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On the Reaction of Dialkyl Acylphosphonate with 2-Methylthiazolium Salts[1)]

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Dialkyl acylphosphonate worked as an acylating agent on 2-methylthiazolium and thiazolinium salts in the presence of base, to give 2-acylidenethiazoline and thiazolidine derivatives, respectively. Dialkyl [1-aryl(alkyl)-1-dialkylphosphatomethyl]phosphonate was also isolated as a by-product in the same reaction. Dialkyl acylphosphonate afforded 2-acylidenethiazolines in better yield compared with acyl chlorides and showed on apparent affinity for carbanions.

Application of diethyl benzoylphosphonate to 1,2,3-trimethylbenzimidazolium iodide, however, formed a dimeric salt, 1,1′,3,3′-tetramethyl-2,2′-(2-phenyltrimethylene)di(benzimidazolium)diiodide in addition to 2-(1,3-dimethylbenzimidazolin-2-ylidene)acetophenone. On the basis of the reactivity difference between the 2-methylthiazolium and 2-methylimidazolium salts and the kinetic experiments, the mechanism of the acylating reaction was proposed.

Keywords——C-acylation; dialkyl acylphosphonate; 2-methylthiazolium salts; 2-acylidenethiazolines; reaction mechanism

Thiamine and 2-free azolium salts react with dialkyl acylphosphonate under basic conditions, following rearrangement of phosphonate to the phosphate structure, to give dihydro-4H-1,4-azine by ring enlargement (Chart 1).[3)] As acylphosphonate is known as an acylating reagent of the hydroxyl group and even of the active methylene group in special cases,[4)] we tried applying the reagents to heterocycles having an active methyl group.

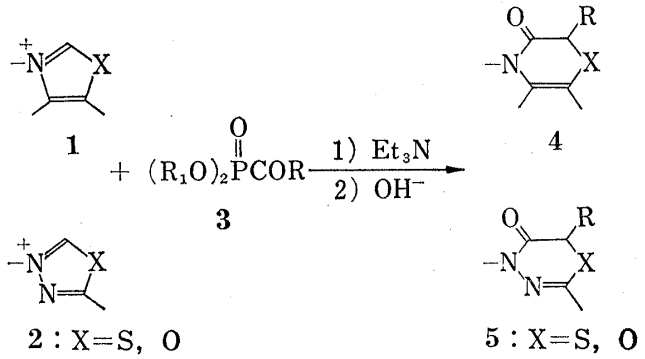

Chart 1

Reaction of 2,3-dimethylbenzothiazolium iodide (**6**) with equimolar diethyl benzoylphosphonate in the presence of 1,5-diazabicyclo[5,4,0]undecene-5 (DBU) in dimethyl formamide (DMF) suspension afforded pale yellow crystals, mp 181°, in 51% yield, which were identified as 2-(3-methylbenzothiazolin-2-ylidene)acetophenone (**7**).[5–8)] This compound (**7**) gave benzoic acid, phenylglyoxilic acid and 3-methylbenzothiazolone (**8**) by ozonolysis and 2-acetyl-2-(3-methylbenzothiazolin-2-ylidene)acetophenone (**9**) by acetylation with acetic anhydride, and α-(2-N-methylanilinoethyl)benzylalcohol (**10**) by catalytic hydrogenation using Raney Ni (Chart 2).

1) This paper constitutes Part XC of a series on Studies on Pyrimidine Derivatives and Related Compounds. Part LXXXIX: A. Takamizawa, H. Sato, and I. Makino, *Vitamins* (Japan), **49**, 177 (1975).
2) Location: *Fukushima-ku, Osaka, 553, Japan.*
3) A. Takamizawa, H. Harada, H. Sato, and Y. Hamashima, *Heterocycles*, **2**, 521 (1974).
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5) E.B. Knott, *J. Chem. Soc.*, **1955**, 916; *ibid.*, **1955**, 937.
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8) A. Mistr, V. Laznicka, and M. Vavra, *Collection Czech. Chem. Commun.*, **36**, 150 (1971).

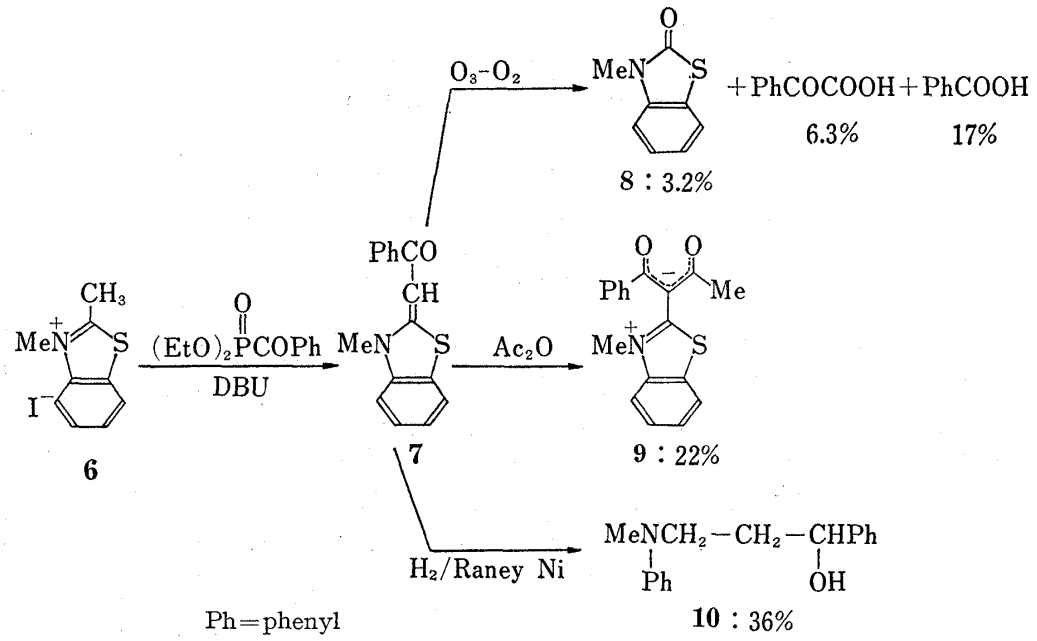


Chart 2

Reaction conditions and results applied in the acylation reaction with acylphosphonate to various 2-methylthiazolium and thiazolinium salts are shown in Table I. Satisfactory results were obtained among various acyl groups, *i.e.*, substituted benzoyl, thenoyl and froyl, *etc.*, using DBU as a base. Compared with the acylation by acyl chloride, acylphosphonate gave a superior yield. Chromatographic refinement of the mother liquid in the reaction of **11a, k** with **3a, d, f** afforded a by-product (**13a—c**), which showed a typical double doublet proton signal according to the P–O–CH–P system in its proton magnetic resonance spectrum and **13a** was identical with diethyl (1-phenyl-1-diethylphosphatomethyl) phosphonate obtained by the alternative procedure[9] (Chart 3). Clearly, this by-product was formed by addition of diethylphosphite which was eliminated as a leaving group in the acylation reaction with unreacted acylphosphonate, following rearrangement from the resulting phosphonate to the phosphate structure. Thus, two equivalent moles of acylphosphonate are necessary in this acylation reaction.

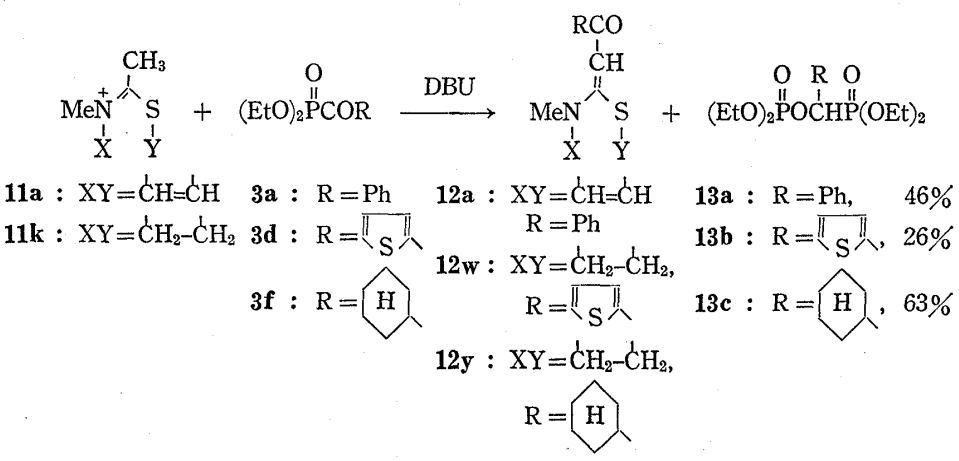
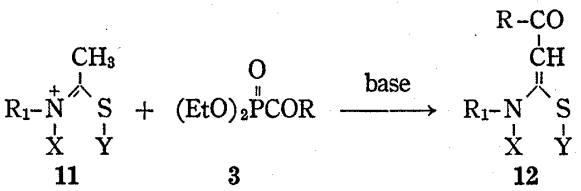


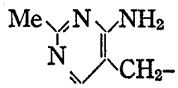
Chart 3

9) S.J. Fitch and K. Moedritzer, *J. Am. Chem. Soc.*, **84**, 1876 (1962).

TABLE I. Reactions of 2-Methylthiazolium and Thiazolinium Salts with Diethyl Acylphosphonate

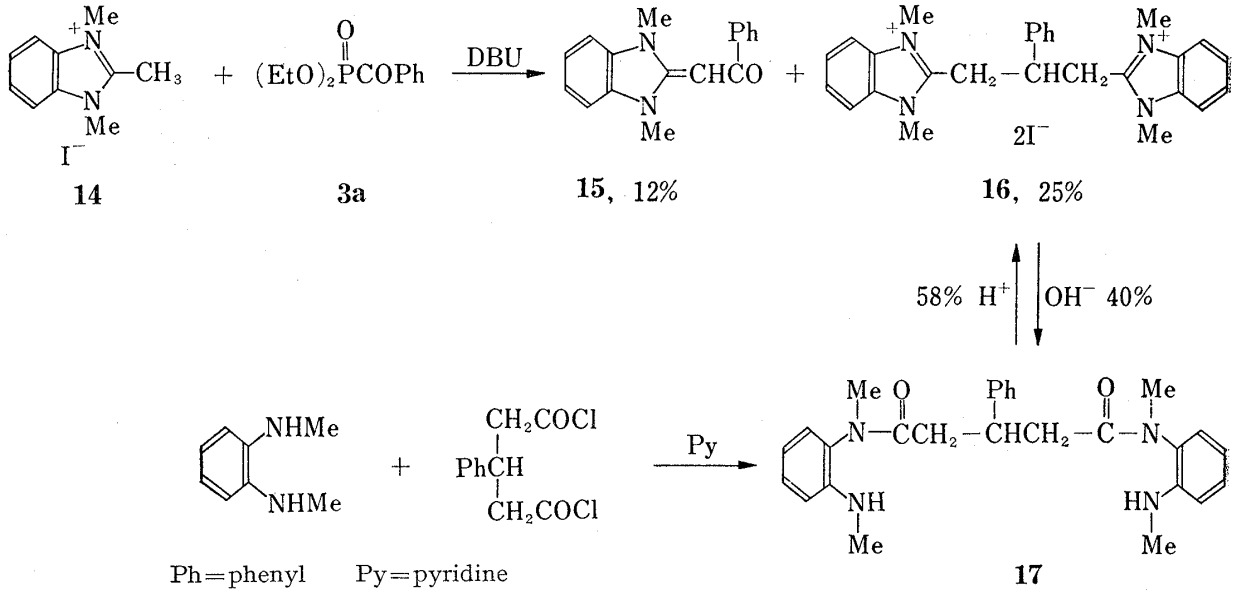


11 3 12

11			3			Base	Temp. (°C)	12		Yield (%)
No.	R_1	X Y	No.	R	mole			No.	mp(°C)	
11a	Me	CH=CH	**3a**	Ph	1.2	DBU	−20	**12a**	149	60
11a	Me	CH=CH	**3a**	Ph	1.2	Et_3N	0—5	**12a**		24
11a	Me	CH=CH	**3a**	Ph	1.2	DABCO	−5—0	**12a**		19
11a	Me	CH=CH	**3a**	Ph	2.4	DBU	−20	**12a**		73
11a	Me	CH=CH	**3b**	*p*-Cl–Ph	2.4	DBU	−20	**12b**	174	66
11a	Me	CH=CH	**3c**	*p*-Me–Ph	2.4	DBU	−20	**12c**	141	69
11a	Me	CH=CH	**3d**		2.4	DBU	−20	**12d**	140	77
11a	Me	CH=CH	**3e**		1.2	DBU	−20	**12e**	98	65
11a	Me	CH=CH	**3f**		1.2	DBU	−20	**12f**	oil	66
11b		CH=CH	**3a**	Ph	2.4	DBU	−20	**12g**	245 (decomp.)	80
11c	CH_2=CH–CH_2–	CH=CH	**3a**	Ph	2.4	DBU	−20	**12h**	70	37
11d	CH≡C–CH_2–	CH=CH	**3a**	Ph	1.2	DBU	−20	**12i**	154—156 (decomp.)	28
11e	Me	Me–C=C  OH	**3a**	Ph	1.2	DBU	−20	**12j** ( OH)	205	30
								12k ( OBz)	141	17
11e	Me	Me–C=C  OH	**3a**	Ph	4.0	DBU	−20	**12k**		67
11f	Me	Me–C=C–COOEt	**3a**	Ph	1.2	DBU	−20	**12l**	233	70
11g	Me	CH=C–Ph	**3a**	Ph	1.2	DBU	−20	**12m**	215	79
11h	Me	CH=C–Ph-*p*-Cl	**3a**	Ph	1.2	DBU	−20	**12n**	277	73
11i	Me	CH=C–Ph-*p*-OMe	**3a**	Ph	1.2	DBU	−20	**12o**	242	73
11j	Me	Me–C=CH	**3g**	*m*-Br–Ph	1.2	DBU	−20	**12p**	185	37
11j	Me	Me–C=CH	**3b**	*p*-Cl–Ph	1.2	DBU	−20	**12q**	177	47
11j	Me	Me–C=CH	**3c**	*p*-Me-Ph	1.2	DBU	−20	**12r**	229	75
11j	Me	Me–C=CH	**3h**	*p*-MeO–Ph	1.2	DBU	−20	**12s**	154	67
11j	Me	Me–C=CH	**3a**	Ph	2.4	DBU	−20	**12t**	175	79
11j	Me	Me–C=CH		PhCOCl	2.4	DBU	−20	**12t**		27
11k	Me	CH_2–CH_2	**3a**	Ph	2.4	DBU	−40	**12u**	127	82
11k	Me	CH_2–CH_2	**3i**	*o*-Me–Ph	2.4	DBU	−40	**12v**	143	76
11k	Me	CH_2–CH_2	**3d**		2.4	DBU	−40	**12w**	140	86
11k	Me	CH_2–CH_2	**3e**		1.2	DBU	−40	**12x**	166	69
11k	Me	CH_2–CH_2	**3f**		1.2	DBU	−40	**12y**	69	30

Ph=phenyl

Application of the acylation reaction to the 1,2,3-trimethylbenzimidazolium salt (**14**) lead to different results from those obtained with the thiazolium salts, giving a dimeric salt (**16**, mp 280°) in 25% yield in addition to acylidene imidazoline (**15**, mp 160°, 12%). The higher formation of the dimeric product (**16**) than the acylidene imidazoline derivative was quite interesting. The salt product (**16**) was hydrolyzed to the amide (**17**) by alkaline and the amide was cyclized to the starting dimeric salt by the acid treatment. The structure of the amide was confirmed finally by the alternate synthesis from N,N′-dimethyl-*o*-phenylenediamine and 3-phenylglutalyl chloride (Chart 4).

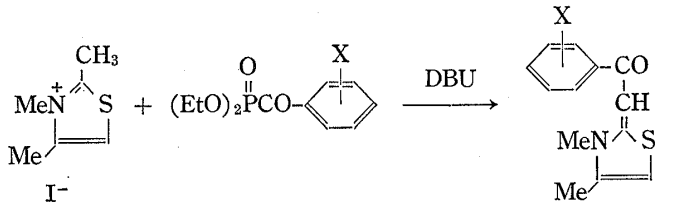


14 **3a** **15**, 12% **16**, 25% **17**

Chart 4

Kinetic experiments on the reaction of 2,3,4-trimethylthiazolium iodide (**11j**) with diethyl substituted benzoylphosphonate (**3h**; X=*p*-OMe, **3c**; *p*-Me, **3a**; H, **3b**; *p*-Cl, **3g**; *m*-Br) and the reaction of 2,3-dimethyl-5-*p*-substituted phenylthiazolium iodide (**11i**; X=OMe, **11g**; H, **11h**; Cl) with diethyl benzoylphosphonate were carried out and the pseudo first-order rate

Table II. Pseudo First-order Rate Constants for the Reaction of 2,3,4-Trimethylthiazolium iodide (**11j**) with Diethyl Substituted Benzoylphosphonate (**3a—c, g, h**) at 22°



11j

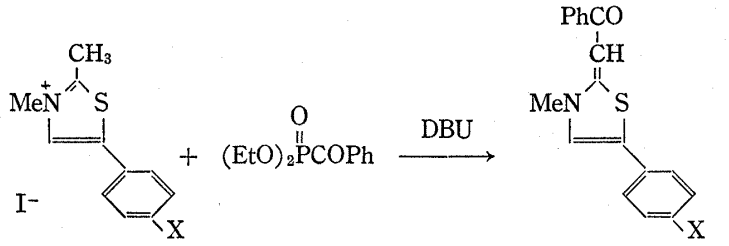
3g : X=*m*-Br
3b : X=*p*-Cl
3a : X=H
3c : X=*p*-Me
3h : X=*p*-OMe

12p : X=*m*-Br
12q : X=*p*-Cl
12t : X=H
12r : X=*p*-Me
12s : X=*p*-OMe

	m-Br	*p*-Cl	H	*p*-Me	*p*-OMe
k min^{-1}	10.5	2.53	0.45	0.18	0.05

Ph=phenyl

Table III. Pseudo First-order Rate Constants for the Reaction of 2,3-Dimethyl-5-*p*-substituted Phenylthiazolium Iodide (**11g—i**) with Diethyl Benzoylphosphonate (**3a**) at 25.5°



11h : X=*p*-Cl **11g** : X=H **11i** : X=*p*-OMe

3a

12n : X=*p*-Cl **12m**: X=H **12o** : X=*p*-OMe

	p-Cl	H	*p*-OMe
k min^{-1}	0.21	0.32	0.71

Ph=phenyl

constants are shown in Tables II and III. A Hammett plot, shown in Fig. 1, gave a positive ρ value for the former and a negative one for the latter.

Accordingly, the reaction mechanism of the acylation reaction might be as shown in Chart 5. Thus, the carbanion formed by proton abstraction of the active methyl group attacks the carbonyl carbon of the acylphosphonate to form an intermediate (**18**), from which the reaction proceeds in different ways. That is, the compounds having an active methylene group (X=S), like the 2-methylthiazolium salts, eliminate diethylphosphite by a second proton abstraction of the active methylene group to give the acylidene thiazoline derivatives (the passway a), while the compounds in which the activity of the methylene group is considerably low, like benzimidazolium (X=NMe), or those which have no active methylene group, like thiamine and 2-free azolium salts, rearrange from the phosphonate (**18**) to the phosphate structure (**19**) and finally form the dimeric salt (**16**) or ring-expanded products (**4**, **5**) by replacement of the phosphate group inter- or intramolecularly (passway b).

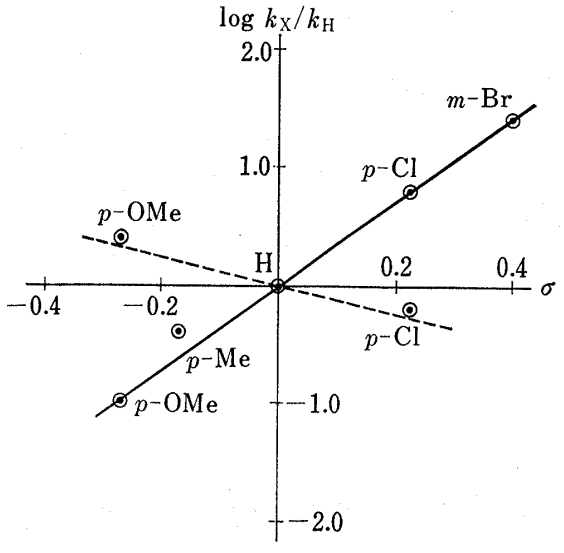


Fig. 1. Plot of log k_X/k_H for the reaction of **11j** with **3a—c, g, h** (Solid Line) and **11g—i** with **3a** (Dotted Line) *vs.* Hammett σ Constants

The wave numbers of the longest wavelength bands in the ultraviolet spectra of **12y**, **u**, **f**, **a**, and **m** are listed in Table IV. The red shift according to the change of the substituent R from the cyclohexane ring to phenyl (**12y→u**, **12f→a**) and the 5-substituent from hydrogen (**12a**) to phenyl (**12m**) were only 31 and 20 nm, respectively, while, the introduction of a double bond into the thiazolidine ring (**12y→12f** and **12u→12a**) caused a larger shift (38 nm). Thus, both substituents R and the 5-phenyl group might be twisted from the chromophoric plane of the acylidenethiazoline skeleton.

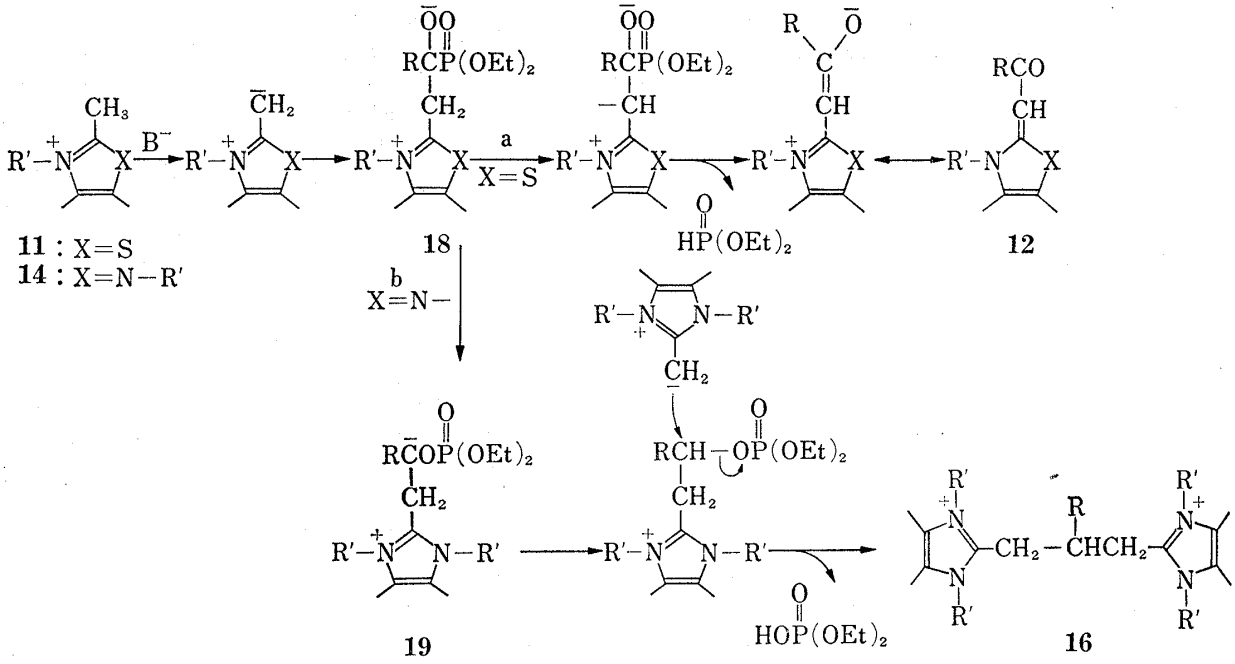
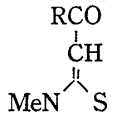


Chart 5

Table IV. The Longest Wavelength of Acylidenethiazolines and Thiazolidines (**12a, f, m, u, y**) in Ultraviolet (UV) Spectra

	No.	X Y	R	UV nm
 **12**	**12y**	$-CH_2-CH_2-$		312
	12u	$-CH_2-CH_2-$	Ph	343
	12f	$-CH=CH-$		350
	12a	$-CH=CH-$	Ph	381
	12m	$-CH=C<_{Ph}$	Ph	401

Ph=phenyl

Experimental[10]

Diethyl Acylphosphonates——Diethyl acylphosphonates were obtained according to Takamizawa, *et al.*,[11] and **3e**, **3f**, **3g** and **3i** showed bp 110—114° (0.1 mmHg) (8.7%), bp 94° (0.1 mmHg) (88%), bp 125—130° (8×10^{-4} mmHg) (51%) and bp 120—123° (3×10^{-3} mmHg) (59%), respectively.

2,3-Dimethyl-5-*p*-substituted Phenylthiazolium Iodide (11g—i)——2-Methyl-5-*p*-substituted phenylthiazoles were obtained according to Gabriel.[12] Thiazoles were heated in excess methyl iodide (methyl iodide-chloroform for 5-*p*-methoxyphenyl derivative) at 50° for 2—3 days under nitrogen atmosphere. The reactants were diluted with acetone and the crystals formed were collected by filtration then recrystallized

10) All melting points are uncorrected. Proton magnetic resonance (PMR) spectra were obtained using a Varian A-60 or T-60 spectrometer with tetramethylsilane (TMS) as the internal standard. Signal multiplicities are represented by s (singlet), d (doublet), t (triplet), q (quartet), b (broad), m (multiplet) and dd (double doublet). Chemical shifts are expressed in δ values and coupling constants are in Hz.

11) A. Takamizawa, Y. Sato, and H. Sato, *Chem. Pharm. Bull.* (Tokyo), **15**, 1183 (1967); *ibid.*, **20**, 892 (1972); A. Takamizawa and H. Sato, *ibid.*, **23**, 948 (1975); A. Takamizawa, H. Sato, and I. Makino, *Vitamins* (Japan), **49**, 177 (1975).

12) S. Gabriel, *Chem. Ber.*, **43**, 1283 (1930).

from ethanol. Quaternary salts (**11g—i**) were obtained in almost quantitative yield: **11g**; mp 195—196°. *Anal.* Calcd. for $C_{11}H_{12}NSI$: C, 41.66; H, 3.81; N, 4.42; S, 10.09; I, 40.02. Found: C, 41.48; H, 3.81; N, 4.19; S, 10.18; I, 40.32. **11h**; mp 199°. *Anal.* Calcd. for $C_{11}H_{11}NSICl \cdot 1/2H_2O$: C, 36.63; H, 3.35; N, 3.88. Found: C, 36.50; H, 3.46; N, 3.74. **11i**; mp 245—246°. *Anal.* Calcd. for $C_{12}H_{14}ONSI$: C, 41.51; H, 4.06; N, 4.03; S, 9.23; I, 36.55. Found: C, 41.54; H, 3.97; N, 3.79; S, 9.16; I, 36.49.

General Procedure for the Reaction of 2-Methylazolium Salts with Diethyl Acylphosphonate——To a suspension of 10 mmoles of 2-methylazolium salt and 2.4 mmoles of diethyl acylphosphonate in 20 ml of dry DMF, was added dropwise a solution of 10 mmoles of DBU in 6 ml of triethylamine in nitrogen atmosphere. The mixture was stirred at −20° for 2 hr then at room temperature for 3 hr, and allowed to stand overnight at room temperature. The solvent was removed *in vacuo* at 60°, and water was added to the residue then extracted with ethyl acetate (when precipitate formed during extraction, it was collected by filtration and mixed with the chloroform extract of the filtrate). The extract was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was dissolved in chloroform and passed through a column of silica gel. The chloroform and 5% ethanol–chloroform elution were evaporated to dryness, and the residue was recrystallized from ethyl acetate or ether–ethyl acetate. 1,1′,3,3′-Tetramethyl-2,2′-(2-phenyltrimethylene)-di(benzimidazolium) diiodide (**16**) was precipitated from the aqueous layer after ethyl acetate extraction and recrystallized from methanol. Yields, analytical data, ultraviolet and nuclear magnetic resonance (NMR) spectra are listed in Tables I, V, VI, and VII, respectively.

Table V. Analytical Data of Acylation Reaction Products

No.	Formula	Calcd.				Found			
		C	H	N	S	C	H	N	S
12a	$C_{12}H_{11}ONS$	66.33	5.10	6.45	14.76	66.19	4.85	6.32	14.69
12b	$C_{12}H_{10}ONSCl$	57.26	4.00	5.56	12.74	57.23	3.69	5.39	12.67
			Cl=14.08				Cl=14.23		
12c	$C_{13}H_{13}ONS$	67.52	5.67	6.06		67.44	5.60	6.10	
12d	$C_{10}H_9ONS_2$	53.79	4.06	6.27	28.71	53.88	3.93	6.24	28.72
12e	$C_{10}H_9O_2NS$	57.95	4.38	6.76	15.47	57.87	4.44	6.72	15.29
12f	$C_{12}H_{17}ONS \cdot 1/2H_2O$	62.03	7.81	6.03	13.80	62.07	7.26	5.66	13.98
12g	$C_{17}H_{16}ON_4S$	62.94	4.97	17.27	9.88	62.26	5.15	17.14	9.62
12h	$C_{14}H_{13}ONS$	69.11	5.39	5.76	13.18	69.08	5.21	5.88	13.47
12i	$C_{14}H_{11}ONS$	69.68	4.59	5.80	13.29	69.50	4.61	5.93	13.22
12j	$C_{15}H_{17}O_2NS$	65.43	6.22	5.09	11.64	65.31	6.31	5.18	11.68
12k	$C_{22}H_{21}O_3NS$	69.63	5.58	3.69	8.45	69.76	5.81	3.75	8.39
12l	$C_{16}H_{17}O_3NS$	63.34	5.65	4.62	10.57	63.40	5.39	4.85	10.77
12m	$C_{18}H_{15}ONS$	73.70	5.15	4.78	10.91	73.63	5.15	4.69	10.97
12n	$C_{18}H_{14}ONSCl$	65.95	4.30	4.27	9.78	66.07	4.29	4.16	9.99
			Cl=10.81				Cl=10.98		
12o	$C_{19}H_{17}O_2NS$	70.56	5.30	4.33	9.91	70.60	5.23	4.47	9.86
12p	$C_{13}H_{12}ONSBr$	50.33	3.90	4.52	10.34	50.58	3.78	4.66	10.14
			Br=25.76				Br=25.97		
12q	$C_{13}H_{12}ONSCl$	58.75	4.55	5.27	12.06	58.59	4.38	5.39	12.20
			Cl=13.34				Cl=13.53		
12r	$C_{14}H_{15}ONS$	68.54	6.16	5.71	13.07	68.69	6.14	5.84	12.79
12s	$C_{14}H_{15}O_2NS$	64.34	5.79	5.36	12.27	64.22	5.66	5.37	12.10
12t	$C_{13}H_{13}ONS$	67.50	5.66	6.06	13.86	67.78	5.64	6.35	13.78
12u	$C_{12}H_{13}ONS$	65.72	5.98	6.39	14.62	65.43	5.96	6.26	14.32
12v	$C_{13}H_{15}ONS$	66.92	6.48	6.00	13.74	67.20	6.49	6.20	13.78
12w	$C_{10}H_{11}ONS_2$	53.31	4.92	6.22	28.46	53.07	4.92	6.06	28.39
12x	$C_{10}H_{11}O_2NS$	57.40	5.30	6.69	15.32	57.54	5.40	6.63	15.04
12y	$C_{12}H_{19}ONS$	63.96	8.50	6.22	14.23	64.09	8.54	6.28	14.37
15	$C_{17}H_{16}ON_2$	77.25	6.10	10.60		76.98	6.21	10.56	
16	$C_{27}H_{30}N_4I_2 \cdot 1/2H_2O$	48.16	4.64	8.32		48.19	4.60	8.25	
			I=37.69				I=36.97		
13a	$C_{15}H_{26}O_7P_2$	47.37	6.89	P=16.29		47.23	6.93	P=16.17	
			MW=380.32				MW=407.4		
13b	$C_{13}H_{24}O_7SP_2 \cdot 1/4ether$	41.53	6.10			41.38	6.41		
13c	$C_{15}H_{32}O_7P_2$	46.63	8.35			46.79	8.43		
		P=16.03	MW=386.37			P=16.18	MW=370.1		

MW=molecular weight

Ozonolysis of 2-(3-Methylbenzothiazolin-2-ylidene)acetophenone (7)——Into a solution of 300 mg of **7** in 20 ml of chloroform, a stream of oxygen with excess ozone was passed at room temperature. Next, the mixture was evaporated *in vacuo*. The residue was dissolved in ether and washed with water, dried then concentrated. After the ether solution had reacted with excess diazoethane in ether for an hour, the solvent was evaporated and the residue was separated by thin-layer chromatography (TLC) (Kieselgel GF-15% hexane–ether). The fraction of ethyl benzoate was hydrolyzed with 10% NaOH in aqueous ethanol (50/50) solution at 80° for 3 hr, neutralized with 20% HCl and extracted with chloroform. The material was recrystallized from water (31 mg, 17%) and identified using commercial benzoic acid. The fraction of ethyl phenylglyoxylate was separated twice by TLC (Kieselgel GF-benzene) and the product was identified using ethyl phenylglyoxylate as 2,4-dinitrophenylhydrazone (mp 155°, 23 mg, 4.3%). The fraction of N-methylbenzothiazolone (**8**) was treated with 10% NaOH in the ethanol–water (50/50) solution at 70° for 20 min and evaporated *in vacuo*. The residue was diluted with water, extracted with chloroform, dried and evaporated. The crystalline residue was recrystallized from ether–hexane (8 mg, 3.2%), and was identical with the authentic sample according to Nitta, *et al.*[13]

Acetylation of 2-(3-Methylbenzothiazoline-2-ylidene)acetophenone (7)——A solution of 40 mg of **7** in 4 ml of acetic anhydride was heated at 120° for 40 hr. After evaporation of acetic anhydride under reduced pressure, the residue was dissolved in chloroform and the solution was washed with the sodium carbonate solution, dried, evaporated and separated by TLC (Kieselgel GF-4% methanol-chloroform). Recrystallization from ethyl acetate gave yellow crystals: mp 183° (**9**, 10 mg, 22%). *Anal.* Calcd. for $C_{18}H_{15}NO_2S$: C, 69.89; H, 4.89; N, 4.53; S, 10.36. Found: C, 69.07; H, 4.77; N, 4.74; S, 10.70. UV λ_{max}^{EtOH} nm (ε): 200.0 (31770), 249.5 (16960), 376 (15360). NMR δ_{ppm} ($CDCl_3$): 2.15^s (3H, COMe), 3.30^s (3H, N–Me), 7.1—8.0^m (9H, 2×Ph).

Catalytic Reduction of 2-(3-Methylbenzothiazolin-2-ylidene)acetophenone (7)——A solution of 134 mg of **7** in 1 ml of methanol and 5 ml of ethanol was hydrogenated over Raney Ni at atmospheric pressure for 48 hr. After filtration and evaporation *in vacuo*, the residue was treated with ether and the crystalline starting material (39 mg) was removed by filtration. The filtrate was separated by TLC (Kieselgel GF-2% ethanol–chloroform) and 44 mg (36%) of oily material (**10**) was obtained. *Anal.* Calcd. for $C_{16}H_{19}ON$: C,

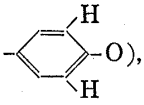
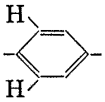
Table VI. Ultraviolet Spectra of the Acylation Products in EtOH

No.	nm (ε)
12a	246.0(9350), 381(24930)
12b	251.5(11530), 385(25770)
12c	255.0(11650), 381(29960)
12d	218.0(9130), 261.0(7740), 276^{sh}(6910), 393(25350)
12e	208.0(9790), 271.5(8470), 386(28050)
12f	207.0(10470), 264.0(1930), 350(24310)
12g[a]	236.0(18240), 275.0(6710), 381(24210)
12h	246.5(9500), 280^{sh}(2050), 382(25740)
12i	247.5(9160), 280^{sh}(1970), 381(24470)
12j	239.5(10210), 275^{sh}(2590), 391(24500)
12k	232.0(21030), 274^{sh}(3890), 282^{sh}(2780), 390(25790)
12l	236.0(11040), 256^{sh}(7490), 313.0(4680), 391(32600)
12m	230.0(8350), 245^{sh}(6840), 312.0(4580), 401(32400)
12n	239.0(19860), 314.5(5370), 404(36470)
12o	244.0(20090), 303.0(7330), 405(32040)
12p	211.5(27480), 239^{sh}(9000), 253^{sh}(6320), 277^{sh}(2400), 390(24730)
12q	213.0^{sh}(19150), 249.5(12730), 390(28430)
12r	214^{sh}(18000), 255.0(11020), 385(28500)
12s	216.5(18400), 269.0(10410), 385(30790)
12t	237.0(9470), 385(25790)
12u	245.0(10720), 278.0(4190), 343(20280)
12v	246.5(5900), 272.0(4320), 326.5(23000)
12w	261.5(8990), 280^{sh}(7810), 355.0(25150)
12x	223.0(4000), 275.0(9780), 350.0(28370)
12y	261.0(4050), 312.0(21990)
15	242.5(16290), 271^{sh}(4830), 278^{sh}(3820), 369(30160)
16	218.5(57420), 258^{sh}(11870), 266^{sh}(14890), 274.5(21150), 282.0(25040)

a) The 12 g spectrum was taken in a MeOH solution.

13) F. Yoneda, T. Ohtaka, and Y. Nitta, *Chem. Pharm. Bull.* (Tokyo), **14**, 698 (1966).

TABLE VII. Proton Magnetic Resonance Spectra of the Acylation Reaction Products in $CDCl_3$ Solution

No.	δ in ppm
12a	3.48^{s} (3H, NMe), 6.35^{b} (1H, =–H), 6.35 and 6.78^{ABq} (2H, J=4.1, Th. 4 and 5-H), 7.30—8.03^{m} (5H, Ph)
12b	3.57^{s} (3H, NMe), 6.33^{b} (1H, =–H), 6.48 and 6.87^{ABq} (2H, J=4.5, Th. 4 and 5-H), 7.37 and $7.93^{A_2B_2}$ (4H, J=8.8, Ph)
12c	2.38^{s} (3H, Me), 3.52^{s} (3H, NMe), 6.35^{b} (1H, =–H), 6.40 and 6.80^{ABq} (2H, J=4.2, Th. 4 and 5-H), 7.22 and $7.87^{A_2B_2}$ (4H, J=8.2, Ph)
12d	3.53^{s} (3H, NMe), 6.22^{b} (1H, =–H), 6.43 and 6.80^{ABq} (2H, J=4.4, Th. 4 and 5-H), 7.05^{dd} (1H, J=5.0 and 3.7, thiophene 4-H), 7.40^{dd} (1H, J=5.0 and 1.2, thiophene 3 or 5-H), 7.60^{dd} (1H, J=1.2 and 3.7, thiophene 5 or 3-H)
12e	3.56^{s} (3H, NMe), 6.31^{d} (1H, J=1.2, =–H), 6.44^{dd} (1H, J=4.3 and 1.2, Th. 5-H), 6.48^{dd} (1H, J=3.5 and 1.8, furan 4-H), 6.84^{d} (1H, J=4.3, Th. 4-H), 7.04^{dd} (1H, J=3.5 and 0.8, furan 3 or 5-H), 7.44^{dd} (1H, J=1.8 and 0.8, furan 5 or 3-H)
12f	1.00—2.62^{m} (11H, cyclohexyl), 3.45^{s} (3H, NMe), 5.69^{b} (1H, =–H), 6.33 and 6.73^{ABq} (2H, J=4.2, Th. 4 and 5-H)
12g[a]	2.32^{s} (3H, pyrimidine 2-Me), 5.12^{s} (2H, CH_2), 6.63^{s} (1H, =–H), 6.82^{d} (1H, J=4.8, Th. 5-H), 6.95^{b} (2H, NH_2), 7.34—8.05^{m} (7H, Ph, pyrimidine 6-H and Th. 4-H)
12h	$4.52^{d,t}$ (2H, J=5.0 and 1.5, CH_2), 4.97—5.50^{m} (2H, $=CH_2$), 5.62—6.67^{m} (2H, 2×=–H), 6.48 and 6.86^{ABq} (2H, J=4.5, Th. 4 and 5-H), 7.25—8.12^{m} (5H, Ph)
12i	2.53^{t} (1H, J=2.5, ≡CH), 4.62^{d} (2H, J=2.5, CH_2), 5.78—6.67^{b} (1H, =–H), 6.45 and 7.03^{ABq} (2H, J=4.5, Th. 4 and 5-H), 7.30—8.12^{m} (5H, Ph)
12j	2.13^{s} (3H, Th. 4-Me), 2.84^{t} (2H, J=6.2, CH_2), 3.44^{s} (3H, NMe), 3.87^{t} (2H, J=6.2, CH_2O), 6.29^{s} (1H, =–H), 7.20—8.17^{m} (5H, Ph)
12k	2.15^{s} (3H, Th. 4-Me), 3.00^{t} (2H, J=6.5, CH_2), 3.43^{s} (3H, NMe), 4.44^{t} (2H, J=6.5, CH_2O), 6.30^{s}(1H, =–H), 7.22—8.17^{m} (10H, 2×Ph)
12l	1.35^{t} (3H, J=7.2, CH_2–$C\underline{H}_3$), 2.56^{s} (3H, Th. 4-Me), 3.44^{s} (3H, NMe), 4.29^{q} (2H, J=7.2, $C\underline{H}_2$–CH_3), 6.38^{s} (1H, =–H), 7.33—8.08^{m} (5H, Ph)
12m	3.51^{s} (3H, NMe), 6.30^{b} (1H, =–H), 6.96^{s} (1H, Th. 4-H), 7.20—8.08^{m} (10H, 2×Ph)
12n[a]	3.67^{s} (3H, NMe), 6.62^{s} (1H, =–H), 7.25—8.10^{m} (9H, 2×Ph), 7.90^{s} (1H, Th. 4-H)
12o	3.53^{s} (3H, NMe), 3.80^{s} (3H, OMe), 6.33^{b} (1H, =–H), 6.83^{d} (2H, J=5.0, ), 6.93^{s} (1H, Th. 4-H), 7.25—8.15^{m} (7H, Ph and )
12p	2.25^{d} (3H, J=1.2, Th. 4-Me), 3.50^{s} (3H, NMe), 6.18^{q} (1H, J=1.2, Th. 5-H), 6.28^{bs} (1H, =–H), 7.10—8.16^{m} (4H, Ph)
12q	2.23^{d} (3H, J=1.2, Th. 4-Me), 3.45^{s} (3H, NMe), 6.15^{q} (1H, J=1.2, Th. 5-H), 6.27^{bs} (1H, =–H), 7.36 and $7.90^{A_2B_2}$ (4H, J=8.8, Ph)
12r	2.18^{d} (3H, J=1.2, Th. 4-Me), 2.38^{s} (3H, Me), 3.42^{s} (3H, NMe), 6.07^{q} (1H, J=1.2, Th. 5-H), 6.23^{b} (1H, =–H), 7.19 and $7.87^{A_2B_2}$ (4H, J=8.4, Ph)
12s	2.18^{d} (3H, J=1.2, Th. 4-Me), 3.42^{s} (3H, NMe), 3.83^{s} (3H, OMe), 6.07^{q} (1H, J=1.2, Th. 5-H), 6.18^{b} (1H, =–H), 6.91 and $7.95^{A_2B_2}$ (4H, J=9.0, Ph)
12t	2.20^{d} (3H, J=1.2, Th. 4-Me), 3.43^{s} (3H, NMe), 6.09^{q} (1H, J=1.2, Th. 5-H), 6.32^{b} (1H, =–H), 7.30—8.05^{m} (5H, Ph)
12u	3.00^{s} (3H, NMe), 2.85—3.80^{m} (4H, Th. 4 and 5-CH_2–CH_2), 6.05^{s} (1H, =–H), 7.25—8.05^{m} (5H, Ph)
12v	2.48^{s} (3H, Me), 2.98^{s} (3H, NMe), 2.88—3.83^{m} (4H, Th. 4 and 5-CH_2–CH_2), 5.73^{b} (1H, =–H), 7.12—7.63^{m} (4H, Ph)
12w	3.02^{s} (3H, NMe), 2.83—3.92^{m} (4H, Th. 4 and 5-CH_2–CH_2), 5.93^{b} (1H, =–H), 7.05^{dd} (1H, J=3.8 and 5.0, thiophene 4-H), 7.44^{dd} (1H, J=5.0 and 1.2,thiophene 3 or 5-H), 7.61^{dd} (1H, J=3.8 and 1.2, thiophene 5 or 3-H)
12x	3.04^{s} (3H, NMe), 2.88—3.83^{m} (4H, Th. 4 and 5-CH_2–CH_2), 6.05^{b} (1H, =–H), 6.48^{dd} (1H, J=3.5 and 1.8, furan 4-H), 7.07^{dd} (1H, J=3.5 and 0.8, furan 3 or 5-H), 7.48^{dd} (1H, J= 1.8 and 0.8, furan 5 or 3-H)
12y	1.00—2.50^{m} (11H, cyclohexyl), 2.91^{s} (3H, NMe), 2.81—3.81^{m} (4H, Th. 4 and 5-CH_2–CH_2), 5.36^{s} (1H, =–H)
15	3.67^{s} (6H, 2×NMe), 5.37^{b} (1H, =–H), 7.17—8.07^{m} (9H, 2×Ph)

No.	δ in ppm
16[a]	3.50—4.38[m] (5H, $CH_2\underline{C}HCH_2$), 3.98[s] (12H, 4×NMe), 7.08—8.08[m] (13H, 3×Ph)
13a	0.93—1.50[m] and 3.62—4.42[m] (12H and 8H, 4×OEt), 5.55[dd] (1H, J=13.5 and 10.5, CH), 7.25—7.70 (5H, Ph)
13b	0.93—1.50[m] and 3.62—4.47[m] (12H and 8H, 4×OEt), 5.83[dd] (1H, J=14.0 and 10.5, CH), 7.00[dd] (1H, J=4 and 1, thiophene 4-H), 7.20—7.50[m] (2H, thiophene 3 and 5-H)
13c	1.37[t] and 3.83—4.48[m] (12H and 8H, J=7.0, 4×OEt), 0.90—2.33[m] (11H, cyclohexyl 4.00—4.75[m] (1H, CH)

a) **12 g, n** and **16** spectra were taken in a dimethyl sulfoxide-d_6 solution.
Ph=phenyl

79.63; H, 7.94; N, 5.80. Found: C, 79.11; H, 8.06; N, 5.65. IR $\nu_{max}^{Chf.}$ cm^{-1}: 3565, 3375 (OH), 1600 (Ph). NMR δ_{ppm} ($CDCl_3$): 1.95[q] (2H, J=7, CH_2–$\underline{CH_2}$–CH), 2.42[s] (1H, OH), 2.88[s] (3H, N–Me), 3.42[t] (2H, J=7.2, CH_2–$\underline{CH_2}$–N), 4.72[t] (1H, J=6.5, CH_2–$\underline{CH}$(OH)–Ph), 6.55—7.45[m] (5H, Ph–N), 7.28[s] (5H, Ph–C).

N,N′-Dimethyl-N,N′-bis(2-methylaminophenyl)-3-phenylglutalamide (17)——a) To a solution of 500 mg of **16** in 10 ml of methanol, was added 1 ml of 40% NaOH and the alkaline solution was heated at 80° for an hour then concentrated *in vacuo* after being left to stand overnight. The residue was extracted with chloroform and the organic layer was dried and evaporated. The oily material was chromatographed on silica gel column and the acetone elution was recrystallized from ethyl acetate–hexane to give 160 mg (48.5%) of colorless flakes: mp 129—130°. *Anal.* Calcd. for $C_{27}H_{32}O_2N_4$: C, 72.95; H, 7.26; N, 12.60; mol. wt., 444.56. Found: C, 72.71; H, 7.25; N, 12.52; mol. wt. ,473.2. IR ν_{max}^{Nujol} cm^{-1}: 3360 (NH), 1655[sh], 1650, 1645[sh] (C=O). NMR δ_{ppm} ($CDCl_3$): 1.65—3.25[m] (5H, CH_2–$\underline{C}H$–CH_2), 2.93[d] (3H, J=5.0, NH–Me), 2.97[d] (3H, J=5.0, NH–Me), 3.15[s] (6H, 2×N–Me), 6.17[b] (2H, 2×NH), 6.40—7.43[m] (13H, 3×Ph).

b) To an ice-cooled solution of 400 mg of N,N′-dimethyl-*o*-phenylenediamine in 1 ml of dry pyridine, was added dropwise 300 mg of freshly distilled 3-phenylglutalylchloride with stirring in argon atmosphere; the mixture was allowed to stand for 2 days. Evaporation, extraction with chloroform, TLC separation (Kieselgel GF-7% methanol–chloroform) and recrystallization from ethyl acetate gave crystals (17 mg, 3%) which were identical with the material obtained above.

Acid Treatment of N,N′-Dimethyl-N,N′-bis(2-methylaminophenyl)-3-phenylglutalamide (17)——A solution of 30 mg of amide (**17**) in 4 ml of 20% HCl was allowed to stand for a week. After evaporation *in vacuo*, the crystalline residue was recrystallized from methanol–ethyl acetate to give 20 mg (58.3%) of **16** dichloride which was identical with the ion-exchange compound (Cl^- form) of **16** diiodide obtained in the reaction of 1,2,3-trimethylbenzimidazolium iodide with diethyl benzoylphosphonate.

Kinetic Experiments——The reaction rates were measured by following the increase of intensity at the longest wavelength of acylidenethiazoline (380—410 nm). A solution containing 0.2 nmole of thiazolium salts and 4.5 nmoles of acylphosphonate in 3.0 ml of dry dimethylformamide was prepared in a ultraviolet cell and the reaction was initiated by adding 1.0 ml of the dimethylformamide solution containing 72 nmoles of DBU followed by rapid mixing by hand. The first reading of intensity was taken at 15 sec after the addition of DBU and thereafter readings were taken at 10 sec intervals for 2 min, after which they were taken at 30 sec intervals for an hour. The concentration [Ct] of acylidenethiazoline derivatives after t sec was obtained from the following equation: $[Ct]=A_t-A_{initial}/A_{infinite}-A_{initial}$, where A_t and $A_{infinite}$ show the intensity after t sec and the intensity observed without increase (after about a half hour), respectively, and $A_{initial}$ shows the intensity before addition of the DBU solution.

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