Synthesis of Testosterone Dimethyl Phosphate, Bornyl Phosphate and Adenosine 5′-Phosphate

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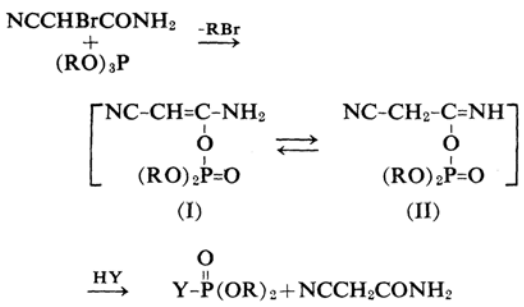
A previous paper described a useful method for the selective phosphorylation of alcohols and the diesters of phosphoric acid by means of α-bromocyanoacetamides and trialkyl phosphites to yield phosphates and pyrophoshates.[1]

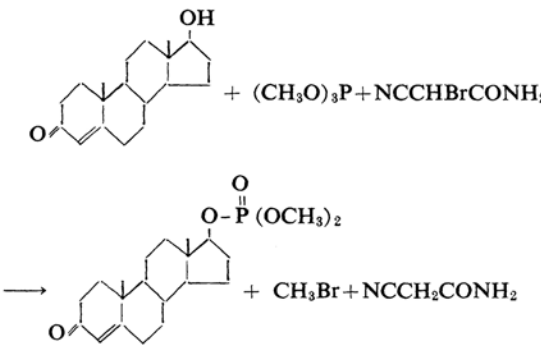
A selective phosphorylation can be effected successfully by this method without isolating the intermediate, enol-phosphate (I) or imidoyl phosphate (II), since it reacts exclusively with nucleophilic reagents, such as alcohols, phenols, diesters of phosphoric acid and amines, under mild conditions.



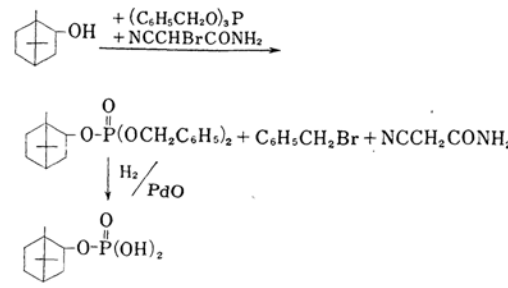
HY : alcohol or diester of phosphoric acid or amine

In the present paper, a successful application of this method to the synthesis of a steroid phosphate, a terpene phosphate and a nucleotide is described.

Müller and his co-workers[2] reported that testosterone dimethyl phosphate was obtained by the oxidation of the dimethyl ester of androst-5-ene-3β, 17β-diol 17-phosphate with chromic acid. It has now been found that testosterone dimethyl phosphate is obtained in a good yield from testosterone and the phosphorylating reagents, i. e., monobromocyanoacetamide and trimethyl phosphite. When trimethyl phosphite was added to a solution of one mole of testosterone and one mole of monobromocyanoacetamide in dry ether at $-40°C$, testosterone dimethyl phosphate was obtained in a 62% yield.

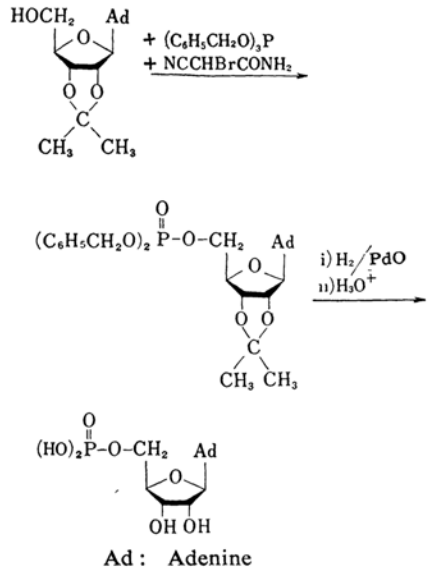


In the next place, a synthesis of bornyl phosphate, which had been reported to be synthesized from borneol and phosphorus oxychloride,[3] by means of the afore-mentioned phosphorylating reagents was tried. It was obtained in a 60% yield by the reaction of borneol with monobromocyanoacetamide and tribenzyl phosphite, followed by hydrogenolysis to remove the benzyl group.



Finally, it was established that adenosine 5′-phosphate[4] was successfully synthesized. Adenosine 5′-phosphate was obtained in a 62% yield when one mole of 2′, 3′-isopropylideneadenosine was treated with one mole of monobromocyanoacetamide and one mole of tribenzyl phosphite, followed by hydrogenolysis and hydrolysis.

1) T. Hata and T. Mukaiyama, This Bulletin, **35**, 1106 (1962).
2) E. Müller, A. Langerbeck and W. Riedel, *Z. physiol. Chem.*, **281**, 29 (1944).
3) C. Neuberg, J. Wagner and K. P. Jacobsohn, *Biochem. Z.*, **188**, 227 (1927).
4) J. Baddiley and A. R. Todd, *J. Chem. Soc.*, **1947**, 648.



Ad: Adenine

Experimental

Testosterone Dimethyl Phosphate.—Into a solution of testosterone (0.20 g.) and monobromocyanoacetamide (0.11 g.) in 20 ml. of dry ether, trimethyl phosphite (0.08 g.) in 10 ml. of dry ether was stirred drop by drop at −40°C. A white precipitate, cyanoacetamide, separated. The solution was kept at room temperature overnight and then filtered. After the removal of methyl bromide and ether, testosterone dimethyl phosphate was obtained as a colorless crystalline solid weighing 0.17 g. (62%) and melting at 144~149°C. The crude product was recrystallized from ether (m. p. 152°C).

Bornyl Phosphate.—Into a solution of borneol (1.54 g.) and monobromocyanoacetamide (1.63 g.) in 100 ml. of dry ether, tribenzyl phosphite (3.80 g.; purity 80%) was stirred drop by drop at room temperature. The solution was further stirred for 2 hr. and then left to stand overnight. After removal of the ether, the residual material was dissolved in aqueous alcohol (50 ml. of 50%), and the solution was shaken with hydrogen at atmospheric pressure over an Adams palladium oxide catalyst, the theoretical amount of hydrogen for the removal of two benzyl groups being taken up in 100 min. The catalyst was removed by filtration, the solution was evaporated to dryness at 40°C under reduced pressure, and the crude bornyl phosphate (1.40 g., 60%) was recrystallized from benzene-petroleum ether (m. p. 155~156°C), alone and in admixture with an authentic sample.

Adenosine 5'-Phosphate.—To a solution of 2', 3'-isopropylideneadenosine (0.31 g.) and tribenzyl phosphite (0.44 g.; purity 80%) in 15 ml. of anhydrous dimethylformamide, monobromocyanoacetamide (0.33 g.) in 10 ml. of anhydrous dimethylformamide was added drop by drop with shaking at room temperature. The solution was then kept at room temperature for 3 days and the solvent evaporated at 30~35°C under reduced pressure (3~4 mmHg). The residual syrup was dissolved in aqueous alcohol (30 ml. of 50%), and the solution was shaken with hydrogen at atmospheric pressure over an Adams palladium oxide catalyst. The absorption of the hydrogen was rapid, the theoretical amount for the removal of two benzyl groups being taken up in 60 min. After the catalyst had been removed by filtration, the filtrate was evaporated at 30°C under reduced pressure to a faintly yellow syrup. The syrup was dissolved in dilute sulfuric acid (5 ml. of a 0.1 N solution), and the solution was set aside for 2 days to effect the hydrolysis of the isopropylidene residue, The sulfuric acid was neutralized with a calculated amount of barium hydroxide (5 ml. of a 0.1 N solution). Barium sulfate was removed by centrifugation, aqueous ammonia (0.1 N) was added to pH 10, and then a saturated solution of barium chloride was added. The precipitate was collected by centrifugation and washed with two portions (10 ml.) of water. The crude barium salt of adenosine 5'-phosphate was suspended in a small amount of water, and dilute hydrochloric acid (1 N) was added to pH 2. The adenosine 5'-phosphate did not crystallize instantly, but, on standing overnight at 0°C, it separated as needles (0.23 g., 66%) (m. p. 187~190°C). Recrystallized from water, it melted at 191°C; the R_f value was 0.70.* The melting point was not depressed in admixture with natural adenosine 5'-phosphate (m. p. 191~192°C).

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* 5% Na_2HPO_4 aq. solution/isoamyl alcohol: 1.0 cm./0.5 cm.