared by the method of Kosolapoff (12, p.2983), and in turn converted to bis(p-aminophenyl)phosphinic acid by well established procedures described by Bauer (3, p.2138). Attempts to convert this compound to the dimethylamino derative were, however, unsuccessful.

Attempts to prepare a Grignard reagent from p-bromodimethylaniline, to be used as an intermediate in the synthesis of bis(p-dimethylaminophenyl)phosphinic acid (I, Figure 1), failed. In view of these experiments, p-dimethylaminophenyllithium was prepared and used according to the directions of Kosolapoff (12, p.2983) for synthesizing arylphosphinic acids using the Grignard reagent. The p-dimethylaminophenyllithium reacted readily with phosphorus oxychloride by this procedure to yield alkali-soluble bis(p-dimethylaminophenyl)phosphinic acid (m.p. 208-210°) (I, Figure 1) which was judged to be identical with our original reaction product $C_{16}H_{21}N_2O_2P$ on the basis of mixed melting point tests. An alkali-insoluble by-product was also isolated which on the basis of analytical data and synthesis was found to be tris(p-dimethylaminophenyl)-phosphine oxide (III, Figure 1), which was probably the same as the hexamethyltriaminotriphenylphosphine oxide described by Bourneuf.

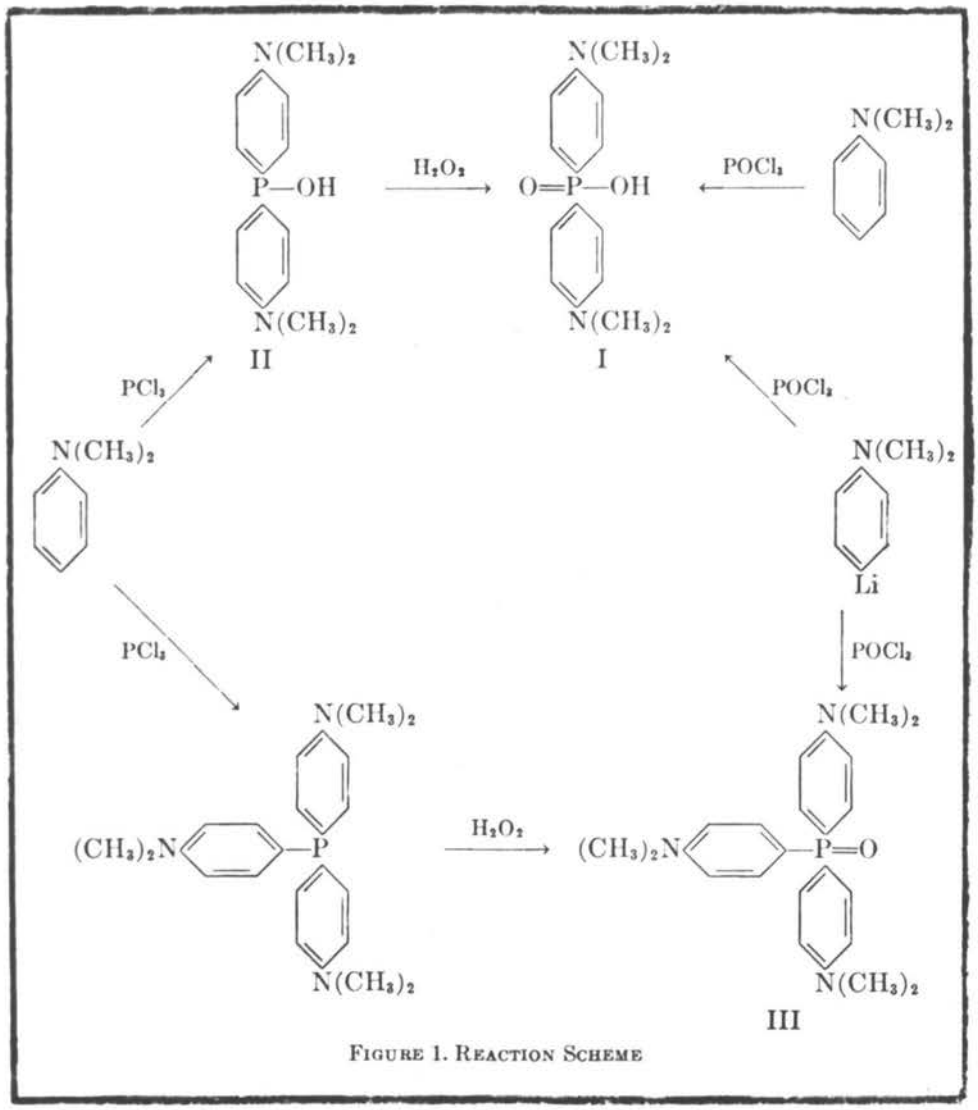

FIGURE 1. REACTION SCHEME

The reaction of phosphorus trichloride and dimethylaniline as described by Bourneuf (5, pp.1808-1815) and Raudnitz (17, pp.745-748) was repeated in this laboratory. The two products obtained, bis-(dimethylaminophenyl)phosphinous acid and tris(dimethylaminophenyl)phosphine were oxidized with three per cent hydrogen peroxide. The two oxidation products were found to be identical with bis(p-dimethylaminophenyl)phosphinic acid (I, Figure 1) and tris-(p-dimethylaminophenyl)phosphine oxide (III, Figure 1) respectively. This proved that phosphorylation of dimethylaniline with phosphorus trichloride also takes place in the para position.

It was thus shown that when dimethylaniline, phosphorus oxychloride, and uric acid were refluxed for long periods necessary to achieve even a small amount of chlorination of the purine nucleus that considerable phosphorylation of the dimethylaniline took place in the para position and only a very small amount of the desired 2,6,8-trichloropurine could be isolated.

Recently, Davoll and Lowy (6, p.2936) report an isolation of only 16-25 per cent yield of trichloropurine from uric acid using dimethylaniline and phosphorus oxychloride as a chlorinating mixture.

In search for a generally useful method of obtaining chloropurines from the corresponding purinones a number of routine chlorinations using other tertiary amines were attempted. In the light of the previous work, triethylamine was chosen as the first tertiary amine to be substituted for dimethylaniline in the reaction mixture. Since triethylamine contained no "phenyl" group, phosphorylation of the phenyl nucleus as a major side reaction was impossible.

In the course of this work it was discovered that in the presence of a limited amount of triethylamine, uric acid was converted to 8-chloroxanthine in yields of from 30-40 per cent; by the substitution of mono-potassium salt of uric acid the yields were consistently above 80 per cent. These results were interesting since in the usual chlorination it is the 8- position which is the last to be chlorinated (9, p.2220).

When these experiments were extended to the use of excess triethylamine coupled with longer reaction time, it was discovered that the reaction not only chlorinated the purine nucleus but the triethylamine proceeded to ammonate the ring. Uric acid under these conditions gave a product, $C_9H_{11}N_5Cl_2$, (I, Figure 2, R = C_2H_5) instead of the expected trichloropurine.

It thus appeared that the product contained a diethylamino-substituent.

In order to determine the position of this substituent a second synthesis was undertaken. Trichloropurine was treated with diethylamine; this gave a product which was found to be identical to (I, R = C_2H_5 Figure 2). The reaction of a secondary amine with trichloropurine has not been previously described, but 2,6-dichloro-7-methylpurine (1, p.1272) has been reported to yield 2-chloro-6-diethylamino-7-methylpurine upon treatment with diethylamine. Since the 6- position is known to be the most reactive in trichloropurine it seemed highly likely that the diethylamino-substituent was in the 6- position. This opinion was confirmed, and the structure of (I, R = C_2H_5 Figure 2) was proved when the reduction product of the 2,8-dichloro-6-diethylaminopurine thus prepared yielded 6-diethylaminopurine (II, R = C_2H_5 Figure 2) which was found to be identical to the reaction product of hypoxanthine, triethylamine and phosphorus oxychloride.

To establish the generality of this reaction xanthine was subjected to reaction with triethylamine and phosphorus oxychloride and the product obtained was found to be 2,6-bis(diethylamino)purine (III, R = C_2H_5 Figure 2).

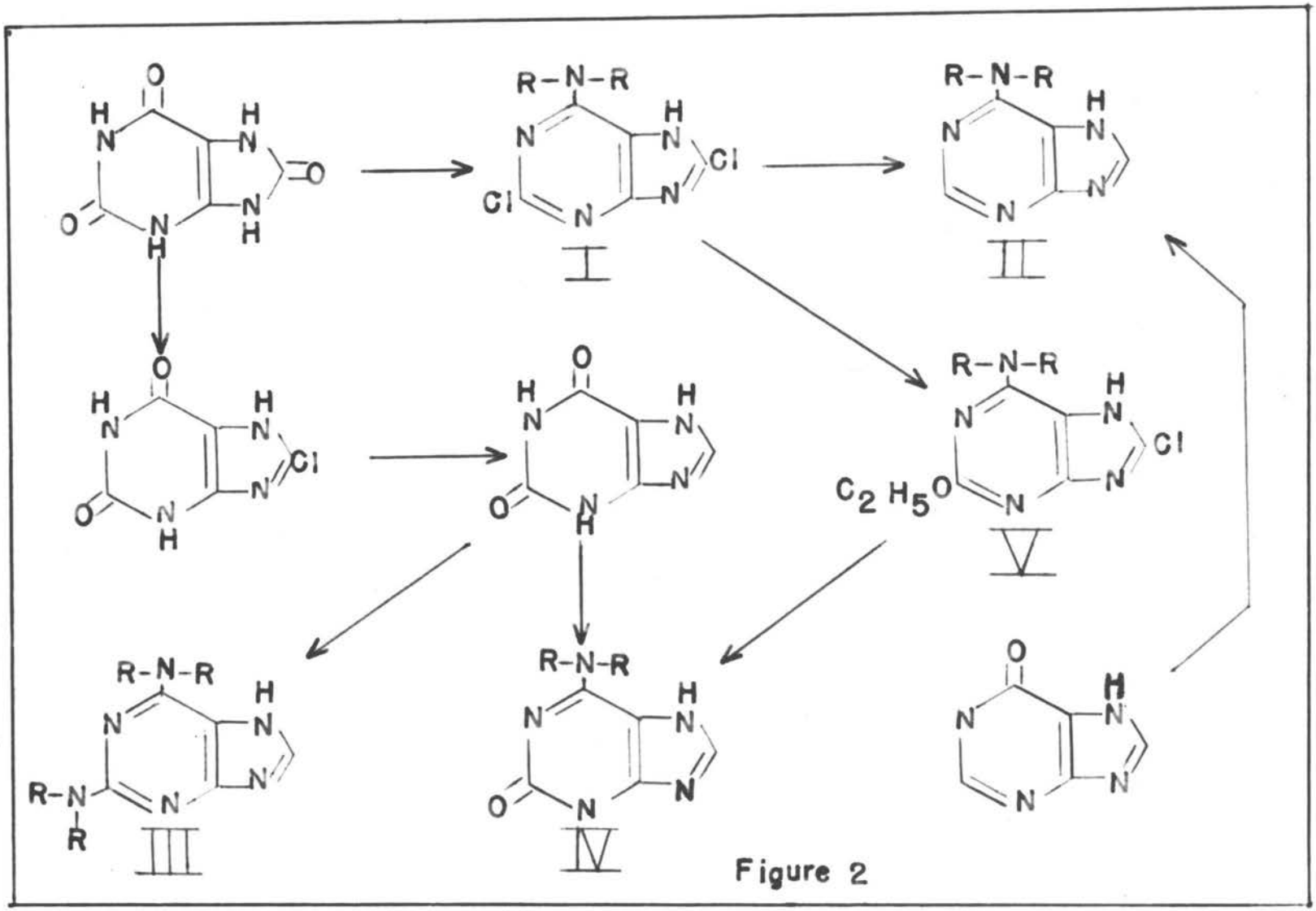

Figure 2

The use of other tertiary amines in the reaction mixture was studied. Trimethylamine, xanthine, and phosphorus oxychloride yielded 2,6-bis(dimethylamino)-purine (III, R = CH_3 Figure 2). It is interesting to note that this reaction could be carried out at atmospheric pressure; this would suggest some type of salt formation in the reaction mixture.

When tri-n-propylamine was used, the reaction product was not the expected 2,6-bis(di-n-propylamino)-derivative but a compound having the empirical formula $C_{11}H_{17}N_5O$ (IV, R = n-C_3H_7 Figure 2). When tri-n-butylamine was used, $C_{13}H_{21}N_5O$ (IV, R = n-C_4H_9) was obtained. It thus appeared that only one of the "hydroxy" groups in xanthine had been replaced by the dialkylamino radical in each case. In order to prove this and to establish the position of the dialkylamino group, the unambiguous synthesis of 6-di-n-butylamino-2-purinone was undertaken.

Using trichloropurine and di-n-butylamine, 2,8-dichloro-6-di-n-butylaminopurine (I, R = n-C_4H_9 Figure 2) was prepared by a procedure similar to that previously employed to synthesize 2,8-dichloro-6-diethylaminopurine (I, R = C_2H_5 Figure 2) (method 2). 2,8-Dichloro-6-di-n-butylaminopurine was then reacted with sodium ethoxide to give 8-chloro-2-ethoxy-6-di-n-butylaminopurine (V, R = n-C_4H_9 Figure 2) by a

procedure similar to that employed by Fischer (9, p.2223) to prepare 8-chloro-2-ethoxy-6-aminopurine from 2,8-dichloro-6-aminopurine. The compound 8-chloro-2-ethoxy-6-di-n-butylaminopurine was then treated with hydriodic acid which cleaved the "ethoxy" group and removed the chlorine atom to give 6-di-n-butylamino-2-purinone (IV, R = n-C_4H_9 Figure 2), which was found to be identical with the product $C_{13}H_{21}N_5O$ obtained from the reaction mixture of tri-n-butylamine, xanthine, and phosphorus oxychloride.

That the compound $C_{11}H_{17}N_5O$ obtained with tri-n-propylamine, xanthine, and phosphorus oxychloride is 6-di-n-propylamino-2-purinone (IV, R = n-C_3H_7 Figure 2) seems highly probable judging from analogous properties and the method of preparation similar to that of 6-di-n-butylamino-2-purinone.

In order to exclude the possibility that the dialkylamination of the purine ring may have been due to the presence of a secondary amine contaminant (in the tertiary amine) only best available grades of tertiary amines were used in these experiments, and only after distillation using a ten plate column.

These purified tertiary amines gave a negative Hinsberg test for the presence of secondary or primary amine contaminants.

Similar reactions involving pyrimidones have been reported. King and coworkers (11, p.1247) have isolated 4,6-dichloro-2methylanilinopyrimidine from the reaction mixture of barbituric acid, phosphorus oxychloride and dimethylaniline. Marshall and Walker (14, p.1010) report the isolation of 2(4)-chloro-6-methyl-4(2)-methylanilino-5-nitropyrimidine from the reaction mixture of phosphorus oxychloride, dimethylaniline, and 6-methyl-5-nitrouracil.

Kawai and Miyoshi (10, pp.20-23) heated 2,4,6-trichloropyrimidine with dimethylaniline and isolated 2,4,6 tris-(methylanilino)pyrimidine.

In principle these reactions appear to be the same. It seems quite probable that the reaction proceeds through the formation of a quaternary salt which decomposes to give the new tertiary amine.

EXPERIMENTAL

Bis(p-dimethylaminophenyl)phosphinic acid (I, Figure 1) Method (1): Redistilled phosphorus oxychloride (80 g.) and 40 g. of dimethylaniline were refluxed in the absence of moisture for 36 hours. The excess phosphorus oxychloride was removed under reduced pressure, the residue treated with 150-200 ml. of water, made alkaline with 6 N sodium hydroxide, and extracted with two 200 ml. portions of ether to remove unreacted dimethylaniline. The aqueous fraction was acidified with glacial acetic acid; crystallization was complete in approximately 12 hours; yield, 8.6 g. (17.1%), m.p. 206-211°. The crude product was treated with a small amount of Norite in a hot ethanol-water mixture, filtered and allowed to crystallize; yield, 8.1 g. of colorless plates, m.p. 209-211°.

When the above operations were repeated under identical conditions except for the addition of 0.2 g. of uric acid and the reaction time allowed to continue only 20 hours, the yield was 16.1 g. (32%), m.p. 209-211°. Anal. Calcd. for $C_{16}H_{21}N_2O_2P$: C, 63.2; H, 6.96; N, 9.20; P, 10.2. Found: C, 63.0; H, 6.83; N, 9.27; P, 10.15.

Method (2): One gram of lithium shot was placed in a three-necked 500 ml. flask containing 50 ml. of

anhydrous ether and equipped with a separatory funnel, stirrer, and a reflux condenser having a moisture-protected outlet. The ether was brought to a gentle reflux and 60 ml. of an anhydrous ethereal solution containing 12 g. of p-bromodimethylaniline was slowly added over a period of two hours. The solution was refluxed two additional hours and then transferred to a separatory funnel.

An ice cold solution (200 ml.) of ether containing 9.0 g. of phosphorus oxychloride was placed in the reaction flask which was then maintained at 0°. The solution of p-dimethylaminophenyllithium was added dropwise with stirring over a period of one hour. After two more hours of stirring at 0°, 125 ml. of 3 N sodium hydroxide was slowly added; the solid matter was removed and set aside. After separation of the ether layer, the aqueous basic solution was acidified with glacial acetic acid and set aside in a refrigerator. A crude precipitate of 1.07 g. (11.7%) of bis-(p-dimethylaminophenyl)phosphinic acid was obtained; m.p. 207-209°. Recrystallization from isopropyl alcohol gave product melting 208-210°. A mixed melting point of this compound and bis(p-dimethylaminophenyl)phosphinic acid prepared by method (1) showed no depression.

Tris(p-dimethylaminophenyl)phosphine oxide (III, Figure 1): The alkali-insoluble material obtained in the previous experiment was repeatedly washed with small portions of cold water and then recrystallized from an ethanol-water mixture; yield, 4.1 g. (50.4%), m.p. 301-306°. Recrystallization from ethanol gave a m.p. 305-306° which could not be raised by further recrystallization. Anal. Calcd. for $C_{24}H_{30}N_3OP$: N, 10.31. Found: N, 10.52, 10.27.

Oxidation of bis(p-dimethylaminophenyl)phosphinous acid (II, Figure 1): One gram of the acid (5, p.1820) was suspended in 40 ml. of 3% hydrogen peroxide and sufficient sulfuric acid was added to effect solution. The solution was then heated just below the boiling point for five minutes, cooled, and treated with 6 N sodium hydroxide until the precipitate which first formed was dissolved. An alkali-insoluble fraction was removed; yield, 0.1 g. m.p. 294-296° (probably impure tris(p-dimethylaminophenyl)phosphine oxide). The filtrate was acidified with glacial acetic acid, cooled, and filtered; yield, 0.72 g., 68.2%. Recrystallization from an ethanol-water mixture gave a white product, bis(p-dimethylaminophenyl)phosphinic acid, m.p. 209-211°. Mixed melting points taken with bis(p-dimethylaminophenyl)phosphinic acid prepared by method (1) and method (2) gave no depression.

Oxidation of tris(p-dimethylaminophenyl)phosphine: Tris(p-dimethylaminophenyl)phosphine (5, p.1820) (0.8 g.) was oxidized under the identical conditions used for the bis compound. The yield of tris(p-dimethylaminophenyl)-phosphine oxide was 0.8 g. (95.8%); m.p. 300-301°. After several recrystallizations from ethanol-water mixtures and then ethanol this product melted at 302-303°. Mixed melting point of this compound and tris-(p-dimethylaminophenyl)phosphine oxide prepared by the use of p-dimethylaminophenyllithium was 305-306°. Anal. Calcd. for $C_{24}H_{30}N_3OP$: N, 10.31. Found: N, 10.26.

Bis(p-aminophenyl)phosphinic acid: A mixture composed of 3.0 g. of bis(p-chlorophenyl)phosphinic acid, (12, p.2983) 40 ml. of 28% aqueous ammonia, and 5.0 g. of freshly prepared cuprous oxide was placed in a high pressure bomb and heated at 155°. After 12 hours the bomb was cooled and the contents removed and filtered. The excess ammonia in the filtrate was removed by gentle heating in vacuo. Glacial acetic acid (5 ml.) was added to dissolve the precipitated copper hydroxides; the solution was diluted to 40 ml. and heated to boiling and the copper was precipitated with hydrogen sulfide. The brown filtrate was clarified with Norite and placed in a refrigerator. An almost colorless precipitate was obtained; yield, 0.83 g. (32.4%), m.p. 233-236°.

Recrystallization from glacial acetic acid gave a m.p. 242-243°. Anal. Calcd. for $C_{12}H_{13}N_2O_2P$: N, 11.75. Found: N, 11.66.

8-Chloroxanthine (8-chloro-2,6-purinedione): To 250 ml. of redistilled phosphorus oxychloride was added 30 g. of the mono-potassium salt of uric acid (7, p.837) and 35 ml. of triethylamine which had been refractionated and dried over sodium. The solution was refluxed for four and one half hours during which time all the mono-potassium urate went into solution. The excess phosphorus oxychloride was then removed using a steam bath and reduced pressure until a light tan syrup remained which was poured onto 200 g. of chipped ice. The solution was then allowed to stand at room temperature for three hours and then refrigerated overnight to complete crystallization. The precipitate was removed by filtration, washed with cold water, acetone, and finally dried at 110°. The yield of crude, slightly yellow, 8-chloroxanthine was 23.1 g. (85.5%).

Further purification was affected by crystallization of the ammonium salt (8, p.2237). Two grams of crude 8-chloroxanthine was suspended in 30 ml. of water containing 5 ml. of con. ammonium hydroxide and the mixture brought to boiling to effect complete solution. The product was decolorized with charcoal and then refrigerated at 4° for twenty-four hours, and filtered.

The white ammonium salt was washed with 5 ml. of ice water and again dissolved in 30 ml. of boiling water. The hot solution was acidified with dilute hydrochloric acid which precipitated the white 8-chloroxanthine. The product was filtered, washed with cold water and dried for one hour at 130°, yield 1.7 g. Anal. Calcd. for $C_5H_3ClN_4O_2$: C, 32.10; H, 1.61; Cl, 19.1. Found: C, 32.06; H, 2.11; Cl, 19.0.

The compound thus obtained was established as 8-chloroxanthine by methylation of the crude product with methyl iodide in the manner employed by Fischer (8, p.2237). One gram of crude 8-chloroxanthine gave 0.61 g. of 8-chlorocaffeine, m.p. 188°.

The 8-chloroxanthine was also reduced to xanthine by a modification of the Fischer (8, p.2238) procedure. Two grams of crude 8-chloroxanthine was suspended in 30 ml. of hydroiodic acid (Sp. G. 1.50, preserved by the addition of hypophosphorus acid) and the solution was boiled gently until the 8-chloroxanthine dissolved. (5 min) The xanthine was then isolated as described by Fischer (8, p.2238). The crude yield of white xanthine was 1.7 g. This material was purified by recrystallization of the sodium salt according to the procedure of Biltz and Beck (4, p.168). Anal. Calcd. for $C_5H_4N_4O_2$: N, 36.85. Found: N, 36.80.

2,8-Dichloro-6-diethylaminopurine (I, R = C_2H_5 Figure 2) Method (1): A mixture of 100 ml. of redistilled phosphorus oxychloride, 5.0 g. of mono-potassium urate and 30 ml. of triethylamine, was refluxed for thirteen hours. The excess phosphorus oxychloride was removed under reduced pressure and the brown syrupy residue poured slowly with vigorous stirring onto 150 g. of chipped ice. The aqueous solution was kept at 0° for one-half hour and then filtered. The precipitate was partially dried using a hot air fan until nearly all the water had been removed. The rather gummy precipitate was then extracted in a Soxhlet extractor with 250 ml. of ether for five hours. Evaporation of the ether left a residue which was dissolved in 100 ml. of boiling heptane; upon cooling 2.5 g. of white needles were isolated, m.p. 210-220°. Recrystallization from 95% ethanol gave 2.1 g. of colorless needles m.p. 224-225°. A final recrystallization from heptane raised the m.p. to 225-225.5°.

2,8-Dichloro-6-diethylaminopurine was found to be insoluble in dilute hydrochloric acid but soluble in dilute sodium hydroxide. Anal. Calcd. for $C_9H_{11}Cl_2N_5$: C, 41.55; H, 4.23; N, 26.9. Found: C, 41.68, 40.96; H, 4.43, 3.89; N, 26.7.

2,8-Dichloro-6-diethylaminopurine Method (2): To a solution of 5 ml. of diethylamine in 25 ml. of

water was added 1.0 g. of trichloropurine (6, p.2936), and the mixture refluxed for one half-hour. The condenser was then removed and the excess diethylamine was allowed to slowly distill away. The solution was then cooled and acidified to congo red paper with dilute hydrochloric acid. An immediate white precipitate was noted, which was filtered, washed with water and then recrystallized from 95% ethanol; yield 0.8 g. of colorless needles, m.p. 225°. A mixed m.p. of this compound and 2,8-dichloro-6-diethylaminopurine obtained by method (1) was 225-225.5°.

2,8-Dichloro-6-diethylaminopurine Method (3): A mixture of 40 ml. of phosphorus oxychloride, 2.5 g. of trichloropurine, and 15 ml. of triethylamine was refluxed for thirteen hours. The product was isolated as described in method (1); yield 1.1 g. of 2,8-dichloro--6-diethylaminopurine. One recrystallization from 95% ethanol gave a m.p. of 225°. The product was identical with that prepared by both by method (1) and method (2) as judged by mixed melting points.

6-Diethylaminopurine (II, R = C_2H_5 Figure 2)

Method (1): A mixture consisting of four grams of colorless hypoxanthine, prepared from adenine by the method of Kruger (13, pp.444-445), 75 ml. of redistilled phosphorus oxychloride and 20 ml. of triethylamine was vigorously refluxed for four hours. After removing the

excess phosphorus oxychloride the remaining brown syrup was poured onto 200 g. of chopped ice. After thirty minutes the mixture was brought to a pH of 9 with concentrated ammonium hydroxide, and then placed in a refrigerator overnight to effect crystallization. The yield was 3.8 g. of tan colored needles which were recrystallized from an ethanol-water mixture to yield 3.0 g. of a colorless product, m.p. 222-223°. A second recrystallization from benzene did not change the melting point. Anal. Calcd. for $C_9H_{12}N_5$: C, 56.6; H, 6.81; N, 36.7. Found: C, 56.7; H, 6.89; N, 36.7.

6-Diethylaminopurine Method (2): 2,8-Dichloro-6-diethylaminopurine, 0.5 g. together with 10 g. of hydriodic acid (Sp. G. 1.5), was placed in a small beaker. The solution was slowly heated to boiling and then boiled gently for ten minutes, cooled, diluted with 5 ml. of water and made slightly basic with concentrated ammonium hydroxide. The precipitate which formed was collected, washed with water, dried and recrystallized from benzene to yield 0.15 g. of a crystalline product m.p. 220-221°. A second recrystallization from benzene raised the m.p. to 221-223°. A mixed melting point of this product with 6-diethylaminopurine prepared by method (1) was 221-223°.

2,6-Bis(diethylamino)purine (III, R = C_2H_5 Figure 2): Xanthine, 6.0 g. and 35 ml. of triethylamine and 100 ml. of phosphorus oxychloride were refluxed for three and one-half hours. After the removal of the excess phosphorus oxychloride the syrupy residue was poured onto 300 g. of chopped ice. The aqueous solution was made ammoniacal, brought to a pH of 9, and placed in a refrigerator for twenty-four hours. The hardened gummy precipitate was then removed by filtration, washed with water and dried. The crude product (5.1 g.) was recrystallized from Skellysolve "B" yielding 4.8 g. of a light tan powder m.p. 112-115°. This material was purified further by sublimation under reduced pressure. A pure white product was obtained in this manner, m.p. 114-116°. The sublimed material was again recrystallized from Skellysolve "B" to give a product m.p. 116.5-117.5°. It was noted that if the 2,6-bis(diethylamino)purine was allowed to recrystallize slowly from Skellysolve "B" extremely large crystals were formed, however, if the cooled solution was scratched with a glass rod, 2,6-bis(diethylamino)purine crystallized in small crystals almost immediately. Anal. Calcd. for $C_{13}H_{22}N_6$: C, 59.60; H, 8.41; N, 32.05. Found: C, 59.55, 59.39; H, 8.69, 8.36; N, 32.23, 31.68.

A picrate of 2,6-bis(diethylamino)purine was made

which after two recrystallizations from ethanol gave a m.p. 173-174°. Anal. Calcd. for $C_{19}H_{25}N_9O_7$: C, 46.43; H, 5.12. Found: C, 46.67; H, 5.34.

2,6-Bis(dimethylamino)purine (III, R = CH_3 Figure 2): Four g. of xanthine was suspended in 60 ml. of phosphorus oxychloride and the solution was cooled to 0°. Anhydrous trimethylamine, 20 ml., was added and the mixture was gradually allowed to warm up to room temperature and then refluxed for fifteen minutes. The solution was again cooled to 0°, and an additional 10 ml. of trimethylamine added, and the solution was again refluxed for a total of four hours. The reaction product was then isolated in the manner used in the preparation of 2,6-bis(diethylamino)purine. The crude product, 2.5 g. of a gray powder was sublimed under reduced pressure to yield 2.1 g. of a colorless product. Recrystallization from xylene gave 2.0 g. m.p. 252-254°. A second recrystallization from 95% ethanol gave a m.p. 254-255°. Anal. Calcd. for $C_9H_{14}N_6$: C, 52.40; H, 6.80: N, 40.77. Found: C, 52.36; H, 7.03; N, 40.68.

6-Di-n-propylamino-2-purinone (IV, R = n-C_3H_7 Figure 2): Xanthine, 1.5 g. and 13 ml. of tri-n-propylamine and 50 ml. of phosphorus oxychloride were vigorously refluxed for four and one-half hours. The phosphorus oxychloride was then removed under reduced

pressure and the syrupy residue poured onto 200 g. of chopped ice. The aqueous solution was brought to a pH of 9 with concentrated ammonium hydroxide and the solution was concentrated (using a heating fan) until the layer of excess tri-n-propylamine had evaporated, then the solution was cooled, filtered, and the precipitate washed with water. The yield was 1.5 g. of a white powder which was recrystallized first from ethanol, then from methanol, to yield 1.1 g. of colorless fine needles, m.p. 290.5-291.5°. Anal. Calcd. for $C_{11}H_{17}N_5O$: C, 56.20; H, 7.23; N, 29.0. Found: C, 56.75; H, 7.33; N, 29.0.

6-Di-n-butylamino-2-purinone (IV, R = n-C_4H_9 Figure 2) Method (1): A mixture consisting of 1.0 g. of xanthine and 15 ml. of tri-n-butylamine and 45 ml. of phosphorus oxychloride was refluxed for three and one-half hours. The product was isolated in a manner identical with that used in the preparation of 6-di-n-propylamino-2-purinone. The yield was 0.6 g. which after recrystallization first from ethanol and then from methanol gave 0.3 g. of colorless crystals m.p. 279-280°. Anal. Calcd. for $C_{13}H_{31}N_5O$: C, 59.3; H, 7.93 N, 26.6. Found: C, 59.3; H, 7.96; N, 26.3.

2,8-Dichloro-6-di-n-butylaminopurine (I, R = n-C_4H_9 Figure 2): To a solution consisting of 10 ml. of di-n-butylamine, 30 ml. of water, and 20 ml. of

ethanol was added 3.0 g. of trichloropurine. The solution was refluxed for an hour, cooled and acidified with dilute hydrochloric acid. The crude, white precipitate was washed with water, dried and recrystallized from 95% ethanol to yield 2.2 g. of white needles m.p. 165-167°. A second recrystallization from heptane raided the m.p. to 168-169°. Anal. Calcd. for $C_{13}H_{19}Cl_2N_5$: C, 49.40; H, 6.02. Found: C, 49.45; H, 6.47.

8-Chloro-2-ethoxy-6-di-n-butylaminopurine (V, R = n-C_4H_9 Figure 2): One gram of 2,8-dichloro-6-di-n-butylaminopurine was dissolved in an alcoholic solution of sodium ethoxide, prepared by dissolving 1.0 g. of sodium in 10 ml. of absolute ethanol. This solution was placed in a sealed glass tube and heated in an oven (temperature 130°) for three and one-half hours. The contents of the tube were diluted with 10 ml. of water and then acidified with acetic acid. The white solid was collected washed with a little cold water, recrystallized from an ethanol-water mixture yielding 0.8 g. m.p. 162-164°. A small amount was recrystallized from 95% ethanol for analytical purposes; m.p. 164-165°. A mixed melting point of this product and the starting material, 2,8-dichloro-6-di-n-butylaminopurine was below 125°. Anal. Calcd. for $C_{15}H_{24}N_5ClO$: C, 55.4; H, 7.40. Found: C, 55.4; H, 7.56.

6-Di-n-butylamino-2-purinone (IV, R = n-C_4H_9 Figure 2) Method (2): To 10 ml. of hydriodic acid (Sp. G. 1.5, preserved with hypophosphorus acid) was added 0.6 g. of 8-chloro-2-ethoxy-6-di-n-butylaminopurine. The solution was boiled gently for five minutes, and then vigorously boiled for an additional ten minutes. The cooled reaction mixture was then diluted with 5 ml. of cold water and made slightly alkaline with concentrated ammonium hydroxide. The white precipitate thus obtained was washed several times with cold water and then recrystallized from methanol. The yield was 0.3 g. of product m.p. 275-277°. A second recrystallization from methanol raised the m.p. to 278.5-279.5°. A mixed melting point of this product and 6-di-n-butylamino-2-purinone prepared by method (1) was 278.5-280°.

2-(6)-Chloro-6-(2)-diethylaminopurine: Into a 500 ml. flask was placed 15.0 g. of xanthine, 200 ml. of phosphorus oxychloride and 10 ml. of triethylamine. The solution was refluxed; every twenty minutes 10 ml. of additional triethylamine was added until a total of 65 ml. had been used. The solution was then refluxed twelve hours more and the reaction mixture processed in the usual manner. The crude product, 6.5 g. of brown gum, was extracted with heptane using a Soxhlet extractor. Upon cooling the heptane solution 0.4 g. of

crude material separated from the more heptane soluble 2,6-bis(diethylamino)purine. The crude product was dissolved in an isopropanol-water mixture, decolorized with charcoal and allowed to crystallize. A second recrystallization from the same solvent gave a white product m.p. 224-226°. A final recrystallization from heptane gave fine needles m.p. 225-227°. Anal. Calcd. for $C_9H_{12}ClN_5$: C, 47.89; H, 5.34. Found: C, 47.62, 47.58; H, 5.44, 5.39.

The isolation of this product from subsequent similar runs could not be consistently repeated. None of this material could be isolated when the preparation of 2,6-bis(diethylamino)purine was carried out in the usual manner.

SUMMARY

Dimethylaniline and phosphorus oxychloride have been shown to react after extended periods of refluxing to give bis(p-dimethylaminophenyl)phosphinic acid. The structure of bis(p-dimethylaminophenyl)phosphinic acid, tris(p-dimethylaminophenyl)phosphine oxide, bis(p-dimethylaminophenyl)phosphinous acid, and tris(p-dimethylaminophenyl)phosphine have been established. Bis(p-aminophenyl)phosphinic acid has been prepared.

The reaction of uric acid, xanthine and hypoxanthine with phosphorus oxychloride in the presence of various aliphatic tertiary amines has been shown to result in the replacement of the "hydroxy" group in the 6- and in some cases the 2- and 6- positions of the purine nucleus to give the corresponding dialkylamino- or bis(dialkylamino)- purine in good yield. The structures of a number of these dialkylaminopurines have been established by synthesis.

8-Chloroxanthine has been prepared in good yield from the mono-potassium salt of uric acid by the action of phosphorus oxychloride and a limited amount of triethylamine. An excess of triethylamine in the same reaction has been found to yield 2,8-dichloro-6-diethylaminopurine.

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