1-C-Phenyl-1-amino-1-deoxy-*threo*-D-glyceritol Hydrochloride.—A suspension of 10 g. of PbO–$BaSO_4$ in 50 ml. of water was hydrogenated and then mixed with 50 ml. of 2 *N* hydrochloric acid and 12 g. of compound II-T produced from II-T and phenyllithium, and then hydrogenated with shaking. When the absorption of hydrogen reached 1115 ml. (at 15°), hydrogenation was stopped. The catalyst was removed by filtration through activated carbon and the filtrate was concentrated under reduced pressure at 40–50° to give crystals which were recrystallized from ethanol (m.p. 175–180°). Further recrystallization gave 5.6 g. of colorless needles, m.p. 178–179.5°, $[\alpha]D$ −10° (*c* 1, water).

Anal. Calcd. for $C_9H_{14}ClNO_2$: C, 53.02; H, 6.93; N, 6.87. Found: C, 53.18; H, 6.65; N, 7.10.

1-C-phenyl-1-acetylamino-1-deoxy-*threo*-D-glyceritol.—To a cold solution of 5.4 g. of 1-C-phenyl-1-amino-1-deoxy-*threo*-D-glyceritiol hydrochloride was added methanolic sodium methylate (prepared from 0.16 g. of sodium and 30 ml. of methanol) and 2.7 g. of acetic anhydride with cooling. The reaction mixture was set aside for 2 days at room temperature. Crystals obtained by concentrating the reaction mixture under reduced pressure were extracted with hot ethyl acetate. From the ethyl acetate solution, after standing at room temperature, 2.5 g. of colorless needles separated (m.p. 125–127°), and another gram of the same substance was obtained from the mother liquor; $[\alpha]D$ −86° (*c* 0.92, ethanol), R_f 0.73 (1-butanol saturated with water).

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.92; H, 7.41; N, 6.82.

N-Acetyl-D-phenylglycinaldehyde.—To a suspension of 1-C-phenyl-1-acetylamino-1-deoxy-*threo*-D-glyceritol (3.1 g.) in benzene (250 ml.) was added 6.6 g. of lead tetraacetate with stirring. When 10 ml. of acetic acid was added to the mixture, a brown precipitate appeared whose color disappeared after 2.5 hr. The precipitate was filtered and a sirup was obtained by concentration of the filtrate. The sirup gave only one spot of R_f 0.846, different from that of the raw material (R_f 0.73), on the paper chromatogram developed with 1-butanol saturated with water; $[\alpha]D$ −25.4° (*c* 1.06, benzene).

N-Acetyl-D-(−)-phenylglycine.—A mixture of N-acetyl-D-phenylglycinaldehyde (2.62 g.), acetic acid (45 ml.), water (10 ml.), and bromine (0.8 ml.) was stirred at room temperature for 3 hr. After removal of bromine by aeration, the reaction mixture was extracted with a benzene–ethyl acetate mixture. The extract was shown to contain the raw material by its ability to reduce Tollens reagent. The extract (1.5 g.) was reoxidized for 8 hr. by bromine in 60% aqueous acetic acid (120 ml.) in the presence of sodium acetate (3 g.). After aeration, the reaction mixture was extracted with 270 ml. of ethyl actate, and the ethyl acetate solution was concentrated to a sirup (1.1 g). The hot water extract from the sirup was stirred with 70 ml. of cation exchange resin (IR 120) for 5 min. to remove sodium ion. After removal of the resin, the water solution (300 ml.) was concentrated to give crystals. The crystals were dissolved in hot water and, after standing at room temperature, there appeared a small amount of precipitate which had no optical activity. Colorless needles obtained by concentration of the mother liquor had the following physical constants which agreed with those of N-acetyl-D-(−)-phenylglycine.[6]: m.p. 189–191°, $[\alpha]D$ −140° (*c* 0.5, water).

Acknowledgment.—The authors are indebted to the members of the Laboratory of Organic Analysis, Tokyo Institute of Technology, for the microanalyses.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OKLAHOMA STATE UNIVERSITY, STILLWATER, OKLA.]

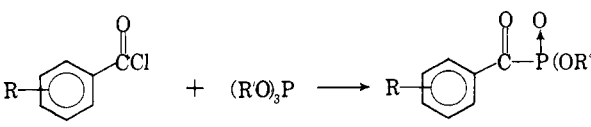
The Reactions of Aroyl Halides with Phosphites. Esters of Aroylphosphonic Acids[1,2]

BY K. DARRELL BERLIN AND H. ANNETTE TAYLOR[3]

RECEIVED MARCH 2, 1964

Esters of aroylphosphonic acids were conveniently synthesized by treatment of phosphites with aroyl chlorides *via* a Michaelis–Arbuzov rearrangement. Infrared and proton magnetic resonance spectral analyses were recorded for all esters and support the proposed structures. Dipole moment measurements and n.m.r. data indicate no preferred conformation for dimethyl benzoylphosphonate, dimethyl *p*-anisoylphosphonate, and dimethyl (*p*-chlorobenzoyl)phosphonate. Carbon–phosphorus bond cleavage in the esters is effected by dilute acid or base, although the reaction is much faster with the latter. Mechanisms are presented for the cleavage processes.

The Michaelis–Arbuzov rearrangement as applied to acyl halides has been largely restricted to phosgene,[4,5] chloroformates,[6] acid halides of fatty acids,[7] acid halides of a few dibasic aliphatic acids,[8] carbamoyl chlorides,[9,10] acetyl chloride,[11,12] and benzoyl chloride.[11,12] We have synthesized a series of disubstituted aroylphosphonates in order to observe the effects of different substituents on the ring and variations in the phosphorus ester groups on the course of the reaction (Table I). The esters obtained (Ia–i) were pale yellow, high-boiling, viscous liquids which were extremely sensitive to moisture and decomposed readily to benzoic acid derivatives and dialkyl hydrogen phosphonates. The reactions are very exothermic and proceed rapidly at room temperature to give homogeneous solutions. Alkyl halides formed *in situ* usually distilled from the reaction flask or were removed by the nitrogen stream used to main-



Ia, R = H, R′ = CH_3
b, R = *p*-OCH_3, R′ = CH_3
c, R = *p*-OCH_3, R′ = C_2H_5
d, R = *p*-OCH_3, R′ = *i*-C_3H_7
e, R = *p*-OCH_3, R′ = C_4H_9
f, R = *p*-OCH_3, R′ = $CH_2CH{=}CH_2$
g, R = *p*-Cl, R′ = CH_3
h, R = *o*-Cl, R′ = CH_3
i, R = *p*-$(CH_3)_3C$, R′ = CH_3

(1) We gratefully acknowledge support by the National Institutes of Health, GM 10367-01. Partial support by the Research Foundation of the Oklahoma State University is also acknowledged.

(2) Presented in part at the Oklahoma Tetrasectional Meeting of the American Chemical Society, Ponca City, Okla., March, 1964.

(3) Abstracted in part from the thesis of H. A. Taylor submitted in partial fulfillment of the requirements for the Master of Science degree at Oklahoma State University, May, 1964.

(4) M. I. Kabachnik and P. A. Rossiiskaya, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 48 (1957); *Chem. Abstr.*, **51**, 10,366 (1957).

(5) A. N. Pudovik and R. N. Platonova, *Zh. Obshch. Khim.*, **29**, 507 (1959); *Chem. Abstr.*, **54**, 254 (1960).

(6) A. E. Arbuzov and A. A. Dunin, *J. Russ. Phys. Chem. Soc.*, **46**, 295 (1914); *Chem. Abstr.*, **8**, 2551 (1914).

(7) B. Ackerman, T. A. Jordan, C. R. Eddy, and D. Swern, *J. Am. Chem. Soc.*, **78**, 4444 (1956).

(8) R. D. Moss, U. S. Patent 3,012,054 (1961); *Chem. Abstr.*, **57**, 4698 (1962).

(9) B. A. Arbuzov and N. I. Rizpolozhenskii, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 847 (1952); *Chem. Abstr.*, **47**, 10,457 (1953).

(10) B. A. Arbuzov and N. I. Rizpolozhenskii, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 854 (1952); *Chem. Abstr.*, **47**, 9903 (1953).

(11) M. I. Kabachnik and P. A. Rossiiskaya, *Bull. Acad. Sci. U.S.S.R., Classe Sci. Chim.*, 364 (1945); *Chem. Abstr.*, **40**, 4688 (1946).

(12) M. I. Kabachnik and P. A. Rossiiskaya, *ibid.*, 597 (1945); *Chem. Abstr.*, **41**, 88 (1947).

TABLE I

PREPARATION OF DIALKYL AROYLPHOSPHONATES

Compound, phosphonate	B.p. °C.	B.p. mm.	Yield, %	Phosphite: acid chloride, moles	Calculated C	Calculated H	Calculated P	Found C	Found H	Found P
Dimethyl benzoyl- (Ia)	146	2.5[a]	81.0	4:3	...	..	...	...	..	...
Dimethyl *p*-anisoyl- (Ib)	170	2.5	61.6	4:3	49.19	5.37	12.68	48.92	5.56	12.55
Diethyl *p*-anisoyl- (Ic)	158	0.4	79.6	4:3	52.94	6.29	11.38	52.89	6.27	11.56
Diisopropyl *p*-anisoyl- (Id)[b]	...	...	..	1:1	...	..	10.32	...	...	10.38
Di-*n*-butyl *p*-anisoyl- (Ie)	175	2	43.9	4:3	58.53	7.68	9.43	58.40	7.61	9.16
Diallyl *p*-anisoyl- (If)[b]	...	...	..	4:3	...	..	...	...	..	...
Dimethyl (*p*-chlorobenzoyl)- (Ig)	136	1.5	57.3	4:3	43.48	4.06	12.46	43.56	4.35	12.26
Dimethyl (*o*-chlorobenzoyl)- (Ih)	102–109	0.1	50.7	4:3	43.48	4.06	12.46	43.25	4.34	12.44
Dimethyl (*p*-*t*-butylbenzoyl)- (Ii)	171–173	1.2	44.4	6:5	57.77	7.09	11.46	57.24	7.00	10.72

[a] Reference 8. [b] Owing to difficulties in purification, the ester was converted to its 2,4-dinitrophenylhydrazone which was analyzed (Table II).

tain anhydrous conditions. Vacuum distillation was only partially successful in providing pure samples of the esters as decomposition was observed in all cases, leaving polymeric tars. In view of the accumulated evidence on the Michaelis–Arbuzov rearrangement,[13] the reaction studied herein appears to follow the classic sequence. Apparently the quasiphosphonium salt is highly unstable and decomposes instantly to give the aroylphosphonate and alkyl halide.

The corresponding 2,4-dinitrophenylhydrazones were easily prepared from each of the liquid esters. Characterization of the solid derivatives was based upon elemental analysis (Table II) and infrared spectra

TABLE II

PREPARATION OF DIALKYL AROYLPHOSPHONATE 2,4-DINITROPHENYLHYDRAZONES

Parent compound, phosphonate	M.p., °C.	Calculated N	Calculated P	Found N	Found P
Dimethyl benzoyl- (Ia)	198–199	14.21	7.86	14.05	7.58
Dimethyl *p*-anisoyl- (Ib)	203–204	13.20	7.30	12.75	6.92
Diethyl *p*-anisoyl- (Ic)	177–178	12.39	6.85	12.13	6.75
Diisopropyl *p*-anisoyl- (Id)	144–146	11.66	6.45	11.61	6.20
Di-*n*-butyl *p*-anisoyl- (Ie)	127–129	11.02	6.09	11.26	5.85
Diallyl *p*-anisoyl- (If)	123–125	11.76	6.50	11.65	6.57
Dimethyl (*p*-chloro- benzoyl)- (Ig)	164–167	13.07	7.22	13.04	7.03
Dimethyl (*o*-chloro- benzoyl)- (Ih)	112–113	13.07	7.22	12.92	7.08
Dimethyl (*p*-butyl- benzoyl)- (Ii)	155–156	12.44	6.88	12.65	6.65

(Table IV), which were quite complex but conspicuously lacked the carbonyl band present in the spectra of the aroylphosphonates. The infrared spectra of ester Ia–i (Table III) showed peaks characteristic of conjugated

TABLE III

INFRARED SPECTRA OF DIALKYL AROYLPHOSPHONATES (CM.$^{-1}$)

Compd.	C=O	P→O	P—O—C	Compd.	C=O	P→O	P—O—C
Ia	1650	1258	1034	If[a]	..	..	..
Ib	1648	1269	1033	Ig	1647	1263	1032
Ic	1650	1264	1025	Ih	1672	1261	1036
Id	1644	1257	998	Ii	1639	1266	1031
Ie	1639	1263	1030				

[a] A pure sample of this compound was not isolated.

carbonyl (1659–1709 cm.$^{-1}$), phosphoryl (1257–1269 cm.$^{-1}$), and the P–O–C– (alkyl) linkage (998–1036

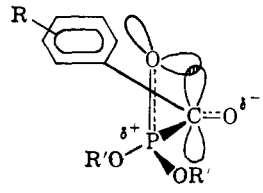
(13) For a summary of important data, see K. D. Berlin, C. Hildebrand A. South, D. M. Hellwege, M. Peterson, E. A. Pier, and J. G. Verkade, *Tetrahedron*, **20**, 323 (1964).

TABLE IV

INFRARED SPECTRA OF DIALKYL AROYLPHOSPHONATE 2,4-DINITROPHENYLHYDRAZONES (CM.$^{-1}$)

Compd.	P→O	P–O–C	Aromatic NO_2	Compd.	P→O	P–O–C	Aromatic NO_2
Ia	1283	1030	1509, 1349	If	1261	1020	1495, 1333
Ib	1285	1033	1503, 1338	Ig	1279	1041	1510, 1340
Ic	1260	1032	1495, 1332	Ih	1253	1010	1503, 1336
Id	1263	1009	1508, 1338	Ii	1280	1041	1509, 1335
Ie	1277	1031	1499, 1336				

cm.$^{-1}$) which approximate those published by Bellamy,[14] by Ketelaar,[15] and by Ackerman.[7] In general, α-diketones are known to show absorption in the range 1710–1730 cm.$^{-1}$ for the carbonyl groups while aryl aldehydes usually exhibit a peak from 1695 to 1715 cm.$^{-1}$.[14] The remarkably low range (1639–1672 cm.$^{-1}$) frequencies for absorption of the carbonyl group in the series of aroylphosphonates (Table III) suggests an alteration in the electronic ground state of the carbon–oxygen bond. It is conceivable that interaction of a filled nonbonding orbital on oxygen of the phosphoryl group with the π-orbital of the carbon atom of the carbonyl group could occur and could result in a shift of the carbonyl stretching frequency to a longer wave length. Molecular models imply, assuming sp^2-hybridization on oxygen of the phosphoryl group, that overlap of the type postulated is probably maximum when the P→O bond is perpendicular to the plane composed of the aryl ring, carbon, and phosphorus.[16]



Proton magnetic resonance spectral studies of phosphorus esters are rare, although P^{31} spectra are plentiful. The phenomenon of P^{31}–H^1 splitting through oxygen was first observed by Axtmann[17] in trialkyl phosphates in 1959. Examination of the trimethyl phosphite spectrum indicates that such splitting also occurs in

(14) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954.

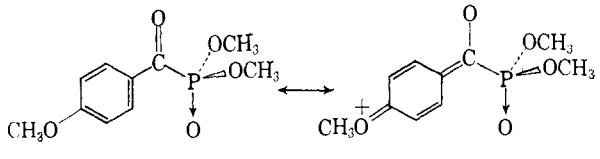
(15) J. A. A. Ketelaar and H. R. Gersmann, *Rec. trav. chim.*, **78**, 190 (1958).

(16) We thank Dr. O. Chapman for bringing this possibility to our attention.

(17) R. C. Axtmann, W. E. Shuler, and J. H. Eberly, *J. Chem. Phys.*, **31**, 850 (1959).

trivalent phosphorus esters. The series of dialkyl aroylphosphonates exhibited doublets in the region of 4.0 δ for the methyl ester protons and similar doubling of the α-protons in the diethyl and diisopropyl esters (Table V). The complexity of the spectrum of di-*n*-butyl *p*-anisoylphosphonate (Ie) prevented evaluation of the doubling. In view of work by Prohaska and Siddall[18,19] concerning splitting of proton resonances in several alkyl esters of phosphorus acids which also contained a phenyl group attached directly to phosphorus, it was expected that perhaps certain protons in the aroylphosphonates would exhibit doubling. The resonance doubling in the organophosphorus compounds studied by Prohaska and Siddall was suggested to be the result of the magnetic anisotropy of the benzene ring whose influence on nearby protons resulted from a preferred conformation in the molecule. The absence of such splitting in the methyl and ethyl esters would seem to indicate that the alkyl ester groups contained equivalent protons.

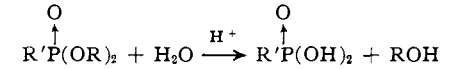
Although models and the n.m.r. spectra suggest free rotation around the C–P bond, certain analogous systems prompt the question of a preferred conformation in the aroylphosphonates. Acyclic α-diketones are suspected to favor an angle of 180° between the carbonyl dipoles.[20] In addition, the Raman spectra of compounds in the bis(dialkylphosphinothioyl) series are consistent for structures with the phosphorothioyl groups opposed.[21] Dipole moment measurements at 25 ± 0.1° in carbon tetrachloride gave values of 2.93 ± 0.05 for Ia, 3.20 ± 0.05 for Ib, and 2.64 ± 0.05 D. for Ig.[22] The moments approximate the values found for a series of carbamoylphosphonates[23] and for a series of dialkyl alkylphosphonates[24] which possess free rotation around the C–P bonds. Interestingly, the dipole moments of benzaldehyde, *p*-anisaldehyde, and *p*-chlorobenzaldehyde have been reported as 2.75, 3.70, and 2.03 D., respectively.[25] The surprisingly lower value of the moment for Ib compared to *p*-anisaldehyde prompts the speculation that the powerful electron-donating ability of the methoxyl function causes an increase in the electronic density on the carbonyl carbon atom. Consequently, the lifetime of the conformation in which



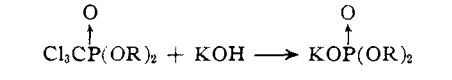
the carbonyl and phosphoryl groups are opposed might increase sufficiently to lower the over-all moment. Apparently the methyl groups are free to rotate and are magnetically equivalent with respect to the aryl group as observed by n.m.r. at 60 Mc.[26]

Interestingly, the dialkyl aroylphosphonates present an opportunity to examine the effect of different substituents in *para*-disubstituted benzene derivatives on the relative chemical shift[27] ν_0 of the two proton groups in these A_2B_2 systems. Richards and Schaefer[28] as well as Cox[29] have shown that chemical shifts in such compounds vary markedly with changes in substituents, but little significance has been assigned to the ν_0 value. In the series of dialkyl *p*-anisoylphosphonates examined, ν_0 was nearly constant (75–78 c.p.s.; Table V). Considerably smaller values occur with the chloro (44 c.p.s.), methyl[30] (51 c.p.s.), and *t*-butyl (40 c.p.s.) groups in the *para* position. No other published spectra on phosphorus compounds are available for comparison, but ν_0 values of 27, 15, and 49 c.p.s. are recorded for *p*-chloroacetophenone,[30,31] *p*-chlorobenzaldehyde,[31] and *p*-methoxybenzoic acid,[31] respectively. The small values shown for *p*-methoxyaniline (3 c.p.s.), *p*-methoxytoluene (15 c.p.s.), and *p*-ethoxyaniline (4 c.p.s.)[31] imply a possible characteristic distinction of *para*-disubstituted compounds with both substituents of the electron-donating type. Carbonyl compounds with a *p*-chloro group fall into a middle range of 15–44 c.p.s. The disubstituted aroylphosphonates and other carbonyl compounds substituted with electron-donating groups appeared to have very high field separation values, ranging from 49 to 78 c.p.s. Whether changes in the π-electron system or the σ-bonds are important is problematical.[32]

Normally, carbon–phosphorus bonds in phosphorus esters are resistant to cleavage *via* alcoholysis or hydrolysis such as with the phosphonates.[33] Prolonged heating under reflux with constant boiling hydrochloric acid suffices for hydrolysis of esters of most phosphonic and



phosphinic acids without risk of breaking the carbon–phosphorus link which is comparable in strength to the carbon–carbon bond. The situation is more favorable under alkaline conditions, however, although the process is most facile when the carbon atom is bonded to powerful electron-withdrawing substituents as shown.[34,35]



Alcoholic sodium hydroxide is reported to cleave the aroylphosphonate II under mild conditions, but no mechanism was postulated.[11] Partial hydrolysis of a

(18) T. H. Siddall and C. A. Prohaska, *J. Am. Chem. Soc.*, **84**, 2502 (1962).

(19) T. H. Siddall and C. A. Prohaska, *ibid.*, **84**, 3467 (1962).

(20) M. S. Newman, Ed., "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 9, p. 450.

(21) P. J. Christen, L. M. Van Der Linde, and F. N. Hooge, *Rec. trav. chim.*, **78**, 161 (1959).

(22) We thank Dr. J. G. Verkade, Department of Chemistry, Iowa State University, for these measurements.

(23) B. A. Arbuzov and T. G. Shavska, *Izvest. Akad. Nauk S.S.S.R. Otdel. Khim. Nauk*, 875 (1952), *Chem. Abstr.*, **47**, 10458 (1953); an average value found was 2.96 D.

(24) B. A. Arbuzov and P. I. Rakov, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 237 (1950); *Chem. Abstr.*, **44**, 8713 (1950).

(25) L. G. Wesson, "Tables of Electric Dipole Moments," The Technology Press, Cambridge, Mass., 1948.

(26) Critical discussions of magnetic nonequivalence are available in the literature; see: E. I. Snyder, *J. Am. Chem. Soc.*, **85**, 2624 (1963), and H. S. Gutosky, *Pure Appl. Chem.*, **7**, 33 (1963).

(27) The relative chemical shift ν_0 is designated to represent the difference in chemical shift of the two proton groups, that is, $\nu_0 = \nu_A - \nu_B$.

(28) R. E. Richards and T. P. Schaefer, *Trans. Faraday Soc.*, **54**, 1280 (1958).

(29) P. F. Cox, *J. Am. Chem. Soc.*, **85**, 380 (1963).

(30) K. D. Berlin and M. Hellwege, unpublished results.

(31) L. F. Bhacca, L. F. Johnson, and J. N. Shoolery, "Nuclear Magnetic Resonance Spectra Catalog," Varian Associates, National Press, 1962.

(32) An attempt to correlate existing data with a molecular orbital description may be helpful and has been promised; see ref. 29.

(33) P. C. Crofts, *Quart. Rev.* (London), **12**, 624 (1960).

(34) I. S. Bengelsdorf, *J. Am. Chem. Soc.*, **77**, 6611 (1955).

(35) It is known that even the thermally stable tertiary phosphine oxides suffer carbon–phosphorus bond cleavage in the presence of strong base at high temperatures. For a review of some of the work in this area, see K. D. Berlin and G. B. Butler, *Chem. Rev.*, **60**, 243 (1960).

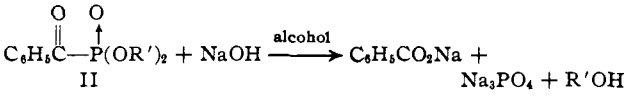
TABLE V

PROTON MAGNETIC RESONANCE SPECTRA OF DIALKYL AROYLPHOSPHONATES (δ)

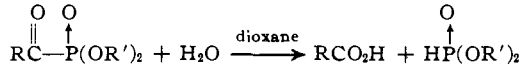
		Ester protons								A_2B_2 aromatic protons		
		H_α			H_β			p-Substituents		Chemical		
Compd.	Type[c]	δ	$J_{H\alpha-H\beta}$	P–H	Type	δ	J_{P-H}	Group	δ	shifts, δ	J_{AB}[d]	ν₀, c.p.s.
Ia	D	3.82	..	11	..	..	..	...	..	...	..	..
Ib	D	3.80	..	11	..	..	..	CH_3O	3.80	6.90, 8.13	9	75
Ic	Q (split)	4.16	7	[a]	T	1.34	7	CH_3O	3.87	6.98, 8.27	9	73
Id	H (split)	4.15	8	[a]	D	1.27	6	CH_3O	3.83	6.90, 8.20	8	78
Ie	[b]	[b]	[b]	[b]	[b]	[b]	[b]	CH_3O	3.82	6.93, 8.22	9	77
Ig	D	3.90	..	11	..	..	..	Cl	..	7.53, 8.25	9	44
Ih	D	3.87	..	11	..	..	..	...	..	...	..	..
Ii	D	3.84	..	11	..	..	..	$(CH_3)_3C$	1.33	7.48, 8.15	9	40

[a] Although splitting was evident, the P^{31}–H^1 coupling constant was not obtained due to overlap of resonance signals. [b] Spectrum too complex and not resolved at 60 Mc. [c] D, doublet; H, heptet; Q, quartet; T, triplet. [d] J_{AB} 

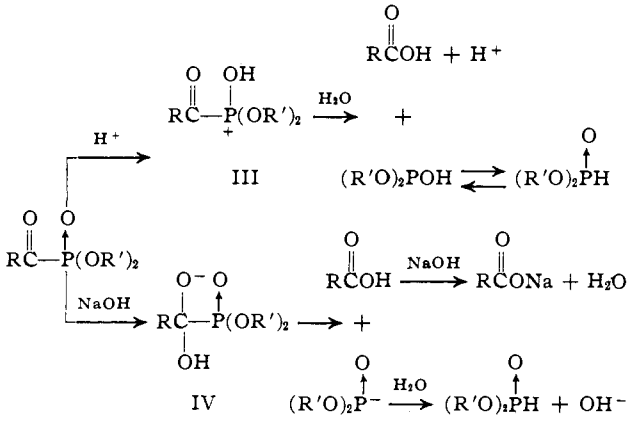
similar ester in aqueous dioxane clearly shows that the carbon–phosphorus linkage is severed in preference



to the phosphorus–oxygen linkage.[36] A comparison



of the acid- and base-catalyzed hydrolysis of Ib indicated the latter reaction to be infinitely more rapid; Ib and aqueous sodium hydroxide mixed at room temperature gave nearly quantitative yields of the insoluble sodium salt of *p*-anisic acid in a few mixtures. In contrast, an acid-catalyzed reaction showed practically no change in composition after stirring 4 hr. at room temperature. From the products previously identified[11] and from our results a mechanism can be postulated for both the acid- and base-catalyzed reactions.



These suggested mechanisms also find analogy in the Aldol-type condensations of dialkyl phosphites with carbonyl compounds already summarized in the literature.[38] The large difference in rate of hydrolysis is difficult to explain. However, in the acid-catalyzed hydrolysis, protonation of the phosphoryl group is probably a highly reversible process since the development of a positive charge on phosphorus attached to a carbonyl function would require considerable energy.[37]

In contrast, creation of IV is reminiscent of the intermediate found in the basis hydrolysis of an ester of a carboxylic acid.[38] Indeed, IV decomposes to the carboxylic acid and a stable anion.

Experimental[39]

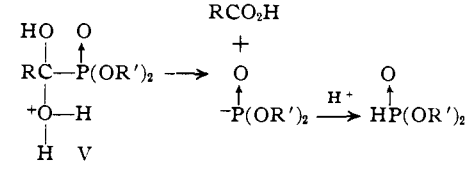
Reagents.—The reagents used were commercial materials and, when necessary, were redistilled before using. Copies of n.m.r. spectra are available from the senior author.

Preparation of *p*-Anisoyl Chloride.—Under anhydrous conditions a mixture of 76.0 g. (0.50 mole) of *p*-anisic acid (m.p. 184°) and 238.0 g. (2.0 moles) of thionyl chloride (b.p. 79° (741 mm.)) was stirred for 2 days at room temperature during which time evolution of hydrogen chloride and sulfur dioxide was observed. After excess thionyl chloride was distilled, the homogeneous reaction mixture was fractionated to yield a colorless product boiling at 255–260° (741 mm.), 79.0 g. (92.6%, lit.[40] b.p. 106–107° (4 mm.)). The freshly distilled product was kept in a desiccator over anhydrous calcium chloride to prevent hydrolysis which was found to occur within 5 min. exposure to the atmosphere. This method gives yields superior to any other reported process.

Preparation of Dialkyl Aroylphosphonates.—The data in Table I were accumulated in experiments performed in essentially the following manner, a modification of that described by Kabachnik.[11] To the acid chloride (0.03 mole) under nitrogen, was added the phosphite (0.04 mole) at such a rate that the temperature of the reaction mixture did not exceed 35°. A yellow color appeared in the solution, and, in the cases of trimethyl or triethyl phosphite, methyl or ethyl chloride was rapidly evolved in the exothermic reaction. The products were purified by vacuum distillation and identified by elemental analyses, infrared spectra (Table III), and n.m.r. spectra (Table V). Exceptional cases occurred with diallyl *p*-anisoylphosphonate (If), which was not distilled, and diisopropyl *p*-anisoylphosphonate (Id), which yielded only *p*-anisic acid upon attempted distillation. Com-

(36) B. Ackerman, T. A. Jordan, C. R. Eddy, and D. Swern, *J. Am. Chem. Soc.*, **78**, 4444 (1956).

(37) An alternative mechanism is also possible, namely, initial protonation of the oxygen atom of the carbonyl function in a slow step. Rapid attack of water on the carbonium ion would be expected to give the species V which could decompose to the benzoic acid derivative and the phosphorus



anion. Rapid protonation of the latter would also be expected.

(38) For a general discussion, see J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 12.

(39) All melting points are corrected. All boiling points are uncorrected. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and Galbraith Laboratories, Knoxville, Tenn. We thank Mr. G. Neuberger for technical assistance in the synthesis of these compounds.

(40) L. M. Yagupol'skii and V. I. Troitskaya, *Zh. Obshch. Khim.*, **27**, 518 (1957); *Chem. Abstr.*, **51**, 15517 (1957).

pound If was identified by characterization of the 2,4-dinitrophenylhydrazone; Id was identified by infrared and n.m.r. spectra taken on the crude compound and characterization of the pure 2,4-dinitrophenylhydrazone.

Preparation of Dialkyl Aroylphosphonate 2,4-Dinitrophenylhydrazones.—The data in Table II were accumulated in experiments performed in essentially the following manner. A stock solution of 2,4-dinitrophenylhydrazine was prepared by placing 6 g. of the reagent (m.p. 198–199°) in 30 ml. of concentrated sulfuric acid and adding this mixture to 40 ml. of water and 140 ml. of 95% ethanol. To 25 ml. of this solution was added 0.5 g. of the dialkyl aroylphosphonate to give a precipitate of the corresponding highly colored 2,4-dinitrophenylhydrazone. Methanol was used to recrystallize all of the derivatives.

Acid Hydrolysis of Dimethyl *p*-Anisoylphosphonate (Ib).—A flask was charged with 2.44 g. (0.01 mole) of Ib and 10 ml. of 0.1 *N* hydrochloric acid. The reaction mixture was stirred for 4 hr. at room temperature without any noticeable change in composition. After stirring for 24 hr. the mixture deposited 1.50 g. (98.7%) of *p*-anisic acid.

Basic Hydrolysis of Dimethyl *p*-Anisoylphosphonate (Ib).—In a system identical with that used for acid hydrolysis was added 2.44 g. (0.01 mole) of Ib and 10 ml. of 0.1 *N* sodium hydroxide. Within 15 min. a heavy white precipitate was observed in the reaction mixture. The solid material was filtered off and the free *p*-anisic acid was regenerated from its sodium salt by treatment with 0.1 *N* hydrochloric acid. The acid (1.43 g., 94.1%) had m.p. 184° after recrystallization from ether.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO 22, CALIF.]

Tertiary Amine Oxide Rearrangements. III. The Mechanism of the Demethylation of Nicotine[1]

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The metal complex catalyzed rearrangement of nicotine N-oxide has been shown, by the combined use of thin layer and gas chromatography, to yield formaldehyde and nicotine, N-methylmyosmine, nornicotine, myosmine, nicotyrine, and cotinine. A simple unified mechanism is capable of rationalizing the formation of these nicotine alkaloids, as well as of all other known metabolites of nicotine.

Nicotine (I) is metabolized in animals and plants to give a variety of products of which only nornicotine (II) may be accounted for by a simple demethylation. Other metabolic products of nicotine include: nicotine 1′-oxide (III) ("oxynicotine"),[3] 3-methylaminopropyl 3′-pyridyl ketone (IV) ("pseudooxynicotine"),[4] 3-nicotinoylpropionic acid (V),[4,5] N-methylmyosmine (VI)[6] (which in aqueous solution is present, by a reversible dehydration–hydration, in equilibrium with IV in the form of its cyclic aminoketal IVa), nicotyrine (VII),[3d,6c,7] γ-3-pyridyl-γ-methylaminobutyric acid (VIII)[8–10] (which cyclizes spontaneously at pH 7 into its lactam cotinine (IX)[11,12]), desmethylcotinine (X),[9,11] γ-3-pyridyl-γ-oxo-N-methylbutyramide (XI),[13] γ-3-pyridyl-γ-hydroxybutyric acid (XII),[14] and myosmine (XIII), a naturally occurring nicotine alkaloid[15] also formed by autoxidation of nicotine.[3d]

In the preceding paper[16] the rearrangement of N-benzyldimethylamine oxides was shown to proceed concurrently along two pathways giving formaldehyde and the appropriate benzaldehyde, in a ratio determined (in the absence of steric factors) by the available α-protons (*i.e.*, adjacent to nitrogen) and by their relative acidities. In the case of nicotine 1′ oxide (III), this rearrangement may occur in the following three possible ways, since three different types of α-proton exist in III: A. Loss of the proton from the N-methyl group, leading to the methylolamine (XIV) known to give formaldehyde and nornicotine (II). Since there are three such protons available, this reaction will have a high statistical probability and is the expected route for N-demethylation. Nicotine-methyl-^{14}C has been found to give radioactive respiratory carbon dioxide *in vivo*,[17] in agreement with the expected conversion of formaldehyde to carbon dioxide *via* formic acid.

B. Another pathway, on the basis of the rearrangement of the N-benzyldimethylamine oxides,[16] is by loss of a proton from the α-position adjacent to the pyridine ring, giving a tertiary hydroxynicotine (IVa), the cyclic ketal of 3-methylaminopropyl 3′-pyridyl ketone (IV). The expected facile dehydration of the tertiary hydroxyl would give the conjugated N-methylmyosmine (VI).

C. Proton removal from the other α-position of the pyrrolidine ring gives a new secondary hydroxynicotine (XV), the cyclic acetal of α-3-pyridyl-γ-methylaminobutyraldehyde (XVa). Ready dehydrogenation of this aldehyde to the acid yields the known γ-3-pyridyl-γ-methylaminobutyric acid (VIII), easily ring closing to form its lactam, cotinine (IX), which may also arise directly from an oxidation or dehydrogenation of the cyclic acetal XV. Nicotine metabolism in rabbit[18] forms a hydroxynicotine with the properties of a cyclized

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