An X-Ray Examination of Long-chain Alkyl Dihydrogen Phosphates and Dialkyl Hydrogen Phosphates and Their Sodium Salts.

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A series of long-chain alkyl dihydrogen phosphates and one of dialkyl hydrogen phosphates (even members, C_{12}—C_{18}), and their sodium salts, have been prepared, and their *X*-ray spacings determined. The structures of these compounds are discussed.

In view of their relation to the phosphatides, we have examined a series of long-chain alkyl phosphates, even members C_{12}—C_{18}, of which only the hexadecyl have previously been studied. Biehringer (*Ber.*, 1905, **38**, 3974) prepared monohexadecyl dihydrogen phosphate by the action of phosphoric oxide on hexadecanol, a reaction shown later by Cherbuliez and Weniger (*Helv. Chim. Acta*, 1946, **29**, 2006) to yield both mono- and di-esters. Plimmer and Burch (*J.*, 1929, 297) prepared monohexadecyl dihydrogen and an impure dihexadecyl hydrogen phosphate, by the action of phosphoryl chloride on hexadecanol. Christiansen (*J. Biol. Chem.*, 1940, **135**, 399) criticised this work, and pointed out that Plimmer and Burch's method of isolation of the monoester depends on the solubility of the barium salt, which is, in fact, insoluble. As will be seen later, however, Christiansen's method of extraction is not free from criticism.

Investigation of the above methods of preparation shows that both give rise to mixtures of mono- and di-esters, which are difficult to separate. To a certain extent it is possible to direct the phosphoryl chloride reaction by the addition of quinoline or pyridine, which favour mono- and di-ester formation respectively; nevertheless, the products are invariably mixtures.

We have therefore used diphenyl phosphorochloridate and phenyl phosphorodichloridate, and have removed the phenyl groups by catalytic hydrogenolysis (cf. Brigl and Müller, *Ber.*, 1939, **72**, 2121; Van der Neut, Uhlenbroek, and Verkade, *Rec. Trav. chim.*, 1953, **72**, 395). As the latter authors showed, it is important to use an alkali-free catalyst in order to avoid the formation of acid sodium salts of the type, $RO{\cdot}PO(OH)_2,RO{\cdot}PO(OH){\cdot}ONa$. The diphenyl alkyl phosphates are low-melting solids or oils which can be purified by distillation *in vacuo*. When kept for some months they develop an odour of phenol, but they are substantially unchanged after several days' refluxing in 90% acetic acid and the only practicable way of removing the phenyl groups is catalytic hydrogenolysis.

The alkyl dihydrogen phosphates are similar to the fatty acids in solubility and in crystalline appearance, and they melt roughly 10° higher than the fatty acid of the same carbon content. They are dibasic acids, but the completely neutralised sodium salts are easily hydrolysed, and could not be obtained homogeneous enough for *X*-ray examination. Sodium hydrogen salts can be prepared pure, but these also tend to pass into quarter sodium salts.

This unusual type of salt was first described by Wagner-Jauregg and Wildermuth (*Ber.*, 1944, **77**, 481), who crystallised neutral disodium hexadecyl phosphate from acetic acid, and obtained a salt with a Na : P ratio of 1 : 2. Wagner-Jauregg, Lennartz, and Kothay (*Ber.*, 1941, **74**, 1513) had previously prepared quarter sodium salts of cholesteryl dihydrogen phosphate. Rose (*J. Amer. Chem. Soc.*, 1947, **69**, 1384) and Hunter, Roberts, and Kester (*ibid.*, 1948, **70**, 3224) obtained quarter quinoline salts of 1 : 3-phosphatidic acids, and Friedman and Seligman (*ibid.*, 1951, **73**, 5292) showed by infrared examination that the quarter sodium salt of β-naphthyl dihydrogen phosphate was an individual compound and not a mixture of sodium naphthyl hydrogen phosphate and naphthyl dihydrogen phosphate. Van der Neut *et al.* (*loc. cit.*) have characterised quarter sodium salts of the fatty acid esters of ethylene glycol dihydrogen phosphates, and converted them into the sodium-free phosphates by treatment with an ion-exchange resin (Amberlite IR-100H).

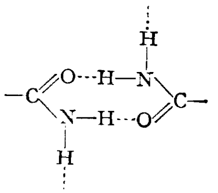
The quarter salts can be prepared by quarter-titrating the alkyl dihydrogen phosphates, by crystallising the sodium hydrogen alkyl phosphates from 90% acetic acid, or by adding a solution of alkyl dihydrogen phosphate to 10% aqueous sodium chloride. The last method is of interest in connection with the work of Christiansen (*loc. cit.*) who, in his preparation of hexadecyl dihydrogen phosphate, added a sodium chloride solution to the latter; this would certainly contaminate his product with the quarter salt. Quarter salts are not readily freed from cations by mineral acids and, in agreement with van der Neut *et al.* (*loc. cit.*), we found that this is best achieved by the use of an ion-exchange resin.

In view of the anomaly in Plimmer and Burch's paper, pointed out by Christiansen (see above), we examined the barium salts, and found that those of the higher alkyl dihydrogen phosphates (C_{12}—C_{18}) are insoluble in water (on the other hand, barium salts of lower members, at least up to C_6, are soluble in cold water, but are precipitated on boiling).

Dialkyl hydrogen phosphates are similar in appearance, and close in m. p., to the monoalkyl esters, from which they are readily distinguished, however, by exhibiting spherulite formations on solidication. They are monobasic, and form only one sodium salt, which is reconverted into the acid by crystallisation from acetic acid. We found no evidence for the existence of an acid salt similar to the quarter salt of the monoalkyl compounds.

X-*Ray Investigation.*—This was carried out as described by Clarkson and Malkin (*J.*, 1934, 666), Cu-K_α radiation, $\lambda = 1{\cdot}54$ Å, being used.

The results are of the expected type, and there is no indication that the presence of the large phosphate group causes any significant change in structure from the monoclinic and orthorhombic forms (tilted and vertical chains, respectively) found for fatty acids and hydrocarbons. In some cases the chains are inclined to the reflecting planes at a smaller angle than is usually found (40—45° compared with an average of about 60° for tilted forms of other long-chain compounds), and this may result merely from the larger size of the phosphate group, or it may be due to the possibility of lateral hydrogen bonding. It is of interest that long-chain fatty acid amides, which are capable of this type of bonding (see inset), are also tilted at the same low angle (44°; unpublished work).



Alkyl dihydrogen phosphates. These exist in two forms, termed A and B, in accordance with the terminology of Piper, Malkin, and Austin (*J.*, 1926, 2310). The B-form, which is the stable form, is obtained from solvents, whilst the A-form, which slowly reverts to the B-form at room temperature, is obtained when the melt solidifies. The long spacings of both forms are linear when plotted against carbon content, and the intercepts at C = 0, which are a measure of the size of the end groups, are 8·3 (A-form) and 7·8 Å (B-form). The results (Table 1) agree with a bimolecular structure $-O{\cdot}PO(OH)_2\ (HO)_2PO{\cdot}O-$ with the long chains tilted across the reflecting planes at angles of 41° (A-form) and 37° (B-form). No difference in m. p. was found for the two forms.

TABLE 1. *Long and short spacings for alkyl dihydrogen phosphates.*

	A-form					B-form		
	Long spacing	Short spacings				Long spacing	Short spacings		
C_{12}	29·0	4·60 w	4·13 s	3·78 s	3·54 w	26·5	4·5 s	4·18 w	3·79 s
C_{14}	32·6	4·64 w	4·14 s	3·79 s	3·53 w	29·5	4·5 s	4·19 w	3·82 s
C_{16}	35·8	4·61 w	4·12 s	3·86 s	3·53 w	32·6	4·52 s	4·14 w	3·76 s
C_{18}	39·3	4·63 w	4·16 s	3·86 s	3·54 w	35·8	4·5 s	4·16 w	3·77 s

s = strong, w = weak, m = moderate, v = very.

Sodium alkyl hydrogen phosphates. The long spacings, plotted against carbon content, are linear, and give an intercept at C = 0 of 9·5 Å. The results (Table 2) agree with a bimolecular structure $-O{\cdot}PO(OH)(ONa)\ (NaO)(HO)PO{\cdot}O-$ with the hydrocarbon chains tilted at an angle of 40° to the reflecting planes.

Quarter sodium salts of alkyl dihydrogen phosphates. The long spacings are linear, with an intercept C = 0 of 9·5 Å. The results (Table 2) agree with a bimolecular structure

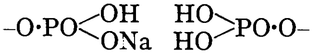
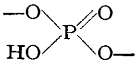
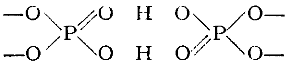

$-\mathrm{O{\cdot}PO}{<}^{\mathrm{OH}}_{\mathrm{ONa}}\ {}^{\mathrm{HO}}_{\mathrm{HO}}{>}\mathrm{PO{\cdot}O}-$ with the hydrocarbon chains tilted at an angle of 56°. The short spacings are quite different from those of either the sodium alkyl hydrogen phosphates or the alkyl dihydrogen phosphates.

TABLE 2. X-*Ray spacings for sodium salts of alkyl dihydrogen phosphates.*

	RO·PO·(OH)ONa						$(\mathrm{RO{\cdot}PO{\cdot}(OH)_2}$ (HO)(NaO)PO·OR)					
	Long spacing	Short spacings					Long spacing	Short spacings				
C_{12}	28·9	5·39 w	4·66 w	4·48 m	3·76 s	3·57 vw	35·2	4·77 w	4·23 s	4·03 vw	3·75 vw	3·57 m
C_{14}	32·6	5·39 w	4·69 w	4·46 m	3·76 s	3·56 vw	39·5	4·81 w	4·19 s	4·07 vw	3·68 vw	3·58 m
C_{16}	36·1	5·34 w	4·59 w	4·44 m	3·8 s	3·62 vw	43·8	4·74 w	4·19 s	4·05 vw	3·81 vw	3·61 m
C_{18}	40·1	5·46 w	4·74 w	4·43 m	3·86 s	3·47 vw	48·2	4·73 w	4·17 s	4·00 vw	3·83 vw	3·61 m

Dialkyl hydrogen phosphates. The long spacings (Table 3) are linear and correspond to molecules tilted at an angle of 45°. The intercept at C = 0 is ≈4 Å, or slightly under a half of that found for the monoalkyl phosphates. This suggests a unimolecular structure (I) rather than the bimolecular structure (II), since the double phosphate end groups, which include hydrogen bonds, could not be accommodated in a length of 4 Å.


(I)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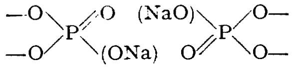

(III)

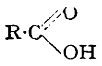
No evidence of polymorphism was observed.

Sodium dialkyl phosphates. The *X*-ray data indicate that these crystallise in double molecules lying vertically across the reflecting planes (*i.e.*, increase in long spacing per carbon atom 1·29 Å, intercept 9 Å) (cf. III).

TABLE 3. X-*Ray spacings for dialkyl hydrogen phosphates and sodium dialkyl phosphates.*

	Long spacing	Short spacings					
		$\mathrm{(RO)_2PO{\cdot}OH}$					
C_{12}	26·3	5·3 vw	4·90 vw	4·5 vs	3·85 s	3·61 m	3·4 vw
C_{14}	30·0	5·27 vw	4·87 vw	4·49 vs	3·80 s	3·61 m	3·4 vw
C_{16}	33·8	5·34 vw	4·89 vw	4·54 vs	3·80 s	3·60 m	3·4 vw
C_{18}	37·4	5·30 vw	4·88 vw	4·51 vs	3·87 s	3·61 m	3·4 vw
		$\mathrm{(RO)_2PO{\cdot}ONa}$					
C_{12}	40·3	6·07 m	5·33 vw	4·86 w	4·49 w	4·12 vs	3·73 vw
C_{14}	45·3	6·10 m	5·32 vw	4·80 w	4·51 w	4·16 vs	3·73 w
C_{16}	50·7	6·16 m	5·35 vw	4·81 w	4·47 w	4·14 vs	3·73 w
C_{18}	55·8	6·19 m	5·39 vw	4·82 w	4·51 w	4·11 vs	3·72 w

As mentioned earlier, the dialkyl phosphates do not form acid salts. This, at first sight, is surprising, particularly in view of the formal resemblance to fatty acids (IV and V) which form unusually stable acid salts (cf. Piper, *J.*, 1929, 231; Malkin, *Ber.*, 1930, **63**, 1807).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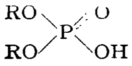
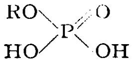
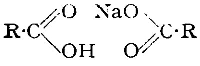

(V)


(VI)


(VII)

It is not easy to explain why (IV) and (VI) should form acid salts of the type (VII), whilst (V) does not. A clue to this anomaly is perhaps to be found from the *X*-ray results. Both fatty acids and their salts, and alkyl dihydrogen phosphates and their monosodium salts, which combine respectively to form acid salts, have the same type of bimolecular structure. On the other hand, dialkyl phosphates and their salts have single and double molecular structures respectively, which presumably make their combination to form acid salts less probable.

EXPERIMENTAL

Hexadecyl Diphenyl Phosphate.—Diphenyl phosphorochloridate (8·0 g., 0·03 mole) was added slowly with shaking to a solution of hexadecan-1-ol (4·8 g., 0·02 mole) in dry pyridine (10 ml.). The flask was stoppered and set aside for 48 hr.; then the contents were poured into ice-cold N-hydrochloric acid (200 ml.). The heavy oil which separated was extracted with ether, and the ethereal layer was washed with N-hydrochloric acid (3 times), 5% sodium hydrogen carbonate (5 times), and water (5 times). After being dried (Na_2SO_4), the ether was removed, and the residue was distilled to give *hexadecyl diphenyl phosphate* (8·1 g., 85%), b. p. 190—195°/10^{-3} mm., m. p. 20—21° (Found: C, 71·1; H, 8·9; P, 6·8. $C_{28}H_{43}O_4P$ requires C, 70·9; H, 9·1; P, 6·6%).

The following were prepared similarly:

Octadecyl diphenyl phosphate (80% yield), b. p. 215—220°/10^{-3} mm., m. p. 31—32° (Found: C, 72·1; H, 9·2; P, 6·5. $C_{30}H_{47}O_4P$ requires C, 71·7; H, 9·4; P, 6·2%).

Diphenyl tetradecyl phosphate (88%), b. p. 190—5°/3 × 10^{-3} mm., m. p. 11—12° (Found: C, 69·7; H, 8·7; P, 7·2. $C_{26}H_{39}O_4P$ requires C, 70·0; H, 8·8; P, 7·0%).

Dodecyl diphenyl phosphate (82%), b. p. 210—215°/10^{-1} mm. m. p. −4° to −3° (Found: C, 68·8; H, 8·3; P, 7·1. $C_{24}H_{35}O_4P$ requires C, 68·9; H, 8·4; P, 7·4%).

Hexadecyl Dihydrogen Phosphate.—A suspension of platinic oxide (Adams) (0·8 g.) in glacial acetic acid (20 ml.) was shaken in hydrogen until absorption ceased (160 ml.; theor., 146 ml.). The catalyst was then well washed with 2N-hydrochloric acid, water, and finally glacial acetic acid, by decantation. Hexadecyl diphenyl phosphate (8 g.) in glacial acetic acid (100 ml.) was added to the catalyst, and the solution was shaken in hydrogen until absorption ceased (5 hr.; uptake 2990 ml.; theor., 3040 ml.). The catalyst was filtered off and washed with chloroform, and the solvents were removed from the filtrate *in vacuo*. The residue, crystallised from light petroleum (b. p. 40—60°), yielded 4·8 g. (90%) of white plates, m. p. 75—76° (Found: C, 59·8; H, 10·9; P, 9·8. Calc. for $C_{16}H_{35}O_4P$: C, 59·7; H, 10·9; P, 9·6%).

Equivalent weights were determined by titration in alcohol with aqueous 0·1N-sodium hydroxide, with bromocresol-purple and phenolphthalein for the first and the second end-point respectively (Found: 326, 165. Theor., 322; 161).

The following were prepared in the same manner:

Octadecyl dihydrogen phosphate (90%), m. p. 83° (Found: C, 61·2; H, 10·8; P, 9·2%; equiv., 353, 174. $C_{18}H_{39}O_4P$ requires C, 61·7; H, 11·2; P, 9·0%; equiv., 350, 175).

Tetradecyl dihydrogen phosphate (81%), m. p. 69° (Found: C, 57·2; H, 10·5; P, 10·8%; equiv., 290, 196. $C_{14}H_{31}O_4P$ requires C, 57·2; H, 10·6; P, 10·6%; equiv., 294, 197).

Dodecyl dihydrogen phosphate (75%), m. p. 59·5° (Found: C, 54·2; H, 10·0; P, 12·1%; equiv., 270, 132. $C_{12}H_{27}O_4P$ requires C, 54·2; H, 10·2; P, 11·7%; equiv., 266, 133).

Sodium Hexadecyl Hydrogen Phosphate.—To a warm solution of hexadecyl dihydrogen phosphate (320 mg., 0·001 mole) in neutral ethanol (15 ml.) was added 0·1N-sodium hydroxide (11 ml.). On cooling, the sodium *salt* separated (320 mg.) as colourless long, thin prisms [Found: C, 55·9; H, 10·0; P, 9·5%; equiv. (phenolphthalein), 345. $C_{16}H_{34}O_4PNa$ requires C, 55·8; H, 9·9; P, 9·0%; equiv., 344]. The following were prepared similarly:

Sodium octadecyl hydrogen phosphate (95%) (Found: C, 58·1; H, 10·2; P, 8·7%; equiv., 375. $C_{18}H_{38}O_4PNa$ requires C, 58·1; H, 10·2; P, 8·4%; equiv., 372).

Sodium tetradecyl hydrogen phosphate (86%) (Found: C, 53·6; H, 9·4; P, 9·7%; equiv., 318. $C_{14}H_{30}O_4PNa$ requires C, 53·2; H, 9·5; P, 9·8%; equiv., 316).

Sodium dodecyl hydrogen phosphate (75%) (Found: C, 49·6; H, 9·2; P, 10·6%; equiv., 280. $C_{12}H_{26}O_4PNa$ requires C, 50·1; H, 9·0; P, 10·8%; equiv., 288).

Quarter Sodium Salt of Hexadecyl Dihydrogen Phosphate.—*Method* 1. To hexadecyl phosphate (0·32 g., 0·001 mole) in warm ethanol (5 ml.) 0·1N-sodium hydroxide (5 ml., 0·0005 mole) was added. On cooling, the quarter sodium salt (0·3 g., 90%) separated as colourless flat prisms (Found: C, 58·0; H, 10·4; P, 9·2%; equiv., 218. $C_{32}H_{69}O_8P_2Na$ requires C, 57·7; H, 10·5; P, 9·8%; equiv., 222).

Method 2. Sodium hexadecyl hydrogen phosphate (0·17 g.) was crystallised twice from aqueous acetic acid (3 ml., 90% acid), yielding 0·12 g. (74%) of the quarter sodium salt (Found: equiv., 219).

Method 3. Hexadecyl dihydrogen phosphate (0·32 g.) was dissolved in ethanol (20 ml.) and the solution was poured into 10% aqueous sodium chloride (50 ml.). The quarter salt separated, and was filtered off and washed with water. Crystallisation from glacial acetic acid afforded 0·25 g. of product of equiv. 225.

X-Ray powder photographs of salts made by all three methods were identical.

The following were made by method 2.

Quarter sodium salt of octadecyl dihydrogen phosphate (94%) (Found : C, 60·2; H, 10·5; P, 8·6%; equiv., 244. $C_{36}H_{77}O_8P_2Na$ requires C, 59·8; H, 10·8; P, 8·6%; equiv., 241.

Quarter sodium salt of tetradecyl dihydrogen phosphate (82%) (Found : C, 55·1; H, 9·9; P, 10·1%; equiv., 203. $C_{28}H_{61}O_8P_2Na$ requires C, 55·1; H, 10·1; P, 10·1%; equiv., 204).

Quarter sodium salt of dodecyl dihydrogen phosphate (72%) (Found : C, 51·7; H, 9·5; P, 11·3%; equiv., 194. $C_{24}H_{53}O_8P_2Na$ requires C, 52·0; H, 9·7; P, 11·2%; equiv., 198).

Conversion of Quarter Sodium Salt of Hexadecyl Dihydrogen Phosphate into Hexadecyl Dihydrogen Phosphate. A solution of the quarter salt (0·5 g.) in warm acetic acid (250 ml.) was diluted to 500 ml. with chloroform and allowed to percolate down a column (60 cm. × 2 cm.) of Amberlite IR-120 resin during 2 hr. The eluant, together with 100 ml. of washings, was concentrated to dryness *in vacuo*, and the residue (0·43 g., 92%), m. p. 75—76°, was shown to be hexadecyl dihydrogen phosphate by its *X*-ray powder photograph.

Didodecyl Hydrogen Phosphate.—Phenyl phosphorodichloridate (4·2 g., 0·02 mole) was added dropwise to a warm solution of dodecan-1-ol (7·4 g., 0·04 mole) in dry pyridine (15 ml.). The solution was kept for 48 hr., after which it was poured into N-hydrochloric acid (200 ml.), and the precipitated oil was extracted with ether. The ethereal solution was washed with N-hydrochloric acid (3 times), 5% sodium hydrogen carbonate (5 times), and water (5 times), and dried (Na_2SO_4). The ether was then removed at 20 mm. and traces of pyridine at 0·5 mm. pressure.

The residual oil (9·9 g.) was dissolved in glacial acetic acid (100 ml.), and after the addition of platinic oxide (Adams; 0·5 g.), the solution was shaken in hydrogen until absorption ceased (3 hr.; 1600 ml.). The catalyst was filtered off and washed with chloroform, and the solvents were removed from the filtrate *in vacuo*. The residue, crystallised from methanol, yielded didodecyl hydrogen phosphate (5·9 g., 70%) as soft white plates, m. p. 59° (Found : C, 66·3; H, 11·7; P, 7·0%; equiv., 432. $C_{24}H_{51}O_4P$ requires C, 66·3; H, 11·8; P, 7·2%; equiv., 435).

The following were prepared identically :

Dioctadecyl hydrogen phosphate (84%), m. p. 82° (Found : C, 71·9; H, 12·4; P, 5·1%; equiv., 599. $C_{36}H_{75}O_4P$ requires C, 71·7; H, 12·6; P, 5·2%; equiv., 603).

Dihexadecyl hydrogen phosphate (80%), m. p. 75° (Found : C, 70·3; H, 12·1; P, 6·1%; equiv., 542. $C_{32}H_{67}O_4P$ requires C, 70·3; H, 12·4; P, 5·7%; equiv., 547).

Ditetradecyl hydrogen phosphate (74%), m. p. 68° (Found : C, 68·8; H, 12·0; P, 6·5%; equiv., 497. $C_{28}H_{59}O_4P$ requires C, 68·4; H, 12·2; P, 6·3%; equiv., 491).

Sodium Dioctadecyl Phosphate. Dioctadecyl phosphate (0·6 g.) was dissolved in warm ethanol (20 ml.), and 0·1N-sodium hydroxide solution (10 ml.) was added. After cooling, the precipitated *sodium salt* was filtered off, and washed with ethanol and ether (yield, 0·58 g.; colourless flakes) (Found : C, 69·0; H, 11·4; P, 4·6. $C_{36}H_{74}O_4PNa$ requires C, 69·2; H, 11·7; P, 4·9%).

The following were made in a similar manner :

Sodium dihexadecyl phosphate (Found : C, 67·4; H, 11·7; P, 5·0. $C_{32}H_{66}O_4PNa$ requires C, 67·6; H, 11·7; P, 5·4%).

Sodium ditetradecyl phosphate (Found : C, 65·3; H, 11·3; P, 6·15. $C_{25}H_{58}O_4PNa$ requires C, 65·5; H, 11·5; P, 6·1%).

Sodium didodecyl phosphate (Found : C, 62·9; H, 11·1; P, 6·9. $C_{24}H_{50}O_4PNa$ requires C, 63·0; H, 11·1; P, 6·8%).

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