($MgSO_4$), the solvent was removed under reduced pressure, and the residue was fractionally distilled to give benzaldehyde (2.10 g, 19.79 mmol, 79%), benzyl alcohol (2.25 g, 20.80 mmol, 83%), and unreacted dibenzyl ether (0.55 g, 2.77 mmol, 11%).

**Reaction of Dibenzyl Ether with Ethyl Azodicarboxylate.**—A mixture of dibenzyl ether (1.14 g, 5.74 mmol) and **1** (1.00 g, 5.74 mmol) was heated at 140° for 30 min to give a colorless solid: ir (neat) 3280 (NH), 1740 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 7.36 (m, 10 H, aromatic), 6.48 (s, 1 H), 4.82 (m, 2 H, $OCH_2C_6H_5$), 4.25 and 4.27 (2 q overlapping, $J$ = 7.5 cps, 4 H, $CO_2CH_2$), 1.27 (t, $J$ = 7.5 cps, 6 H, $CCH_3$).

A small fraction of the product (50 mg) was refluxed with $H_2O$ (0.2 ml) for 30 min and extracted with $CDCl_3$ (2 × 0.3 ml). Nmr analysis of the combined $CDCl_3$ extracts indicated that they contained equimolar amounts of benzaldehyde (δ 9.88, s, 1 H, CHO), benzyl alcohol (δ 4.60, s, 2 H, $CH_2O$), and **6** (δ 1.22, t, 6 H, $CCH_2CH_2CH_2$).

**Reaction of Dibenzyl Thioether with Ethyl Azodicarboxylate.**—A mixture of dibenzyl thioether (1.23 g, 5.74 mmol) and **1** (1.00 g, 5.74 mmol) was heated at 140° for 30 min to give a white solid mass: ir (neat) 3280 (NH), 1740 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 7.25 (m, 10 H, aromatic), 6.50 (s, 1 H), 3.92 (m, 2 H, $SCH_2C_6H_5$), 4.16 and 4.17 (2 q overlapping, $J$ = 7.5 cps, 4 H, $CO_2CH_2$), 1.22 (t, $J$ = 7.5 cps, 6 H, $CCH_3$). A small fraction of the product (50 mg) ws refluxed under $N_2$ with 1 $N$ HCl (0.2 ml) for 1 hr and extracted with $CDCl_3$ (2 × 0.3 ml). Nmr analysis of the combined $CDCl_3$ extracts indicated that they contained equimolar amounts of benzaldehyde (δ 9.88, s, 1 H, CHO), benzyl mercaptan (δ 3.66, s, 2 H, $CH_2S$), and **6** (δ 1.22, t, 6 H, $CCH_2CH_2CH_2C$).

**Determination of Unreacted Dibenzyl Ether or Dibenzyl Thioether by Glc.**—A known amount (2.87 mmol) of the reaction mixture between **1** and the appropriate ether was transferred quantitatively into a 25-ml volumetric flask and diluted to the mark with a 1 $N$ HCl solution in a $H_2O$–EtOH (1:1) mixture. The mixture was analyzed against a standard of the dibenzyl ether (2.87 mmol) or the dibenzyl thioether (2.87 mmol) following the same procedure as used in the determination of tertiary amines.

**Registry No.**—**1**, 1972-28-7; **6**, 4114-28-7; **8**, 10465-78-8; **9**, 10465-81-3; **12**, 38910-96-2; **14**, 38910-97-3; **15**, 38910-98-4; $N$-methylpiperidine, 626-67-5; $N$-benzylpiperidine, 2905-56-8; dibenzyl ether, 103-50-4; dibenzyl thioether, 538-74-9.

**Acknowledgment.**—The authors gratefully acknowledge support of this project by McNeil Laboratories, Inc., Fort Washington, Pa. The authors wish to express their appreciation to Mr. T. L. Gruen for his technical assistance.

# Phosphorino[4,3-*d*]pyrimidines. III. Synthesis, Resolution, and Properties of 4-Substituted Phosphorino[4,3-*d*]pyrimidines[1]

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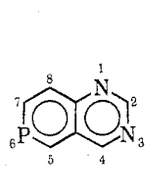
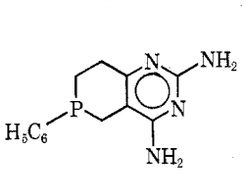
*Received October 27, 1972*

A family of 4-substituted 6-phenylphosphorino[4,3-*d*]pyrimidines has been prepared with 4-amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile as the key starting material. Pmr, $^{31}P$ nmr, infrared, and mass spectral data support the structures. Treatment of 4-amino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-*d*]-pyrimidine with benzyl bromide gave the corresponding phosphonium salt, which was resolved *via* its dibenzoyl tartrate salts. Ammonium bromide converted the diastereomers back to the enantiomeric bromides. Attempted methylation of 5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-*d*]pyrimidine-4-thiol gave 5,6,7,8-tetrahydro-4-(methylthio)-6-phenylphosphorino[4,3-*d*]pyrimidine 6-sulfide *without* quaternization of the phosphorus atom. Spectral data for all of these compounds are briefly discussed.

Phosphorino[4,3-*d*]pyrimidines (**1**) represent a very recent[3] and intriguing family of compounds in the area



**1**



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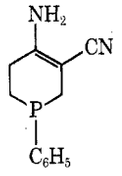

**3**

of fused carbon–phosphorus heterocycles. The 5,6,7,8-tetrahydro derivatives are prochiral about the asymmetric phosphorus atom, and 4-substituted pyrimidines, such as adenine and 6-mercaptopurine, are well known for their biological and medicinal value.[4] Recent evidence also indicates that quinazolines substituted at the 6 position, particularly heteroatom substituents, are of potential use as antimetabolites.[5] Additionally, C–P heterocycles which possess organic functionality are extremely rare in the literature[6,7] and hence very little is known of the biological activity conveyed by the phosphorus atom. The first reported[3] phosphorinopyrimidine was the 2,4-diamino derivative **2** prepared in a direct condensation of the 2-enamine nitrile **3** with guanidine. Interestingly, recent literature[8] suggests that a method of choice for the synthesis of 4-substituted fused pyrimidines involves the utilization of 2-enamino nitriles as their triethyl orthoformate adducts.

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(2) National Science Foundation Faculty Fellow, 1971–1972; NSF Trainee, 1970–1972; Predoctoral candidate, 1970–1972.

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(4) J. H. Lister, "Fused Pyrimidines, Part II Purines," D. J. Brown, Ed., in "The Chemistry of Heterocyclic Compounds," A. Weissberger and E. C. Taylor, Ed., Wiley-Interscience, New York, N. Y., 1971.

(5) J. Davoll, A. M. Johnson, H. J. Davies, O. D. Bird, J. Clarke, and E. F. Elslager, *J. Med. Chem.*, **15**, 812 (1972); E. F. Elslager, J. Clarke, L. M. Werbel, and D. F. Worth, *ibid.*, **15**, 827 (1972); J. Davoll, J. Clarke, and E. F. Elslager, *ibid.*, **15**, 837 (1972).

(6) K. D. Berlin and D. M. Hellwege, *Top. Phosphorus Chem.*, **6**, 1 (1969).

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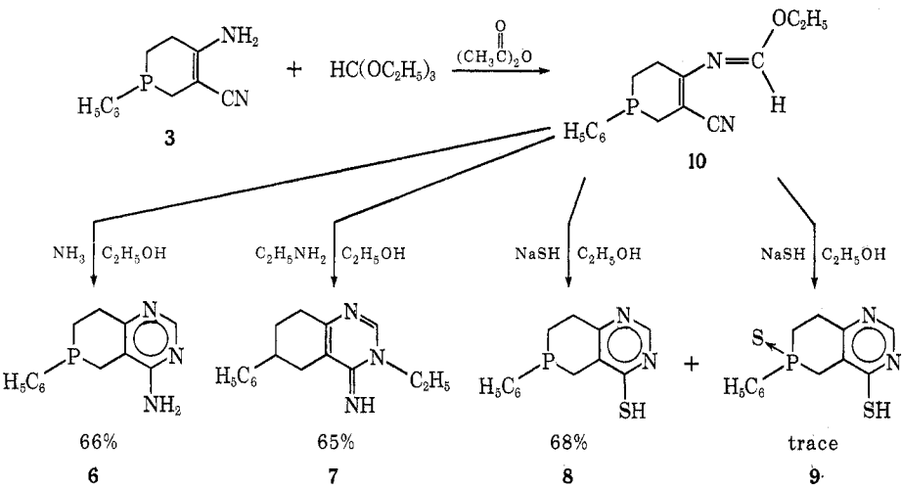
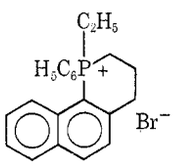
SCHEME I

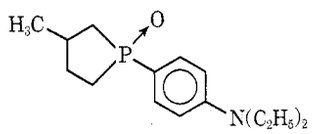



In view of the potential biological activity, novel structure, and stereochemistry of the title compounds, we elected to attempt the preparation of 4-substituted 5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-*d*]pyrimidines from 4-amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile (**3**).

The resolution of cyclic phosphorus compounds (and acyclic) has generally been effected by two basic methods: (a) quaternization of phosphorus to form phosphonium salts which may be resolved *via* anion exchange with reagents such as hydrogen silver L(+)- and D(−)-dibenzoyltartaric acids;[9] and (b) by blocking the phosphorus atom for reaction, generally by conversion to the phosphine oxide, and utilizing some other functionality for resolution. Thus, **4** has been resolved by Chen and Berlin[10] utilizing method a and **5** has been resolved *via* method b by Ostrogovich and Kerek[11] using camphor-13-sulfonic acid.




4




5

The synthesis of 4-substituted 6-phenylphosphorino[4,3,-*d*]pyrimidines **6**, **7**, and **8** was accomplished as outlined in Scheme I. 4-Amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile (**3**) was prepared according to known procedure[12] from bis(2-cyanoethyl)-phenylphosphine.[13] The ethoxymethylene derivative **10** (Scheme I), formed by boiling the 2-amino nitrile **3** in excess solution of 50:50 triethyl orthoformate and acetic anhydride, was used in crude form in reaction with either anhydrous amine (to give **6** or **7**) or anhydrous ethanolic sodium hydrosulfide (to give **8**) to effect pyrimidine formation. Derivatives such as **10** can be and have been isolated[14] but are generally used as crude material. The mechanisms involved in these transformations may be similar to those proposed by Taylor and coworkers[8,14] utilizing carbocyclic 2-enamine nitriles. It has been proposed that the yield-limiting factor in analogous reactions was the formation of the ethoxymethylene derivative.[8] The narrow range of yields (65–68%) for **6**, **7**, and **8** is additional evidence that the formation of the ethoxymethylene derivative may be the yield-limiting step in the sequence. Thus, in spite of the large size of the phosphorus atom (covalent radius 1.10 Å)[15] compared to carbon (covalent radius 0.77 Å),[15] any inherent strain in the six-membered C–P heterocycle is not sufficient to prevent formation of the fused-ring system.

The importance of acetic anhydride to the initial condensation is clearly illustrated in the synthesis of **8**. Attempted formation of **8** without the presence of acetic anhydride resulted in a yield of only 26%. With acetic anhydride, the return was increased to 66%. The function of the acetic anhydride may be to remove the ethanol converted in the reaction to ethyl acetate, which thereby helps to drive the reaction to completion. This assumes that the initial formation of **10** is an equilibrium-controlled reaction. An interesting facet in the synthesis of **8** is that a small amount of the phosphine sulfide **9** is also formed. Evidently, the phosphine is capable of abstracting sulfur from $H_2S$ or NaSH (an apparent redox reaction). This type of exchange ($\geqslant P \rightarrow \geqslant P{=}S$) appears to be rare, although removal of sulfur by phosphorus from carbon[16,17] or phosphorus[18] is known. A possible analogous process is the formation of phosphine oxides *via* treatment of a phosphine with hydroxylamine.[19] The proposed structures of **6**, **7**, and **8** are supported by elemental analysis and their respective ir, pmr, $^{31}P$ nmr, and mass spectral properties.

In an ancillary experiment to confirm the structure,

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(14) E. C. Taylor and P. K. Loeffler, *J. Amer. Chem. Soc.*, **82**, 3147 (1960).

(15) L. A. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 224.

(16) E. J. Corey, *Pure Appl. Chem.*, **14**, 19 (1967).

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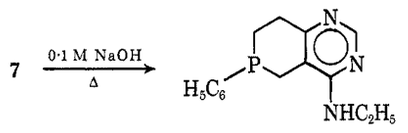
(19) M. D. Martz and L. D. Quin, *J. Org. Chem.*, **34**, 3195 (1969).

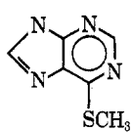
**7** was rearranged to **11** by boiling the former in 0.1 *M* NaOH, known conditions for the classic Dimroth rearrangement.[20]



**11**

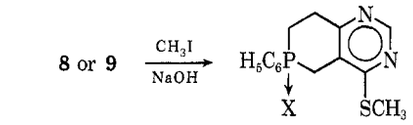
The pmr spectra of both reactant and product show anomalous features. The spectrum of **7** displays two sets of quartets of approximate equal intensity for the *N*-methylene group. Decoupling experiments (irradiating $NCH_2CH_3$ and observing $NCH_2CH_3$) reveal the collapse of the double set of quartets to a crude singlet. In an inverse decoupling experiment the observed triplet of the $NCH_2CH_3$ collapsed to a singlet. A third decoupling experiment (irradiation of =NH and observation of the $NCH_2CH_3$) showed some type of magnetic interaction, but did not cause the methylene to go to a simple quartet. Observing the spectrum in the presence of $D_2O$ did not reveal any change in the coupling pattern. Although Brown[20] did not record any secondary splitting of this type in his discussion of the pmr spectra of *N*-methyl-4-iminoquinazolines, we have tentatively attributed this phenomenon in our system to syn–anti isomerism about the imino nitrogen and/or nonequivalence of the methylene hydrogens owing to restricted rotation. The distance between the imine hydrogen and other protons in the molecule could conceivably preclude the observation of any other splitting as a result of syn–anti isomerism. Curiously, the pmr spectrum of **11** in $DCCl_3$ shows a complete doubling of all resonance lines in an approximate intensity ratio of 3:1. A Courtauld model of **11** indicates considerable hindered rotation of the $-NHC_2H_5$ group. This steric barrier to rotation could result in conformers in which the $-NHC_2H_5$ group is syn or anti with respect to the *P*-phenyl ring. Experimental evidence supporting this explanation is: (1) the relative intensity of the doubled spectrum is solvent-dependent, and (2) the spectrum (in *o*-$C_6H_4Cl_2$) is temperature dependent with only one set of resonance signals observable at 125°.

Recent reports concerning the biological activity and potential chemotherapeutic usefulness of 6-(methylthio)purine[21] and the predicted increased water



solubility of phosphonium salts prompted us to investigate the chemistry of **6** and **8**. Of particular interest were the relative reactivities of the following groups: $-\ddot{S}H$ *vs.* $C_6H_5\ddot{P}$ (alkylation *vs.* quaternization), $-\ddot{S}CH_3$ *vs.* $C_6H_5\ddot{P}$, and $-\ddot{N}H_2$ and/or pyrimidine ring N *vs.* $C_6H_5\ddot{P}$. Specifically, the question arose of competitive alkylation involving the thiol function in the presence of a phosphine without carbon–phosphorus bond formation or cleavage (in the presence of base) and whether it would be possible to quaternize a tertiary phosphine in the presence of a methylthio or nitrogen functional group.

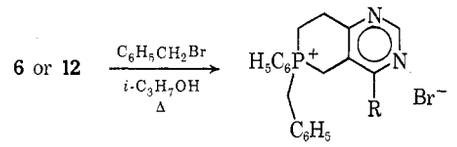
The methylation of **8** and **9** to form the methylthio derivatives **12** (89%) and **13** (71%) was accomplished



**12**, X = —
**13**, X = S

with 10% sodium hydroxide and methyl iodide. Surprisingly, derivatives **12** and **13** are volatile and are readily purified by vacuum sublimation (83–90°, 0.05 mm). Quaternization of phosphorus during the preparation of **12** was *not* observed and there was also no evidence of carbon–phosphorus bond cleavage. Hence, with respect to methylation, **8** is an exact chemical analog of aminopyrimidinethiols in which one can methylate the mercapto group in the presence of the amino function.[22]

The formation of phosphonium salts **14** and **15** from phosphines **6** and **12**, respectively, indicate that



**14**, R = $SCH_3$
**15**, R = $NH_2$

the tertiary phosphine in these phosphorino[4,3-*d*]-pyrimidines is a stronger base and/or a more powerful nucleophile than the 4-methylthio or the 4-amino group. The assignment of the phosphonium structure is rigorously supported by infrared, nmr, mass spectral, and elemental analysis; except for the latter, the analyses are similar to those of the simpler precursor pyrimidines. However, most significantly, the highly positive $^{31}P$ nmr absorption of the phosphine precursors (*ca.* $\delta$ 44 relative to $H_3PO_4$; see Table I)

TABLE I
$^{31}P$ CHEMICAL SHIFTS OF C–P HETEROCYCLES

| Compd | $\delta$ | Solvent | Concn, % |
|---|---|---|---|
| **3** | +46.9 | $HCCl_3$ | 5 |
| **6** | +44.0 | DMSO | 5 |
| **7** | +44.6 | DMSO | 5 |
| **8** | +39.6 | DMSO | 5 |
| **11** | +44.7 | DMSO | 5 |
| **12** | +44.4 | $CH_3OH$ | 5 |
| **14** | −18.6 | $HCCl_3$ | 10 |
| **15** | −18.6 | DMSO | 10 |
| **17** | −29.0 | DMSO | 5 |

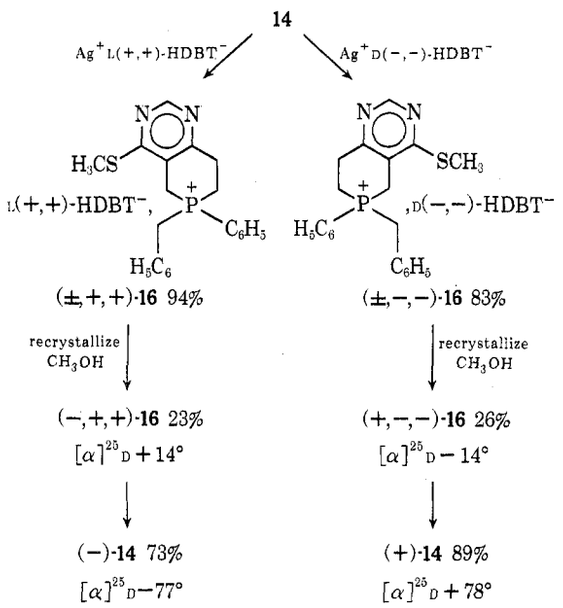
is shifted to a highly negative $\delta$ $^{31}P$ nmr absorption in the phosphonium salts (*ca.* $\delta$ −18; Table I). This shift from positive to negative $^{31}P$ absorption is characteristic of a conversion from a phosphine to a phosphonium salt and is well documented.[23] The reaction

(20) D. J. Brown and B. T. England, *Aust. J. Chem.*, **21**, 2813 (1968).
(21) J. A. Montgomery and K. Hewson, *J. Med. Chem.*, **15**, 571 (1972).
(22) D. J. Brown and S. F. Mason, "The Pyrimidines," in "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience, New York, N. Y., 1962.
(23) M. M. Crutchfield, C. H. Dungan, J. H. Letcher, V. Mark, and J. R. Van Wazer, *Top. Phosphorus Chem.*, **5**, 1 (1967).

is complete and specific for the phosphine, as indicated by the loss of all absorption for $^{31}P$ at positive $\delta$ in the nmr. (Even after extended time averaging, absorption at positive $\delta$ was not observable.)

The resolution of racemic **14** was achieved by the successful isolation of the enantiomer (+)-**14** and (−)-**14**. Conversion of racemic **14** to a mixture of diastereomeric hydrogen D(−,−)-dibenzoyltartrate salts [(+,−,−)-**16** and (−,−,−)-**16**] is shown in Scheme II.

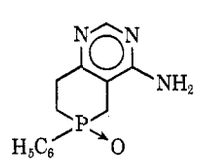
SCHEME II




Subsequent separation of (+,−,−)-**16** and (−,−,−)-**16** could be realized by repeated recrystallizations from a minimal amount of methanol.

Four recrystallizations were sufficient to purify 375 mg of (+,−,−)-**14** to a constant specific rotation, $[\alpha]^{25}D$ −14°, and a sharp melting point, 164.5–165°. The pure diastereomer (+,−,−)-**16** underwent satisfactory metathesis with ammonium bromide to form optically active (+)-**14**, $[\alpha]^{25}D$ +78° ($CH_3OH$), 89%, mp 250–251°. In a parallel but *separate* resolution (+)-**14** was isolated with a specific rotation of $[\alpha]^{25}D$ +77°. The equal but opposite values obtained for the specific rotations of enantiomeric **14** (Scheme II) and enantiomeric **16** [(+,−,−)-**16** and (−,+,+)-**16**], coupled with the reproducibility of the values, is strong evidence that complete resolution has been achieved.

Attempts to prepare the salt of phosphine **6** and L-mandelic acid were unfruitful. A crystalline product was not obtained even after repeated crystallization attempts. However, it is interesting that when this mixture was treated with aqueous NaOH to decompose the salt, **6** was not obtained, but instead the phosphine oxide **17** was isolated. Whether **17** is the result




**17**

of simple air oxidation of **6** or was oxidized by some other material in solution is not known at this time.

Salts **14**–**16** have been characterized by spectral data and elemental analyses. The inclusion of solvent of crystallization, or of stoichiometric amounts of dibenzoyltartaric acid or its anions, was an anticipated difficulty which was not encountered.[10]

The predominant mass spectral fragment ions of all phosphorino[4,3-*d*]pyrimidines are listed in the Experimental Section. In general, these compounds give molecular ions of good intensity. However, phosphonium salts **14** and **15** do not show molecular ions such as Aguiar and coworkers[24] observed in certain C–P heterocycles (evaporated into the spectrometer above 300°) but instead show *m/e* $M^+$ − HBr as the largest major ion. The loss of HBr possibly results from electron impact within the ionizing region of the spectrometer and not from thermal decomposition on the probe. If thermal decomposition occurred, HBr would be observed in the spectrum, and it was *not* found. This situation is not true in the case of **16**, the hydrogen dibenzoyltartrate salt. Decomposition of the sample occurs in the probe at about 160°. Elimination of benzoic acid (identified by comparison with the known mass spectrum) is noted in the spectrum. The spectrum of the main sample is obtained at a probe temperature of *ca.* 200°. Benzoic acid must come from decomposition and cannot be a contaminant because benzoic acid is volatile at room temperature in the mass spectrometer.

## Experimental Section

Melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus in evacuated, sealed tubes. Infrared spectra were determined on a Beckman IR-5A spectrometer as potassium bromide pellets. Nuclear magnetic resonance spectra were determined on a Varian A-60 MHz high-resolution spectrometer and a Varian XL-100 MHz spectrometer. Mass spectra were determined on a LKB-9000 prototype, single-focusing magnetic sector instrument. Rotations were determined on a Rudolf Model 80 polarimeter at the sodium D line using a 2-dm cell. Elemental microanalyses were determined by Galbraith Laboratories, Knoxville, Tenn.

**4-Amino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-*d*]pyrimidine (6).**—A mixture of the 2-enamino nitrile **3**[12] (10.8 g, 0.05 mol), 80 ml (72 g, 0.49 mol) of triethyl orthoformate, and 80 ml of acetic anhydride was boiled for 1 hr. The solution of ethoxymethylene derivative **10** was concentrated to a residual oil by distillation under vacuum (70°, 0.1 mm). Anhydrous, saturated $C_2H_5OH$–$NH_3$ (200 ml, saturated at 0°) was added to the residue and the solution was stirred overnight. (After approximately 5 hr of stirring, a precipitate formed.) The mixture was filtered and the residue was washed with 25 ml of cold $C_2H_5OH$ on the filter to yield 6.5 g, mp 194–197° of **6**. The filtrate and washings were combined and evaporated to dryness on the rotary evaporator. Trituration of the resulting oil with acetone followed by filtration gave an additional 0.8 g (mp 196–197°) of **6** for a total yield of 7.3 g (66%). Sublimation (190–200°, 0.001–0.0005 mm) gave pure **6**, mp 196–197° (lit.[3] mp 196–197°). A mixture melting point of **6** with an authentic sample showed no depression and the respective spectral properties were identical.

**3-Ethyl-5,6,7,8-tetrahydro-4(3*H*)-imino-6-phenylphosphorino-[4,3-*d*]pyrimidine (7).**—The crude ethoxymethylene derivative **10** was prepared as in the previous experiment. Anhydrous ethylamine (20 g) in 200 ml of absolute ethanol was added to crude **10** with stirring. After a short period of time (*ca.* 15 min), a large amount of precipitate formed. Stirring was continued overnight. The black reaction mixture was filtered, and the

(24) A. M. Aguiar, H. Aguiar, and D. Daigle, *J. Amer. Chem. Soc.*, **87**, 672 (1965).

residue was washed on the filter with two 50-ml portions of cold anhydrous ethanol to give 8.8 g (65%, dried at 78°, 1 mm) of **7** as a clean white powder. Sublimation of this sample at 135–140° (0.0001–0.0005 mm) afforded an analytical sample: mp 147–149° (s.t.); ir (KBr) 3.04, 6.14, 6.38, 7.0, 7.2 μ; pmr (DCCl$_3$) δ 1.4 (t, 3, Hz, NCH$_2$CH$_3$), 1.9–2.8 (m, 6, phosphorin ring), 4.0 (m, 2, NCH$_2$CH$_3$), 5.6 (s, broad, 1, =NH), 7.3 (m, 5, –C$_6$H$_5$), 7.65 (s, 1, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 271 (80), 242 (11), 194 (27), 181 (10), 180 (100), 162 (28), 107 (10), 28 (12). The $^{31}$P magnetic resonance absorption of **7** occurred at δ +39.6 (5% in DMSO) from 85% H$_3$PO$_4$.

*Anal.* Calcd for C$_{15}$H$_{18}$N$_3$P: N, 15.50; P, 11.44. Found: N, 15.36; P, 11.22.

**5,6,7,8-Tetrahydro-6-phenylphosphorino[4,3-*d*]pyrimidine-4-thiol (8).**—A mixture of the 2-amino nitrile **3** (9.0 g, 0.0416 mol) and triethyl orthoformate (100 ml, 90 g, 0.6 mol) was boiled for 2 hr. Volatiles were then removed by distillation under reduced pressure (70°, 0.05 mm) to yield the crude ethoxymethylene derivative **10**. Sodium hydrosulfide in anhydrous C$_2$H$_5$OH (300 ml, 1.5 *N*) was added and the mixture was boiled for 12 hr. The C$_2$H$_5$OH was removed by rotary evaporation and the residual solid was dissolved in hot H$_2$O (*ca.* 150 ml). The aqueous solution was treated with decolorizing charcoal and filtered. Acidification of the hot filtrate was achieved with glacial CH$_3$CO$_2$H (H$_2$S was evolved). The precipitated product was washed with water and ethanol and dried. Two sublimations of the crude yellow product at 180–190° (0.002–0.001 mm) gave 3.1 g (26%) of analytically pure phosphine **8**: mp 230–231.5°; ir (KBr) 3.18, 3.28, 3.38, 6.24 μ; pmr (DMSO-*d*$_6$) δ 1.9–3.8 (m, 6, phosphorin ring), 2.95 (s, broad, 1, SH), 7.2 (m, 5, C$_6$H$_5$), 8.0 (s, 1, 2-H); mass spectrum (70 eV) *m/e* (rel intensity) 260 (100), 259 (18), 261 (18), 245 (17), 227 (20), 183 (21), 169 (42), 151 (16), 109 (13), 107 (11), 91 (25), 78 (12), 65 (11), 28 (11). The 40.5-MHz nmr spectrum of **8** showed $^{31}$P absorption at δ +44.59 (5% in DMSO) relative to 85% H$_3$PO$_4$.

*Anal.* Calcd for C$_{13}$H$_{13}$N$_2$PS: N, 10.77; P, 11.92; S, 12.31. Found: N, 10.90; P, 11.80; S, 12.43.

In a second preparation, equal volumes of triethyl orthoformate and acetic anhydride were used. The yield of **8** was increased to 66% in what was otherwise an identical experiment.

**4-(Ethylamino)-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-*d*]pyrimidine (11).**—A mixture of the iminopyrimidine **7** (1 g) and 50 ml of NaOH (0.1 *N*) was boiled for 1 hr. The resulting oil was separated from the water and dissolved in HCCl$_3$. The HCCl$_3$ solution was evaporated to dryness on the rotary evaporator and the residual oil was dissolved in acetone. After 2 days, during which time no crystallization occurred, the acetone solution was evaporated to dryness on the rotary evaporator to give **11** (0.7 g, 70%) as a crystalline solid. An analytical sample was obtained by sublimation at 135–140° (0.0001–0.0005 mm): mp 134–138° (s.t.); ir (KBr) 3.02, 3.4, 6.26 μ (the pmr spectrum shows two absorptions, a high-intensity and low-intensity signal, for each proton); pmr (DCCl$_3$) high intensity (low intensity) δ 1.25 (1.22) (t, 3, NHCH$_2$CH$_3$), 2.0–3.2 (m, 6, phosphorin ring), 3.25 (pentet, 2, NHCH$_2$CH$_3$), 4.8 (5.25), (s, 1, NHCH$_2$CH$_3$), 7.25 (7.3) (m, 5, C$_6$H$_5$), 8.38 (8.45) (s, 1, 2-H); mass spectrum (70 eV) *m/e* (rel intensity) 271 (100), 271 (18), 270 (13), 256 (20), 243 (15), 228 (25), 180 (16), 162 (13). The $^{31}$P magnetic resonance adsorption of **11** occurred at δ +44.74 (5% in DMSO) relative to 85% H$_3$PO$_4$.

*Anal.* Calcd for C$_{15}$H$_{18}$N$_3$P: N, 15.50; P, 11.44. Found: N, 15.45; P, 11.18.

**5,6,7,8-Tetrahydro-4-(methylthio)-6-phenylphosphorino[4,3-*d*]pyrimidine (12).**—Methyl iodide (3.0 g, 0.021 mol) was added to a solution of pyrimidine **8** (5.2 g, 0.02 mol) in 35 ml of 2 *N* NaOH. The mixture was shaken vigorously and allowed to stand for 30 min while the product precipitated. The mixture was filtered, and the residue was washed (H$_2$O) while on the filter and subsequently dried under vacuum (56°, 1 mm). The crude material was then sublimed (80–90°, 0.1–0.02 mm) to yield 4.9 g (89%) of pure **12**: mp 96–98°; ir (KBr) 6.47, 6.56, 6.95, 7.06 μ; pmr (DMSO-*d*$_6$) 2.55 (s, 3, SCH$_3$), 2.1–3.2 (m, 6, phosphorin ring), 7.25 (m, 5, C$_6$H$_5$), 8.15 (s, 1, 2-H); mass spectrum (70 eV) *m/e* (rel intensity) 274 (100), 275 (27), 273 (10), 259 (27), 241 (33), 201 (11), 109 (10). The 40.5-MHz nmr spectrum of **12** showed $^{31}$P absorption at δ +44.45 (5% in CH$_3$OH) relative to 85% H$_3$PO$_4$.

*Anal.* Calcd for C$_{14}$H$_{15}$N$_2$PS: N, 10.22; P, 11.31; S, 11.68. Found: N, 10.07; P, 11.16; S, 11.76.

**5,6,7,8-Tetrahydro-4-(methylthio)-6-phenylphosphorino[4,3-*d*]pyrimidine 6-Sulfide (13).**—Methyl iodide (0.79 g, 0.15 mol) was added to a solution of crude **9** (0.38 g, 0.13 mol) in 15 ml of 10% NaOH. The mixture was shaken vigorously and allowed to stand for 15 min while the product precipitated. The mixture was filtered and the residue was recrystallized (C$_2$H$_5$OH–H$_2$O). Subsequent sublimation (80–90°, 0.05 mm) of the residue gave **13**: mp 146–148° (0.28 g, 71%); ir (KBr) 6.46, 6.58, 6.98, 7.04, 7.48, 9.05 μ; pmr (DMSO-*d*$_6$) δ 2.55 (s, 3, SCH$_3$), 2.1–4.0 (m, 6, phosphorin ring), 7.6 (m, 3, *m*-C$_6$H$_5$), 7.85–8.15 (m, 2, *o*-C$_6$H$_5$), 8.8 (s, 1, 2-H); mass spectrum (70 eV) *m/e* (rel intensity) 306 (100), 308 (11), 307 (17), 305 (13), 304 (68), 291 (28), 290 (10), 273 (37), 271 (14), 260 (21), 243 (10), 165 (11), 135 (10), 109 (13), 92 (10), 91 (11), 65 (10), 63 (19).

*Anal.* Calcd for C$_{14}$H$_{15}$N$_2$PS$_2$: N, 9.15; P, 10.14; S, 20.92. Found: N, 9.02; P, 10.34; S, 20.76.

**Preparation of 5,6,7,8-Tetrahydro-4-(methylthio)-6-benzyl-6-phenylphosphorinia[4,3-*d*]pyrimidine Bromide (14).**—Benzyl bromide (1.7 g, 0.01 mol) was added to a warm solution of pyrimidine **12** (2.74 g, 0.01 mol) in 50 ml of 2-propanol. The solution was boiled for 1 hr. The solution was concentrated on the rotary evaporator to approximately 35 ml (a small amount of crystal formation was noted at this point), diluted with 100 ml of ethyl acetate, and allowed to crystallize overnight. The precipitate was filtered out and recrystallized (C$_2$H$_5$OH–ethyl acetate) to give 3.2 g (74%) of pure **14**: mp 249–251°; ir (KBr) 6.48, 7.05, 7.45, 11.51, 12.08 μ; pmr (DCCl$_3$) δ 2.45 (s, 3, SCH$_3$) 2.0–5.0 (m, 6, phosphorin ring), 5.18 and 5.45 (pair of doublets, $J_{PCH}$ = 16.4, $J_{HCH}$ = 3.7 Hz, –CH$_2$C$_6$H$_5$), 7.25 (s, 5, –CH$_2$C$_6$H$_5$), 7.4–7.7 (m, 3, *m*-C$_6$H$_5$), 7.7–8.0 (m, 2, *o*-C$_6$H$_5$), 8.62 (s, 1, 2-H); mass spectrum (70 eV) *m/e* (rel intensity) 364 (33), 365 (11), 363 (11), 350 (12), 349 (51), 274 (24), 273 (40), 271 (13), 121 (13), 109 (12), 92 (18), 91 (100), 82 (11), 80 (12), 65 (15). The $^{31}$P nmr spectrum of **14** showed absorption at δ –18.6 (10% in CH$_3$OH) relative to 85% H$_3$PO$_4$.

*Anal.* Calcd for C$_{21}$H$_{22}$BrN$_2$PS: N, 6.29; P, 6.96; S, 7.19. Found: N, 6.21; P, 6.89; S, 7.16.

**Preparation of 4-Amino-5,6,7,8-tetrahydro-6-benzyl-6-phenylphosphorinia[4,3-*d*]pyrimidine Bromide (15).**—Benzyl bromide (0.86 g, 0.01 mol) was added to a warm solution of pyrimidine **6** (1.22 g, 0.01 mol) in 50 ml of 2-propanol and the solution was boiled for 1 hr. The solution was subsequently concentrated to *ca.* 15 ml on the rotary evaporator, diluted with 50 ml of ethyl acetate, and allowed to stand overnight. The mixture was filtered and the residue was recrystallized (C$_2$H$_5$OH–ethyl acetate) to give 1.6 g of **15** (mp 248–251°, 79%): ir (KBr) 2.94, 3.19, 3.45, 5.99, 6.15, 6.34, 6.94 μ; pmr (DMSO-*d*$_6$) δ 2.7–4.2 (m, 6, phosphorin ring), 3.6 (s, 2, NH$_2$), 4.4 (d, 2, $J_{PCH}$ = 15.4 Hz, CH$_2$C$_6$H$_5$), 7.15 (m, 5, CH$_2$C$_6$H$_5$), 7.5–8.05 (m, 5, –C$_6$H$_5$), 8.18 (s, 1, 2-H); mass spectrum (70 eV) *m/e* (rel intensity) 333 (66), 334 (17), 332 (32), 243 (32), 242 (66), 241 (12), 166 (12), 164 (13), 134 (22), 121 (31), 109 (19), 107 (17), 92 (17), 91 (100), 82 (17), 80 (21), 65 (35), 28 (40). The $^{31}$P nmr spectrum of **15** showed absorption at δ –18.6 (10% in CH$_3$OH) relative to 85% H$_3$PO$_4$.

*Anal.* Calcd for C$_{20}$H$_{21}$BrN$_3$P: N, 10.16; P, 7.49. Found: N, 9.76; P, 7.22.

**Preparation and Resolution of (±)-5,6,7,8-Tetrahydro-4-(methylthio)-6-benzyl-6-phenylphosphorinia[4,3-*d*]pyrimidine Hydrogen D(–,–)-Dibenzoyltartrate [(±,–,–)-16].**—The phosphonium salt **14** (2.225 g, mmol) dissolved in 50 ml of CH$_3$OH was slowly added to a suspension of silver hydrogen D(–,–)-dibenzoyltartrate[9] (2.79 g, 6 mmol) in boiling CH$_3$OH and the mixture was heated for 30 min. The white Ag HDBT slowly dissolved during the reaction. After *ca.* 10 min of heating, AgBr precipitated as a gray solid. The mixture was cooled and filtered to give AgBr (0.78 g, 83%) and a rose-colored, CH$_3$OH solution of **16**. The CH$_3$OH solution was concentrated on the rotary evaporator to *ca.* 20 ml, treated with 50 ml of ethyl acetate, and allowed to stand overnight. The mixture was then filtered to give 1.9 g of crude white **16**, mp 154–158°, [α]$^{25}$D –46° (*c* 0.0100, CH$_3$OH). The filtrate was concentrated to *ca.* 20 ml, diluted with ethyl acetate, and filtered to give a second fraction of **16** as a rose-colored solid (1.0 g, mp 126–153°). Determination of the optical rotation of this fraction was not possible because of the color. The total yield was 2.9 g (83%). The first fraction was leached with boiling 2-propanol to give a residue of 1.6 g, [α]$^{25}$D –42° (*c* 0.0100, CH$_3$OH). Three subsequent recrystallizations (CH$_3$OH) of the first fraction produced 0.4 g (23%) of material with a narrow, constant melting range (mp 164.5–165°)

and of constant specific rotation, $[\alpha]^{25}D$ −14° (*c* 0.0120, $CH_3OH$). Subsequent recrystallizations of this material failed to cause any variance in these analytical data. The direction in which the rotation had changed, *i.e.*, from negative toward positive, indicated that the diastereomer isolated was (+,−,−)-**16**: ir (KBr) 5.80, 6.45, 6.93, 7.33, 7.44, 7.84 μ; mass spectrum *m/e* (rel intensity) $M^+$ 722 absent, the spectrum of benzoic acid is observed at a probe temperature of *ca.* 160°, 391 (29), 364 (13), 349 (18), 317 (19), 290 (19), 274 (11), 273 (12), 257 (13), 109 (14), 105 (12), 92 (15), 91 (100), 77 (17), 65 (18), 51 (10), 48 (18), 47 (27), 45 (15), 44 (63), 43 (11), 28 (42).

*Anal.* Calcd for $C_{39}H_{35}N_2O_3PS$: C, 64.82; H, 4.84; N, 3.88; P, 4.29. Found: C, 64.75; H, 4.87; N, 3.77; P, 4.17.

In a parallel but separate experiment, 0.82 g (31%) of (+,−,−)-**16** [mp 164.5–165°, $[\alpha]^{25}D$ −14° (*c* 0.0120, $CH_3OH$)] was obtained from 5.3 g of (±,−,−)-**16** prepared as previously described.

The mother liquors of the initial recrystallizations from both experiments were combined and evaporated to dryness. The residue was recrystallized ($CH_3OH$) to give 3.3 g of (±,−,−)-**16** enriched in the (−,−,−)-**16** diastereomer, $[\alpha]^{25}D$ −84° (*c* 0.0120, $CH_3OH$).

**Metathesis of (+)-5,6,7,8-Tetrahydro-4-(methylthio)-6-benzyl-6-phenylphosphorinia[4,3-*d*]pyrimidine Hydrogen D(−,−)-Dibenzoyltartrate [(+,−,−)-16 to the Corresponding Bromide [(+)-14].**—A solution of (+,−,−)-**16** (0.375 g, 0.00052 mol) and $NH_4Br$ (0.1 g, 0.001 mol) in 25 ml of $CH_3OH$ was boiled for 1 hr and allowed to stand overnight. The $CH_3OH$ was evaporated on the rotary evaporator and the residue was extracted with hot $HCCl_3$ (4 × 25 ml). The $HCCl_3$ extracts were evaporated to dryness and the residue was recrystallized ($CH_3OH$–ethyl acetate) to give 211 mg (89%) of enantiomer (+)-**14**, $[\alpha]^{25}D$ +76° (*c* 0.00873, $CH_3OH$). Recrystallization of this sample ($CH_3OH$–ethyl acetate) gave 174 mg of (+)-**14**, mp 250–251°, $[\alpha]^{25}D$ +78° (*c* 0.00696, $CH_3OH$). The infrared spectrum of (+)-**14** was identical with the infrared spectrum of racemic **14**.

In like manner, the 0.82 g of (+,−,−)-**16** from the separate but parallel resolution underwent metathesis with $NH_4Br$ to give, after two recrystallizations ($CH_3OH$–ethyl acetate), 0.44 g (87%) of (+)-**14**, mp 250–251°, $[\alpha]^{25}D$ +77° (*c* 0.0120, $CH_3OH$).

Similarly, the 3.3 g, $[\alpha]^{25}D$ −84°, of residual (±,−,−)-**16** enriched in (−,−,−)-**16** diastereomer was subjected to metathesis with $NH_4Br$ to give 1.9 g $[\alpha]^{25}D$ −16° (*c* 0.0120, $CH_3OH$), mp 249–251°, 93%, of (±)-**14** enriched in (−)-**14** (20% optical purity).

**Preparation and Resolution of (±)-5,6,7,8-Tetrahydro-4-(methylthio)-6-benzyl-6-phenylphosphorinia[4,3-*d*]pyrimidine Hydrogen L(+,+)-Dibenzoyltartrate [(±,+,+)-16].**—The levorotary enriched phosphonium bromide (±)-**14**, $[\alpha]^{25}D$ −16°, 1.9 g, 4.2 mmol, and silver hydrogen L(+,+)-dibenzoyltartrate[8] (2.325 g, 5 mmol) were allowed to react in the same manner utilized for the D(−,−) isomer to give 3.2 g (94%) of (−,+,+)-enriched (±,+,+)-**16**, mp 137–152°. Three recrystallizations of this material were sufficient to produce 433 mg (23%) of (−,+,+)-**16** with a constant melting point and constant specific rotation, mp 165–166°, $[\alpha]^{25}D$ +14° (*c* 0.0120, $CH_3OH$).

**Metathesis of (−)-5,6,7,8-Tetrahydro-4-(methylthio)-6-benzyl-6-phenylphosphorinia[4,3-*d*]pyrimidine Hydrogen L(+,+)-Dibenzoyltartrate [(−,+,+)-16] to the Corresponding Bromide [(−)-14].**—Utilizing the procedure previously described for metathesis, 433 mg (0.6 mmol) of (−,+,+)-**16** and 0.2 g (2 mmol) of $NH_4Br$ reacted to give, after two recrystallizations, (−)-**14**, 194 mg (73%), mp 250–251°, $[\alpha]^{25}D$ −77° (*c* 0.0120, $CH_3OH$). The infrared spectrum of (−)-**14** was identical with the infrared spectrum of racemic **14**.

**Preparation of 4-Amino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-*d*]pyrimidine 6-Oxide (17).**—Phosphorinopyrimidine **6** (2.43 g, 0.01 mol) in 25 ml of $C_2H_5OH$ and a solution of D(−)-mandelic acid (1.52 g, 0.01 mol) in 25 ml of $C_2H_5OH$ were mixed and the solution was boiled for 1 hr. The solvent was subsequently evaporated and the resulting oil was submitted to recrystallization attempts utilizing a variety of solvents. After *ca.* 8 weeks, crystallization had not occurred. Hence, the solvents were removed *via* rotary evaporator and the resulting oil was treated with 200 ml of 10% NaOH to decompose any salt present and to remove the mandelic acid. The reaction mixture was filtered to give a light brown powder. Recrystallization of this powder, with the aid of Nuchar, from $C_2H_5OH$–$H_2O$, gave 1.9 g of **17** as white crystals: mp 294–296°; 73%; ir (KBr) 3.02, 3.18, 6.03, 6.34, 6.40, 6.49, 6.75, 6.88 μ; pmr (DMSO-$d_6$) δ 2.0–3.3 (m, 6, phosphorin ring), 6.72 (s, 2, $NH_2$), 7.56 (m, 3, *m*- and *p*-$PC_6H_5$), 7.64–7.88 (m, 2, *o*-$PC_6H_5$), 8.18 (s, 1, 2-H); mass spectrum (70 eV) *m/e* (rel intensity) 259 (100), 260 (17), 258 (21), 182 (21), 135 (21), 134 (56), 107 (14), 54 (10), 47 (19). The 40.5-MHz nmr spectrum of **17** showed $^{31}P$ absorption at δ −29.0 (5% in DMSO) relative to 85% $H_3PO_4$.

*Anal.* Calcd for $C_{13}H_{14}N_3OP$: N, 16.22; P, 11.97. Found: N, 16.11; P, 11.84.

**Registry No.**—**3**, 23848-09-1; **6**, 38626-62-9; **7**, 38626-63-0; **8**, 38626-64-1; **9**, 38626-65-2; **10**, 38626-66-3; **11**, 38626-67-4; **12**, 38626-68-5; **13**, 38626-69-6; (±)-**14**, 38626-70-9; (+)-**14**, 38626-71-0; (−)-**14**, 38626-72-1; **15**, 38626-73-2; (±,−,−)-**16**, 38626-74-3; (+,−,−)-**16**, 38626-75-4; (−,−,−)-**16**, 38626-76-5; (±,+,+)-**16**, 38677-76-8; (−,+,+)-**16**, 38677-77-9; (+,+,+)-**16**, 38626-77-6; **17**, 38626-78-7; triethyl orthoformate, 122-51-0; silver hydrogen, D(−,−)-dibenzoyltartrate, 38823-92-6; silver hydrogen L(+,+)-dibenzoyltartrate, 38823-93-7; D(−)-mandelic acid, 611-71-2.