Oxidation of the 2-*sec*-butyl isomer by the procedure used for the oxidation of 2-(1-phenylethyl)pyrrole gave on distillation 2-methylbutyric acid: bp 165–175°; $n^{25}D$ 1.4048; $[\alpha]^{25}D$ +15.31 ± 0.01° (neat) (lit.[18] bp 176–177.5°; $n^{25}D$ 1.4042). The ir spectrum of the acid was identical with that obtained from an authentic sample. Assuming that the value of $[\alpha]^{25}D$ +20.5° [6,17] represents the rotation of 100% optically pure acid, the 2-methylbutyric acid obtained on oxidation was 75% optically pure. The isomerization from the N to the 2 position occurred with 77% retention of configuration.

The structure of the 2-(*sec*-butyl)-3,5-dimethylpyrrole was confirmed by synthesis from 2,4-dimethylpyrrylmagnesium bromide and *sec*-butyl bromide. The glpc retention times and nmr and ir spectra were identical with those of authentic samples.

(+)-3-(*sec*-Butyl)-2,5-dimethylpyrrole was purified by glpc (12 ft × 0.375 in. 20% Apiezon L column at 170°): purity, 99.4%; mp 28°; d^{28} 0.8859 g/ml; $[\alpha]^{25}D$ +30.1 ± 0.2° (*c* 8.46, CCl_4); $\nu_{max}^{CCl_4}$ 3840 cm^{-1} (N–H); λ_{max}^{MeOH} 211 mμ (ε 6900); nmr spectrum, 0.75 (triplet, 3 H), 1.05 (doublet, 3 H), 1.34 (multiplet, 2 H), 2.00 (singlet, 3 H), 2.03 (singlet, 3 H), 2.31 (multiplet, 1 H), 5.46 (doublet, 1 H), 6.95 ppm (singlet, 1 H).

Anal. Calcd for $C_{10}H_{17}N$: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.25; H, 11.06; N, 9.21.

(18) K. B. Wiberg and T. W. Hutton, *J. Amer. Chem. Soc.*, **78**, 1640 (1956).

Oxidation produced 2-methylbutyric acid: $n^{25}D$ 1.4056; $[\alpha]^{25}D$ +15.11 ± 0.01° (neat); 74% optical purity. The isomerization to the 3 position occurred with 76% retention of configuration.

The glpc retention time and the ir and nmr spectra of the product obtained from reaction of 2,5-dimethylpyrrylmagnesium bromide with *sec*-butyl bromide were identical with those obtained from the 3-*sec*-butyl isomer produced on pyrolysis.

Registry No.—N-(1-Phenethyl)pyrrole, 17289-34-8; (+)-N-(1-phenethyl)pyrrole, 13245-05-1; N-(*sec*-butyl)-pyrrole, 17289-36-0; (+)-N-(*sec*-butyl)pyrrole, 13245-04-0; (+)-N-(1-phenylethyl)-2,5-dimethylpyrrole, 17289-38-2; (+)-N-(*sec*-butyl)-2,5-dimethylpyrrole, 17289-39-3; (+)-2-(1-phenylethyl)pyrrole, 13245-06-2; (+)-3-(1-phenylethyl)pyrrole, 13245-07-3; (+)-2-(*sec*-butyl)pyrrole, 17289-42-8; (+)-3-(*sec*-butyl)pyrrole, 17289-43-9; (+)-2-(1-phenylethyl)-3,5-dimethylpyrrole, 17289-44-0; (−)-3-(1-phenylethyl)-2,5-dimethylpyrrole, 17289-45-1; (+)-2-(*sec*-butyl)-3,5-dimethylpyrrole, 17289-46-2; (+)-3-(*sec*-butyl)-2,5-dimethylpyrrole, 17289-47-3.

Studies on Pyrimidine Derivatives and Related Compounds. LVIII.[1] Reaction of Dialkyl Acylphosphonates with 3-Benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium Halides (Takamizawa Reaction 7)

AKIRA TAKAMIZAWA, YOSHIO HAMASHIMA, AND HISAO SATO

Shionogi Research Laboratory, Shionogi and Company, Ltd., Fukushima-ku, Osaka, Japan

Received March 19, 1968

The novel reactions of 3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium salts (**9a–c**) with diethyl benzoyl- or diethyl acetylphosphonate (**3a** or **b**) producing 2-phenyl-3-oxo-4-benzyl-5-methyl-6-(2-benzoyloxy)ethyl-2,3-dihydro-4H-1,4-thiazine (**8**) and 2-methyl-3-oxo-4-benzyl-5-methyl-6-(2-benzoyloxy)ethyl-2,3-dihydro-4H-1,4-thiazine (**17**) afforded 2-(1-diethylphosphoroyl)benzyl-3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium salts (**10a–c**) or 2-(1-diethylphosphoroyl)ethyl-3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium bromide (**16**) as the intermediates. 3-Alkylimino-2,3-dihydro-4H-1,4-thiazine derivatives (**20–22** and **24**) were also obtained by the reaction of **10b** or **16** with ammonia or primary amines. The reaction of **10b** with dimethylamine gave 2-phenyl-3-dimethylamino-4-benzyl-5-methyl-6-(2-benzoyloxy)ethyl-4H-1,4-thiazine (**23**). The reaction of **16** with dimethylamine gave **17** unexpectedly. The rearrangement of **10b** to **8** was kinetically studied by measuring the successive changes in the ultraviolet absorption spectra. The mechanism of this novel reaction involving ring conversion was discussed. The reaction mechanism of thiamine with dialkyl acylphosphonates producing 1-alkyl-3-(2-hydroxy)ethyl-4,9-dimethyl-1,6-dihydropyrimido[4′,5′:4,5]pyrimido[2,3-*d*][1,4]thiazine (**4**) was also discussed briefly.

In previous papers,[2–4] we reported that the reaction of thiamine (B_1) with dialkyl acylphosphonate involving a novel conversion of thiazolium moiety into thiazine afforded tricyclic 1-alkyl-3-(2-hydroxy)ethyl-4,9-dimethyl-1,6-dihydropyrimido[4′,5′:4,5]pyrimido-[2,3-*d*][1,4]thiazine (**4**), which was quite easily hydrolyzed to give 2-alkyl-3-oxo-4-(2-methyl-4-aminopyrimidin-5-yl)methyl-5-methyl-6-(2-hydroxy)-ethyl-2,3-dihydro-4H-1,4-thiazine (**5**). 1,4-Thiazine derivatives (**7** and **8**) were directly obtained in fairly good yields in the case of thiazolium salts containing no functional groups such as the pyrimidine C-4 amino group (Scheme I). This is new reaction for dialkyl acylphosphonate. The present paper is aimed to elucidate the reaction mechanism of thiazolium salts with acylphosphonates using 3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium halides and diethyl benzoyl- and diethyl acetylphosphonates. The information obtained here offers data useful for the elucidation of the Perkow reaction mechanism.

Reaction of Thiazolium Salts with Diethyl Benzoyl- and Diethyl Acetylphosphonate.—We already reported[5] that the reaction of the so-called "neutral form" of benzyl thiazolium salt (**6**) with diethyl benzoylphosphonate (**3a**) gave 2-phenyl-3-oxo-4-benzyl-5-methyl-6-(2-hydroxy)ethyl-2,3-dihydro-4H-1,4-thiazine (**7**) and its benzoate (**8**). In this paper the reactions of 3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium halides (**9a–c**) with **3a** and diethyl acetylphosphonate (**3b**) in the presence of triethylamine in N,N-dimethylformamide are described.

The 1:1 adducts (**10a–c**) of **9a–c** and **3a** were obtained in approximately 80% yields by the reactions of **9a–c** with **3a**; each gave the nitrate (**10d**) on treat-

(1) Part LVII: A. Takamizawa, Y. Hamashima, S. Sakai, and S. Nagakura, *Bull. Chem. Soc. Jap.*, **41** (No. 9) (1968).

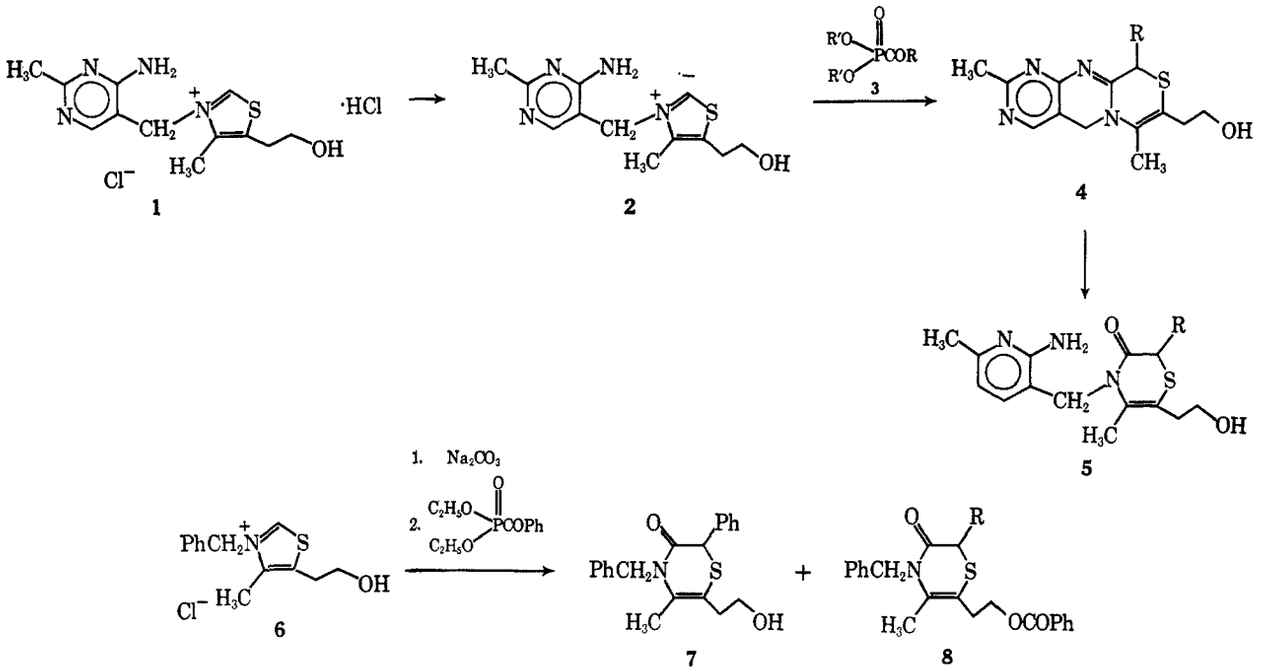
(2) A. Takamizawa, Y. Hamashima, Y. Sato, H. Sato, S. Tanaka, H. Ito and Y. Mori, *J. Org. Chem.*, **31**, 2951 (1966).

(3) A. Takamizawa, Y. Hamashima, Y. Sato, and H. Sato, *Chem. Pharm. Bull.* (Tokyo), **15**, 1178 (1967).

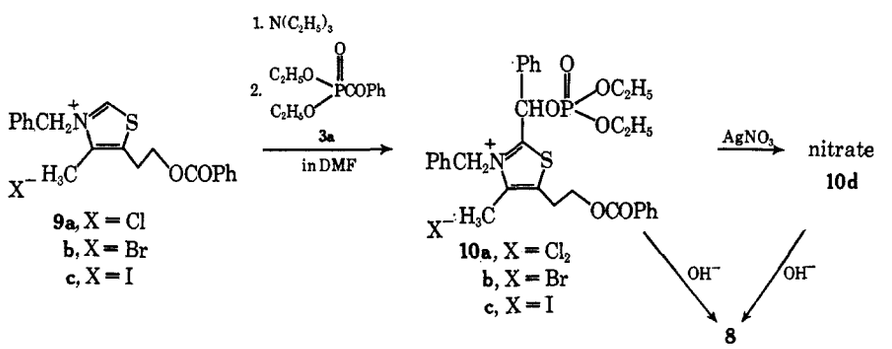
(4) A. Takamizawa, Y. Sato, and H. Sato, *ibid.*, **15**, 1183 (1967).

(5) A. Takamizawa and Y. Sato, *ibid.*, **14**, 742 (1966).

SCHEME I

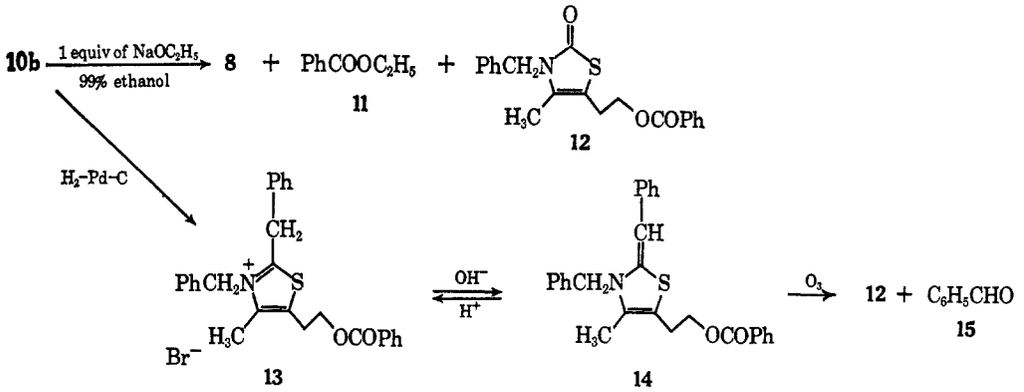


SCHEME II

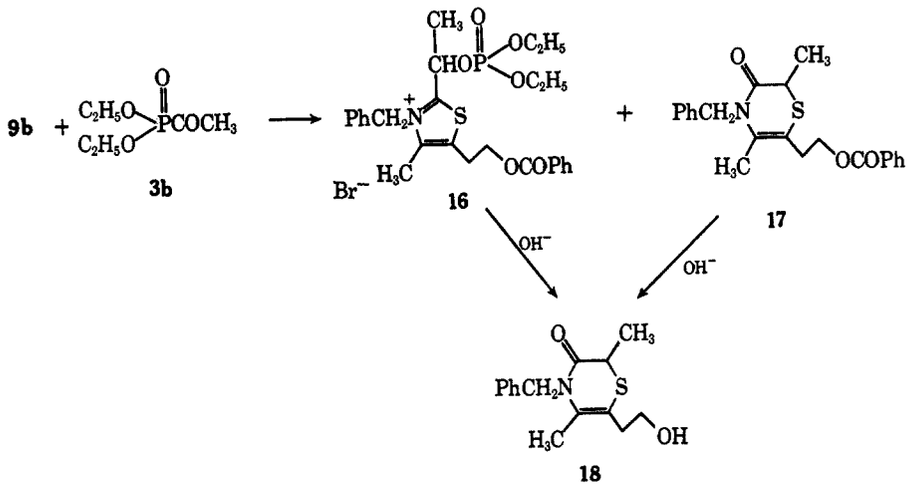


ment with silver nitrate and were easily converted into **8** by alkali (Scheme II). These facts reveal that **10a–d** are intermediates of a novel reaction leading to 1,4-thiazine derivatives from the reaction of thiazolium salts with acylphosphonate. The ir spectrum of **10a–d** showed strong ester bands, P=O and P—O—C, but no hydroxyl or carbonyl absorption band was observed. Accordingly, the diethoxyphosphinoyl group of **3a** can be thought to be introduced intact, though its benzoyl group may change the original form. There was no distinctive difference between the uv absorption spectrum of **10** and that of **9**. The nuclear magnetic resonance spectrum (nmr) of **10b**, for example, showed a 15 H multiplet signal at τ 1.95–2.83, a 1 H multiplet signal at 3.12–3.20, which did not disappear with an addition of deuterium oxide, a 4 H multiplet methylene signal at 6.12, a 6 H methyl signal of two ethoxyphosphinoyl groups as two triplets of doublets at 8.87 and 8.92 (J_{HH} = 7.0, J_{PH} = 1.1 Hz), a 2 H singlet methylene signal at 3.97, and a singlet methyl signal at 7.56. The latter two signals showed very similar signal patterns and chemical-shift values as **9b**, but no C-2 methine signal was detected. From the above data, **10b** might still have the thiazolium moiety, and **3a** was assumed to be substituted at the thiazole C-2 position in a form of $C_6H_5CHP(O)(OC_2H_5)_2$. In this case, there might be another possibility that **10** might have a six-membered-ring structure in view of its easy and facile conversion into a 1,4-thiazine derivative. This notion, however, was discarded on the basis of the following evidence. Ethyl benzoate (**11**) and 3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolin-2-one (**12**) were obtained by careful treatment of **10b** with an equimolar amount of sodium ethoxide. Furthermore, hydrogenation of **10b** over a palladium–charcoal catalyst consumed an equimolar amount of hydrogen to give a colorless oily product (**13**), which was neutralized to afford **14**, (Scheme III). The ir absorption spectrum of **14** showed ester bands at 1713 and 1278 and strong bands due to conjugated double bond at 1573 and 1552 cm^{-1}. The uv absorption spectrum exhibited the absorption maxima at 229.5 mμ (ϵ 17,800), 267 (6110), and 365 (8510), but these bands disappeared by adding hydrochloric acid and reproduced the absorption curve of **13**, indicating that the highly conjugated system disappeared on protonation. The nmr spectrum of **14** showed a 1 H singlet at τ 4.63, and a 2 H singlet methylene signal at 5.18. These signals changed on a proton addition, namely, the signal at 4.63 disappeared with the concurrent appearance of a 2 H singlet at 5.68, and a 2 H singlet signal at 5.18 shifted to lower field (4.03). The behavior of these proton signals are explained as

SCHEME III



SCHEME IV



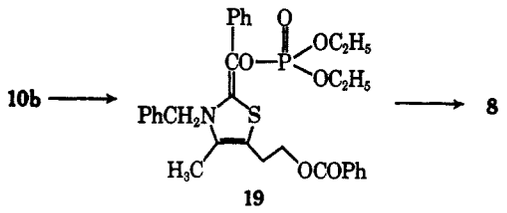
follows. The signal at τ 4.63 was assigned to a benzylidene proton at the thiazole C-2 and that of 5.18 to benzyl methylene protons at the nitrogen. The two groups changed into two benzyl groups owing to formation of a thiazolium moiety by adding acid. Furthermore, chemical evidence for the structure of **14** was obtained by ozonolysis of **14** which gave **12** and benzaldehyde (**15**) (Scheme III). Based on the data mentioned above the structure of **14** was determined to be 2-benzylidene-3-benzyl-4-methyl-5-(2-benzoyloxy)-ethylthiazoline.

Reaction of **9b** with **3b** was also found to proceed analogously, providing **16** in a moderate yield together with a small amount of **17** (Scheme IV). The elemental analysis of **16** corresponded to the 1:1 adduct of **9b** and **3b**. The ir spectrum showed strong ester bands at 1712 and 1280, P=O band at 1265, and P—O—C bands at 1026 and 969 cm^{-1}, but no hydroxyl absorption band was observed. The nmr signal showed a 2 H singlet methylene signal and a typical 4 H CH_3–$CH<$ signal composed of a doublet and a quintet;[6] this splitting was caused by a coupling of the methine proton with phosphor nucleus. Treatment of **16** with alcoholic sodium hydroxide gave **18** in a good yield. These data indicated that **16** had an analogous structure to that of **10** and it was concluded to be that of 2-(1-diethylphosphoroyl)ethyl-3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium bromide. Upon reconsidering the matter of **10b**, the existence of C_6H_5—$CHOP(O)(OC_2H_5)_2$ systems was confirmed. The structure of **17** was determined on the basis of the following evidence. The ir spectrum showed an amide carbonyl band at 1665 cm^{-1}. The uv absorption spectrum showed a curve very similar to that of **8**. The nmr signal showed a typical CH_3—$CH<$ signal composed of a doublet and a quartet. These data indicated that **17** had a structure analogous to **8**, and it was concluded to be that of 2,5-dimethyl-3-oxo-4-benzyl-6-(2-benzyloxy)-ethyl-2,3-dihydro-4H-1,4-thiazine. Compound **17** was hydrolyzed to give **18**.

Kinetic Studies of the Rearrangement of 10b in Alkaline Medium.—In the process of obtaining **8** from **10** a deprotonation might first occur on the benzyl group substituted at the C-2 position of the thiazole moiety by an alkaline treatment in a similar manner as observed for the change from **13** to **14**. The absorption maxima at 229 and 276 mμ of **10b** immediately disappeared by the addition of alkali, and simultaneously the strong maximum appeared at 373.5 mμ. The new absorption spectrum returned to that of **10b** again by an immediate addition of acid. The intensity of the band at 373.5 mμ decreased slowly and finally disappeared, and the spectrum indicated a similar pattern to that of **8** (uv max 229 and 282 mμ). Accordingly, it is probable that **10b** may be rearranged to **8** *via* **19** as an intermediate (Scheme V). The rate of the rearrangement of **19** to **8** was determined by measuring the successive decrease in the absorption intensity at 373.5 mμ as a function of time. Compound **8** was ob-

(6) J. W. Emsley, J Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press Ltd., Oxford, England, 1966, p 1062.

SCHEME V



tained in nearly theoretical yield upon degradation of **10b** in the similar reaction conditions (See Experimental Section). Figure 1 shows examples of the behavior at 15 and 5°. These rate constants were obtained under excess hydroxide concentrations. The logarithms of the observed ϵ at 15 and 5° for the rearrangement of **18** to **8** were plotted against time. Over the time range between 30 sec and 60 min the plots were found to fit to a straight line with a slope of −0.031 and −0.016. The mean values of k_{calcd} from the data of Figure 1 and the equation $\log \epsilon = -0.4343 kt + \log \epsilon_0$ are 1.19×10^{-3} and 6.11×10^{-4} M^{-1} sec^{-1} at 15 and 5°, respectively.

Reactions of 10b and 16 with Amines.—The alkaline treatment of **10b** or **16** produced **8** or **17** in good yields. The reaction of **10b** with methylamine gave a colorless solid, whose structure was assumed to be **20** (Scheme VI) with regard to the reaction between **10b** and sodium hydroxide affording **8**. The ir spectrum showed ester bands at 1720 and 1278, and a C=N band at 1633 cm^{-1}. In the uv spectrum, the absorption maxima appeared at 228 mμ (ϵ 22,500), 282 (3840), and 301 (4150); the latter maximum shifted to 311 (3340) by adding hydrochloric acid. The nmr spectrum showed a 2 H AB-type quartet benzyl signal at τ 4.04 and 5.39 (J = 16.0 Hz), a 1 H singlet signal at 4.82, and a singlet N-methyl signal at 6.97. These signals were changed by adding several drops of concentrated hydrochloric acid; namely, the benzyl methylene signal shifted to τ 3.76 and 4.90 as the AB quartet (J = 16.0 Hz); the 1 H singlet signal at 4.48; and the N-methyl signal at 6.85 as a doublet (J = 5.5 Hz). These data mentioned above support the structural relation between **20** and **20a**. Another possibility of the structure with thiazoline moiety in **20′** or of the equilibria of **20′a** ⇌ **20′b** was excluded by the uv and nmr data. Accordingly, the structure of **20** was concluded to be that of 2-phenyl-3-methylimino-4-benzyl-5-methyl-6-(2-benzoyloxy)ethyl-2,3-dihydro-4H-1,4-thiazine. The reaction of **10b** with benzylamine afforded **21** as a colorless oil in a good yield. The hydrochloride of **21** was obtained as colorless needles. The reaction of **10b** with ammonia similarly gave **22** as an oil. The reaction of **10b** with dimethylamine afforded a light brown oil (**23**), whose structure was confirmed by the following data. The ir spectrum showed a strong C=C band at 1582 cm^{-1}. The absorption maxima in the uv region appeared at 231 mμ (ϵ 25,500), 281 (7240), and 365 (2500). These absorption maxima disappeared by adding acid with the concurrent appearance of maxima at 228 mμ (ϵ 22,800) and 332 (3490). The nmr spectrum showed a 2 H singlet methylene signal at τ 5.38 and a 6 H singlet N-dimethyl signal at 7.56. On an addition of a proton, these signals shifted toward lower field, the former appeared at τ 4.24 and 4.69 as AB-type quartet, and the latter at 6.60 as a broad singlet. Furthermore,

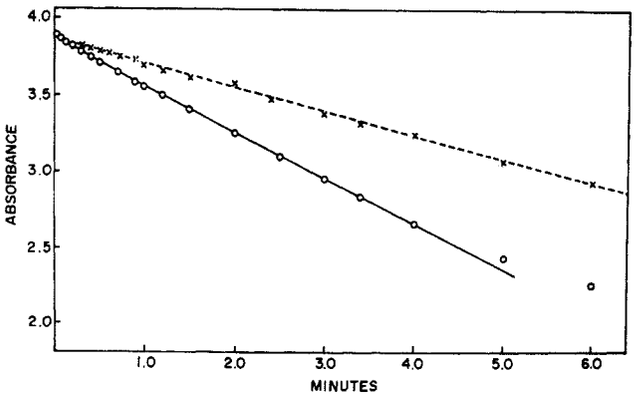


Figure 1.—Disappearance of 2-(1-diethylphosphoroyl)benzylidene-3-benzyl-4-methyl-5-(2-benzoyloxy)ethyl-4-thiazoline (**19**) at 15 (———) and 5° (– – – –).

a 1 H signal newly appeared at τ 4.17, which was assigned to the C-2 proton in **23a**. These spectral data indicate the unambiguous structure for **23** and the equilibrium between **23** and **23a**. The structures of **20**–**23** were also supported on the basis of the following evidence. The reaction of **16** with methylamine afforded **24** as colorless crystals. The ir spectrum showed a strong C=N band at 1619 cm^{-1}. The ultraviolet absorption spectrum showed maxima at 229 mμ (ϵ 20,800), 284 (4760), and 296 (5320) in a neutral medium; at 229 (20,400), 283 (2830), and 309 (3890) in an acidic medium. The nmr spectrum showed a 3 H singlet N-methyl signal at τ 6.99 and a typical 4 H CH_3—CH< signal as a doublet and a quartet. Contrary to our expectation **17** was obtained as an oil by the reaction of **16** with dimethylamine.

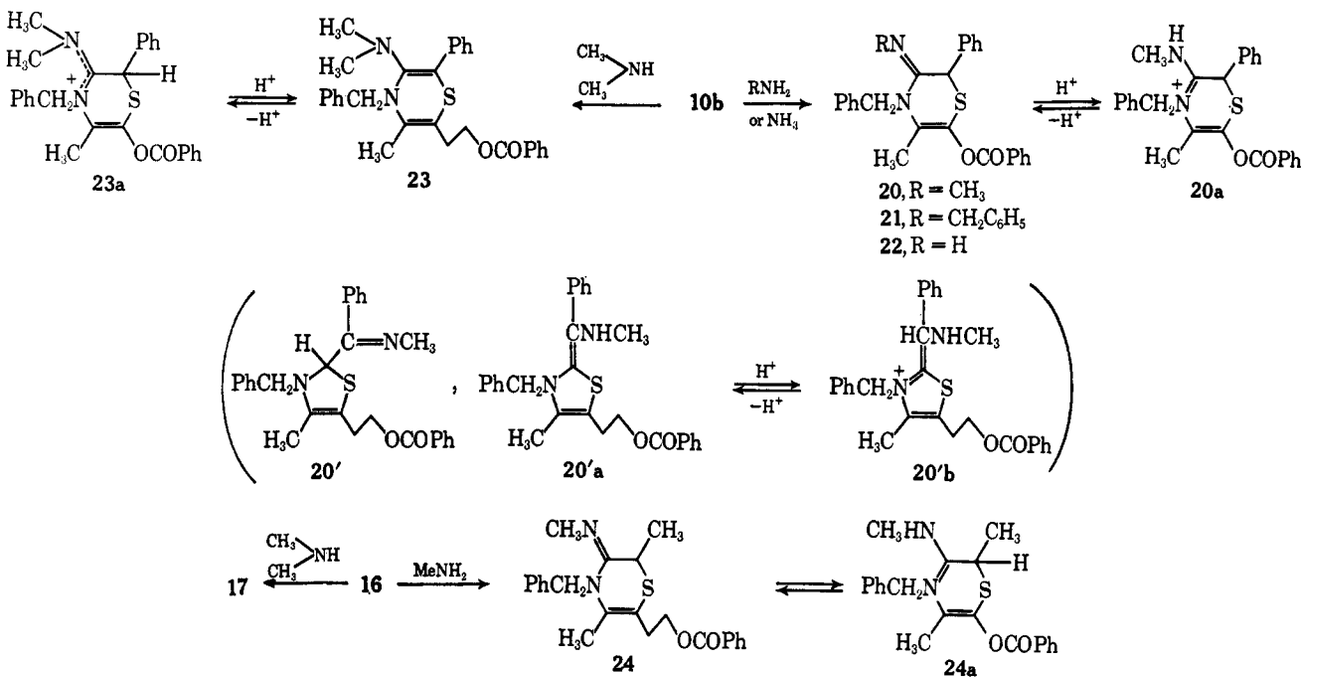
Discussion

As described above, **10** retains a thiazolium moiety which is expanded to give **8** by the presence of base. It seems probable that the reaction will proceed by way of Scheme VII. Previously we reported[7] that dialkyl acylphosphonates are convenient acylating agents. In this case, thiazolium ylide **a** produced by treatment of **9** with triethylamine reacts with the acylphosphonate to give betain **b**. This makes a nucleophilic attack on the pentavalent phosphorous to give a cyclic oxyphosphorane **c**. The benzyl carbon of the C_6H_5–C–P system in **c** is electron deficient; the rearrangement occurs easily and results in **10**. This assumption is supported by the fact that the reaction of **9** with **3b** proceeds more slowly than that of **9** with **3a** (see Experimental Section). In view of the spectral consideration mentioned above, it is obvious that **10** produces **d** by deprotonation, followed by a ring expansion to give **8**. Both spectral data and the experimental results support the assumption that the rearrangement reaction is first order.

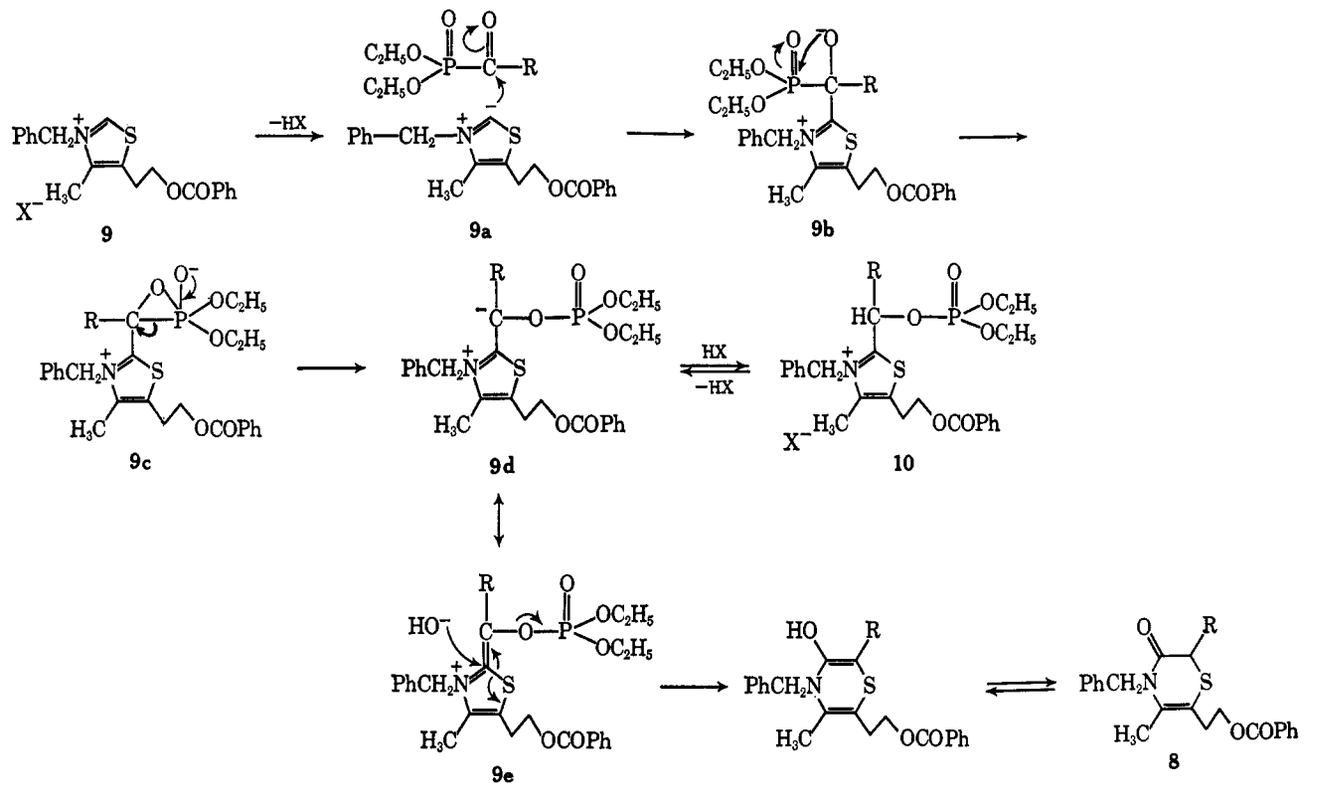
The mechanism of the reaction of thiamine with dialkyl acylphosphonate to give **4** can be easily and reasonably explained by the facts that **19**–**24** were produced from the reaction of **10b** or **16** with amines as described. In thiamine, the amino group at the pyrimidine C-4 position shows similar behavior to that of the amines described above and gives **4** by the way

(7) A. Takamizawa, Y. Sato, and S. Tanaka, *Yakugaku Zasshi*, **85**, 298 (1965).

SCHEME VI



SCHEME VII



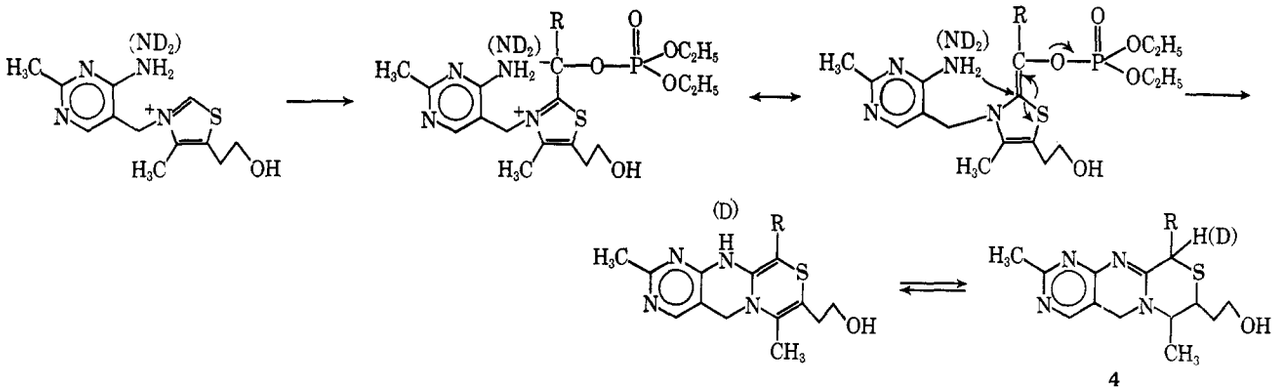
described in Scheme VIII. This assumption is also supported by the fact that, when deuterioaminothiamine was used, a deuterium on the pyrimidine C-4 amino group was introduced into the C-1 position of **4** as previously described.[2]

Various mechanisms have been reported on the Perkow reaction. Recently Hudson, *et al.*,[8] suggested that the enol phosphate formation proceeded most likely by the initial attack at carbonyl carbon followed by rearrangement of the phosphorous to carbonyl oxygen. More recently, from the data of the reaction of certain phenacyl bromides with triethyl phosphite, Borowitz, *et al.*,[9] suggested that the Perkow reaction involved an initial attack of triethyl phosphite on the carbonyl carbon followed by rearrangment to oxygen. The isolation of **10** and **16** in our case offers a suggestion for the elucidation of the Perkow reaction mechanism (Scheme IX).

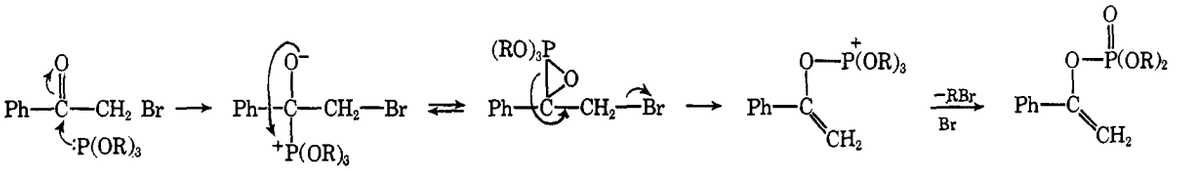
(8) P. A. Chopard, V. M. Clark, R. F. Hudson, and A. J. Kirby, *Tetrahedron*, **21**, 1961 (1965).

(9) I. J. Borowitz, M. Anshel, and S. Firstenberg, *J. Org. Chem.*, **32**, 1723 (1967).

SCHEME VIII



SCHEME IX



Experimental Section[10]

2-(1-Diethylphosphoroyl)benzyl-3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium Halides (10a–c). 10a.—To an ice-cooled suspension of **9a** (3.73 g) and triethylamine (2.2 g) in N,N-dimethylformamide (40 ml) was added **3a** (2.42 g) in nitrogen atmosphere, and the mixture was stirred at 0–5° for 15 min; then the mixture reacted at room temperature for 15 hr resulting in a dark green solution. The solution was concentrated *in vacuo* leaving a green crystalline residue, which was washed with ether and acetone. The light green residue was recrystallized from acetonitrile or ethanol affording **10a** as colorless needles (5.18 g): mp 150–151° dec; ir (Nujol) 1716 and 1270 (COO), 1256 (P=O), and 1028, 1108, and 986 cm^{-1} (P—O—C).

Anal. Calcd for $C_{31}H_{35}ClNO_6PS$: C, 60.43; H, 5.72; Cl, 5.76; N, 2.28; P, 5.02; S, 5.20. Found: C, 60.12; H, 5.84; Cl, 6.06; N, 2.40; P, 4.83; S, 5.21.

10b was obtained by a method similar to that for **10a** using 2.01 g of **9b**, 1.1 g of triethylamine and 1.21 g of **3a** in N,N-dimethylformamide (20 ml). Recrystallization of the solid from ethanol gave colorless rhombs (2.83 g, 88%): mp 148° dec; uv max (95% C_2H_5OH) 230 mμ (ε 18,200), 271 (8720), and 276 (8740).

Anal. Calcd for $C_{31}H_{35}BrNO_6PS$: C, 56.36; H, 5.34; Br, 12.09; N, 2.12; P, 4.69; S, 4.85; C_2H_5O, 13.62. Found: C, 56.46; H, 5.43; Br, 11.84; N, 2.05; P, 4.39; S, 4.58; C_2H_5O, 13.64.

10c gave light brown needles (acetone): yield, 73.2%; mp 119° dec.

Anal. Calcd for $C_{31}H_{35}INO_6PS$: C, 52.62; H, 4.99; I, 17.95; N, 1.98; P, 4.32; S, 4.54. Found: C, 52.41; H, 5.14; I, 18.01; N, 1.92; P, 4.21; S, 5.12.

2-(1-Diethylphosphoroyl)benzyl-3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium Nitrate (10d).—To a solution of **10b** (0.21 g) in methanol (5 ml) was added 0.062 g of silver nitrate in water. Precipitated silver bromide was removed by centrifugation. The residue, after removal of the solvent, was extracted with chloroform. The extract was washed, dried, and concentrated leaving a colorless crystalline residue, which was recrystallized from methanol–benzene to give **10d** as colorless needles (0.15 g): mp 138–139°; ir (Nujol) 1340 and 1326 cm^{-1} (NO_3).

Anal. Calcd for $C_{31}H_{35}N_2O_9PS$: C, 57.93; H, 5.49; N, 4.36; P, 4.82; S, 4.99; Found: C, 57.85; H, 5.73; N, 4.26; P, 4.60; S, 5.78.

(10) All melting points were obtained using a stirred Yamato Kagaku silicon oil bath. Infrared spectra were measured using a Jasco DS-201B recording spectrophotometer, and ultraviolet curves were obtained using a Hitachi EPS-3 recording spectrophotometer. Proton magnetic resonance spectra were obtained using a Varian A-60 apparatus with tetramethylsilane as the internal standard.

Similar reaction of **10a** or **10c** with silver nitrate also gave **10d** (83 and 62%, respectively).

Alkaline Degradation of 10a–d. General Procedure.—To 20 ml of 10% alcoholic sodium hydroxide (75%) was added 1.3 g of **10b**; the mixture was stirred at 10° for 2 hr, after which the mixture was concentrated and extracted with chloroform. The chloroform extract was washed, dried, and concentrated leaving a light brown oily residue, which crystallized on standing. Recrystallization from ether gave 0.79 g (89%) of **8** as colorless needles, mp 107–108°, which proved to be identical with an authentic sample by ir comparison.

Treatment of 10b with Equimolar Amount of Sodium Ethoxide.—To a cooled solution of 1.98 g of **10b** in 36 ml of ethanol was added dropwise 0.075 g of sodium in 6 ml of ethanol, and the mixture was stirred at −50° for 1.5 hr, after which the mixture was allowed to warm to room temperature and left overnight, The mixture was concentrated and extracted with chloroform. To the residue after removal of the solvent was added acetone precipitating colorless solid (0.45 g of **10b** recovered), which was filtered off and the filtrate was concentrated and submitted to silica gel chromatography. Elution with acetone gave a light brown oil, which was a mixture of three components. The mixture was rechromatographed over alumina and eluted with ether to give 0.04 g of ethyl benzoate (**11**) as the first fraction. From the second fraction was obtained 0.19 g of **8** as colorless crystals. From the following fraction was obtained 0.07 g of colorless crystals, mp 77–78°, which proved to be identical with **12** by mixture melting point and ir comparison.

Catalytic Hydrogenation of 10b with Palladium-Charcoal.—**10b** (0.66 g) was dissolved in 15 ml of methanol and hydrogenated at atmospheric pressure and room temperature over 1 g of 5% palladium-charcoal catalyst. Complete hydrogenation was observed after approximately 32 ml of hydrogen had been consumed within 15 min. The solution was freed of the catalyst by suction filtration and the filtrate was concentrated, neutralized, and extracted with chloroform. The crystalline residue after removal of the solvent was recrystallized from ether giving **14** as yellow plates (0.2 g): mp 107–108°; nmr ($CDCl_3$) τ 1.84–3.18 [m, 15, (C_6H_5)$_3$], 4.36 (s, 1, C_6H_5—CH=), 5.18 (s, 2, C_6H_5—CH_2—), 5.55 and 7.08 (t, 4, >—CH_2—CH_2—O—, J = 6.3 Hz), and 8.03 (s, 3, CH_3) in a neutral medium; 1.52–3.00 [m, 15, (C_6H_5)$_3$], 4.03 (s, 2, C_6H_5—CH_2—), 5.68 (s, 2, thiazole C_2—CH_2—C_6H_5), 5.50 and 6.61 (t, 4, >—CH_2—CH_2—O—, J = 6.2 Hz), and 7.52 (s, 3, CH_3) on addition of 2–3 drops of concentrated hydrochloric acid.

Anal. Calcd for $C_{27}H_{25}NO_2S$: C, 75.86; H, 5.90; N, 3.28; S, 7.49; mol wt, 427.54. Found: C, 75.93; H, 5.72; N, 3.29; S, 7.69; mol wt, 433 (chloroform).

Ozonolysis of 14.—Through a solution of **14** (0.05 g) in chloroform (15 ml) was passed 0.006 g of ozone at −30°; the mixture was stirred at the temperature for 30 min. The mixture was

decomposed by the addition of 0.5 g of powdered zinc, 0.5 ml of acetic acid, and 1 ml of water. The mixture was filtered; the filtrate was neutralized with sodium carbonate; and the chloroform layer was separated. The residue after removal of the solvent was submitted to alumina chromatography and eluted with ether. From the first fraction was obtained 0.003 g of benzldehyde, which was identical with authentic benzaldehyde as shown by gas chromatographical identification. From the second fraction was obtained 0.005 g of colorless crystals, mp 76–78°, which were proved to be identical with **12** by infrared comparison.

2-(Diethylphosphoroyl)ethyl-3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium Bromide (16).—To a solution of 2.09 g of **9b** in 15 ml of N,N-dimethylformamide was added 1.1 g of triethylamine, and the mixture was stirred for 20 min, after which 0.9 g of **3b** was added; the mixture was allowed to react at room temperature for 8 hr and left overnight. The reaction mixture was concentrated *in vacuo*, and the resulting oil was extracted with acetone (0.27 g of triethylamine hydrobromide was obtained as insoluble material). The extract was concentrated; the residue, after washing with hot ether, was dissolved in chloroform and submitted to the silica gel column chromatography to yield **16** as a light brown oil (1.8 g): R_f 0.12 (SiO_2–methanol) and R_f 0.46 (SiO_2–acetone); nmr ($CDCl_3$) τ 1.92–2.97 [m, 10, $(C_6H_5)_2$], 3.90 (quintet, 1, CH_3–CH–O–P, $J_{HH} = J_{PH} = 6.5$ Hz), 4.02 (s, 2, $C_6H_5CH_2$–), 5.35 (t, 2, >–CH_2–CH_2–O–, $J = 5.6$ Hz), 5.96 (quintet of doublets, 2, CH_3–CH_2–O, $J_{HH} = J_{PH} = 7.0$ Hz), 5.98 (quintet of doublets, 2, CH_3–CH_2–O, $J_{HH} = J_{PH} = 7.0$ Hz), 6.52 (t, 2, >–CH_2–CH_2–O, $J = 5.6$ Hz), 7.54 (s, 3, CH_3), 8.05 (d, 3, CH_3–CH<, $J = 6.5$ Hz), 8.75 (triplet of doublets, 3, CH_3–CH_2–O, $J_{HH} = 7.1$ Hz, $J_{PH} = 1.0$ Hz), and 8.78 (triplet of doublets, 3, CH_3–CH_2–O, $J_{HH} = 7.1$ Hz, $J_{PH} = 1.0$ Hz).

Anal. Calcd for $C_{26}H_{33}BrNO_6PS$: C, 52.17; H, 5.56; Br, 13.35; N, 2.34; P, 5.18. Found: C, 53.00; H, 5.87; Br, 12.96; N, 2.41; P, 5.29.

The ether extract was submitted on alumina column chromatography. Elution with ether gave 0.35 g of **17** as a colorless oil: ir (film) 1718, 1276 (COO), and 1665 cm^{-1} (CO); uv max (95% C_2H_5OH) 229.5 mμ (ϵ 17,900), 276 (2890) shoulder, 282 (3130), 292 (2580) shoulder; nmr ($CDCl_3$) τ 1.93–2.63 [m, 10, $(C_6H_5)_2$], 2.82 (s, 5, C_6H_5–CH_2–), 4.91 and 5.55 (AB quartet, 2, C_6H_5–CH_2–, $J = 16.0$ Hz), 5.55 (t, 2, >–CH_2–CH_2–O, $J = 6.5$ Hz), 6.60 (q, 1, CH_3–CH<, $J = 6.8$ Hz), 7.35 (t, 2, >–CH_2–CH_2–O, $J = 6.5$ Hz), 8.07 (s, 3, CH_3), and 8.54 (d, 3, CH_3–CH<, $J = 6.8$ Hz).

Anal. Calcd for $C_{22}H_{23}NO_3S$: C, 69.27; H, 6.08; N, 3.67; S, 8.39. Found: C, 68.90; H, 6.21; N, 4.09; S, 8.58.

Alkaline Treatment of 16. A.—To a cooled solution of 0.3 g of sodium in 10 ml of ethanol was added dropwise an ethanol solution of **16** (1.0 g). The temperature was maintained for 1.5 hr below 5°, after which the mixture was stirred at room temperature for 2 hr. The residue, after removal of the solvent, was extracted with chloroform and chromatographed over alumina. Elution with ether gave 0.2 g of **18** as a colorless oil: R_f 0.42 (alumina–ether); ir (film) 3380, 1045 (OH), and 1652 cm^{-1} (CO); uv max (95% C_2H_5OH) 230 mμ (ϵ 5920) shoulder and 290 (2460); nmr ($CDCl_3$) τ 2.76–2.83 (m, 5, C_6H_5), 5.00 and 5.27 (AB quartet, 2, C_6H_5–CH_2–, $J = 16.5$ Hz), 6.58 (t, 2, >–CH_2–CH_2–O, $J = 6.5$ Hz), 6.73 (q, 1, CH_3–CH<, $J = 7.1$ Hz), 7.67 (t, 2, >–CH_2–CH_2–O, $J = 6.5$ Hz), 8.23 (s, 3, CH_3), and 8.66 (d, 3, CH_3–CH<, $J = 7.1$ Hz).

Anal. Calcd for $C_{15}H_{19}NO_2S$: C, 64.96; H, 6.91; N, 5.05; S, 11.55. Found: C, 64.72; H, 7.17; N, 5.01; S, 11.50.

B.—A solution of **16** (0.3 g) in 15 ml of 10% sodium hydroxide–ethanol was warmed at 60° for 1.5 hr, after which the mixture was concentrated and extracted with chloroform. The extract was washed, dried, and concentrated leaving oily residue, which was chromatographed over alumina. Elution with ether gave 0.08 g of colorless oil, which proved to be identical with **18** obtained above (A) by infrared comparison.

2-Phenyl-3-methylimino-4-benzyl-5-methyl-6-(2-benzoyloxy)ethyl-2,3-dihydro-4H-1,4-thiazine (20) was obtained as colorless plates (ether) by a method similar to that mentioned using methylamine and **10b**: mp 123–124°; yield, 87.2%.

Anal. Calcd for $C_{28}H_{28}N_2O_2S$: C, 73.66; H, 6.18; N, 6.14; O, 7.01; S, 7.02; mol wt, 456.58. Found: C, 73.43; H, 6.22; N, 6.19; O, 7.29; S, 6.78; mol wt, 453 (acetone).

2-Phenyl-3-benzylimino-4-benzyl-5-methyl-6-(2-benzoyloxy)ethyl-2,3-dihydro-4H-1,4-thiazine (21) was obtained as light brown oil by a method similar to that mentioned using benzylamine and **10b**. The hydrochloride, was obtained as colorless needles from methanol–acetone: mp 198–200° dec; ir (Nujol) 1711, 1281 (COO), and 1586 cm^{-1} (C=N); nmr (D_2O) τ 2.15–2.80 [m, 10, $(C_6H_5)_2$], 2.86 (s, 5, C_6H_5), 3.53 and 4.86 (AB quartet, 2, $J = 17.1$ Hz), 4.86 (s, 1, C_6H_5—CH<), 5.03 and 5.45 (AB quartet, 2, $J = 16.0$ Hz).

Anal. Calcd for $C_{34}H_{33}ClN_2O_2S$: C, 71.78; H, 5.85; Cl, 6.23; N, 4.92; O, 5.62; S, 5.63. Found: C, 71.65; H, 5.97; Cl, 6.43; N, 4.99; O, 5.90; S, 5.58.

2-Phenyl-3-imino-4-benzyl-5-methyl-6-(2-benzoyloxy)ethyl-2,3-dihydro-4H-1,4-thiazine (22).—To an ice-cooled and stirred 8% alcoholic ammonia solution (20 ml) was added dropwise 1.0 g of **10b** in ethanol. The temperature was maintained for 1 hr below 5°, after which the mixture was stirred at room temperature for 2 hr. The residue, after removal of the solvent and excess of ammonia, was extracted with chloroform. The chloroform extract was washed, dried, and concentrated leaving an oily residue, which was not crystallized and not distillable. The hydrochloride (0.4 g) was obtained as colorless cubes [mp 190° dec; ir (Nujol) 1720, 1276 (COO) and 1598 cm^{-1} (C=N)].

Anal. Calcd for $C_{27}H_{27}ClN_2O_2S$: C, 67.70; H, 5.68; Cl, 7.40; N, 5.68; O, 6.68; S, 6.69. Found: C, 68.45; H, 5.96; Cl, 7.67; N, 5.77; O, 6.72; S, 6.76.

2-Phenyl-3-dimethylamino-4-benzyl-5-methyl-6-(2-benzoyloxy)-ethyl-4H-1,4-thiazine (23).—To a stirred and ice-cooled 10% dimethylamine solution in ethanol (20 ml) was added 1.5 g of **10b** in ethanol. The temperature was maintained for 2 hr below 5°, after which the mixture was stirred at room temperature for 5 hr. After removal of the solvent and excess of dimethylamine, the residue was extracted with chloroform. The chloroform extract was washed, dried, and concentrated leaving an oily residue. The residue was purified by alumina column chromatography, and **23** was obtained as a light brown oil (0.4 g).

Anal. Calcd for $C_{29}H_{30}N_2O_2S$: C, 74.01; H, 6.42; N, 5.95; S, 6.81. Found: C, 74.02; H, 6.65; N, 5.40; S, 6.55.

2-Methyl-3-methylimino-4-benzyl-5-methyl-6-(2-benzoyloxy)-ethyl-4H-1,4-thiazine (24).—To a cooled solution of **16** (1.0 g) in ethanol (15 ml) was added 10 ml of alcoholic methylamine (8.6%). The temperature of the mixture was maintained for 2 hr below 10°, after which the mixture was stirred at room temperature for 1 hr. After removal of the solvent and excess of methylamine the residue was extracted with chloroform. The chloroform extract was washed, dried, and submitted to the alumina-column chromatography. Elution with ether gave a mixture of two compounds as yellow oil (0.28 g), which was rechromatographed over silica gel. Elution with ether gave 0.025 g of colorless oil, which proved to be identical with **17** by infrared comparison. From the second fraction was obtained crystals, which were recrystallized from ether to give **24** as colorless rhombs (0.13 g): mp 90–92°; nmr ($CDCl_3$) τ 1.95–2.67 (m, 5, C_6H_5), 2.85 (s, 5, C_6H_5—CH_2—), 4.49 and 5.33 (AB quartet, 2, C_6H_5—CH_2—, $J = 16.0$ Hz), 5.58 (t, 2, >—CH_2—CH_2—O, $J = 6.3$ Hz), 5.95 (q, 1, CH_3—CH<, $J = 7.0$ Hz), 6.99 (s, 3, =N—CH_3), *ca.* 7.4 (m, 2, >—CH_2—CH_2—O), 8.06 (s, 3, C_5—CH_3), and 8.69 (d, 3, CH_3—CH<, $J = 7.0$ Hz); nmr ($CDCl_3$ + 3 drops of concentrated HCl) τ 1.96–2.63 (m, 5, C_6H_5), 2.77 (s, 5, C_6H_5—CH_2—), 4.23 and 4.87 (AB quartet, 2, C_6H_5—CH_2—, $J = 17.0$ Hz), 5.35 (t, 2, >—CH_2—CH_2—O, $J = 6.0$ Hz), 5.75 (q, 1, CH_3CH<, $J = 7.0$ Hz), 6.82 (d, 3, N—CH_3, $J = 5.0$ Hz), 7.23 (m, 2, >—CH_2—CH_2—O) and 8.57 (d, 3, CH_3—CH<, $J = 7.0$ Hz).

Anal. Calcd for $C_{28}H_{26}N_2O_2S$: C, 70.03; H, 6.64; N, 7.10; S, 8.12. Found: C, 70.17; H, 6.85; N, 7.04; S, 7.96.

Reaction of 16 with Dimethylamine.—To a solution of **16** (1.0 g) in ethanol (15 ml) was added 10 ml of alcoholic dimethylamine (10%) with stirring. The temperature was maintained for 3 hr below 10°, after which the mixture was stirred at room temperature for 5 hr. After removal of the solvent and excess of dimethylamine, the residue was extracted with chloroform. The chloroform extract was washed, dried, and submitted to the alumina chromatography.

Elution with ether gave brown oils, which were rechromatographed over silica gel. First 0.18 g of colorless oil was obtained, which proved to be identical with **17** obtained above by ir comparison. From the second fraction was obtained light brown crystals, which were recrystallized from ether to give 0.01 g of **12** as colorless crystals, mp 75–77°, undepressed by admixture with an authentic sample.

Alkaline Hydrolysis of 17.—A solution of **17** (0.5 g) and sodium hydroxide (1.0 g) in diluted ethanol (10 ml) was stirred at room

temperature for 5 hr; the mixture was concentrated and extracted with chloroform. The chloroform extract was washed, dried, and concentrated to leave light brown oil. The residue was chromatographed over alumina. Elution with ether gave 0.32 g of **18** as colorless oil, which proved to be identical with an authentic sample by ir comparison.

Kinetic and Rate Constant Measurements.—The rates of rearrangement of 2-(1-diethylphosphoroyl)benzyliden-3-benzyl-4-methyl-5-(2-benzoyloxy)ethyl-4-thiazoline (**19**) were measured by following the decrease of the intensity at 373.5 mμ, using a Hitachi EPS-3 spectrophotometer equipped with a thermostated cell holder. A solution containing 2.9 ml of 9.3×10^{-1} *M* **10b** in 95% ethanol was prepared in 4 ml with 1-cm cuvettes and temperature equilibration. Reaction was initiated by the addition of 0.1 ml of temperature-equilibrated solution of 6.06×10^{-2} *M* sodium hydroxide in 95% ethanol from a blow-out pipet, followed by rapid mixing with hands. The first reading of intensity was taken about 15 sec after the addition, and thereafter readings were taken at 10-sec intervals during 2 min, after which readings were taken at 30-sec intervals. All the plots of log ε against time were linear for at least 50 min. The rate constants were reproducible within ±4% of the average. The extinction coefficient of **19** at 373.5 mμ in 2×10^{-3} *N* NaOH at 15° was obtained by extrapolating of the plot of log ε against time to the moment at which sodium hydroxide solution was added into ethanolic solution of **10b**. Five determinations gave values between 8210 and 8450 M^{-1} cm^{-1}, with an average of 8300 M^{-1} cm^{-1}.

Product Identification.—The uv spectrum of a solution that initially contained 9.3×10^{-5} *M* **10b** in 95% ethanol containing 2×10^{-3} sodium hydroxide showed, after complete disappearance of the absorbance at 373.5 mμ, a band with uv max (95% C_2H_5OH) 229 mμ (ε 17,500) and 282 (3320). Under the same condition the spectrum of authentic 2-phenyl-3-oxo-4-benzyl-5-methyl-6-(2-benzoyloxy)ethyl-2,3-dihydro-4H-1,4-thiazine (**8**) had uv max (95% C_2H_5OH) 229 mμ (ε 18,000) and 282 (3410).

Registry No.—**10a**, 17511-94-3; **10b**, 17511-95-4; **10c**, 17511-96-5; **10d**, 17511-97-6; **14**, 17528-36-8; **16**, 17528-37-9; **17**, 17511-98-7; **18**, 17528-38-0; **20**, 17511-99-8; **21** HCl, 17512-00-4; **22**, 17528-39-1; **23**, 17512-01-5; **24**, 17512-02-6.

Acknowledgments.—The authors are grateful to Professor Emeritus E. Ochiai and Professor S. Nagakura of Tokyo University for their valuable discussions.

Synthesis and Determination of the Absolute Configurations of the Enantiomeric 1,2-Epoxy-1-phenylcyclohexanes

GIANCARLO BERTI, BRUNO MACCHIA, FRANCO MACCHIA, AND LUIGI MONTI

Institutes of Organic and Pharmaceutical Chemistry, University of Pisa, 56100 Pisa, Italy

Received April 30, 1968

The enantiomeric forms of 1,2-epoxy-1-phenylcyclohexane have been prepared through a sequence involving conversion of the racemic epoxide into a mixture of 1-phenyl- and 2-phenyl-*trans*-2-dimethylaminocyclohexanols, separation and resolution of this mixture with tartaric and dibenzoyltartaric acids, and reconversion of the resolved amino alcohols into the epoxide. The absolute configurations and optical purities of the (+)-epoxide and of several other phenylcyclohexane derivatives have been determined through a series of stereospecific reactions leading to (+)-2-phenyladipic acid; application of the partial resolution method of Horeau to two of the intermediates has provided further confirmation for the stereochemical assignments.

The optically active forms of 1,2-epoxy-1-phenylcyclohexane (**2**) were needed for an extention of previous work on the stereochemistry of the ring opening of aryl-substituted cyclohexene oxides.[1-3] Since no practical method could be seen for a direct resolution of the racemic epoxide, a preparation involving cyclization of an appropriate optically active precursor appeared as the most promising approach. Racemic **2** was therefore treated with aqueous dimethylamine under pressure; this reaction had been repeatedly reported to give exclusively the amino alcohol **3**,[4-6] but it was found that the product actually consisted of a mixture of the two *trans* compounds **1** and **3**, in a ratio of about 1:2, and of some of the *cis* glycol **13**. The latter product evidently derives from the hydrolysis of **2**, which is known to proceed exclusively by *cis* opening of the ring in the absence of acids.[7]

The necessity of separating the two amino alcohols **1** and **3** prior to their resolution introduced an unforeseen complication in the planned route to the optically active epoxide; luckily enough, however, it was found that the separation of isomers and the resolution could be easily carried out in one sequence, since the (+)-tartrate of (−)-**3** crystallized out in fairly good purity on treatment of the crude mixture of bases with (+)-tartaric acid. A subsequent treatment of the bases recovered from the mother liquor with (−)-dibenzoyltartaric acid gave the corresponding salt of (+)-**1**. The separation–resolution could be completed by further treatments with (−)-tartaric acid and (+)-dibenzoyltartaric acid, which led to the isolation of (+)-**3** and (−)-**1**. About 70% of the initial mixture was thus recovered in the form of bases of high optical purity.

The structures of the isomeric amino alcohols **1** and **3** were assigned on the basis of the fact that (+)-**1** was easily oxidized with Jones reagent to the ketone (−)-**4**, while (+)-**3** was recovered unchanged from a similar treatment.

The amino alcohols **1** and **3** were reconverted into the epoxide **2** through the corresponding quaternary hydroxides. Both (−)-**1** and (+)-**3** gave the dextrorotatory epoxide **2**; (+)-**1** and (−)-**3**, the levorotatory enantiomer. All four products had specific rotations of at least ±117°, the highest value observed being +121.2° (in benzene). The close coincidence of the four values indicates that 121.2° probably corresponds very nearly to optical purity. This was confirmed

(1) G. Berti, F. Bottari, B. Macchia, and F. Macchia, *Tetrahedron*, **21**, 3277 (1965).
(2) G. Berti, F. Bottari, B. Macchia, and F. Macchia, *ibid.*, **22**, 189 (1966).
(3) G. Berti, B. Macchia, and F. Macchia, *ibid.*, **24**, 1755 (1968).
(4) J. Levy and J. Sfiras, *Bull. Soc. Chim. Fr.*, **49**, 1837 (1931).
(5) A. M. Mandrou, P. Potin, and R. Wylde-Lachazette, *ibid.*, 1546 (1962).
(6) N. B. Chapman and D. J. Triggle, *J. Chem. Soc.*, 4835 (1963).
(7) C. L. Stevens, H. T. Hanson, and K. G. Taylor, *J. Amer. Chem. Soc.*, **88**, 2769 (1966).