Dimethyl Selenoxide Oxidation of Trivalent Phosphorus Compounds, Thio- and Selenophosphoryl Compounds, and Thiocarbonyl Compounds. Stereochemical Studies and Selective Modification of the Thiocarbonyl-Containing Nucleic Acid Components[1]

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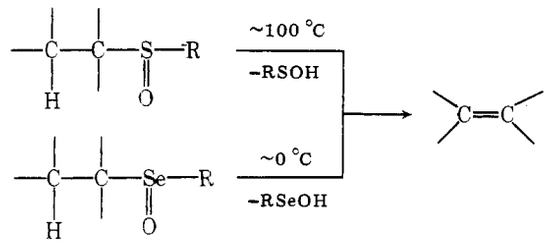
Received September 7, 1977

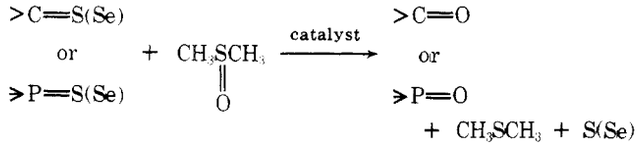
Dimethyl selenoxide was found to be an excellent oxidizing agent which converts P^{III} compounds, thio- and selenophosphoryl compounds, and thiocarbonyl compounds into their phosphoryl or carbonyl analogues under very mild conditions in the absence of catalysts. For this reason it is a reagent of choice for selective modification of the thiocarbonyl-containing minor components of transfer ribonucleic acids such as thiouracils and the corresponding thionucleosides and thionucleotides. The oxidation of cyclic six-membered phosphites and thio(seleno)phosphates with dimethyl selenoxide is accompanied by retention of configuration at phosphorus. In contrast, the oxidation of chiral acyclic P^{III} compounds as well as the conversion of chiral phosphine sulfides and selenides into phosphoryl derivatives proceed with inversion of configuration around the phosphorus atom. The mechanism of the dimethyl selenoxide oxidations is discussed.

The application of organic selenium reagents in organic synthesis has attracted increasing interest in recent years.[2] In comparison with sulfur reagents, the corresponding selenium analogues are usually more reactive, which allows the performance of desired reactions under milder conditions. The best illustration is the synthesis of olefins from sulfoxides and selenoxides involving the syn elimination of sulfenic and selenenic acid, respectively. It has been found that, in contrast to thermal decomposition of sulfoxides to olefins taking place under forced conditions,[3] the elimination of selenoxides occurs spontaneously at room temperature or below. This difference in behavior of sulfoxides and selenoxides is most probably a



consequence of the greater basicity of the selenynyl oxygen atom. It was expected, therefore, that the increased reactivity of selenoxides vs. sulfoxides may be also observed in other reactions.

Recently, we reported[4] a convenient method of oxidation of carbon and phosphorus compounds containing the thiono(seleno) groups >C=S(Se) and >P=S(Se) by dimethyl

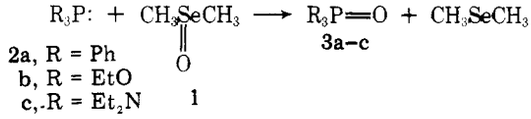


sulfoxide. This reaction is, however, catalyzed by strong acids or iodine and in the majority of cases it takes place at elevated temperatures. For this reason the above oxidation method cannot be applied to oxidation of the acid and thermally labile compounds. Moreover, its application as a method for selective modification of the thiocarbonyl-containing minor components in transfer ribonucleic acids[5] is, for the same reasons, of limited value.

This fact prompted us to investigate the reaction of dimethyl selenoxide (Me_2SeO, **1**) with trivalent phosphorus compounds, thio- and selenophosphoryl compounds, and thiocarbonyl compounds hoping to effect their oxidation under milder conditions and in the absence of an electrophilic catalyst. This was found to be the case and the results of this study are reported here.

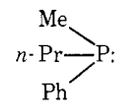
Results and Discussion

Oxidation of Trivalent Phosphorus Compounds by Dimethyl Selenoxide (1). It was found that treatment of P^{III} compounds (**2**) with dimethyl selenoxide (**1**) at room tem-

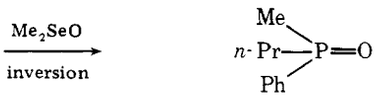


perature yielded the corresponding phosphoryl derivatives (**3**) and dimethyl selenide as the reduction product. The reaction is quantitative and practically complete after 1 h as evidenced by TLC. It should be pointed out that oxidation of triphenylphosphine (**2a**) by **1** was achieved under these mild conditions, whereas the analogous oxidation by dimethyl sulfoxide[6] requires higher temperature and acid catalysis.

If the reactions of P^{III} compounds with dimethyl selenoxide (**1**) are stereospecific it would be the preferred reagent for oxidation of chiral phosphines. With this in mind we have examined oxidation of optically active methyl-*n*-propylphenylphosphine (**4**)[7] by **1** and found that it resulted in the



(*S*)-**4**, $[\alpha]_{589}$ +15.21° (78% o.p.)
(*R*)-**4**, $[\alpha]_{589}$ −4.6° (23% o.p.)
(*S*)-**4**, $[\alpha]_{589}$ +9.36° (48% o.p.)



(*S*)-**5**, $[\alpha]_{589}$ −14.80° (74% o.p.)
(*R*)-**5**, $[\alpha]_{589}$ +4.31° (21.5% o.p.)
(*S*)-**5**, $[\alpha]_{589}$ −9.25° (46% o.p.)

formation of optically active phosphine oxide (**5**)[8] with nearly full *inversion of configuration at phosphorus*.

We used also in the present study optically active *O*-methyl ethylphenylphosphinite (**6**) and *S*-ethyl ethylphenylthiophosphinite (**7**) as model compounds. Asymmetric synthesis

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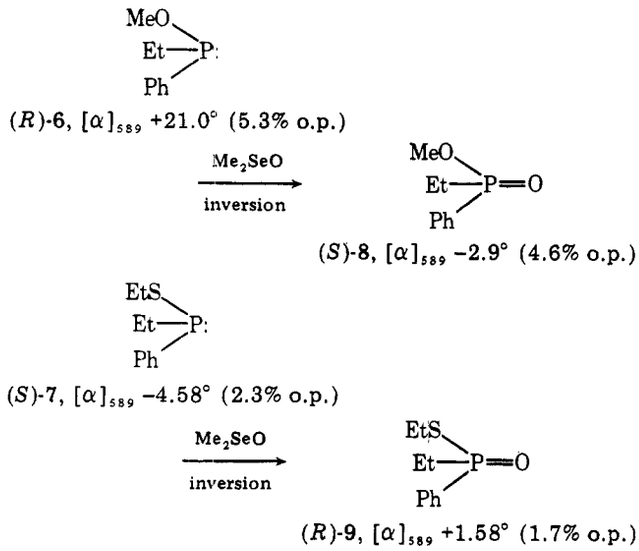


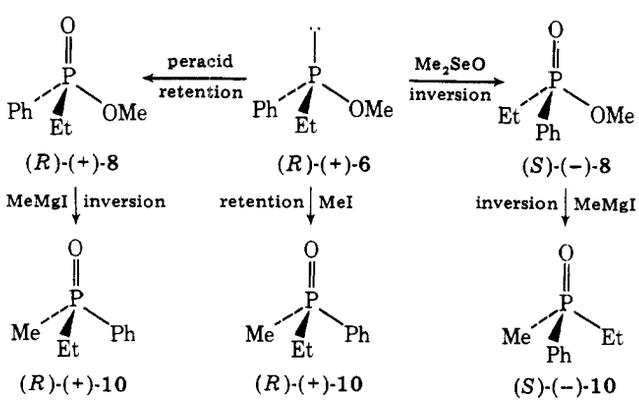
and stereochemistry of these P^{III} esters has recently been reported from this laboratory.[9] The results concerning oxidation of **6** and **7** by **1** are shown below.

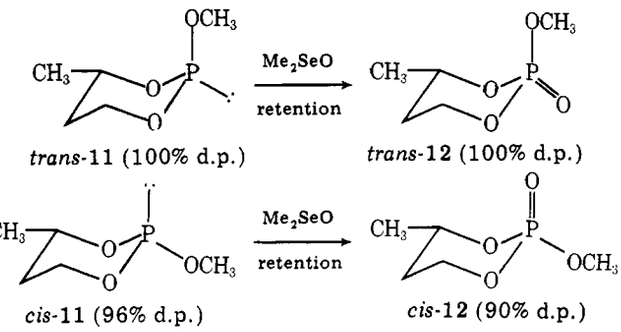
When (*R*)-(+)-**6**, $[\alpha]_{589}$ + 21.0°, was treated with **1**, (−)-*O*-methyl ethylphenylphosphinate (**8**), $[\alpha]_{589}$ −2.9°, was obtained. In order to establish the optical purity as well as the chirality at phosphorus of (−)-**8** it was further treated with methylmagnesium iodide to give (*S*)-(−)-methylethylphenylphosphine oxide (**10**), $[\alpha]_{589}$ −0.99° (4.3% optical purity). Since the latter reaction is known to proceed with inversion of configuration around phosphorus,[10] it follows that oxidation of the ester **6** by dimethyl selenoxide (**1**) is accompanied by inversion of configuration at the chiral phosphorus atom and the ester (−)-**8** should have the *S* configuration. In accord with this finding oxidation of (*R*)-(+)-**6**, $[\alpha]_{589}$ + 15.0°, by means of *m*-chloroperbenzoic acid gave (*R*)-(+)-**8**, $[\alpha]_{589}$ +1.4°, with retention of configuration at phosphorus.

The results discussed above together with the direct conversion of (*R*)-(+)-**6** into (*R*)-(+)-**10** in the Arbuzov reaction[9a] enabled us to construct a new diligostatic, three-reaction cycle involving one ligand metathesis[11] (see Scheme I).

In the series of experiments with optically active acyclic P^{III} compounds we have demonstrated that Me_2SeO oxidation proceeds with inversion of configuration at phosphorus. However, when diastereomeric 2-methoxy-4-methyl-1,3,2-dioxaphosphorinanes (**11**)[12a] were used as model compounds net *retention of configuration at phosphorus* was observed. Thus, treatment of the diastereomerically pure *trans*-**11** with **1** at room temperature gave pure *trans*-phosphate **12**. Oxidation of *cis*-**11** containing 4% of the trans isomer with **1** at −10 °C yielded *cis*-phosphate **12**[12b] having a diastereomeric purity of 90%.

Scheme I





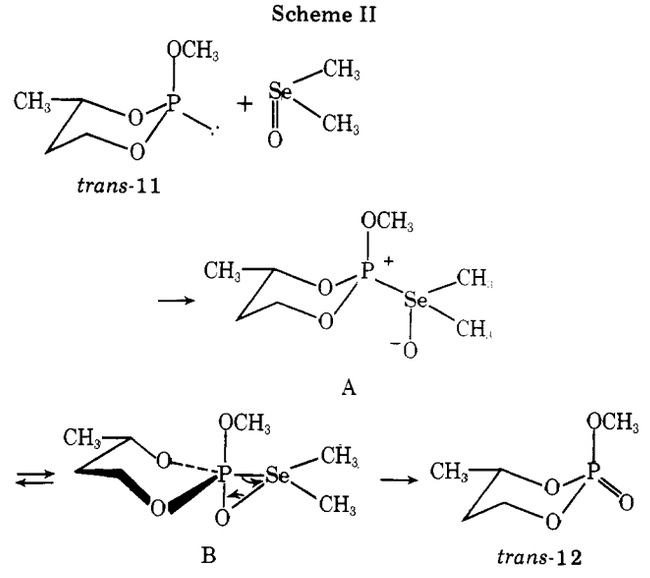
Retention at phosphorus observed in the oxidation of cyclic phosphites by Me_2SeO may be easily explained by the mechanistic sequence proposed in Scheme II.

It is reasonable to assume that the first step in the reaction between cyclic phosphites and **1** is the nucleophilic attack of phosphorus on the selenium atom of **1**, resulting in the formation of the "zwitterion" A. It may undergo then internal cyclization to give the intermediate phosphorane B, in which the six-membered ring spans two equatorial positions, the methoxy group and the three-membered ring oxygen atom occupy apical positions, and selenium occupies an equatorial position. This situation seems to us to be most convenient from the point of view of apicophilicity of substituents at phosphorus in trigonal-bypiramidal species.[13] Decomposition of the five-coordinate phosphorus intermediate B gives the phosphoryl compound with retention of configuration at phosphorus.

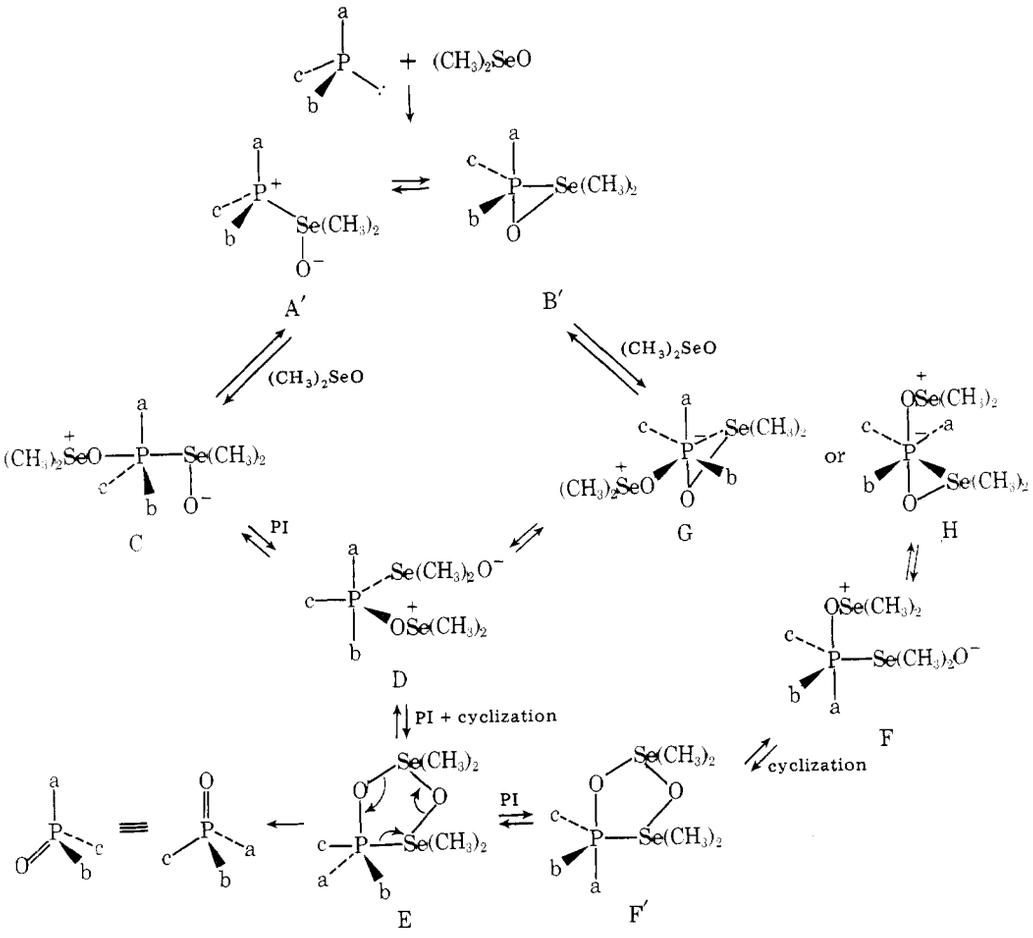
Since optically active acyclic trivalent phosphorus compounds were found to be oxidized by **1** with inversion of configuration at phosphorus, a different course of events should be considered (see Scheme III).

One can also assume that the phosphonium salt A′ and the pentacovalent phosphorus intermediate B′ are formed from **1** and acyclic P^{III} compounds.[14] However, the next step cannot be decomposition because it should give phosphoryl derivatives with retained configuration at phosphorus. We believe, therefore, that the second molecule of **1** attacks intermediate species A′ and B′ by means of the nucleophilic oxygen atom. The reaction of **1** with A′ should produce the phosphorane C, which after two permutational isomerizations (PI) and internal cyclization[15] should give the phosphorane E. Decomposition of E as depicted in Scheme III yields phosphoryl compound, dimethyl selenoxide, and dimethyl selenide. The overall stereochemistry of this cycle is inversion of configuration at phosphorus. If the phosphorane B′ is subjected to

Scheme II



Scheme III



nucleophilic attack by 1 the formation of two pentacoordinate phosphorus species D and F may be expected. The latter, after internal cyclization and one permutational isomerization, should also give the final pentacovalent phosphorus intermediate E, collapsing to the reaction products.

The transient formation of the hexacoordinate phosphorus anions G and H during the nucleophilic attack of 1 on B′ is an attractive hypothesis.[16]

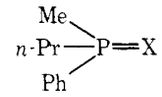
According to the mechanistic consideration presented above the opposite steric courses of the Me_2SeO oxidation of cyclic and acyclic systems may be attributed to the well-known difference in the sensitivity of cyclic and acyclic phosphorus compounds toward nucleophiles.[17]

Oxidation of Thio- and Selenophosphoryl Compounds by Dimethyl Selenoxide (1). As expected, dimethyl selenoxide (1) also reacts rapidly with thio- and selenophosphoryl compounds (13) at room temperature to give phosphoryl compounds (3), dimethyl selenide, and sulfur or selenium. The reaction is practically quantitative and the yields of the isolated phosphoryl derivatives 3 exceed 90%. Some representative examples are shown below.

$$R_3P{=}X + 1 \longrightarrow R_3P{=}O + CH_3SeCH_3 + X$$

13a, R = Ph; X = Se — 3a,b,d
b, R = EtO; X = Se
c, R = *n*-Bu; X = S

Since the stereochemistry and mechanism of the conversion of thio- and selenophosphoryl compounds into oxygen analogues have recently attracted attention in many laboratories[18] as well as in connection with our studies on the stereochemistry of this conversion by means of dimethyl sulfoxide,[4b,c] we have investigated the stereochemistry of the reaction now reported. It was found that oxidation of the optically active (*S*)-(−)-methylphenyl-*n*-propylphosphine sulfide



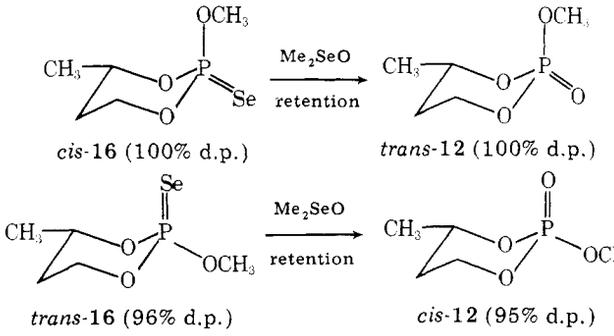
(*S*)-14, X = S, $[\alpha]_{589}$ −18.73° (84.2% o.p.)
(*S*)-15, X = Se, $[\alpha]_{589}$ −19.48° (100% o.p.)

(*R*)-5, $[\alpha]_{589}$ +14.4° (72% o.p.)
(*R*)-5, $[\alpha]_{589}$ +20.0° (100% o.p.)

(**14**)[19] and (*S*)-(−)-methylphenyl-*n*-propylphosphine selenide (**15**)[20] by 1 leads to (*R*)-(+)-phosphine oxide (**5**)[8] and is accompanied *by inversion of configuration at phosphorus.*

Conversely, oxidation of cyclic *cis*- and *trans*-2-methoxy-2-seleno-4-methyl-1,3,2-dioxaphosphorinane (**16**)[18] by 1 was found to take place with full *retention at phosphorus* to give *trans*- and *cis*-phosphate **12,** respectively.

The results described above show that the steric course of oxidation of cyclic and acyclic thio- and selenophosphoryl

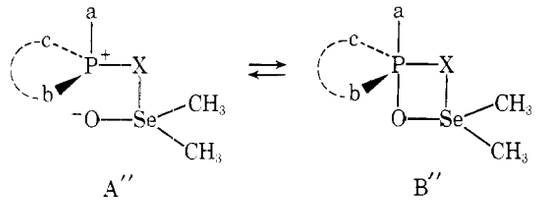


cis-16 (100% d.p.) — *trans*-12 (100% d.p.)

trans-16 (96% d.p.) — *cis*-12 (95% d.p.)

compounds by dimethyl selenoxide and by dimethyl sulfoxide[4b,c] is the same.

As in the case of the oxidation of cyclic 1,3,2-dioxaphosphorinanes and acyclic P^{III} compounds by Me_2SeO, the different stereochemistry of the oxidation of cyclic and acyclic thio(seleno)phosphoryl systems may be rationalized by assuming the formation of the intermediate adduct A″ or phosphorane B″, the mode of decomposition of which is dependent on the nature of substituents connected with the phosphorus atom.



A″ B″

X = S, Se

In the case of cyclic six-membered systems, which are less susceptible to nucleophilic attack at phosphorus, the intramolecular decomposition of these intermediates should be favored and would involve retention at phosphorus. On the other hand, nucleophilic attack of the second molecule of Me_2SeO on A″ or B″ containing acyclic substituents, followed by loss of dimethyl selenide and sulfur or selenium, would provide an alternative route to phosphoryl compounds accompanied by inversion at phosphorus.

Oxidation of Thiocarbonyl Compounds by Dimethyl Selenoxide (1). Selective Modification of 4-Thiouracil Nucleosides and Nucleotides. The present study on application of dimethyl selenoxide (1) as oxidizing agent was extended to thiocarbonyl compounds. In contrast to the electrophile-catalyzed Me_2SO oxidation,[4a,c] treatment of simple thioureas (17) with Me_2SeO itself at room temperature results in a clean conversion to the corresponding ureas (18).

$$(RNH)_2C{=}S + 1 \longrightarrow (RNH)_2C{=}O + CH_3SeCH_3 + S$$

17a–e 18a–e

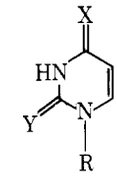
17a, R = H
b, R = *i*-Pr
c, R = *t*-Bu
d, R = c-Hex
e, R + R = $-CH_2CH_2-$

This new and extremely mild oxidation procedure of the thiocarbonyl group is of great importance from the point of view of chemical modification of nucleic acids. Following the discovery of 4-thiouridine in tRNA of *E. coli*,[21] many methods have been developed for the chemical transformation of the thio base[22] in order to elucidate the biochemical role of this minor component of tRNA. In the course of our studies we have used Me_2SO in the presence of acids or catalytic amounts of iodine.[5] However, as it has been mentioned above, there are some limitations connected with this method. This prompted an investigation of the Me_2SeO oxidation of thiouracils and higher nucleic acid components containing a thiocarbonyl group.

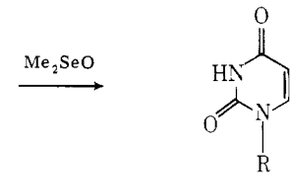
The reaction between thiouracils **19a–d** and 1 was carried out in methanol or methanol–chloroform mixture at 40 °C for ~6 h and it has been shown by TLC to give uracil **20a** isolated in 80–90% yields. Oxidation of 4-thiouridine (**19d**) by Me_2SeO in ethanol at room temperature afforded uridine (**20b**) in 82% yield.

Finally, oxidation of uridylyl-(3′-5′)-4-thiouridine (21) by Me_2SeO was investigated in order to show that the internucleotidic bond is stable under the reaction conditions. Also in this case quantitative conversion of the unprotected **21** into **22** was achieved at room temperature in ethanol solution.

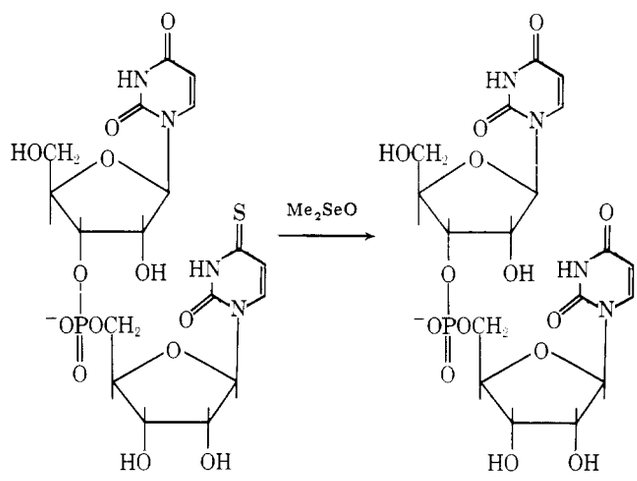
It should be pointed out that the ease with which thiouracils, 4-thiouridine, and thionucleotide **21**, are oxidized by



19a, Y = S; X = O; R = H
b, Y = O; X = S; R = H
c, Y = S; X = S; R = H
d, Y = O; X = S; R = ribofuranosyl



20a, R = H
b, R = ribofuranosyl



21, UpU^s[4] 22, UpU

Me_2SeO as well as the fact that no degradation of the sugar moiety and no breaking of the internucleotide bond was observed under the experimental conditions employed could permit selective modification of the 4-thiouracil residues in tRNA. Studies in this direction are in progress in our Laboratory.

Experimental Section

General. Melting points and boiling points are uncorrected. ^1H NMR spectra were recorded on a R12B Perkin-Elmer spectrometer (Me_4Si as internal standard). ^{31}P NMR spectra were obtained on a Jeol JNM-C-60 H1 spectrometer (85% H_3PO_4 as external standard). In this paper the new convention of positive ^{31}P signals to low field from H_3PO_4 is used. IR spectra were recorded on a Spektromom 2000 spectrophotometer. Thin-layer chromatograms for analytical purposes were run on glass plates (5 × 20 cm) coated with a 2-mm layer of silica gel GF_{254} (Merck). Column chromatography was done on silica gel (Merck, 100–200 mesh) using the Laboratory Data Control set containing dual wavelength UV absorbance detector (254 and 280 nm), constametric IIG, and recorder 3402 units. GLC analysis was carried out with Varian Aerograph Model 1520 flame ionization gas chromatograph. Optical activity measurements were made with a Perkin-Elmer 241 MC photopolarimeter; concentrations of the solutions were about 2 g/100 mL.

Dimethyl selenoxide (1) was prepared according to Poetzold et al.[23] from dimethyl selenide via the dibromo derivative.[24]

Oxidation of Triphenylphosphine (2a) by Dimethyl Selenoxide (1). To a solution of triphenylphosphine (**2a**) (1.3 g, 0.005 mol) in chloroform (5 mL) an excess of **1** (0.75 g, 0.006 mol) in chloroform (5 mL) was added at room temperature. The reaction progress was controlled by TLC (R_f 0.88 and 0.12 for **2a** and **3a**, respectively). After 1 h dimethyl selenide was distilled off and trapped by an ethanol solution of mercury(II) chloride [0.5 g of $(CH_3)_2Se{\cdot}HgCl_2$, yield 91%, mp 150–152 °C (lit.[25] 151–153 °C)]. After cooling, chloroform (5 mL) was added and the organic layer was washed with water (3 × 3 mL), dried,

Table I. Oxidation of Trivalent Phosphorus, Thio(seleno)phosphoryl and Thio(seleno)carbonyl Compounds by Dimethyl Selenoxide 1

Substrate	Registry no.	Product	Registry no.	Yield, %	Physical data (lit. data)
2a, Ph_3P	603-35-0	**3a,** Ph_3PO	791-28-6	100	mp 156–158 °C (mp 154–157 °C[26])
2b, $(EtO)_3P$	122-52-1	**3b,** $(EtO)_3PO$	78-40-0	83	bp 90 °C (8 mmHg), n^{23}_D 1.4058, δ_{31P} − 1.0
2c, $(Me_2N)_3P$	1608-26-0	**3c,** $(Me_2N)_3PO$	680-31-9	84	bp 100 °C (0.2 mmHg)
13a, Ph_3PSe	3878-44-2	**3a,** Ph_3PO		100	mp 155–158 °C
13b, $(EtO)_3PSe$	2651-89-0	**3b,** $(EtO)_3PO$		92	bp 80 °C (15 mmHg), n^{20}_D 1.4062
13c, *n*-Bu_3PS	3084-50-2	**3d,** *n*-Bu_3PO	814-29-9	76	bp 90 °C (0.9 mmHg), δ_{31P} +43.7 (δ_{31P} +43.2[27])
17a, $(H_2N)_2CS$	62-56-6	**18a,** $(H_2N)_2CO$	631-62-9	81	mp 148–151 °C (mp 140–151 °C[28])[a]
17b, $(i\text{-}PrNH)_2CS$	2986-17-6	**18b,** $(i\text{-}PrNH)_2CO$	4128-37-4	84	mp 188–192 °C (mp 192 °C[29])
17c, $(t\text{-}BuNH)_2CS$	4041-95-6	**18c,** $(t\text{-}BuNH)_2CO$	5336-24-3	86	mp 239–242 °C (mp 242 °C[30])
17d, $(c\text{-}C_6H_{11}NH)_2CS$	1212-29-9	**18d,** $(c\text{-}C_6H_{11}NH)_2CO$	2387-23-7	93	mp 225–228 °C (mp 229–230 °C[31])
17e, c-$NHCH_2$-$CH_2NHC(=S)$	96-45-7	**18e,** c-$NHCH_2$-$CH_2NHC(=O)$	120-93-4	77	mp 130–135 °C (mp 131 °C[32])

[a] Mp refers to the complex of urea with oxalic acid, $2Co(NH_2)_2{\cdot}H_2C_2O_4$.

and evaporated to give triphenylphosphine oxide (**3a**) (1.35 g, 100%, mp 154–157 °C). Recrystallization from benzene–petroleum ether afforded analytically pure phosphine oxide **3a** [1.2 g, mp 156–158 °C (lit.[26] mp 154–157 °C)].

The experimental results concerning oxidation of triethyl phosphite (**2b**) and hexaethyl phosphorotriamidite (**2c**) are given in Table I.

Conversion of (*R*)-(−)-Methylphenyl-*n*-propylphosphine (4) to Phosphine Oxide (*R*)-(+)-5 by Means of Dimethyl Selenoxide (1). To a solution of **4** (0.24 g, 0.0014 mol), $[\alpha]_{589}$ −4.6° (toluene), in chloroform (5 mL) a small molar excess of **1** in chloroform was added. After 15 min, chloroform and dimethyl selenide were removed and water (5 mL) was added to the residue. The aqueous layer was extracted with chloroform (3 × 5 mL) and the organic layer was dried over $MgSO_4$ and evaporated. The residue was distilled to give (*R*)-(+)-methylphenyl-*n*-propylphosphine oxide (**5**), 0.16 (64%), $[\alpha]_{589}$ +4.31° (methanol), δ_{31P} +42.46 ppm.

Under the same conditions phosphine (*S*)-(+)-**4,** $[\alpha]_{589}$ +15.21° (toluene) and $[\alpha]_{589}$ +9.36° (toluene), was converted into phosphine oxide (*S*)-(−)-**5,** having $[\alpha]_{589}$ −14.80° (methanol) and $[\alpha]_{589}$ −9.25° (methanol), respectively.

Reaction of (*R*)-(+)-*O*-Methyl Ethylphenylphosphinite (6) with Dimethyl Selenoxide (1). To a stirred solution of **6** (0.6 g, 0.0035 mol), $[\alpha]_{589}$ +21.0° (benzene), in chloroform (5 mL) **1** (0.5 g, 0.004 mol) in methanol or chloroform (5 mL) was added at −20 °C. After stirring at room temperature for 10 min the reaction mixture was treated with water (10 mL) and the reaction product was extracted with chloroform (3 × 10 mL). The chloroform layer was dried over anhydrous $MgSO_4$ and evaporated to afford (*S*)-(−)-*O*-methyl ethylphenylphosphinate (**8**) purified by distillation: 0.55 g (84%); bp 95–98 °C (0.5 mmHg); n^{22}_D 1.5213; $[\alpha]_{589}$ −2.9° (methanol); δ_{31P} +49.95 ppm.

Oxidation of (*R*)-(+)-*O*-Methyl Ethylphenylphosphinite (6) by *m*-Chloroperbenzoic Acid. To a solution of **6** (0.5 g, 0.003 mol), $[\alpha]_{589}$ +15.0° (benzene), in ether (5 mL) a solution of *m*-chloroperbenzoic acid (0.75 g, 0.0043 mol) in ether (15 mL) and benzene (1 mL) was added at room temperature. After the usual workup and distillation at 0.2 mmHg, phosphinate (*R*)-(+)-**8** was obtained, $[\alpha]_{589}$ +1.4° (*c* 4.5, methanol). The ester was identical in all respects with that prepared as described above.

Reaction of (*S*)-(−)-*S*-Ethyl Ethylphenylthiophosphinite (7) with Dimethyl Selenoxide (1). A solution of 0.6 g (0.003 mol) of **7,** $[\alpha]_{589}$ −4.58° (neat), in chloroform (10 mL) was treated with an equimolar amount of **1** (0.375 g) in chloroform (5 mL) at −10 °C. After stirring for 10 min at room temperature water (20 mL) was added to the reaction mixture. The aqueous layer was extracted with chloroform (3 × 10 mL). The combined chloroform extracts were dried and evaporated to give the crude (*R*)-(+)-*S*-ethyl ethylphenylthiophosphinate (**9**) purified by distillation: 0.5 g (78%); n^{21}_D 1.5298; $[\alpha]_{589}$ +1.58° (benzene); δ_{31P} +53.3 ppm.

Conversion of (*S*)-(−)-*O*-Methyl Ethylphenylphosphinate (8) to (*S*)-(−)-Methylethylphenylphosphine Oxide (10). A solution of methylmagnesium iodide prepared from methyl iodide (0.55 g) and magnesium (0.08 g) in ether (20 mL) was treated with **8,** $[\alpha]_{589}$ − 2.9° (0.55 g, 0.003 mol) in ether (5 mL). The reaction was then quenched with saturated aqueous ammonium chloride (10 mL). The layers were separated and the aqueous layer was extracted with chloroform (3 × 10 mL). The organic layers were combined, dried, and evaporated. After distillation at 0.4 mmHg (*S*)-(−)-methylethylphenylphosphine oxide (**10**) was obtained: 0.3 g (60%); $[\alpha]_{589}$ −0.99° (methanol); δ_{31P} +44.55 ppm. The material was identical by TLC with **10** prepared by us in another study.[9]

Oxidation of *trans*-2-Methoxy-4-methyl-1,3,2-dioxaphosphorinane (11) by Dimethyl Selenoxide (1). A solution of *trans*-**11** (1.5 g, 0.01 mol) in benzene (10 mL) was treated with **1** (1.375 g, 0.011 mol) in benzene (5 mL) at room temperature. After a few minutes benzene and dimethyl selenide were removed and chloroform (20 mL) was added. The organic layer was washed with water, dried, and evaporated to give *trans*-2-methoxy-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (**12**) isolated by distillation: 0.72 g (85%); bp 95 °C (0.1 mmHg). The product was diastereomerically pure by GLC.

Oxidation of *cis*-11 by 1. To a solution of **11** (1.5 g, 0.01 mol) consisting of *cis*-**11** (96%) and *trans*-**11** (4%) in benzene–chloroform (15 mL–5 mL) a solution of **1** (1.375 g, 0.011 mol) in chloroform (5 mL) was added at −10 °C. The workup as described above gave *cis*-2-methoxy-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (**12**) as a 90% diastereomerically pure sample (GLC assay); 1.38 g (82%); bp 92 °C (0.1 mmHg).

Reaction of Triphenylphosphine Selenide (13a) with Dimethyl Selenoxide (1). A solution of triphenylphosphine selenide (**13a**) (0.345 g, 0.001 mol) in chloroform (10 mL) was treated with **1** (0.13 g, 0.00104 mol) in chloroform (2 mL). After 15 min dimethyl selenide was distilled off and trapped by an ethanol solution of mercury(II) chloride (0.103 g of $(CH_3)_2Se{\cdot}HgCl_2$, yield 94%). To a residual solution, after cooling, chloroform (10 mL) was added and selenium (0.079 g, 100%) was filtered off. The chloroform solution was washed with water, dried, and evaporated to give triphenylphosphine oxide (**3a**); 0.278 g (100%); mp 155–158 °C; R_f 0.20 for **3a,** R_f 0.78 for **13a** (benzene–ethyl acetate, 1:1).

The experimental results concerning oxidation of triethyl selenophosphate (**13b**) and tri-*n*-butylphosphine sulfide (**13c**) are given in Table I.

Conversion of (*S*)-(−)-Methylphenyl-*n*-propylphosphine Sulfide (14) to (*R*)-(+)-Methylphenyl-*n*-propylphosphine Oxide (5) by Means of Dimethyl Selenoxide (1). To a solution of **14** (0.215 g, 0.001 mol), $[\alpha]_{589}$ −18.73° (methanol), in chloroform (5 mL) was added a solution of **1** (0.1375 g, 0.0011 mol) in chloroform (2 mL). After few minutes methanol (5 mL) was added to the reaction mixture and sulfur (0.029 g, 90%) was filtered off. The filtrate was evaporated and water (10 mL) was added to the residue. The aqueous layer was extracted with ether (3 mL) and then with chloroform (3 × 3 mL). The combined organic extracts were dried and evaporated. The residue was distilled to give 0.137 g (76%) of (*R*)-(+)-methylphenyl-*n*-propylphosphine oxide (**5**), $[\alpha]_{589}$ +14.4° (methanol).

Conversion of (*S*)-(−)-Methylphenyl-*n*-propylphosphine Selenide (15) to (*R*)-(+)-Methylphenyl-*n*-propylphosphine Oxide (5) by Means of Dimethyl Selenoxide (1). A solution of **15** (54 mg, 0.00022 mol), $[\alpha]_{578}$ −19.48° (methanol), in benzene (5 mL) was treated with **1** used in small molar excess. Selenium (17.2 mg, 100%) was filtered off and the filtrate evaporated. The residue was treated with water (3 mL) and the aqueous phase was extracted with chloroform (3 × 3 mL). The organic layer was dried and evaporated to give **5** isolated by distillation: 32 mg (80%); $[\alpha]_{589}$ +20.0 (methanol); δ_{31P} +42.4 ppm.

Oxidation of *cis*-2-Methoxy-2-seleno-4-methyl-1,3,2-dioxaphosphorinane (16) by Dimethyl Selenoxide (1). To a solution of *cis*-**16** (1.15 g, 0.005 mol) in chloroform (10 mL) an equimolar amount

of **1** in chloroform was added. After a few minutes dimethyl selenide formed and was distilled off and trapped by an ethanol solution of mercury(II) chloride [0.47 g of $(CH_3)_2Se{\cdot}HgCl_2$, 93%]. The reaction mixture was then treated with chloroform (5 mL), cooled, and filtered in order to remove selenium (0.39 g, 100%). The chloroform solution was washed with water, dried, and evaporated to afford ***trans*-12** purified by distillation: 0.7 g (83%); bp 94 °C (0.2 mm). The product was identical (^{31}P NMR and GLC assay) with an authentic sample.[12b]

Oxidation of *trans*-16 by 1. Oxidation of *trans*-**16** (1.15 g, 0.005 mol) as a 96% diastereomerically pure sample according to the procedure described above gave selenium (0.39 g, 100%) and *cis*-**12** (0.74 g, 88%) having a diastereomeric purity 95% (GLC assay).

Oxidation of Thiourea (17a) by Dimethyl Selenoxide (1). To a solution of **17a** (0.76 g, 0.01 mol) in a mixture of chloroform and ethanol (5 mL, 1:1) a solution of **1** (1.375 g, 0.011 mol) in chloroform (5 mL) was added at room temperature. After 1 h sulfur (0.28 g, 87%) was filtered off. The filtrate was concentrated and treated with an acetone solution of oxalic acid. After 12 h the complex of urea (**18a**) with oxalic acid, $2CO(NH_2)_2{\cdot}H_2C_2O_4$, that crystallized was collected: 1.7 g (81%); mp 148–151 °C (lit.[28] mp 140–151 °C).

Oxidation of Diisopropylthiourea (17b) by 1. 17b (0.8 g, 0.005 mol) was dissolved in a mixture of chloroform and methanol (5 mL, 1:1) and treated with an equimolar amount of **1** in chloroform. After 1.5 h methanol (15 mL) was added to the reaction mixture and sulfur (0.13 g, 81%) filtered off. The filtrate was evaporated and the residue was crystallized from ethanol to give diisopropylurea (**18b**): 0.61 g (84%); mp 188–192 °C (lit.[29] mp 192 °C).

Oxidation of other thioureas (**17c, 17d,** and **17e**) was carried out according to the procedure described above. The results are summarized in Table I.

Oxidation of Thiouracils 19 by Dimethyl Selenoxide (1). General Procedure. Thiouracil **19** (0.005 mol) dissolved in a mixture of methanol (2.5 mL) and chloroform (2.5 mL) was treated with **1** (0.0055 mol). The reaction mixture was heated at 40 °C for 6 h. Dimethyl selenide which distilled off during the reaction was trapped by an ethanol solution of mercury(II) chloride. After cooling and addition of methanol, sulfur was filtered off. Then, the solution was evaporated and the crude product, **20,** was isolated by column chromatography on silica gel (GF_{254}).

The purity of uracil **20** was controlled by TLC using isopropyl alcohol–ammonia–water (7:1:2) as developing system; in the case of uridine (**20b**) butanol–water (86:14) was used: R_f 0.78 for **19a,** 0.80 for **19b,** 0.89 for **19c,** 0.40 for **19d,** 0.72 for **20a,** and 0.18 for **20b.**

From **19a, 19b,** and **19c** uracil **20a** was obtained in 90, 85, and 79% yield, respectively. Oxidation of 4-thiouridine (**19d**) afforded uridine **20b** in 82% yield.

Synthesis of Uridylyl-(3′-5′)-4-thiouridine (21). To a solution of the calcium salt of 2′-*O*-tetrahydropyranyl-5′-*O*-acetyluridine 3′-phosphate[33] (100 mg, 2×10^{-4} mol) Dowex 50X(H^+) was added. After few minutes the ion exchanger was filtered off and the filtrate was concentrated at 10 °C. The residue was coevaporated with three portions of pyridine and dissolved in anhydrous pyridine (3 mL). To this solution 2′-3′-isopropylidene-4-thiouridine[34] (300 mg) in pyridine (10 mL) was added and then dicyclohexylcarbodiimide (0.5 g). The reaction mixture was left to stand for 72 h at room temperature and then treated with water (12 mL) and pyridine (10 mL). After 8 h the reaction solution was extracted with petroleum ether in order to remove unreacted carbodiimide, filtered, and evaporated. The residue was kept with a dioxane–ammonia (1:1, 10 mL) mixture for 12 h at room temperature. After evaporation of solvents the concentrate was dissolved in ethanol and acetic acid and refluxed for 20 min. Then the solution was concentrated at 0.2 mmHg and coevaporated with methanol. The residue was dissolved in pyridine and chromatographed on a paper Whatman 3MM using isopropyl alcohol–ammonia–water (7:1:3) as solvent system. The fraction containing the title compound **21,** R_f 0.20, was extracted with water. Evaporation of the water solution afforded **21**;[35] 35 mg (30%).

Compound **21** (3 mg) was dissolved in water (0.1 mL) and treated with aqueous ammonia (pH 8) and then with the pancreatic ribonuclease solution. After the incubation for 5 h the mixture was chromatographed on a glass plate covered with cellulose using isopropyl alcohol–ammonia–water (7:1:2) as developing system. Two spots, R_f 0.13 and 0.38, were observed which correspond to uridine 3′-phosphate and 4-thiouridine, respectively.

Conversion of 21 to 22 by Means of Dimethyl Selenoxide (1). A sample of 13 mg (2×10^{-5} mol) of **21** was dissolved in ethanol and treated with **1** in methanol. After 24 h the solvents were evaporated and the product, **22,** was isolated by preparative TLC using butanol–water (86:14) as developing system: R_f 0.52.

In order to confirm the structure it was dissolved in aqueous pyridine solution and treated with the pancreatic ribonuclease solution for 48 h at room temperature. The solution was concentrated and subjected to paper electrophoresis on Whatman No 1 paper. Two spots, R_f 1.00 and 0.17, were observed which correspond to uridine 3′-phosphate and uridine, respectively.

Acknowledgment. We thank Dr. J. Omelańczuk for providing us with the results of oxidation of optically active phosphinite **8** with *m*-chloroperbenzoic acid.

Registry No.—**1,** 4371-90-8; (*R*)-**4,** 13153-89-4; (*S*)-**4,** 701-03-1; (*R*)-**5,** 17170-48-8; (*S*)-**5,** 1515-99-7; (*R*)-**6,** 57322-07-3; (*S*)-**7,** 62621-07-2; (*S*)-**8,** 65665-33-0; (*R*)-**9,** 65665-34-1; (*S*)-**10,** 26515-05-9; *trans*-**11,** 7735-81-1; *cis*-**11,** 7735-85-5; *trans*-**12,** 33996-03-1; *cis*-**12,** 33996-04-2; (*S*)-**14,** 13153-91-8; (*S*)-**15,** 34641-79-7; *cis*-**16,** 33996-02-0; *trans*-**16,** 33996-01-9; **19a,** 141-90-2; **19b,** 591-28-6; **19c,** 2001-93-6; **19d,** 13957-31-8; **20a,** 66-22-8; **20b,** 58-96-8; **21,** 22249-22-5; **22,** 2415-43-2; 2′-*O*-tetrahydropyranyl-5′-*O*-acetyluridine 3′-phosphate calcium salt, 65665-35-2; 2′,3′-isopropylidene-4-thiouridine, 14795-36-9.

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(15) We assumed that the formation of the five-membered ring is more probable in apical and equatorial positions.
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Retention at phosphorus observed during oxidation of cyclic phosphites **11** may be also explained by assuming that the second Me_2SeO molecule attacks the intermediate A to give the phosphorane in which the six-membered ring spans apical and equatorial positions, the methoxy group occupies an equatorial position, and the selenium and oxygen atoms of two Me_2SeO molecules forming the five-membered ring are in equatorial and apical position, respectively.
On the other hand, inversion at phosphorus observed in the case of oxidation of acyclic trivalent phosphorus compounds may be a consequence of a nucleophilic attack of A′ by means of the negatively charged oxygen atom on the second Me_2SeO molecule and the decomposition of this intermediate via the cyclic phosphorane in which the selenium and oxygen atoms of two Me_2SeO molecules forming the five-membered ring occupy two equatorial positions. These mechanistic possibilities are currently being investigated.
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Heavy-Atom Effect in Photoisomerization of 4-Pyrones and 4-Pyridones

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Received March 21, 1977

Internal and external heavy-atom effects were applied to determine the excited state involved in photoisomerization of 2,6-dimethyl-3,5-bis(para-substituted phenyl)-4-pyrones to 3,6-bis(para-substituted phenyl)-4,5-dimethyl-2-pyrones. A similar method was used in the photorearrangement of 1,2,6-trimethyl-3,5-bis(para-substituted phenyl)-4-pyridones to 1,4,6-trimethyl-3,5-bis(para-substituted phenyl)-2-pyridones. Both 4-pyrones and 4-pyridones phosphoresce at 77 K from the π,π^* triplet state and show a shorter phosphorescence lifetime with increasing atomic number of the halogen substituents. Quantum yields of both the photoisomerization and intersystem crossing of these 4-pyrones and 4-pyridones are not internally dependent on the atomic number of the substituent. Addition of the heavy-atom solvent (*n*-butyl bromide) decreases quantum yield of photoisomerization and increases intersystem crossing efficiency from the singlet to triplet excited states. This photoisomerization was not quenched by dienes, indicating that the photoisomerization of both 4-pyrones and 4-pyridones proceeds via their π,π^* singlet.

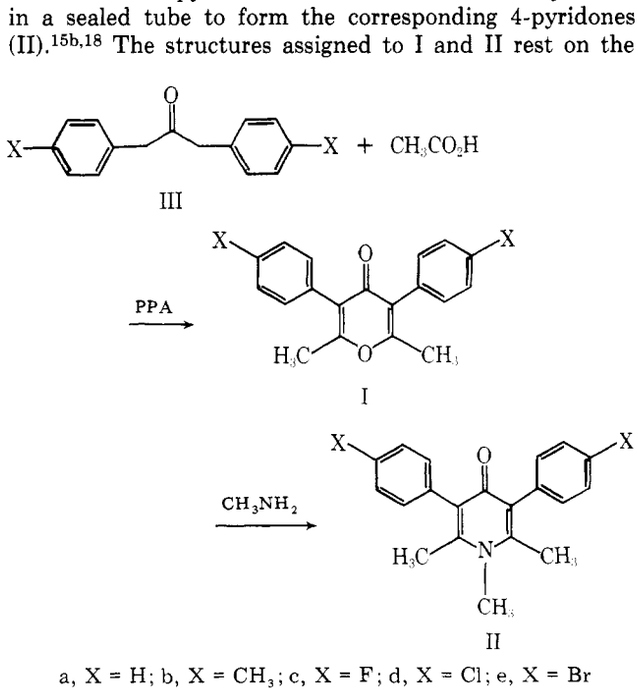
Although internal and external heavy-atom effects on photophysical processes have been extensively investigated using the spectroscopic and theoretical methods,[2-5] studies on a heavy-atom effect on a photochemical reaction have been relatively few until the discovery by Cowan and Drisco[6] that the photodimerization of acenaphthylene was beneficially perturbed when a heavy-atom solvent was present. Somewhat later, a heavy-atom effect was widely utilized in the photochemical cycloaddition of acenaphthylene to acrylonitrile,[7] pentadiene,[8] cyclopentadiene,[9] and maleic anhydride.[10] The effect was also observed in the photochemical isomerization of bicyclo[4.2.1]nona-2,4-dienes[11] and bromostilbenes[12] and in the photoabstraction–cyclization of methyl *o*-benzyloxyphenylglyoxylate.[13]

We recently reported the photoisomerization of 4-pyrones to 2-pyrones[14] and of 4-pyridones to 2-pyridones.[15] Evidence was given to support the idea that the photorearrangement of the 4-pyridone[15] occurred in the excited singlet state, although the photoexcited state responsible for the photoisomerization of 4-pyrones[14] was not determined and further study has remained.

We now wish to report a study illustrating an application of a heavy-atom effect in determining the excited state involved in the photoisomerization of 4-pyrones. Emission spectra of 2,6-dimethyl-3,5-bis(para-substituted phenyl)-4-pyrones (I) were measured and the quantum yield in the photoisomerization of I, perturbed internally or externally by a heavy atom, was also determined. A similar study was extended to the photorearrangement of 1,2,6-trimethyl-3,5-bis(para-substituted phenyl)-4-pyridones (II). Comparison of the internal and external heavy-atom effects in the photoisomerization of I with those in the photorearrangement of II was anticipated to determine the nature of the excited state involved in the photoreaction of I, since the excited state responsible for the photoreaction of II was firmly established.[15]

Results and Discussion

2,6-Dimethyl-3,5-bis(para-substituted phenyl)-4-pyrones (I) were prepared by condensation of para,para'-disubstituted bibenzyl ketone (III) with acetic acid in the presence of polyphosphoric acid (PPA) as employed for the synthesis of Ia.[16,17] These 4-pyrones were condensed with methylamine in a sealed tube to form the corresponding 4-pyridones (II).[15b,18] The structures assigned to I and II rest on the



a, X = H; b, X = CH_3; c, X = F; d, X = Cl; e, X = Br

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