5-Benzoyl-2-thiouracils (Table I).—One-tenth mole of the appropriate thiourea was added to 250 ml. of absolute ethanol containing 0.1 mole of sodium ethylate. To this was added 24.8 g. (0.1 mole) of ethyl ethoxymethylenebenzoylacetate.[13] This was set aside for 3 days. The alcohol was partially evaporated, cold water was added and the product precipitated by addition of acetic acid. The 5-benzoyl-2-thiouracils were recrystallized from ethanol.

5-Acetyl-2-thiouracils (Table I).—Two-tenths mole of the thiourea was treated with 30.4 g. (0.2 mole) of ethyl ethoxymethyleneacetoactate[14] and 0.2 mole of sodium ethylate in the manner described in the above paragraph. The resulting 5-acetyl-2-thiouracils were recrystallized from a mixture of ethanol and ethyl acetate.

5-Acetyl-3-β-methoxyethyl-2-methylthio-4(3H)-pyrimidinone.—A solution was made of 11.4 g. (0.05 mole) of 5-acetyl-3 β-methoxyethyl-2-thiouracil in 60 ml. of 2 *N* NaOH. This was stirred and 7.1 g. (0.05 mole) of methyl iodide was added dropwise. After standing for two hours at room temperature, the solid was collected and recrystallized from a mixture of ethyl acetate and light petroleum ether; yield 5 g. (41%), m.p. 94°.

Anal. Calcd. for $C_{10}H_{14}N_2O_3S$: C, 49.58; H, 5.83; N, 11.57. Found: C, 49.91; H, 5.87; N, 11.70.

5-Acetyl-3-isopropyl-2-methylthio-4(3H)-pyrimidinone.—To 100 ml. of methanol was added 21 g. (0.1 mole) of 5-acetyl-3-isopropyl-2-thiouracil, 5.4 g. (0.1 mole) of sodium methylate and 14.1 g. (0.1 mole) of methyl iodide. The solution was allowed to stand for several hours and then evaporated to dryness on the steam-bath. The sodium iodide was separated by the addition of ether. The filtrate was evaporated to yield an oil which crystallized upon standing. This was recrystallized three times from light petroleum ether; yield 12 g. (53%).

(13) L. Panizzi, *Gazz. chim. ital.*, **73**, 13 (1943) [*C. A.*, **39**, 1871 (1945)].

(14) L. Claisen, *Ann.*, **297**, 16 (1897).

Anal. Calcd. for $C_{10}H_{14}N_2O_2S$: N, 13.33. Found: N, 13.57.

5-Carbethoxy-2-methylthio-3-phenyl-4(3H)-pyrimidinone.—To 200 ml. of 2% aqueous sodium hydroxide was added 27.6 g. (0.1 mole) of 5-carbethoxy-3-phenyl-2-thiouracil. The mixture was stirred mechanically and the solid dissolved. To this was added, dropwise, 12.6 g. (0.1 mole) of dimethyl sulfate. After 0.5 hour the product had separated. This solid was collected, dried and recrystallized from ethyl acetate; yield 28 g. (96%), m.p. 128°.

Anal. Calcd. for $C_{14}H_{14}N_2O_3S$: C, 57.93; H, 4.86; N, 9.65. Found: C, 57.76; H, 4.94; N, 9.61.

5-Cyano-3-isopropyl-2-thiouracil.—Five grams of 5-cyano-3-isopropyl-2-thiocytosine was added to 35 ml. of 3 *N* HCl. The acid solution was refluxed for 3 hours. The mixture was cooled and the insoluble 5-cyano-3-isopropyl-2-thiouracil was collected and recrystallized from ethyl alcohol; yield 4 g. (80%), m.p. 84–85°.

Anal. Calcd. for $C_8H_9N_3OS$: C, 49.23; H, 4.65; S, 16.40. Found: C, 48.99; H, 5.14; S, 16.39.

Alkaline Hydrolysis of 5-Carbethoxy-2-thiouracils.—Ten grams of the 5-carbethoxy-2-thiouracil was boiled with 50 ml. of 3 *N* NaOH for 2–4 hours. The cooled solution was filtered and the filtrate acidified with dilute hydrochloric acid. The product was collected and recrystallized from ethanol. The following 5-carboxythiouracils were obtained in yields of 50–75%.

5-Carboxy-3-phenyl-2-thiouracil, m.p. 248° dec. *Anal.* Calcd. for $C_{11}H_8N_2O_3S$: C, 53.23; H, 3.25. Found: C, 53.31; H, 3.45.

5-Carboxy-3-*n*-hexyl-2-thiouracil, m.p. 154°. *Anal.* Calcd. for $C_{11}H_{16}N_2O_3S$: S, 12.52; N, 10.93. Found: S, 12.65; N, 10.72.

INDIANAPOLIS, INDIANA

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY AND SOCONY MOBIL OIL CO., INC., RESEARCH AND DEVELOPMENT LABORATORY]

Disubstituted Phosphine Oxides. III. Addition to α,β-Unsaturated Nitriles and Carbonyl Compounds[1]

BY ROBERT CLAY MILLER,[2] JOHN S. BRADLEY[3] AND LYLE A. HAMILTON

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Two disubstituted phosphine oxides have been added to α,β-unsaturated nitriles, esters, ketones and amides in the presence of traces of sodium ethoxide. Hydrolysis of the nitrile, ester and amide adducts gave 3-disubstituted phosphinylpropionic acids (V). Similar additions to diethyl maleate and hydrolysis gave 1-disubstituted phosphinylsuccinic acids which can be decarboxylated to form V.

Unsymmetrical tertiary phosphine oxides have been prepared by the base-catalyzed addition of two disubstituted phosphine oxides (I) to α,β-unsaturated nitriles, esters, ketones and an amide. Analogous reactions of the structurally similar dialkyl phosphonates (II)[4] have been reported by Pudovik[5] and others.[6] II has been added to α,β-unsaturated nitriles[5a–c,6] esters[5a,b,d–f,6] amides[5e,g] and ketones.[5a,h,6]

While a few of the additions were carried out with di-*n*-octylphosphine oxide (Ia),[7,8] most of the reactions involved a previously unreported analog, dibenzylphosphine oxide (Ib). Because of the greater ease of removal of the less soluble higher melting dibenzylphosphine oxide adducts from the reaction mixture, the yields were higher than for similar di-*n*-octylphosphine oxide addition products. The dibenzylphosphine oxide was prepared

(1) Presented at the Delaware Valley Regional Meeting, Philadelphia, Pa., February 16, 1956. Taken from a dissertation submitted by R. C. M. to the Temple University Graduate Council in partial fullfillment of the requirements for the degree of Doctor of Philosophy.

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(3) Taken from a thesis submitted by J. S. B. to the Department of Chemistry, Temple University, in partial fulfillment of the requirements for the degree of Master of Arts.

(4) The nomenclature of organophosphorus compounds used in this paper follows that outlined in *Chem. Eng. News*, **30**, 4515 (1952).

(5) A few of the many papers by Pudovik and co-workers are as follows: (a) A. N. Pudovik and B. A. Arbuzov, *Doklady Akad. Nauk S.S.S.R.*, **73**, 327 (1950); *C.A.*, **45**, 2853 (1951); (b) *J. Gen. Chem. U.S.S.R.*, **21**, 2035 (1951); (c) A. N. Pudovik and N. I. Plakatina, *Sbornik Statei Obshchei Khim.*, **2**, 831 (1953); *C. A.*, **49**, 6821 (1955); (d) A. N. Pudovik, *Zhur. Obshchei Khim.*, **22**, 1143 (1952); *C. A.*, **47**, 4836 (1953); (e) A. N. Pudovik and D. Kh. Yarmukhametova, *Izvest. Akad. Nauk, S.S.S.R., Otdel. Khim. Nauk*, 721 (1952); *C. A.*, **47**, 10467 (1953); (f) A. N. Pudovik, *ibid.*, 926 (1952); *C. A.*, **47**, 10467 (1953); (g) A. N. Pudovik, *Doklady Akad. Nauk S.S.S.R.*, **85**, 349 (1952); *C. A.*, **47**, 5351 (1953); (h) A. N. Pudovik, *Zhur. Obshchei Khim.*, **22**, 1371 (1952); *C. A.*, **47**, 4837 (1953).

(6) B. Bochwic and J. Michalski, *Nature*, **167**, 1035 (1951).

(7) R. H. Williams and L. A. Hamilton, THIS JOURNAL, **74**, 5418 (1952).

(8) R. H. Williams and L. A. Hamilton, *ibid.*, **77**, 3411 (1955).

by treating benzylmagnesium chloride with di-*n*-butyl phosphonate.

$$3C_6H_5CH_2MgCl + (n\text{-}C_4H_9O)_2P(O)H \xrightarrow[2,\ H^+,\ H_2O]{1,\ Et_2O,\ C_6H_6} (C_6H_5CH_2)_2P(O)H + C_6H_5CH_3 + Mg(OC_4H_9)Cl$$

Ib

Oxidation of Ib with 30% H_2O_2 gave the known dibenzylphosphinic acid, $(C_6H_5CH_2)_2P(O)OH$.

The base-catalyzed addition reactions of I were carried out in the same manner as the dialkyl phosphonate additions to an activated double bond, such as acrylonitrile.

$$(RO)_2P(O)H + CH_2{=}CHCN \xrightarrow[\text{trace RONa}]{ROH} (RO)_2P(O)CH_2CH_2CN$$

II III

An alcoholic solution of I and an activated olefin was treated with catalytic amounts of sodium ethoxide in ethanol. The reactions were moderately exothermic.

$$R_2P(O)H + R'CH{:}CR''Y \xrightarrow[\text{trace EtONa}]{EtOH} R_2P(O)CH(R')CH(R'')Y$$

I IV

R = $C_6H_5CH_2$ (Ib), n-C_8H_{17} (Ia)
R′ = H, CH_3, C_6H_5, $COOC_2H_5$
R″ = H, CH_3
Y = CN, $COOC_2H_5$, $CONH_2$, $COCH_3$, COC_6H_5

The addition products of I and II with α,β-unsaturated nitriles and carbonyl compounds are believed to have similar structures. The phosphinyl group adds to the electropositive β-carbon atom to form a phosphorus-substituted derivative of a propionic acid. Pudovik and Arbuzov[5a] proved that β-attack had occurred in the dialkyl phosphonate case by acid hydrolysis of III to yield 3-dihydroxyphosphinylpropionic acid, $(HO)_2P(O)CH_2CH_2COOH$. The mechanism of the addition reaction of I to an activated olefin is presumed to be similar to that proposed for dialkyl phosphonate additions.[5b] This would involve a base-catalyzed chain mechanism.

$$R_2P(O)H + RONa \longrightarrow R_2P(O)Na + ROH$$

$$R_2P(O)Na + \overset{\delta^+}{C}H_2{=}CH{-}\overset{\delta^-}{C}{\equiv}N \longrightarrow (R_2P(O)CHCHCN)^-Na^+$$

$$(R_2P(O)CH_2CHCN)^-Na^+ + R_2P(O)H \longrightarrow R_2P(O)CH_2CH_2CN + R_2P(O)Na$$

The addition products (IV) containing such reactive Y substituents as ester, amido and nitrile groups have been hydrolyzed with aqueous alkali to the parent carboxylic acids without altering the stable tertiary phosphine oxide linkage.

$$IV \xrightarrow[2,\ H^+]{1,\ H_2O,\ OH^-} R_2P(O)CH(R')CH(R'')COOH$$

V

In this manner, the adducts of Ib with acrylonitrile (VI), ethyl acrylate (VII) and acrylamide (VIII) have been converted to the same carboxylic acid, 3-dibenzylphosphinylpropionic acid. Similarly, 3-di-*n*-octylphosphinylpropionic acid has been obtained by hydrolysis of the adducts of Ia with VI, VII and VIII.

In order to prove that, in the case of phosphine oxide additions, the addition of the phosphinyl group was at the β-carbon atom of the activated olefin rather than at the α-position, Ib was added to diethyl maleate, a symmetrically activated olefin, to form a liquid ester adduct. Hydrolysis of the crude product gave a high-melting dibasic carboxylic acid whose analysis and infrared spectrum is in agreement with that expected of 2-dibenzylphosphinylsuccinic acid (IXb).

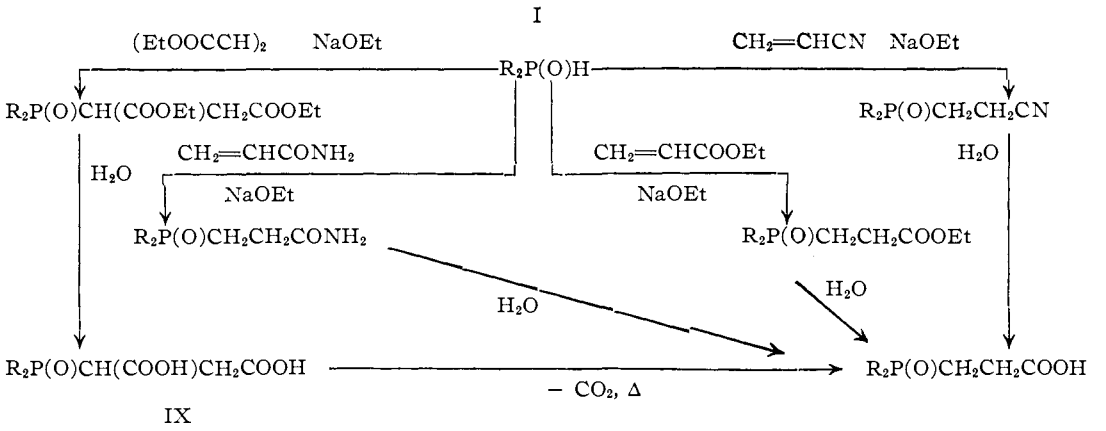
$R_2P(O)CH(COOH)CH_2COOH$ $(HO)_2P(O)CH_2COOH$
R = n-C_8H_{71} (IXa) X
R = $C_6H_5CH_2$ (IXb)

Heating IXb to its melting point resulted in the loss of one mole of carbon dioxide. The similarity of the structure of IX and the easily decarboxylated acetoacetic acid is evident. Furthermore, a phosphorus analog of acetoacetic acid, dihydroxyphosphinylacetic acid (X), was found to lose one equivalent of carbon dioxide when heated to a temperature greater than 200°. Therefore it is not unreasonable to expect IX to undergo a decarboxylation reaction in which the carboxy group attached to the carbon atom bearing the phosphinyl group is eliminated. The decarboxylated product was found to be identical to the hydrolysis product of the adduct of Ib and VII. Hence, the addition of Ib to VII (as well as VI and VIII) must have involved the attack of the phosphinyl group at the β-carbon atom of the activated olefin.

A similar addition of Ia to diethyl maleate followed by hydrolysis gave a dibasic acid IXa. On heating the acid above its melting point, decarboxylation occurred yielding 3-di-*n*-octylphosphinylpropionic acid. The addition of I to α,β-unsaturated esters, amide and nitrile and the conversion to a common carboxylic acid is shown in the chart.

Several unsuccessful attempts to prove β-attack by means of alkylation reactions of alkali salts of I were made. Formation of the potassium salt of Ia followed by treatment with 3-chloropropionitrile failed to yield a product identical to the adduct of Ia and VI. Instead, a high-melting nitrogen-, potassium- and halogen-free organophosphorus compound was obtained whose structure could not be determined. Similarly, the sodium salt of Ib was treated with ethyl 2-bromopropionate. Hydrolysis of the crude product gave an impure acidic material which resisted purification. This mixture may have contained some of the desired acid product as obtained from the hydrolysis of the adduct of Ib and VII.

The additions of Ib to ethyl methacrylate, ethyl crotonate (XI), ethyl cinnamate, methacrylonitrile and 3-butenenitrile (XII) have been similarly carried out, and the hydrolysis products obtained. Several of the carboxylic acids formed have been methylated by means of diazomethane. In the addition involving XII, isomerization of the olefinic bond to form the conjugated isomer apparently occurs prior to the addition reaction. Hydrolysis of this adduct



gives the same acid as obtained from hydrolyzing the adduct of Ib and XI.

$$CH_2{=}CHCH_2CN \underset{\longleftarrow}{\xrightarrow{NaOEt}} CH_3CH{=}CHCN$$

$$R_2P(O)H + CH_3CH{=}CHCN \xrightarrow{NaOEt} R_2P(O)CH(CH_3)CH_2CN$$

A similar base-catalyzed isomerization of XII is reported by Pudovik[5c] prior to the addition reaction with dialkyl phosphonate.

Several base-catalyzed addition reactions of I to α,β-unsaturated ketones also have been made. The addition of Ib to benzalacetone (XIII) and to benzalacetophenone and of Ia to XIII were carried out with the attack occurring at the olefinic linkage. Infrared spectra indicated the absence of olefinic bonds and the presence of a carbonyl linkage. 2,4-Dinitrophenylhydrazones also were prepared.

Experimental

Dibenzylphosphine Oxide.—Several large batches of dibenzylphosphine oxide were prepared according to the method of Williams and Hamilton[7] with minor modifications. A solution of 252.5 g. (1.30 moles) of di-*n*-butyl phosphonate in 1 liter of anhydrous benzene was added over a period of 2 hours to a solution of benzylmagnesium chloride (from 500 g. (3.95 mole) of benzyl chloride, 96.0 g. (3.95 g. atom) of magnesium and 700 ml. of diethyl ether). The stirred, gently refluxing, reaction mixture became very gelatinous toward the end of the addition. The mixture was refluxed on a steam-bath for 30 minutes and then was hydrolyzed with 1500 ml. of 3:1 aqueous H_2SO_4. Two organic layers were obtained which combined upon the addition of 750 ml. of benzene. After the organic layer was washed and evaporated to a volume of 1 liter, 102 g. of white plates, melting at 107.5–109.5°,[9] was obtained. Dilution of the filtrate with 2 liters of *n*-heptane yielded an additional 101 g. of white solid melting at 108–110°. The combined product represents a yield of 68%. Two recrystallizations of 7.0 g. of the combined product from 3:1 *n*-hexane:benzene gave 5.2 g. of white plates, melting at 109.3–110.1°.

Anal. Calcd. for $(C_6H_5CH_2)_2P(O)H$: C, 73.03; H, 6.57; P, 13.5; neut. no., nil. Found: C, 73.32; H, 6.64; P, 13.5; neut. no., 0.8.

Yield values of 65, 69 and 71% were obtained for three other batches, each involving 2–4 moles of benzyl chloride.

Oxidation of a 10-g. sample of dibenzylphosphine oxide by heating on a steam-bath with excess 30% hydrogen peroxide gave 6.8 g. (63.5% yield) of shiny plates of dibenzylphosphinic acid, melting at 189–189.8°. Letts[10] reported a melting point of 192° for this compound.

(9) All melting points uncorrected.

(10) E. A. Letts and R. F. Blake, *J. Chem. Soc.*, **58**, 766 (1890).

Anal. Calcd. for $(C_6H_5CH_2)_2P(O)OH$: P, 12.6; neut. equiv., 246. Found: P, 12.7; neut. equiv., 244.

Addition of Disubstituted Phosphine Oxides to α,β-Unsaturated Nitriles, Esters and an Amide.—A mixture of 0.05 mole of the activated olefin and 0.05 mole of disubstituted phosphine oxide in 25 ml. of absolute ethanol was treated with a few drops of an ethanolic solution of sodium ethoxide (2–6 mole per cent. of the phosphine oxide). The dibenzylphosphine oxide products were formed with a moderate heat evolution, the temperature increasing to 50–60°. The solid products were obtained from the reaction mixture after standing overnight in the refrigerator. The di-*n*-octylphosphine oxide reactions usually were less exothermic, and the mixtures were refluxed for 1–2 hours prior to evaporation of the solvent and recrystallization. The white products were recrystallized from aqueous alcohol (Ib series), and *n*-hexane or *n*-heptane (Ia series). The yields, melting points and analyses are listed in Table I.

The ester, amide and nitrile products were hydrolyzed by refluxing 5–10 g. of the adduct overnight with 4–6 g. of sodium hydroxide in 100–150 ml. of water. Acidification with HCl gave the acid products as white solids. The acids were purified by recrystallization from aqueous alcohol or xylene (acids from Ib) and *n*-hexane (acids from Ia). Table II lists the melting points and analytical data of the acid products.

2-Dibenzylphosphinylsuccinic Acid from Hydrolysis of Dibenzylphosphine Oxide–Diethyl Maleate Adduct.—A solution of 0.015 g. of sodium in 1.5 ml. of absolute ethanol was slowly added to 11.50 g. (0.050 mole) of Ib and 9.00 g. (0.052 mole) of diethyl maleate in 25 ml. of ethanol. The solvent was evaporated, and the uncrystallizable yellow oil was hydrolyzed. After refluxing for 16 hours with 6.0 g. (0.15 mole) of sodium hydroxide in 150 ml. of water, the mixture was acidified with HCl to yield 17.1 g. of a white solid, melting at 216.5–217.5° dec. Recrystallizing twice from 1:1 aqueous alcohol gave 15.9 g. (92% yield) of white powder, melting at 218.0–218.5° dec. The product was dried overnight in a drying pistol (2 mm.) at room temperature, as some decomposition was noted on drying overnight at 100°.

Anal. Calcd. for $(C_6H_5CH_2)_2P(O)CH(COOH)CH_2CO-OH$: P, 9.0; neut. equiv., 173. Found: P, 8.8; neut. equiv., 175.

3-Dibenzylphosphinylpropionic Acid from Decarboxylation of 2-Dibenzylphosphinylsuccinic Acid.—Heating 8.02 g. (0.0231 mole) of 2-dibenzylphosphinylsuccinic acid to its melting point caused the vigorous evolution of carbon dioxide. Cooling yielded 6.85 g. of a yellow glass. Decolorization and crystallization of the glass from 600 ml. of 2:1 aqueous alcohol with charcoal gave 6.30 g. (90% yield) of faintly yellow-tinged needles. Two additional recrystallizations from aqueous alcohol gave white needles, melting at 179.8–180.5°. The melting point was not depressed when mixed with 3-dibenzylphosphinylpropionic acid obtained from the hydrolysis of the adduct of VI, VII or VIII with Ib. Comparison of X-ray diffraction patterns and infrared absorption curves of the two 3-dibenzylphosphinylpropionic acid products showed them to be identical. Treatment of both acid products with an excess of diazomethane in ether gave the same methyl ester, as described in Table I.

TABLE I

ADDITION COMPOUNDS OF DISUBSTITUTED PHOSPHINE OXIDES TO α,β-UNSATURATED NITRILES AND CARBONYL COMPOUNDS, $R_2P(O)CH(R')CH(R'')Y$

R	Substituents R'	R''	Y	Yield, %	M.p., °C.	Phosphorus, % Calcd.	Phosphorus, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sapn. equiv. Calcd.	Sapn. equiv. Found
$C_6H_5CH_2$	H	H	CN	66	109.0–110.0	10.9	10.8	4.9	4.8	..	..
$C_6H_5CH_2$	H	H	$COOCH_3$[a]	60	122.4–123.0	9.8	9.8	..	..	..	..
$C_6H_5CH_2$	H	H	$COOC_2H_5$	78	93.0–93.6	9.4	9.3	..	..	330	331
$C_6H_5CH_2$	H	H	$CONH_2$	90	195.0–195.6	10.3	10.2	4.6	4.5	..	.
$C_6H_5CH_2$	H	CH_3	CN	91	121.5–122.0	10.4	10.5	4.7	4.7	..	..
$C_6H_5CH_2$	CH_3	H	CN	69	93.5–94.1	10.4	10.5	4.7	4.6	..	..
$C_6H_5CH_2$	H	CH_3	$COOC_2H_5$	73	92.7–93.1	9.0	8.9	..	..	344	354
$C_6H_5CH_2$	C_6H_5	H	$COOCH_3$[a]	84	178.2–178.6	7.9	7.9	..	..	..	..
$C_6H_5CH_2$	C_6H_5	H	$COOC_2H_5$	91	138.5–139.0	7.6	7.6	..	..	407	399
$C_6H_5CH_2$	C_6H_5	H	$COCH_3$	70	171.6–172.1	8.2	8.3	..	..	..	..
$C_6H_5CH_2$	C_6H_5	H	COC_6H_5	92	205.6–206.5	7.1	6.9	..	..	..	..
n-C_8H_{17}	H	H	CN	39	53.4–54.2	9.4	9.2	4.3	4.2	..	..
n-C_8H_{17}	H	H	$CONH_2$	27	132.6–133.0	9.0	8.9	4.0	4.0	..	..
n-C_8H_{17}	C_6H_5	H	$COCH_3$	26	62.3–63.0	7.4	7.4	..	..	..	..

[a] Prepared by methylation of the acid with diazomethane.

TABLE II

HYDROLYSIS PRODUCTS OF DISUBSTITUTED PHOSPHINE OXIDE-α,β-UNSATURATED NITRILE, ESTER AND AMIDE ADDUCTS, $R_2P(O)CH(R')CH(R'')COOH$

R	Substituents R'	R''	Yield, %	M.p., °C.	Phosphorus, % Calcd.	Phosphorus, % Found	Neut. equiv. Calcd.	Neut. equiv. Found
$C_6H_5CH_2$	H	H	99[a]	180.6–181.4	10.2	10.2	302	303
$C_6H_5CH_2$	H	CH_3	89[b]	142.5–143.0	9.8	9.7	316	312
$C_6H_5CH_2$	CH_3	H	58[c]	151.0–151.8	9.8	9.8	316	318
$C_6H_5CH_2$	COOH	H	92[c]	218.0–218.5 d.	9.0	8.8	173	175
$C_6H_5CH_2$[e]	C_6H_5	H	85[b]	211.0–212.0[d]	8.2	8.2	378	376
n-C_8H_{17}	H	H	45[c]	81.5–82.1	8.9	8.8	346	347
n-C_8H_{17}	COOH	H	90[c]	97.5–99.0	7.9	7.8	195	197

[a] From hydrolysis of pure nitrile. [b] From hydrolysis of pure ethyl ester. [c] From hydrolysis of crude unreported ethyl ester. [d] If heated slowly. If plunged into a melting point bath heated to 190°, the compound melted, resolidified, and remelted at 210.5–212.0°. [e] Calcd. for $(C_6H_5CH_2)_2P(O)CH(C_6H_5)CH_2COOH$: C, 73.00; H, 6.13. Found: C, 73.05; H, 6.30.

Anal. Calcd. for $(C_6H_5CH_2)_2P(O)CH_2CH_2COOH$: P, 10.2; neut. equiv., 302. Found: P, 10.1; neut. equiv., 302.

A similar addition of di-*n*-octylphosphine oxide to diethyl maleate followed by hydrolysis was carried out to give the analogous 2-di-*n*-octylphosphinylsuccinic acid (see Table II). Decarboxylation gave the same product as obtained by hydrolysis by the adducts of Ia with VI, VII or VIII.

Addition of Disubstituted Phosphine Oxides to α,β-Unsaturated Ketones. 4-Dibenzylphosphinyl-4-phenyl-2-butanone.—A mixture of 11.50 g. (0.050 mole) of Ib and 7.31 g. (0.050 mole) of XIII in 25 ml. of absolute ethanol was treated slowly with a solution of 0.02 g. of sodium in 2 ml. of ethanol. After some evolution of heat, 14.85 g. of a heavy white precipitate was obtained. Two recrystallizations from 2:1 *n*-hexane:benzene mixture gave 13.2 g. (70.1% yield) of long white needles, melting at 171.6–172.1°.

Anal. Calcd. for $(C_6H_5CH_2)_2P(O)CH(C_6H_5)CH_2COCH_3$: C, 76.60; H, 6.69; P, 8.2. Found: C, 76.28; H, 6.65; P, 8.3.

Treatment of 1.42 g. of the adduct with 0.75 g. of 2,4-dinitrophenylhydrazine in 25 ml. of 95% ethanol and 1 ml. of concd. HCl gave 2.00 g. of the yellow dinitrophenylhydrazone, melting at 180–182°. After recrystallization from 3:1 ethanol:ethyl acetate, 1.87 g. of yellow powder was obtained, softening at 146–147° and melting at 181.2–182.0°, if heated slowly in a bath from room temperature. When plunged into a bath heated to 150°, the sample melted momentarily and solidified. Upon further heating, the sample remelted at 181–182°.

Anal. Calcd. for $(C_6H_5CH_2)_2P(O)CH(C_6H_5)CH_2C(CH_3)=NNHC_6H_3(NO_2)_2$: N, 10.1; P, 5.6. Found: N, 9.8; P, 5.5.

4-Di-*n*-octylphosphinyl-4-phenyl-2-butanone.—A solution of 0.20 g. of sodium in 4 ml. of ethanol was added dropwise to a mixture of 15.4 g. of Ia, 8.20 g. of XIII and 25 ml. of ethanol. The solution became light yellow in color, but no noticeable amount of heat was evolved. When refluxed for a few minutes, the mixture became dark red. After evaporation of the ethanol at room temperature, the heavy red oil was diluted with 75 ml. of *n*-hexane. Upon cooling, 8.8 g. of a crude off-white product, melting at 59–62°, was obtained. This was recrystallized four times from *n*-hexane, using charcoal to yield 6.20 g. (26% yield) of white powder, melting at 62.3–63.0°. The infrared spectrum showed strong phosphoryl and carbonyl absorption. No olefinic absorption was detected.

Anal. Calcd. for $(C_8H_{17})_2P(O)CH(C_6H_5)CH_2COCH_3$: P, 7.4. Found: P, 7.4.

Attempted Reaction of the Potassium Salt of Di-*n*-octylphosphine Oxide with 3-Chloropropionitrile.—A solution of 27.4 g. (0.10 mole) of di-*n*-octylphosphine oxide in 200 ml. of anhydrous toluene was refluxed for 20 hours under an atmosphere of nitrogen with 4.13 g. (0.106 g. atom) of potassium. On cooling the cloudy solution, 0.35 g. of unreacted potassium metal was removed. After 9.0 g. (0.10 mole) of 3-chloropropionitrile was added in 50 ml. of toluene, the mixture was refluxed for 3 hours. A cloudy yellow mixture was formed. The mixture was filtered to remove potassium chloride and then evaporated to a volume of 125 ml. on the steam-bath under a stream of nitrogen. A heavy white precipitate formed on cooling. Filtration yielded 14.0 g. of product melting at 145–148°, and a phosphine-smelling filtrate from which no pure product could be isolated. After three recrystallizations from *n*-heptane, 13.1 g. of a

white powder was obtained, melting at 149.5–150.5. This product contained 10.6% phosphorus, but no nitrogen, chlorine or potassium. The infrared spectrum showed strong phosphoryl absorption and nothing else. The structure of this product is unknown.

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The Synthesis of α-D-Glucosamine-1-phosphate and N-Acetyl-α-D-glucosamine-1-phosphate. Enzymatic Formation of Uridine Diphosphoglucosamine[1]

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Procedures for the synthesis of α-D-glucosamine-1-phosphate and N-acetyl-α-D-glucosamine-1-phosphate are described. α-1-Bromo-3,4,6-tri-O-acetylglucosamine hydrobromide was treated with the triethylamine salt of diphenylphosphoric acid. Phenyl groups were cleaved from the resulting diphenyl phosphoric ester and the acetyl groups were removed by treatment with potassium methoxide to give the α-1-phosphoric ester of glucosamine as the crystalline monopotassium salt. N-Acetyl-α-D-glucosamine-1-phosphate is prepared from the dephenylated tri-O-acetyl intermediate by deacetylation under conditions which favor acyl migration from O to N. Some glucosamine-1-phosphate is formed under these conditions and may be separated from the N-acetyl compound with the aid of an ion exchange resin. The N-acetyl-α-glucosamine-1-phosphate is obtained as a crystalline monohydrate of the dipotassium salt. A new nucleotide, uridine diphosphoglucosamine, was formed when synthetic glucosamine-1-phosphate was incubated with uridine triphosphate in the presence of enzyme preparations from rat liver nuclei or from yeast.

The study of biosynthetic reactions involving glucosamine has been hampered by a lack of adequate sources of chemically pure phosphoric esters of this amino sugar. Enzymatically synthesized glucosamine-6-phosphate has been used to establish the enzymatic conversion of the -6-ester to the -1-ester,[2] and the enzymatic acetylation to produce N-acetylglucosamine-6-phosphate.[3] The latter has been shown[4] to be converted to the -1-ester by a specific mutase enzyme. The 1-ester in turn reacts enzymatically with uridine triphosphate to produce uridine diphosphoacetylglucosamine (UDPAG) and inorganic pyrophosphate. Preliminary results indicate that UDPAG may be involved in mucopolysaccharide synthesis[5] but more work, with intermediates of known purity, must be done to establish the pathways involved in the synthesis of this important class of compounds. It is in this area that abundant supplies of synthetic intermediates may be most helpful.

In a previous paper we described the chemical synthesis of D-glucosamine-6-phosphate and N-acetyl-D-glucosamine-6-phosphate.[6] It is the purpose of this paper to describe the chemical synthesis of two other biologically active intermediates, namely, α-D-glucosamine-1-phosphate and N-acetyl-α-D-glucosamine-1-phosphate.

The method of synthesis is indicated in Fig. 1. α-1-Bromo-3,4,6-tri-O-acetylglucosamine hydrobromide[7] was treated with the triethylamine salt of diphenylphosphoric acid. The phosphorylated product, II, was obtained as the crystalline hydrochloride salt. That the reaction yields products of α-configuration was conclusively established by facts to be presented below. After removal of the phenyl groups from II by catalytic hydrogenation, the acetyl groups were cleaved with potassium methoxide and the product was recrystallized as the pure monopotassium salt. It is presumably a zwitterion as depicted in Fig. 1.

N-Acetyl-α-glucosamine-1-phosphate was prepared from II by deacetylation under conditions which favor migration of acetyl groups from O to N. White[8] has shown that N-acetylglucosamine can be formed from tetra-O-acetylglucosamine in ammoniacal methanol. It has been logically assumed[9] that the acetyl group migrates from the 1- to the 2-position. In the present case, the migrating group must come from the 3-, 4- or 6-position and models of the compound in the most probable conformation demonstrate that the acetyl group on carbon atom 3 is in closest juxtaposition with the nitrogen at position 2.

The product obtained by treatment of III with ammoniacal methanol is a mixture of N-acetylglucosamine-1-phosphate and glucosamine-1-phosphate as indicated by paper chromatography, rate of acid hydrolysis and by enzymatic studies. In initial experiments the latter amounted to about 40% of the product. Conducting the hydrogenation at 0° and treating the product with anhydrous ammonia immediately thereafter did not diminish the extent of complete deacetylation. The amount of glucosamine-1-phosphate formed could be reduced to about 20% by the use of greater volumes of methanol as solvent. It is necessary to separate the two phosphoric esters since the ease of crystallization and the purity of the N-acetylglucosamine-1-phosphate are affected by the presence of glucosamine-1-phosphate. Separation of the mixture was accomplished easily with the aid of Dowex-1

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