Phosphorus-31 Nuclear Magnetic Resonance Studies on Hydrobromides of Substituted Triarylphosphines and Other Derivatives[1]

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Phosphorus–proton coupling is observed in methylene chloride solutions of tertiary arylphosphine hydrobromides for most of the 18 phosphines examined. Only those phosphines with strong electron-withdrawing groups on the phenyl ring and thus of weaker basicity do not exhibit P–H coupling. Some ^{31}P NMR data are also given for previously unreported secondary phosphines, Ar_2PH; lithium phosphides, $LiPAr_2$; and methylphosphonium salts, $(Ar_3PMe)Br$.

The basicity of trivalent phosphorus compounds toward protons depends on the electronic and steric properties of the groups attached to phosphorus which affects the availability of the lone pair of electrons.[2,3] Thus, trialkylphosphine hydrohalides are fairly stable in water, under mildly acidic conditions,[2] triphenylphosphine hydrobromide can be isolated from ether with anhydrous HBr and Ph_3P,[4] and other triphenylphosphonium salts[5,6] are stable, while much less basic trivalent phosphorus compounds, such as triorganophosphites and phosphorus halides, can only be protonated in very strong acid such as concentrated H_2SO_4,[7] HSO_3F,[8] or HSO_3F–SbF_5.[9] Observation of direct phosphorus–hydrogen spin–spin coupling (generally about 500 Hz) in either the proton or phosphorus-31 NMR spectrum is proof for the protonation of the phosphorus atom.[7-12] However, it has been shown that proton exchange, rapid on the NMR time scale, can result in collapse of the PH doublet in either the ^{31}P or ^1H NMR spectrum and that a more rapid exchange rate is related to the lower basicity of the phosphorus compound.[10] Thus doublet formation is favored by high basicity of the phosphorus, high acidity of the protonating medium, and lower temperatures.[11] The doublet of protonated triphenylphosphine was not observed in the original studies with HBr(g) and CH_2Cl_2 solution,[10] but was observed with concentrated H_2SO_4[7] and HSO_3F[12] solvent. Triphenylphosphine is therefore on the borderline for observation of the PH NMR doublet, depending on the acidity of the protonating medium. Consequently, we have investigated the behavior of 17 triarylphosphines[13] in CH_2Cl_2(HBr) solution by ^{31}P NMR in order to determine the effect of electron-attracting and electron-withdrawing substituents on the protonation of the phosphine.

In addition, some other new derivatives of the tertiary arylphosphines are reported, including 13 methylphosphonium salts, $(Ar_3PMe)Br$; four lithium phosphides, $LiPAr_2$; and four secondary phosphines, Ar_2PH.

Results and Discussion

When anhydrous HBr is bubbled into a solution of a triarylphosphine in diethyl ether, a precipitate of the hydrobromide, $(Ar_3PH)Br$, usually results.[4] Although these hydrobromides are generally very hygroscopic and difficult to analyze and characterize as the solid, they dissolve in CH_2Cl_2 to give solutions which have the same NMR spectra as solutions of Ar_3P in CH_2Cl_2 with HBr(g) added. The triarylphosphines examined in this group fall into four categories (Table I): (a) those which do not form detectable hydrobromides, either as a precipitate from ether/HBr(g) or in CH_2Cl_2/HBr(g) as observed by NMR; (b) those which form hydrobromides but whose NMR spectra do not exhibit P–H doublets, even under extended HBr treatment; (c) those which form hydrobromides without a PH doublet in the NMR spectrum under normal treatment but which do exhibit the doublet under extended HBr treatment; and (d) those whose hydrobromides exhibit the PH NMR doublet under all the conditions examined.

Generally, this order represents the order of increasing basicity as expected from the inductive and mesomeric effects of the substituents on the phenyl ring. The least basic category (a) includes the three trifluoromethyl compounds: $(4\text{-}CF_3C_6H_4)_3P$, $(3\text{-}CF_3C_6H_4)_3P$, and $(2\text{-}CF_3C_6H_4)_3P$. The next category also includes phosphines with electronegative groups, viz., $(3\text{-}ClC_6H_4)_3P$, $(3\text{-}CH_3OC_6H_4)_3P$, $(4\text{-}FC_6H_4)_3P$, and $(4\text{-}ClC_6H_4)_3P$. Although these tertiary phosphines form hydrobromides as indicated by their slight coordination shifts in CH_2Cl_2/HBr solution compared to their chemical shifts in CH_2Cl_2, the expected doublet in the ^{31}P NMR spectrum due to coupling to the acidic proton directly attached to phosphorus is not observed at ambient temperatures owing to exchange which is rapid on the NMR time scale. In a test experiment, the ^1H NMR of $(4\text{-}ClC_6H_4)_3P$ also does not exhibit a proton doublet due to the acidic proton on phosphorus at ambient temperatures. However, at −20 °C the PH doublet is observed (δ 10.7 ppm, $^1J_{PH}$ = 538 Hz). Since the proton has a rather low-field chemical shift, a 1000-Hz sweep width on a 60-MHz instrument must be used to observe the downfield peak (which is about 420 Hz below the phenyl proton region) of the doublet. At −30 °C, the doublet sharpens somewhat over the −20 °C spectrum as expected.

The third category (c) includes $(C_6H_5)_3P$ and $(4\text{-}Me_3SiC_6H_4)_3P$, which are of intermediate basicity based on these findings. In our original work[10] we had not observed a doublet in the case of triphenylphosphine hydrobromide, which was prepared by bubbling anhydrous gaseous hydrogen bromide into a methylene chloride solution of triphenylphosphine for several minutes followed by nitrogen bubbling for 1 min, or by precipitating the hydrobromide from an ether solution of Ph_3P and redissolving the filtered phosphonium salt in CH_2Cl_2. However, reports indicating that Ph_3P in stronger acids[7,12] does, in fact, exhibit the PH doublet prompted us to use extended HBr treatment. Indeed, after about 6 or 7 min of bubbling HBr into the CH_2Cl_2–phosphine solution, the PH doublet is observed in the fuming solution. Presumably, complex anions, such as HBr_2^- and higher analogues,[14] which are less basic than Br^-, are formed under these conditions. It is also noted that the extended treatment of HBr causes the coordination shift to increase for $(Ph_3PH)^+$ and $[(Me_3SiC_6H_4)_3PH]^+$, which is consistent with more complete protonation as observed below. Category d includes most of the triarylphosphines examined. These form hydrobromides which exhibit the PH doublet upon brief HBr treatment of CH_2Cl_2 solutions. Included in this category of more basic triarylphosphines are those with inductively electron-releasing groups such as $4\text{-}(CH_3)_3CC_6H_4$– and $3\text{-}CH_3C_6H_4$– and also the mesomerically electron-releasing groups such as 2- and $4\text{-}CH_3OC_6H_4$–. The presence of only one electron-releasing group is sufficient in certain instances to change the phosphine from category c to d, e.g., both $(2\text{-}CH_3C_6H_4)$ $(C_6H_5)_2P$ and

Table I. ^{31}P NMR Data for Triarylphosphonium Ions

Registry no.	Compd	$\delta_{Ar_3PH^+}$[a]	δ_{Ar_3P}[a]	Δ[b]	$^1J_{PH}$, Hz
61249-01-2	$[(2\text{-}CH_3OC_6H_4)_3PH]^+$	−17.1	−38.5	21.4	542
61249-02-3	$[(2\text{-}CH_3OC_6H_4)_2(C_6H_5)PH]^+$	−9.0	−27.2	18.2	532
61249-03-4	$[(2\text{-}CH_3OC_6H_4)(C_6H_5)_2PH]^+$	−3.8	−16.3	12.5	525
61249-04-5	$[(2\text{-}CH_3C_6H_4)_3PH]^+$	−12.5	−30.0	17.5	515
61249-05-6	$[(2\text{-}CH_3C_6H_4)_2(C_6H_5)PH]^+$	−10.5	−21.4	10.9	508
61249-06-7	$[(2\text{-}CH_3C_6H_4)_2(4\text{-}CH_3C_6H_4)PH]^+$	−11.5	−22.1	10.6	498
61249-07-8	$[(2\text{-}CH_3C_6H_4)(C_6H_5)_2PH]^+$	−5.2	−13.4	8.2	514
61249-08-9	$[(3\text{-}CH_3C_6H_4)_3PH]^+$	−0.3	−5.3	5.0	513
61249-09-0	$[(3\text{-}ClC_6H_4)_3PH]^+$	−7.1	−4.4	−2.7	
61249-10-3	$[(3\text{-}CH_3OC_6H_4)_3PH]^+$	−1.4	−2.1	0.7	
61249-11-4	$[(4\text{-}CH_3C_6H_4)_3PH]^+$	−0.2	−8.0	7.8	517
61249-12-5	$[(4\text{-}CH_3OC_6H_4)_3PH]^+$	−2.3	−10.8	7.9	514
61249-13-6	$[(4\text{-}CH_3SC_6H_4)PH]^+$	−0.7	−8.3	7.6	515
61249-14-7	$\{[4\text{-}(CH_3)_3CC_6H_4]_3PH\}^+$	−1.2	−9.1	7.9	513
61249-15-8	$[(4\text{-}FC_6H_4)_3PH]^+$	−5.5	−9.0	3.5	
61249-16-9	$[(4\text{-}ClC_6H_4)_3PH]^+$	−6.3	−8.5	2.2	
	$[(4\text{-}ClC_6H_4)_3PH]^+$				538[c]
19287-86-6	$[(C_6H_5)_3PH]^+$	−3.1	−6.0	2.9	
	$[(C_6H_5)_3PH]^+$	−1.0	−6.0	5.0	480[d]
61249-17-0	$\{[4\text{-}(CH_3)_3SiC_6H_4]_3PH\}^+$	−4.2	−5.8	1.6	
	$\{[4\text{-}(CH_3)_3SiC_6H_4]_3PH\}^+$	−1.4	−5.8	4.4	514[d]

[a] Negative shifts (ppm) are upfield from 85% H_3PO_4. [b] $\Delta = \delta_{Ar_3PH^+} - \delta_{Ar_3P}$. [c] Observed in the ^1H NMR at −30 °C. [d] Extended HBr treatment of Ar_3P in CH_2Cl_2.

Table II. NMR Data for Methyltriarylphosphonium Bromides

Registry no.	Compd	δ_P, ppm[a]	δ_{CH_3}	$^2J_{PCH}$, Hz
1779-49-3	$[(C_6H_5)_3PCH_3]Br$	22.7		
61249-18-1	$[(4\text{-}FC_6H_4)_3PCH_3]Br$	21.4, 22.6	3.42	13.8
61249-19-2	$[(4\text{-}ClC_6H_4)_3PCH_3]Br$	22.5, 23.5	3.44	14.4
61249-20-5	$[(4\text{-}CH_3C_6H_4)_3PCH_3]Br$	20.2, 21.8	3.11	12.7
61249-21-6	$[(4\text{-}CF_3C_6H_4)_3PCH_3]Br$	23.6, 24.8	3.86	14.1
35369-39-2	$[(4\text{-}CH_3OC_6H_4)_3PCH_3]Br$	18.8, 19.6	3.00	13.4
50376-14-2	$[(3\text{-}CH_3C_6H_4)_3PCH_3]Br$	21.0, 21.9	3.23	13.6
61249-22-7	$[(3\text{-}CF_3C_6H_4)_3PCH_3]Br$	24.6, 25.4	3.50	15.4
61249-23-8	$[(3\text{-}FC_6H_4)_3PCH_3]Br$	22.1, 23.0	3.58	13.5
61249-24-9	$[(2\text{-}CH_3C_6H_4)_3PCH_3]Br$	22.6, 23.0	3.21	12.8
61249-25-0	$[(2\text{-}CH_3OC_6H_4)_3PCH_3]Br$	19.7, 19.3	2.74	15.3
61249-26-1	$[(2\text{-}CH_3C_6H_4)_2(C_6H_5)PCH_3]Br$	21.3, 22.3	3.24	12.9
61259-98-1	$[(2\text{-}CH_3OC_6H_4)_2(C_6H_5)PCH_3]Br$	19.7, 19.9	2.94	14.3
61249-27-2	$[(2\text{-}CH_3C_6H_4)(C_6H_5)_2PCH_3]Br$	21.4, 22.2	3.26	13.3

[a] Positive chemical shifts (ppm) are downfield from 85% H_3PO_4. The first number is in MeOH solution, the second in dimethyl sulfoxide solution. [b] Parts per million downfield from tetramethylsilane.

$(2\text{-}CH_3OC_6H_4)(C_6H_5)_2P$ are in category d whereas $(C_6H_5)_3P$ is not.

The coordination shift, i.e., the chemical shift upon protonation ($\delta_{PR_3H^+} - \delta_{PR_3}$), is positive (downfield) in all cases except one. A slight upfield coordination shift of $(3\text{-}ClC_6H_4)_3P$ in CH_2Cl_2/HBr is not understood but is probably indicative of very slight protonation. Protonation of triorganophosphites also results in upfield shifts.[7] In general, if the coordination shift is less than 4 ppm in this work, the PH doublet is not observed, and when it is more than 4 ppm, the doublet is present. The phosphines containing ortho substituents show a very large coordination shift upon protonation. However, this is probably due to the unusually high field resonance of the ortho-substituted triarylphosphines[15] themselves caused by a large γ effect[13,16] by interaction with the phosphorus lone pair of electrons. This effect is of course largely lost on protonation. Thus the coordination shifts of the ortho-substituted arylphosphines cannot be compared directly with the other compounds. A larger than normal $^1J_{PH}$ is observed in the $[(2\text{-}CH_3OC_6H_4)_n\text{-}(C_6H_5)_{3-n}PH]^+$ (n = 1, 2, or 3) ions. The cause of this is not clear since a noticeable steric effect of the o-methoxy groups would result in larger CPC bond angles with a resulting lower s character in the PH bond and a correspondingly smaller anticipated $^1J_{PH}$.[11]

Quaternary phosphonium salts of 13 of the triarylphosphines were made by reaction with bromomethane. The NMR data are given in Table II. From the ^{31}P chemical shifts, which range from 18.8 to 22.5 for the para-substituted compounds, 21.0 to 24.6 for the meta-substituted, and 19.7 to 22.6 for the ortho-substituted compounds, it is clear that the unusually large "γ" effect in the ortho-substituted arylphosphines is lost on quaternization. This observation strengthens the thesis that the mechanism of large γ effect[13,16] on the chemical shift of phosphines involves electron pair interaction with the γ substituent. Qualitatively, the ^{31}P chemical shifts of the phosphonium salts with the most strongly electron-withdrawing substituents, viz., $[(3\text{-}CF_3C_6H_4)_3PCH_3]Br$ (δ 24.6 ppm) and $[(4\text{-}CF_3C_6H_4)_3PCH_3]Br$ (δ 23.6 ppm), occur at

Table III. ^{31}P NMR Data for $LiPAr_2$ and Ar_2PH

Registry no.	Compd	δ_P, ppm[a]	$^1J_{PH}$, Hz
50416-93-8	$LiP(2\text{-}CH_3C_6H_4)_2$	−39.3	
61249-28-3	$LiP(3\text{-}CH_3C_6H_4)_2$	−23.9	
39952-43-7	$LiP(4\text{-}CH_3C_6H_4)_2$	−27.2	
61249-29-4	$LiP[4\text{-}(CH_3)_3CC_6H_4]_2$	−29.9	
29949-64-2	$HP(2\text{-}CH_3C_6H_4)_2$	−59.1	219
10177-78-3	$HP(3\text{-}CH_3C_6H_4)_2$	−40.3	214
1017-60-3	$HP(4\text{-}CH_3C_6H_4)_2$	−43.0	212
29949-65-3	$HP[4\text{-}(CH_3)_3CC_6H_4]_2$	−43.9	212

[a] Negative shifts are upfield from 85% H_3PO_4. The lithium phosphides are in THF solution; the secondary phosphines are neat liquids.

Table IV. Melting Points and Analytical Data for Methyltriarylphosphonium Bromides

Compd	Mp, °C	Calcd, % C	Calcd, % H	Found, % C	Found, % H
$[(4\text{-}FC_6H_4)_3PCH_3]Br$	315–317	55.10	3.65	55.40	3.76
$[(4\text{-}ClC_6H_4)_3PCH_3]Br$	230–231	49.55	3.28	49.54	3.38
$[(4\text{-}CH_3OC_6H_4)_3PCH_3]Br$	211–213 (214–216)[a]				
$[(4\text{-}CF_3C_6H_4)_3PCH_3]Br$	256–259	47.08	2.69	47.34	2.75
$[(4\text{-}CH_3C_6H_4)_3PCH_3]Br$	219–220 (220.5–221)[a]				
$[(3\text{-}CH_3C_6H_4)_3PCH_3]Br$	204–206	66.17	6.06	65.90	6.22
$[(3\text{-}FC_6H_4)_3PCH_3]Br$	321–330	55.10	3.65	54.94	3.66
$[(3\text{-}CF_3C_6H_4)_3PCH_3]Br$	243–245	47.08	2.69	46.88	2.58
$[(2\text{-}CH_3C_6H_4)_3]Br$	207–209	66.17	6.06	66.46	6.04
$[(2\text{-}CH_3C_6H_4)_2(C_6H_5)PCH_3]Br$	192–194	65.46	5.76	65.26	5.77
$[(2\text{-}CH_3C_6H_4)(C_6H_5)_2PCH_3]Br$	120–122	64.70	5.43	64.93	5.71
$[(2\text{-}CH_3OC_6H_4)_3PCH_3]Br$	227–230 (234–236)[a]				
$[(2\text{-}CH_3OC_6H_4)_2(C_6H_5)PCH_3]Br$	240–243	60.44	5.32	60.70	5.34

[a] G. Wittig, H. D. Weigmann, and M. Schlosser, *Chem. Ber.*, **94**, 676 (1961).

lowest field and the ^{31}P shifts of phosphonium salts with the most strongly electron-releasing substituents, viz., $[(4\text{-}CH_3OC_6H_4)_3PCH_3]Br$ (δ 18.8 ppm) and $[(2\text{-}CH_3OC_6H_4)_3PCH_3]Br$ (δ 19.7 ppm), occur at highest field of the compounds examined. These shifts are in reasonable agreement with other arylphosphonium salts.[17]

Several of the triarylphosphines were cleaved by lithium in tetrahydrofuran to produce the corresponding lithium diarylphosphides[18] in solution. The phosphorus chemical shifts are given in Table III along with ^{31}P data for the respective secondary phosphines, which are formed by hydrolysis of the lithium phosphide solution. In each class of compound, the γ effect on the chemical shift is noted for the $2\text{-}CH_3C_6H_4$– group.

In summary, protonation studies of substituted arylphosphines indicate that the rate of proton exchange on the phosphorus atom can be qualitatively determined by the presence or absence of a PH doublet in either the ^{31}P or ^1H NMR spectrum, and that these observations are related in a sensible way to the basicities of the phosphines. The unusually large γ effect on the ^{31}P chemical shift in ortho-substituted triarylphosphines, diarylphosphines, and lithium diarylphosphides is not observed in the corresponding methyl quaternary phosphonium salts.

Experimental Section

The ^{31}P NMR spectra were measured in 13-mm nonspinning tubes with an 85% H_3PO_4 reference tube (4 mm) fixed concentrically in the larger tube via a serum stopper. A Varian DP60 spectrometer operating at 24.3 MHz was used with calibrations made by the sideband technique. Chemical shifts are accurate to ±0.5 ppm and coupling constants to about ±10 Hz. Proton spectra were recorded on a Varian Associates A-60A with tetramethylsilane as an internal standard. Melting points were obtained on a Mel-Temp melting point apparatus and are uncorrected. Microanalyses were performed by Dr. Franz Kasler, University of Maryland.

The tertiary phosphines were prepared and characterized in earlier work.[1,13] The hydrobromides were prepared by bubbling anhydrous HBr into approximately 30% solutions of the phosphines in CH_2Cl_2 for a few minutes, and then by passing dry N_2 through the solutions for about 1 min. For extended treatment, the HBr was bubbled into the solutions for 6 or 7 min followed by immediate capping of the tube with a serum stopper in order to prevent the fuming solution from losing HBr.

The quaternary phosphonium salts were prepared as described as follows for $[(4\text{-}CF_3C_6H_4)_3PCH_3]Br$. Analytical data and melting points are given in Table IV.

In a 100-ml two-necked flask equipped with a dry ice condenser, nitrogen and gas inlet tubes, and a magnetic stirrer were placed 2.0 g (4.3 mmol) of $(4\text{-}CF_3C_6H_4)_3P$ and 25 ml of benzene. After the condenser was charged with dry ice and acetone, an excess of methyl bromide was allowed to condense into the vigorously stirred solution. The reaction mixture was stirred for 8 h. An oily solid was formed, which after evaporation of the benzene was recrystallized from 2-propanol and diethyl ether. The yield was 1.5 g (62%) of white solid, mp 256–259 °C. Analyses are given in Table IV.

Lithium diarylphosphides and secondary phosphines were prepared as described for $LiP(2\text{-}CH_3C_6H_4)_2$. In a 200-ml flask equipped with a condenser, magnetic stirrer, and N_2-inlet tube were placed 7.6 g (25 mmol) of $(2\text{-}CH_3C_6H_4)_3P$, 0.7 g (0.1 g-atom) of finely cut Li wire, and 50 ml of THF. After stirring at ambient temperature for 1.5 h, the solution had turned dark red. A ^{31}P NMR spectrum of an aliquot showed major peaks at −30.0 (starting material) and −39.8 ppm (product) with a minor peak at −28 ppm (?). After stirring for 30 h, only one peak at −39.4 ppm is observed in solution. This is attributed to the product of cleavage, $LiP(2\text{-}CH_3C_6H_4)$. Hydrolysis of the red solution by deoxygenated aqueous NH_4Cl gave a colorless solution whose ^{31}P NMR spectrum showed a doublet at −59.1 ppm ($^1J_{PH}$ = 219 Hz). Subsequent evaporation of the THF followed by vacuum distillation of the residue yielded a colorless liquid (2.8 g, 52%), bp 104–106 °C (0.1 mmHg). The ^{31}P NMR data for the other phosphides and secondary phosphines are given in Table III.

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Registry No.—RP (R = Ph_3), 603-35-0; RP (R = $(4\text{-}F(C_6H_4)_3$), 18437-78-0; RP (R = $(4\text{-}ClC_6H_4)_3$), 1159-54-2; RP (R = $(4CH_3C_6H_4)_3$), 1038-95-5; RP (R = $(4CF_3C_6H_4)_3$), 13406-29-6; RP (R = $(4\text{-}CH_3OC_6H_4)_3$), 855-38-9; RP (R = $(3\text{-}CH_3C_6H_4)_3$), 6224-63-1; RP (R = $(3\text{-}CF_3C_6H_4)_3$), 25688-46-4; RP (R = $(3\text{-}FC_6H_4)_3$), 23039-94-3; RP (R = $2\text{-}CH_3C_6H_4)_3$), 6163-58-2; RP (R = $(2\text{-}CH_3O\text{-}C_6H_4)_3$), 4731-65-1; RP (R = $(2\text{-}CH_3C_6H_4)_2Ph$), 18803-09-3; RP (R = $(2\text{-}CH_3OC_6H_4)_2$) Ph), 36802-41-2; RP (R = $(2\text{-}CH_3C_6H_4)Ph_2$), 5931-53-3; methyl bromide, 74-83-9; RP (R = $(4\text{-}(CH_3)_3CC_6H_4)_3$), 13716-12-6.

References and Notes

(1) Taken in part from the Ph.D. Dissertation of A. W. Yankowsky, University

of Maryland, 1970.
(2) W. A. Henderson, Jr., and C. A. Streuli, *J. Am. Chem. Soc.*, **82**, 5791 (1960).
(3) H. Goetz and A. Sidhu, *Justus Liebigs Ann. Chem.*, **682**, 71 (1965).
(4) D. Seyferth, S. O. Grim, and T. O. Read, *J. Am. Chem. Soc.*, **83**, 1617 (1961).
(5) J. C. Sheldon and S. Y. Tyree, Jr., *J. Am. Chem. Soc.*, **80**, 2117 (1958).
(6) J. P. Day and L. M. Venanzi, *J. Chem. Soc. A*, 1363 (1966).
(7) W. McFarlane and R. F. M. White, *Chem. Commun.*, 744 (1969).
(8) (a) L. J. Vande Griend and J. G. Verkade, *J. Am. Chem. Soc.*, **97**, 5958 (1975); (b) L. J. Vande Griend and J. G. Verkade, *Phosphorus*, **3**, 13 (1973).
(9) G. A. Olah and C. W. McFarland, *J. Org. Chem.*, **36**, 1374 (1971).
(10) S. O. Grim and W. McFarlane, *Can. J. Chem.*, **46**, 2071 (1968).
(11) L. J. Vande Griend, J. G. Verkade, C. Jongsma, and F. Bickelhaupt, *Phosphorus*, **6**, 131 (1976).
(12) G. A. Olah and C. W. McFarland, *J. Org. Chem.*, **34**, 1832 (1969).
(13) S. O. Grim and A. W. Yankowsky, *Phosphorus Sulfur*, in press.
(14) M. van den Akker and F. Jellinek, *Recl. Trav. Chim. Pays-Bas*, **86**, 275 (1967).
(15) S. O. Grim, A. W. Yankowsky, S. A. Bruno, W. J. Bailey, E. F. Davidoff, and T. J. Marks, *J. Chem. Eng. Data*, **15**, 497 (1970).
(16) L. D. Quin and J. J. Breen, *Org. Mag. Reson.*, **5**, 17 (1973).
(17) H. Goetz, H. Juds, and F. Marschner, *Phosphorus*, **1**, 217 (1972).
(18) (a) D. Wittenberg and H. Gilman, *J. Org. Chem.*, **23**, 1063 (1958); (b) K. Issleib and H. O. Fröhlich, *Z. Naturforsch. B*, **14**, 349 (1959).

Synthesis of β,γ-Unsaturated Amino Acids

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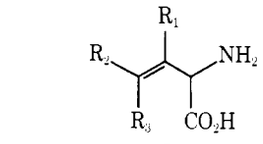
An efficient synthesis and resolution of the β,γ-unsaturated amino acid isodehydrovaline (Ia) is described. The same compound, as its D antipode, was also obtained by a selective degradation of penicillin V. A reasonably efficient synthesis of vinylglycine is reported in detail.

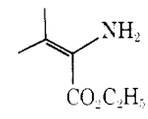
The β,γ-unsaturated amino acids, of the general structure I, are a growing class of natural products. These interesting substances possess potent biological activity,[1] both as enzyme inhibitors[2-4] and as antibiotics.[5] In connection with our interest in penicillin biosynthesis and synthesis[6] we have initiated studies on the synthesis of such compounds and here report these results in detail.

As a synthetic intermediate we required large amounts of the so far unknown substance Ia, which we have called isodehydrovaline, to distinguish it from the well-known α,β isomer, dehydrovaline ethyl ester (II).[7] Substance Ia is closely related to the fungal metabolites β-methylenenorvaline (Ib)[8] and β-methylenenorleucine (Ic).[9] Although a synthesis of Ib has been reported,[8] via a Strecker reaction on α-ethylacrolein, the low yield (0.4%) induced us to investigate alternative routes to Ia. We found that the intermediate in the synthesis of II, methyl α-nitrodimethylacrylate (III),[7] could be efficiently deconjugated by kinetic protonation of the potassium salt IV, yielding the β,γ-unsaturated isomer V, in greater than 90% isolated yield.[10] The success of this deconjugation may reside in the orthogonal and therefore nonconjugated nature of IV, resulting from steric hindrance, as shown in VI. This substance V was smoothly reduced and hydrolyzed in one step with tin and hydrochloric acid to the racemic amino acid Ia (45%). An efficient resolution of this amino acid (Ia) was accomplished by conversion to the chloroacetyl derivative (Schotten–Baumann) and selective deacylation of the L antipode by the use of hog acylase I. A reference sample of the D form of Ia was obtained in a reasonably efficient sequence from penicillin V. Thus conversion of the β-sulfoxide methyl ester of penicillin V, VII, to the known thiazoline VIII by the method of Cooper[11] (treating with trimethyl phosphite), followed by acid-catalyzed conversion to the thiazole IX, yielded thereby a dipeptide containing the intact D-isodehydrovaline unit. Selective hydrolysis of the amide bond was achieved by way of the iminochloride and methanolysis to give the methyl ester of D-isodehydrovaline hydrochloride as X (R = CH_3), which was hydrolysed with aqueous acid to the free amino acid hydrochloride (X, R = H), identical in all respects with that obtained by total synthesis.

A reported synthesis of the naturally occurring parent[12] of this class of β,γ-unsaturated amino acids, vinylglycine (Id),

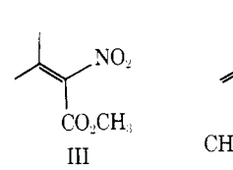


I

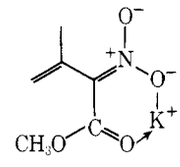


II

Ia, $R_1 = CH_3$; $R_2 = R_3 = H$
b, $R_1 = CH_2CH_3$; $R_2 = R_3 = H$
c, $R_1 = CH_2CH_2CH_3$; $R_2 = R_3 = H$
d, $R_1 = R_2 = R_3 = H$



III



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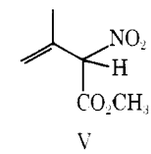

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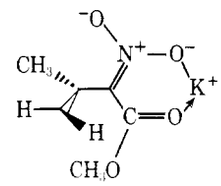
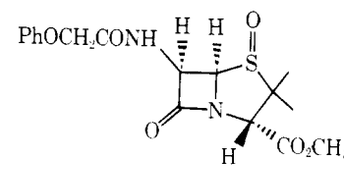
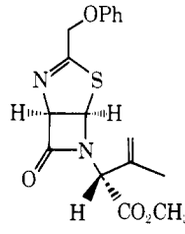


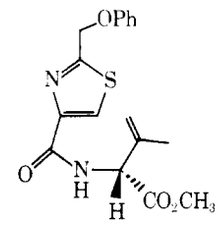
VI



VII



VIII



IX

has proceeded in only modest yield.[1,4,13] We developed a more efficient route to the racemic Id which we report here. Thus 2-hydroxy-3-butenoic acid (XI), readily obtained from acrolein cyanohydrin,[14] was converted (phosphorus tribromide) to the α-bromoacyl bromide (XII, R = Br) which was hydro-