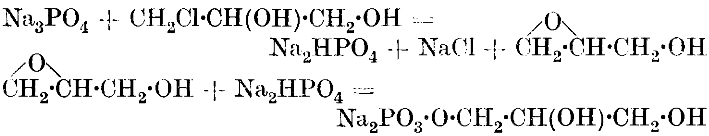
CCLXXXVII.—*The Constitution of the Glycerophosphates.*

By Douglas William Hill and Frank Lee Pyman.

Some years ago King and Pyman (J., 1914, **105**, 1238) synthesised salts of both α- and β-glycerophosphoric acids and showed that the commercial crystalline sodium salt first introduced by Poulenc Frères was sodium β-glycerophosphate. They synthesised calcium α-glycerophosphate by the action of trisodium phosphate upon α-monochlorohydrin and treatment of the product with calcium chloride and represented the reaction by the scheme (1).

(1) $\mathrm{OH\cdot CH_2\cdot CH(OH)\cdot CH_2Cl + (NaO)_3PO \longrightarrow OH\cdot CH_2\cdot CH(OH)\cdot CH_2\cdot O\cdot PO_3Ca}$

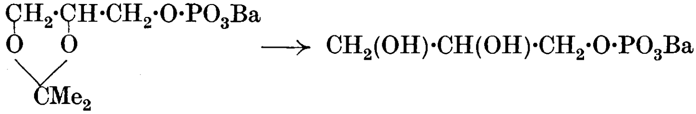
The calcium salt so prepared was well crystallised, forming square leaflets, containing 0·9% H_2O, and had the solubility 1·9% (*i.e.*, grams contained in 100 c.c. of aqueous solution); the corresponding quinine salt became transparent at 153—156°. Later, Bailly (*Compt. rend.*, 1915, **160**, 663) prepared calcium α-glycerophosphate by oxidising sodium allyl phosphate with potassium permanganate and converting the product into the calcium salt; he found the solubility to be 4·95% at 15°. In a later quantitative study (*Compt. rend.*, 1915, **161**, 677) of the interaction of trisodium phosphate and α-monochlorohydrin he found that whilst the reaction proceeds rapidly as regards the formation of sodium chloride and the destruction of trisodium phosphate, which are in molecular agreement throughout, the formation of sodium glycerophosphate takes place much more slowly, and he considered that its formation took place, at least in part, according to equations (2) and (3).



(2) $\mathrm{Na_3PO_4 + CH_2Cl\cdot CH(OH)\cdot CH_2\cdot OH = Na_2HPO_4 + NaCl + \overset{\diagup O \diagdown}{CH_2\cdot CH}\cdot CH_2\cdot OH}$

(3) $\mathrm{\overset{\diagup O \diagdown}{CH_2\cdot CH}\cdot CH_2\cdot OH + Na_2HPO_4 = Na_2PO_3\cdot O\cdot CH_2\cdot CH(OH)\cdot CH_2\cdot OH}$

He found confirmation of this view in the fact that he was able to prepare calcium glycerophosphate from glycide and disodium phosphate, and considered that his results threw doubt on the structure of King and Pyman's α-glycerophosphate, since in his view the addition of disodium phosphate to glycide might yield either the α- or the β-glycerophosphate. As a matter of fact, he found (*Ann. Chim.*, 1916, **6**, 123) that the glycerophosphate from glycide and disodium phosphate gave the reactions of the α-salt intensively. It is conceivable, however, that if the mechanism of the reaction is as Bailly suggests, a small proportion of the β-salt might also be formed, and in this case the calcium α-glycerophosphate of King and Pyman might not be pure. On the other hand, the calcium α-glycerophosphate of King and Pyman is not more, but less soluble in water than that of Bailly, and would therefore appear to be the purer of the two. It is, moreover, not unlikely that a glycerophosphate formed by oxidising an allyl phosphate with permanganate might be contaminated by traces of the corresponding keto-acid or other impurities. The matter thus called for further investigation, and the present authors have now repeated the preparation of calcium α-glycerophosphate by the methods of King and Pyman and of Bailly, and in addition have employed a third method, since described by Fischer and Pfähler (*Ber.*, 1920, **53**, 1606), which is not open to the criticisms applicable to the methods of King and Pyman and of Bailly. This method comprises the formation of barium *iso*propylidene α-glycerophosphate from *iso*propylideneglycerol (of which the constitution was established by Irvine, Macdonald, and Soutar; J., 1915, **107**, 337) and phosphorus oxychloride, followed by hydrolysis of the product with the formation of barium α-glycerophosphate :

(4) 

$$\underset{\underset{CMe_2}{\underbrace{O\quad O}}}{CH_2\cdot CH}\cdot CH_2\cdot O\cdot PO_3Ba \longrightarrow CH_2(OH)\cdot CH(OH)\cdot CH_2\cdot O\cdot PO_3Ba$$

The products prepared by the three methods were converted into the calcium and quinine salts for comparison and it became apparent that the products of King and Pyman and of Fischer and Pfähler were identical and different from that of Bailly. The calcium salts of King and Pyman and of Fischer and Pfähler were indistinguishable in appearance, crystallising in small plates which were almost anhydrous (Found respectively : H_2O, 0·8 and 0·7; in dried salt, Ca, 19·1 and 19·0. Calc. : Ca, 19·1%). The calcium salt of King and Pyman had the solubility 1·8% at 18°, when prepared as described by these authors, but when it was prepared from the barium salt by treatment with sodium carbonate, followed by calcium chloride, the solubility was found to be 2·6% at 18°. The calcium salt similarly prepared from Fischer and Pfähler's barium salt had the solubility 2·5% at 18°. When mixed with quinine hydrochloride, both salts gave a crystalline precipitate of quinine α-glycerophosphate of m. p. 152—153°, which readily gave pure quinine α-glycerophosphate of m. p. 153—154° on crystallisation. The preparation of quinine α-glycerophosphate, m. p. 155°, from Fischer and Pfähler's barium α-glycerophosphate has already been recorded by Karrer and Benz (*Helv. Chim. Acta*, 1926, **9**, 23).

Bailly has stated that when calcium α-glycerophosphate is prepared by the method of King and Pyman, but is precipitated by alcohol instead of by heating an aqueous solution, the product has a solubility of 4·6%. We are unable to confirm this result, the procedure in our hands leading to a calcium α-glycerophosphate containing 1·7% H_2O and of solubility 2·0% at 18°.

The calcium salt prepared by Bailly's method, namely, by the oxidation of sodium allyl phosphate and conversion into the calcium salt, was a white powder of doubtfully crystalline structure. It contained 1 molecule of water of crystallisation (Found: H_2O, 7·0; in dried salt, Ca, 19·1. Calc.: Ca, 19·1%), and its solubility in water was 4·0%. On crystallisation from water it gave a salt of more definitely crystalline structure and of lower solubility. When mixed with quinine hydrochloride, it gave a crystalline deposit of quinine glycerophosphate melting over a wide range, about 135—145°. This salt was difficult to purify, but after several crystallisations from 20% alcohol it gave in 10% yield a quinine salt of m. p. 153—154°. The calcium salt was prepared from the purified quinine salt by adding sodium hydroxide, extracting quinine by means of ether, and adding calcium chloride. It resembled King and Pyman's salt in its solubility (1·8%) and was definitely crystalline, but it contained considerably more water of crystallisation (H_2O, 6·0%). It has been recorded earlier that Bailly was able to prepare a calcium glycerophosphate from the products of interaction of glycide and disodium phosphate. This contained $1H_2O$ and its solubility was 4·7% at 15°.

It appears to us that the conclusions to be drawn from these results are that pure α-glycerophosphates can be prepared by the methods of King and Pyman and of Fischer and Pfähler, and that the characteristics of calcium α-glycerophosphate described by King and Pyman are those of the pure salt. The calcium α-glycerophosphate prepared through the barium salt by the methods of King and Pyman and of Fischer and Pfähler, having a greater solubility (2·6%) than that of King and Pyman, also appears to be a pure salt, judging from its crystalline form and conversion into a homogeneous quinine salt, and we regard it as another modification. For Bailly's calcium α-glycerophosphate containing $1H_2O$ and of much greater solubility (4·95%) there remain the two possibilities (1) that it is a third form of pure calcium α-glycerophosphate, and (2) that it is impure. The character of the quinine salt prepared from it strongly bears out the latter alternative.

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