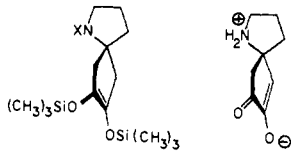
bromotrimethylsilane) to distill at low temperature, leaving a tan solid. To the residue dissolved in absolute ethyl alcohol at 0° was added a solution of excess (sixfold) diazomethane in methylene chloride. The crude product was a mixture of **6**, the *N*-methyl derivative of **6** (10:1 ratio, respectively), and products related to chlorotrimethylsilane (^{1}H nmr absorption at δ 0.0–0.2).[13] The crude product (*ca.* 60% yield of **6**)

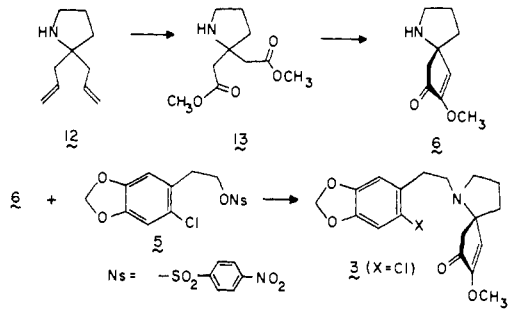


i, X = $-Si(CH_3)_3$ iii

ii, X = H

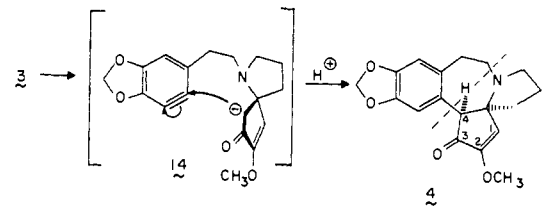
could be used in the next step without loss of efficiency: column chromatography (20% water on neutral alumina) afforded pure **6** in 45–55% yield; ^{1}H nmr ($CDCl_3$) δ 1.7–2.0 (m, CH_2CH_2 in pyrrolidine ring), 2.30 (s, NH), 2.46 (s, CH_2CO), 2.9–3.2 (m, CH_2N), 3.68 (s, CO_2CH_3); ir (neat) 1630, 1725 cm^{-1}; mass spectral mol wt, 157; mp of 3,5-dinitrobenzamide, 236.5–237° dec.

In the presence of diisopropylethylamine in acetonitrile at 55° for 12–15 hr, intermediates **5** and **6** reacted to produce the tertiary amine **3** (X = Cl), in 65–87% yield: mp 109.9–110.7°; ^{1}H nmr ($CDCl_3$) δ 1.8–2.1 (m, CH_2CH_2 in pyrrolidine ring), 2.30 (AB qt, J = 14 Hz, CH_2CO), 2.5–3.1 (br m, 6 H), 3.67 (s, OCH_3), 5.88 (s, OCH_2O), 5.92 (s, C=CH), 6.61 (s, aryl H), 6.72 (s, aryl H); mass spectral mol wt, 349. *Anal.* Found: C, 61.77; H, 5.68; N, 3.96; Cl, 10.32.



Ns = $-SO_2-C_6H_4-NO_2$

Compound **3** (X = Cl) and related derivatives (X = F, Br, I, H) are potentially very versatile intermediates in the synthesis of cephalotaxine (**2**) and cephalotaxinone (**4**). Suitable modification of the functional groups in the cyclopentenone ring of **3** should allow several fundamentally different approaches for the ring closure to give **4** (or **2**). The most direct approach, requiring no functional group protection or modification, is based on the reaction of nucleophiles with benzyne derivatives; this concept has been used with moderate success in numerous simple intramolecular examples[14] but not, to our knowledge, in natural product synthesis. The reaction of **3** (X = Cl) with potassium triphenylmethide (twofold excess) in 1,2-dimethoxyethane at 50° for 2 hr produced (±)-cephalotaxinone (**4**), identical in ir, ^{1}H nmr, and tlc behavior with natural (−)-cephalotaxinone.[15] The yield, after isolation by preparative layer chromatography, was 13–16%. A parallel series of experiments on **3** (X = Br) and **3** (X = I) afforded, at best, similar yields of **4**. The epimer of **4** (at C-4) was not isolated, consistent with inspection of models which indicates that **4** is the more stable isomer and with the expectation that proton exchange at C-4 occurs readily during the reaction and isolation procedures. Even with the present low yield in the ring closure to give **4**, the convergent plan and short sequences allow the preparation of 8–9 g of cephalotaxinone from 100 g of pyrrolidone and from *ca.* 75 g of piperonal.



Reduction of synthetic cephalotaxinone with diisobutylaluminum hydride[16] in benzene for 1 hr at 25° afforded a single product, (±)-cephalotaxine (**2**), identical in ^{1}H nmr, ir, and tlc behavior with (−)-cephalotaxine of natural origin.

Further work is under way to improve the efficiency of the conversion **3** → **4**, so as to provide a truly practical synthesis of cephalotaxine and harringtonine.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (AI-08687).

(13) An alternate series of operations for the conversion **13** → **6** revealed the intermediates. After filtering the crude mixture from the reaction with sodium–potassium alloy, the benzene was removed at reduced pressure to leave a colorless oil containing mainly i (tentatively identified by ^{1}H nmr) which was selectively hydrolyzed with wet ether at 25° to give ii (^{1}H nmr). Addition of bromine to ii in methylene chloride at −78° followed by warming to 25° gave a tan solid, identified as the zwitterion iii by ^{1}H nmr (DMSO-d_6, D_2O) and solubility properties (insoluble in acetonitrile and tetrahydrofuran, soluble in water). Diazomethane reacted with iii to give **6** containing 10% of the *N*-methyl derivative of **6**. The yields are somewhat lower than from the procedure outlined in the discussion, and the operations are more cumbersome.

(14) R. W. Hoffman, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967.

(15) We are indebted to Mr. R. G. Powell of the United States Department of Agriculture, Peoria, Ill., for a generous gift of the natural material.

(16) The use of diisobutylaluminum hydride for this reduction was suggested by Professor R. H. Schlessinger (University of Rochester) based on his studies with material of natural origin.

(17) National Institutes of Health Postdoctoral Fellow, 1972.

(18) National Science Foundation Undergraduate Research Participant, 1971.

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^{1}H and ^{31}P Nuclear Magnetic Resonance Evidence for the Existence of 1,2-Diphenyldiphosphine in Equilibrium with Phenylphosphine and Pentaphenylcyclopentaphosphine

Sir:

Compared with the large number of tetrasubstituted derivatives of diphosphine, P_2H_4, which have been isolated in the last 10 years,[1] only a few derivatives bearing

(1) A. H. Cowley, *Chem. Rev.*, **65**, 617 (1965); E. Fluck, "Preparative Inorganic Reactions," Vol. 5, Interscience, New York, N. Y., 1968, pp 103–156.

still one or more P–H functionality have been described.[2] In particular, the sole representative of the class of disecondary diphosphines R(H)PP(H)R is 1,2-bis(trifluoromethyl)diphosphine[2a] which was isolated from the hydrolysis products of tetrakis(trifluoromethyl)cyclotetraphosphine, $(CF_3P)_4$. The formation of 1,2-diphenyldiphosphine (I), through a metal–halogen exchange reaction (eq 1), has been asserted,[3] but

$$2C_6H_5PHK + BrCH_2CH_2Br \longrightarrow C_6H_5(H)PP(H)C_6H_5 + 2KBr + CH_2CH_2 \quad (1)$$
$$\text{I}$$

further investigations in this field[4] showed that reaction 1 actually follows a different course to give as main products $(C_6H_5P)_5$, $C_6H_5PH_2$, KBr, and CH_2CH_2. The previously postulated product I was in fact neither isolated nor detected.

We wish to report here nmr evidence for the existence of I in equilibrium with its dismutation products, phenylphosphine, $C_6H_5PH_2$, and pentaphenylcyclopentaphosphine, $(C_6H_5P)_5$, prepared by a different means.

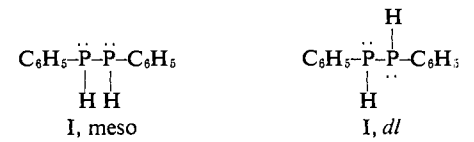
Typically a sealed evacuated nmr sample tube containing 108 mg (0.2 mmol) of $(C_6H_5P)_5$,[5] 110 mg (1 mmol) of $C_6H_5PH_2$, and 0.5 ml of deuterated pyridine with a small amount of TMS was heated for 2 days at 100°. The 100-MHz ^1H nmr spectrum of the resulting mixture was found to be insensitive to further heating and long-term storage. The ^1H nmr spectra (60, 100, 250 MHz; δ downfield from internal TMS) of this sample show an intense doublet (δ 3.89 ppm, J = 200 Hz) for $C_6H_5PH_2$, a complicated pattern (δ 6.5–8.5 ppm) for the aromatic proton resonance, and two symmetrical sets of lines centered respectively on δ_{Ia} 4.37 ppm and δ_{Ib} 4.35 ppm. Each set is the AA′ part of an AA′XX′ system[6] with the following spin coupling parameters: N_1 = 218.6, L_1 = 193.4, K_1 = 196.3, M_1 = 186.7 Hz and N_2 = 218.2, L_2 = 198.2, K_2 = 202.5, M_2 = 179.1 Hz. The ^{31}P nmr spectra (24.3 and 40.5 MHz; δ upfield from external H_3PO_4) show a 1:2:1 triplet (δ +122 ppm, J = 200 Hz) for $C_6H_5PH_2$,[7] a broad peak (δ +4 ppm) attributable to $(C_6H_5P)_5$,[5] and two symmetrical patterns centered on δ'_{Ia} +66 ppm and δ'_{Ib} +70 ppm; the lines of these patterns are somewhat broadened by small unresolved spin couplings but nevertheless they fit correctly with the AA′XX′ systems calculated with the N, K, L, and M values observed in the ^1H nmr spectra. The relationship between the ^{31}P sets (XX′) and the ^1H sets (AA′) was definitively established by (^{31}P) ^1H double resonance experiments. On raising the temperature, the AA′ patterns in the 100-MHz ^1H spectra broaden and coalesce reversibly into a single AA′ pattern, without any loss of the spin coupling information up to 180°; using the coalescence temperature method (T_c = 150 ± 5°, observed on the N doublets) an approximate value of 22 kcal/mol is obtained for $\Delta G^{\ddagger}$ for the rate process involved.

Considering this temperature dependence and the nmr spin coupling constants extracted from the N, K, L, and M parameters (see Table I), we attribute the observed AA′XX′ patterns to the diastereomeric modifications meso and *dl* of the diphosphine I.[8]

Table I. Nmr Coupling Constants[a] in the Diastereomers of 1,2-Diphenyldiphosphine

	$^1J_{PH}$ (J_{AX})[b]	$^2J_{PH}$ ($J_{AX'}$)[b]	$^1J_{PP}$ ($J_{XX'}$)	$^3J_{HH}$ ($J_{AA'}$)
Ia	+206	+12.6	191.5	4.8
Ib	+208.2	+10	190.8	11.7

[a] Uncertainty, ±0.5 Hz. [b] The absolute signs are given assuming that $^1J_{PH}$ is positive.



I, meso

I, *dl*

It should be noted that the $\Delta G^{\ddagger}$ value observed for the interconversion of Ia and Ib is close to the values ($\Delta G^{\ddagger}$ = 22 to 24 kcal/mol) reported for the inversion–rotation process in di(tertiary diphosphines).[9] The coupling constants of Table I should be compared to the parent ones reported for P_2H_4,[10] $(CH_3)_2PP(CH_3)_2$,[11] and $C_6H_5(CH_3)PP(CH_3)C_6H_5$.[12] Particularly noteworthy is the near coincidence of the $^1J_{PP}$ values in Ia and Ib, in light of recent theoretical[13a] and experimental[11,13b] data on the rotational dependence of this coupling constant.

We failed to isolate I in pure form through the usual separation techniques, all the attempts resulting in the recovery of pure phenylphosphine and cyclophosphine. In the sample described above the concentration ratio $[(C_6H_5PH)_2]/[C_6H_5PH_2]$ is 25/75 and this ratio does not change noticeably in the temperature range 30–200°. Starting with variable relative amounts of $C_6H_5PH_2$ and $(C_6H_5P)_5$, the relative amounts of $C_6H_5PH_2$, $(C_6H_5PH)_2$, and $(C_6H_5P)_5$, observed at equilibrium, were in agreement with the stoichiometry of eq 2.

$$5(C_6H_5PH)_2 \rightleftharpoons 5C_6H_5PH_2 + (C_6H_5P)_5 \quad (2)$$

Ring cleavage reactions involving cyclopolyphosphines are not without precedents[14] and it was suggested that the trifluoromethylphosphinidene moiety CF_3P has an important part in such reactions. As

(2) To our knowledge, these are the following: (a) $CF_3(H)PP(H)CF_3$ [W. Mahler and A. B. Burg, *J. Amer. Chem. Soc.*, **80**, 6161 (1958)], (b) $CH_3(H)PP(CF_3)_2$ [A. B. Burg and K. K. Joshi, *ibid.*, **86**, 353 (1964)], (c) $H_2P–PF_2$ [H. W. Schiller and R. W. Rudolph, *Inorg. Chem.*, **10**, 2500 (1971)], (d) $(CF_3)_2PPH_2$ [R. Demuth, J. Grobe, and L. Steiner, *Z. Naturforsch. B*, **26**, 731 (1971)].

(3) K. Issleib and D. Jacob, *Chem. Ber.*, **94**, 107 (1961).

(4) K. Issleib and K. Krech, *ibid.*, **99**, 1310 (1966); we thank Professor Issleib who brought our attention on this further finding of his group.

(5) L. Maier, *Fortshr. Chem. Forsch.*, **8**, 1 (1967).

(6) P. Diehl, R. K. Harris, and R. G. Jones, *Progr. Nuclear Magn. Resonance Spectrosc.*, **3**, 1 (1967).

(7) E. Fluck and K. Issleib, *Chem. Ber.*, **98**, 2674 (1965).

(8) In analogy with the adduct $(CH_3)_3PPCF_3$ [A. B. Burg and W. Mahler, *J. Amer. Chem. Soc.*, **83**, 2388 (1961)], one of the referees suggested $(C_6H_5)H_2PPC_6H_5$ as an alternate structure which could fit with our observed ^1H nmr spectra. Indeed the X part of an ABX_2 system can bear some resemblance with the X part of an AA′XX′ system, but the AB part and the X part of an ABX_2 system cannot be identical in any way. Our ^{31}P nmr data are only compatible with AA′XX′ systems and thus rule out any nonsymetrical structure with respect to the P–P bond.

(9) J. B. Lambert, G. F. Jackson, III, and D. C. Mueller, *ibid.*, **92**, 3093 (1970), and references cited therein.

(10) R. M. Lynden-Bell, *Trans. Faraday Soc.*, **57**, 888 (1961).

(11) E. G. Finer and R. K. Harris, *Mol. Phys.*, **12**, 457 (1967).

(12) H. C. E. McFarlane and W. McFarlane, *Chem. Commun.*, 1589 (1971).

(13) (a) A. H. Cowley and W. D. White, *J. Amer. Chem. Soc.*, **91**, 1913, 1917 (1969). (b) R. W. Rudolph and R. A. Newmark, *ibid.*, **92**, 1195 (1970).

(14) (a) A. H. Cowley, *ibid.*, **89**, 5990 (1967); (b) A. H. Cowley and D. S. Dierdorf, *ibid.*, **91**, 6609, (1969).

regarding the specific type of reaction observed here it should be noted that $(CF_3P)_4$ reacts quantitatively with CH_3PH_2 to give CF_3PH_2 and $(CH_3P)_5$[14a] but the course followed by the reaction, when the phosphine and cyclophosphine are identically substituted, was not considered. The first isolated disecondary diphosphine $(CF_3PH)_2$[2a] has been reported to decompose above 225°, giving mainly $(CF_3P)_4$ and CF_3PH_2, but the reverse reaction was apparently not observed. We are presently investigating some other mixtures $(RP)_n$–RPH_2 to test the generality of the equilibrium giving rise to I.

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A New Simple Method for Rapid Tritium Labeling of Organics Using Organoaluminum Dihalide Catalysts

Sir:

We have recently published[1] a method for rapid deuteration of aromatic compounds using organoaluminum dihalide catalysts promoted by a trace of water. Equilibration of deuterium between two aromatic compounds such as benzene-d_6 and bromobenzene is attained within minutes at room temperature, the exchange being highly selective for aromatic hydrogen atoms and not subject to steric effects in the aromatic ring. D_2O is not a suitable source of deuterium in such deuteration reactions because the catalyst is rapidly hydrolyzed, although small traces of water promote the catalyst activity.

We now report that the same organoaluminum dihalide catalysts with tritiated water as the isotope source and catalyst promoter may be used for instantaneous tritium labeling of a variety of organic compounds.

When tritium labeling is the objective, as distinct from deuterium labeling, traces of high specific activity tritiated water may be used to hydrolyze a solution of the organoaluminum dihalide catalyst in an organic substrate. Adequate tritium labeling of the substrate accompanies this hydrolysis. This method is not suitable for deuterium labeling since substantial exchange with D_2O and not just hydrolysis of some catalyst complex is necessary to achieve reasonably high deuterium isotope ratios. A range of organoaluminum halides has been used as catalysts, ethylaluminum dichloride being the most satisfactory.

Table I shows representative compounds labeled by the present technique in which ethylaluminum dichloride (0.01 g) was added by syringe to the organic substrate (0.2 g) under dry nitrogen, and the solution treated with a drop of tritiated water (0.01 g, 5 Ci/g).

Table I. Compounds Labeled by Tritiated Water Using Ethylaluminum Dichloride Catalyst[a]

% incorporation of tritium into organic compound[b]		
10–100%	1–10%	0.1–1%
Benzene	Furan	Cyclohexene
Toluene	Cyclohexanone	
Naphthalene	1-Methylcyclopentene	
Anthracene	1-Methylcycloheptene	
Pyrene	Triphenylamine	
Azulene		
Anisole		
Pyrrole		
Chlorobenzene		

[a] Reaction conditions: room temperature, 2 min, 50 mCi of HTO. [b] Expressed as per cent of total tritium in reaction mixture.

After approximately 2 min, ordinary water (1 ml) was added to ensure complete hydrolysis of the catalyst. The organic product was analyzed simultaneously for chemical and radiochemical products by means of a gas–liquid chromatograph coupled to an ion-chamber radioactivity detector assembly. In no system was any radioactive or nonradioactive product detected other than the labeled parent compound. The results in Table I are expressed as the percentage of the added tritium that is incorporated into the organic compound. For the conditions stated above, the specific activities of products ranged from 18 mCi/mmol for benzene to 0.2 mCi/mmol for cyclohexene. Higher specific activities are obtained if higher specific activity HTO is used.

Of the hydrocarbons studied, aromatics were labeled with high efficiency while alkenes were tritiated to a lesser extent (Table I). Saturated hydrocarbons have not been successfully labeled by the present technique. A variety of substituted hydrocarbons labeled readily.

Detailed studies of the orientation of isotope after labeling have not yet been carried out. However, oxidation of labeled toluene to benzoic acid with complete retention of tritium activity showed toluene was labeled only in the ring. Nitration of the toluene followed by gas-chromatographic analysis of the mixed nitration products showed a random distribution of tritium in the aromatic ring. This result is in accord with the high selectivity for aromatic proton exchange and absence of steric effects within the aromatic ring observed in the deuteration studies on a wide variety of compounds.[1]

The work of Balaban and coworkers[2–4] may be related to this present study. They labeled a range of organic compounds by using aluminum chloride in prolonged exchange with tritiated water present at a molar concentration about half that of the catalyst. With benzene, exchange was complete in 1.5 hr at room temperature, but with chlorobenzene exchange was incomplete even after 3 hr at 100°. A variety of other compounds exhibited varying degrees of exchange after prolonged times at elevated temperatures.

The present method, using organoaluminim dihalides, is much faster for aromatic compounds than that proposed by Balaban, *et al.*[2] This is exemplified by the instantaneous tritiation of chlorobenzene at room temperature in the present method. Speed of labeling

(1) J. L. Garnett, M. A. Long, R. F. W. Vining, and T. Mole, *J. Amer. Chem. Soc.*, **94**, 5913 (1972).

(2) C. Mantescu and A. T. Balaban, *Can. J. Chem.*, **41**, 2120 (1963).
(3) C. Mantescu, A. Genunche, and A. T. Balaban, *J. Label. Compounds*, **2**, 261 (1966).
(4) C. Mantescu, A. Genunche, D. Duta-Cristu, and A. T. Balaban, *ibid.*, **2**, 267 (1966).