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On the Reaction of Dialkyl Acylphosphonate with 2-Methyl-1,3,4-thiadiazolium Salts[1]

Akira Takamizawa, Yoshihiro Matsushita, and Hiroshi Harada

Shionogi Research Laboratory, Shionogi and Co., Ltd.[2]

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Dialkyl acylphosphonate acted as an acylating agent for the 2-methyl group in 1,3,4-thiadiazolium salts, as well as 2-methylthiazolium and thiazolinium salts, to give 2-acylidenethiadiazoline derivatives. The reaction of diethyl benzoylphosphonate (**1**) with 5-amino-2,3-dimethyl-1,3,4-thiadiazolium iodide (**2c**) gave the N-monobenzoate inner salt (**6**), C-monobenzoate (**7**), C,N-dibenzoate (**8**) and 5-benzoylamido-2-styryl-thiadiazolium hydroxide inner salt (**9**); the extent of N-acylation was greater than that of C-acylation. The structures of the inner salt products (**6** and **9**) were confirmed by an alternative synthesis. A proposed mechanism for the acylphosphonate reaction with 2-methyl-1,3,4-thiadiazolium salts is presented, and is consistent with the ^{13}C-nuclear magnetic resonance chemical shifts of the 2-methyl groups of the 1,3-azolium salts.

Keywords——2-methyl-1,3,4-thiadiazolium salts; dialkyl acylphosphonate; C- and N-acylation; heterocylic zwitterion; reaction mechanism

In a previous paper,[3] we reported that the methyl carbon of 2-methylthiazolium betaine was acylated by dialkyl acylphosphonate. This paper deals with the application of the acylation reaction to 2-methyl-1,3,4-thiadiazolium salts and compares the C- and N-acylation ratios in compounds having amino and methyl groups in the same thiadiazolium nucleus.

The action of diethyl benzoylphosphonate (**1**) on 2,3,5-trimethyl-1,3,4-thiadiazolium iodide (**2a**) in dimethylformamide (DMF) suspension in the presence of 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) provided 2-(3,5-dimethyl-1,3,4-thiadiazolin-2-ylidene)acetophenone (**3a**) in 73% yield; the structure of the product was confirmed by elemental analysis and spectral data. The product **3a** showed a strong absorption band at 367 nm (ε=24400) in the ultraviolet (UV) spectrum due to the enaminoketone chromophore, a strong carbonyl band at 1600 cm^{-1} in the infrared (IR) spectrum and a singlet olefinic proton signal at δ 6.30 which disappeared on D_2O treatment in the nuclear magnetic resonance (NMR) spectrum. These spectral data are characteristic of 2-acylidene thiazoline and thiadiazoline derivatives. 5-Acetamido-2,3-dimethyl-1,3,4-thiadiazolium iodide (**2b**) was obtained by alkylation of 2-acetamido-5-methyl-1,3,4-thiadiazole (**4**) with methyl iodide (the position of alkylation was not clear at this stage and was determined later), accompanied by a small amount of another quaternary base, mp 198—200°, resembling 2-acetamido-3,5-dimethyl-1,3,4-thiadiazolium iodide, although its identity was not confirmed. Treatment of **2b** with 2 moles of **1** gave 2-(5-acetamido-3-methyl-1,3,4-thiadiazolin-2-ylidene)acetophenone (**3b**) and diethyl[1-phenyl-1-diethylphosphatomethyl]phosphate (**5**) in 72 and 75% yields, respectively. Thus, the acylation reaction at the 2-methyl carbon of 1,3,4-thiadiazolium betaine proceeded in the same way as that of the 2-methylthiazolium compounds.

As it seemed of interest to determine whether the active methyl or the amino group was acylated more easily with this reagent, we conducted the acylphosphonate reaction with the 5-amino-2,3-dimethyl-1,3,4-thiadiazolium iodide **2c**, bearing both groups in the same molecule.

1) This paper constitutes Part XCIII of a series: Studies on Pyrimidine Derivatives and Related Compounds. Part XCII: A. Takamizawa and I. Makino, *Vitamins* (Japan), **52**, 127 (1978).
2) Location: *Fukushima-ku, Osaka, 553 Japan.*
3) A. Takamizawa, Y. Matsushita, and H. Harada, *Chem. Pharm. Bull.*, **25**, 991 (1977).

Reaction of the amino derivative (**2c**) with equimolar diethyl benzoylphosphonate (**1**) afforded the N-monobenzoate betaine (**6**), C-monobenzoate (**7**), and C,N-dibenzoate (**8**) in 36, 2.2 and 3.5% yields, respectively. On the other hand, the reaction using 2 mol of benzoylphosphonate (**1**) gave **6**, **8** and a new product (**9**) in 50, 34, and 6.4% yields, respectively. Compound **8** was also obtained from the reaction of **6** or **7** with equimolar benzoylphosphonate. Reaction of **6** with 2 mol of benzoylphosphonate gave **8** and **9** in 50 and 25% yields, respectively. The product **6** was synthesized using benzoylisothiocyanate (**11**) and N-methylthioacetohydrazide (**10**), modifying the synthetic route to the 2-phenyl derivative of **6** reported by Thieme.[4] The inner salt (**6**) gave a salt, 5-benzoylamido-2,3-dimethyl-1,3,4-thiadiazolium iodide (**12**), with

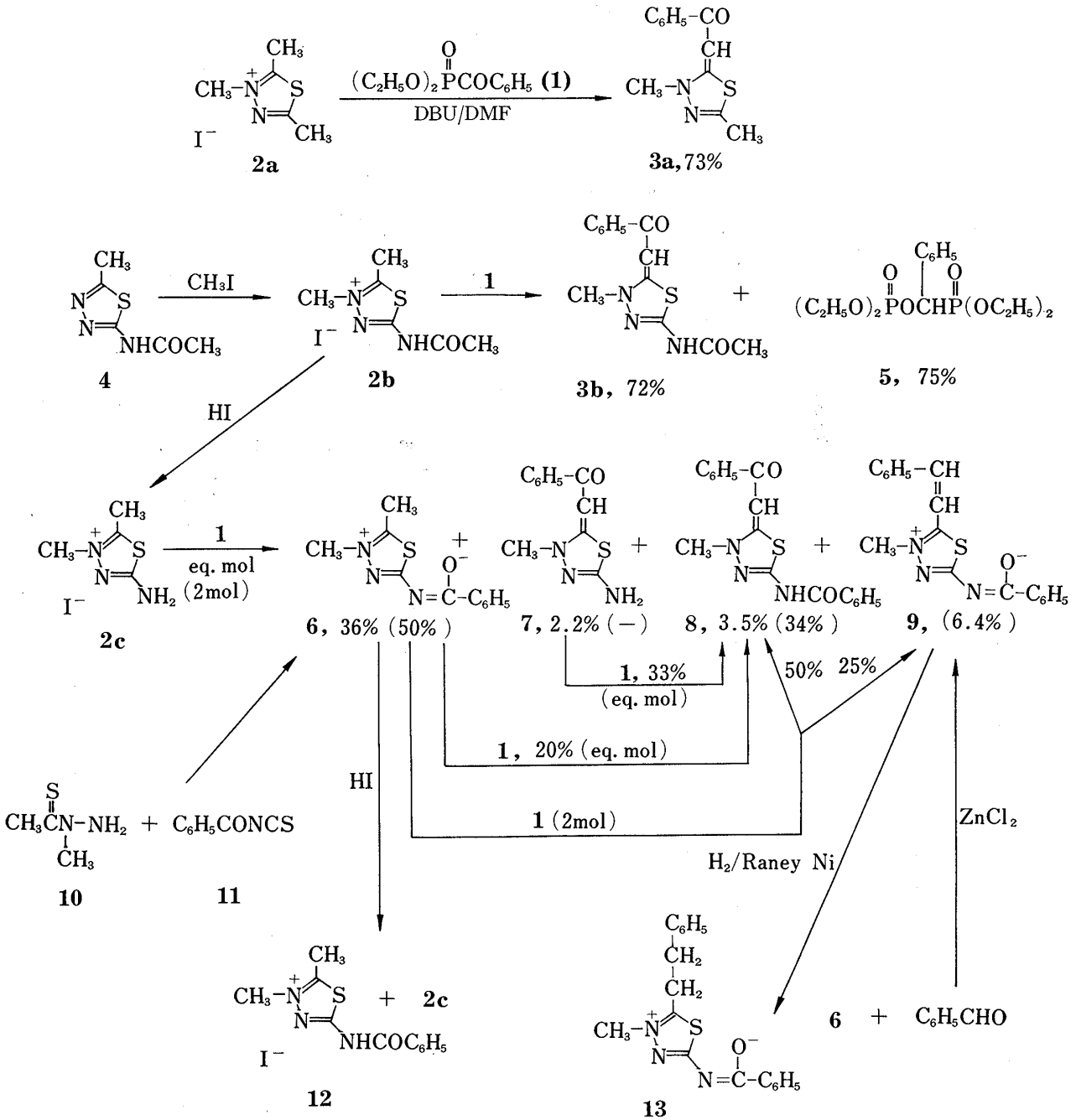

Chart 1

4) von P. Thieme, M. Patsch, and H. König, *Liebig Ann. Chem.*, **764**, 94 (1972).

hydrogen iodide. The identity of the synthetic product with **6** obtained in the acylphosphonate reaction confirmed that N-methylation of **4** with methyl iodide occurred at the nitrogen adjacent to the carbon bearing the methyl substituent.

The product **9** gave the formula $C_{18}H_{15}N_3OS$, with one oxygen less than the C,N-dibenzoate (**8**), on elemental analysis, and showed a strong absorption band at 388 nm (ε=27700) in the UV spectrum. In the NMR spectrum, the N-methyl signal appeared at 4.23 as a singlet, and 12 protons corresponding to phenyl and olefinic protons appeared at 7.33—8.41 as a multiplet. Hydrogenation of **9** over a large amount of Raney Ni catalyst gave colorless crystals (**13**) which gave the formula $C_{18}H_{17}N_3OS$ on elemental analysis, and showed signals for four protons at 2.83—3.43 as a multiplet in the NMR spectrum. The structure of **9** was assumed to be 2-styrylthiadiazolium inner salt based on the above data, and was finally determined to be 5-benzoylamido-3-methyl-2-styryl-1,3,4-thiadiazolium hydroxide inner salt by comparison with the product of the reaction of **6** with benzaldehyde in the presence of zinc chloride, using the synthesis of Kondo *et al.*[5] for 2-styrylthiazoles. This 2-styryl derivative (**9**) was a single compound although its geometry was obscure.

The above results show that acylphosphonate reacts with the 2-methyl group of 2-methyl-1,3,4-thiadiazolium salts as well as 2-methylthiazolium and thiazolinium salts to give 2-acylidene derivatives. However, the formation of the 2-styryl derivatives was observed, in contrast to the case of 2-methylthiazolium and thiazolinium salts. In the acylation reaction using acylphosphonate with a compound having an active methyl group and an amino group in the same molecule, the amino group was acylated more easily than the active methyl group.

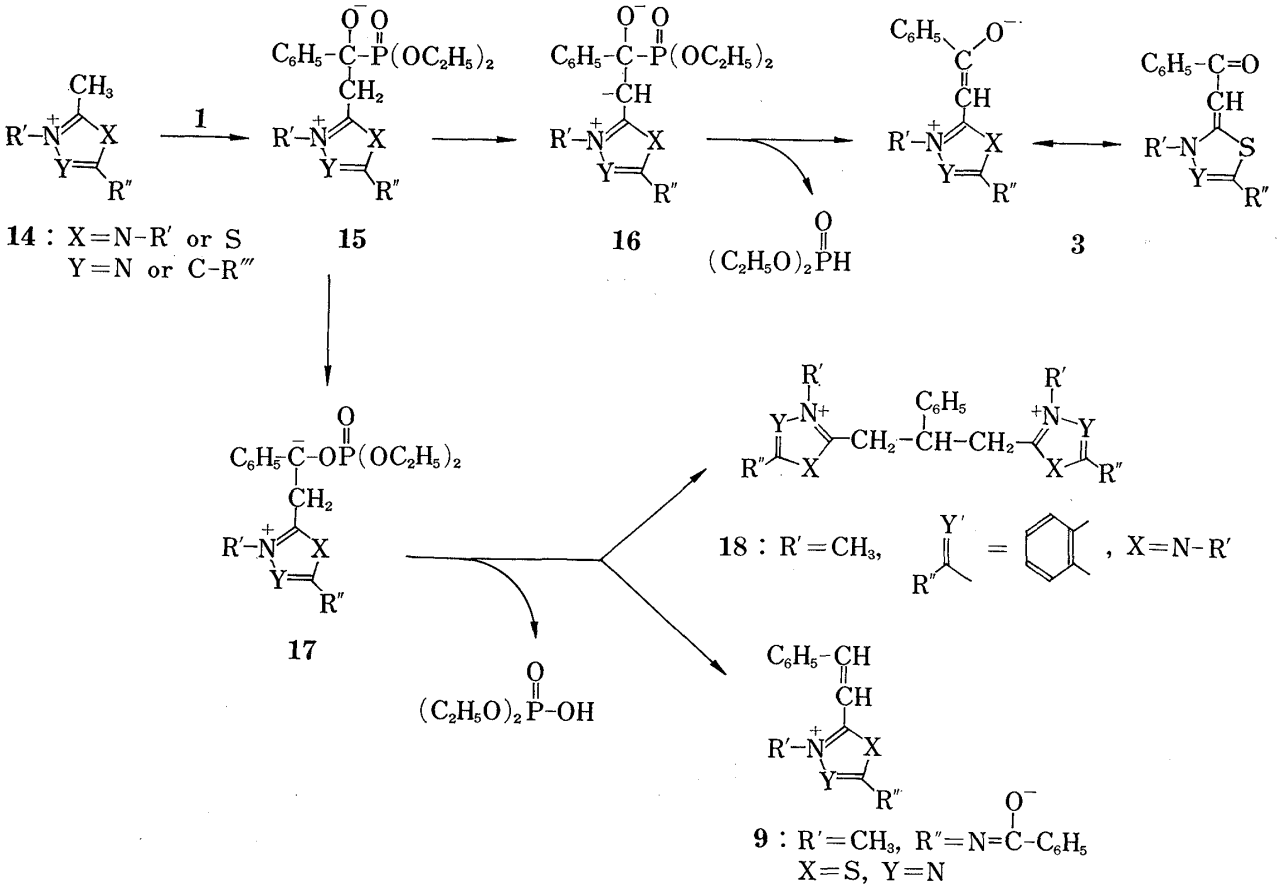

Chart 2

5) H. Kondo and F. Nagasawa, *Yakugaku Zasshi*, **57**, 909 (1937).

The mechanism of the reaction can be explained as reported previously[3] (Chart 2). The 1 : 1 adduct (**15**) of acylphosphonate and 2-methylazolium is formed first, and eliminates diethyl hydrogen phosphite to form a 2-acylidene derivative (**3**) when the activity of the 2-methylene group is relatively high. When this activity is relatively low, the first phosphonate intermediate (**15**) will rearrange into the second intermediate (**17**) having the phosphate structure,[3] as also seen in the ring enlargement reaction of 2-unsubstituted thiazolium salts with dialkyl acylphosphonate,[6] and the intramolecular elimination of diethylphosphate may lead to formation of the 2-styryl derivative (**9**).

In order to evaluate the activity of the 2-methylene group, the ^{13}C chemical shifts of the 2-methyl group in 2-methylazolium salts were determined. They were δ 15.70 for 2,3-dimethylthiazolium iodide, 14.71 for 5-acetamido-2,3-dimethyl-1,3,4-thiadiazolium iodide (**2b**), 13.76 for 5-benzoylamido-2,3-dimethyl-1,3,4-thiadiazolium hydroxide inner salt (**6**) and 10.82 for 1,2,3-trimethylbenzimidazolium iodide. The former two compounds gave only 2-acylidene derivatives (**3**) in the benzoylphosphonate reaction, while the third (**6**) formed a mixture of 2-acylidenethiadiazoline (**8**) and the 2-styryl derivative (**9**), and the last compound afforded mainly 1,1′,3,3′-tetramethyl-2,2′-(2-phenyltrimethylene)-di(benzimidazolium)diiodide (**18**).[3] Azolium salts in which the 2-methyl carbon signals appeared at relatively low field gave 2-acylidene derivatives (**3**) *via* **16**, while those in which the same signals appeared at relatively high field gave mainly the dimeric imidazolium salt (**18**) or, in part, the styrylthiadiazolium salt (**9**) which was formed by elimination of diethylphosphate from **17**. Thus, the order of reactivity in the acylphosphonate reaction coincided with the order of the ^{13}C chemical shifts of the 2-methyl group in the azolium salts. As a correlation between the ^{13}C chemical shifts of substituted methyl carbon and the electronegativities of the substituents has been observed,[7] this finding supports the mechanism shown in Chart 2, although further experiments on the precise correlation between the reactivity and the ^{13}C chemical shifts of the 2-methylene group in azolium salts may be desirable.

Experimental[8]

General Procedure for the Reaction of 2-Methyl-1,3,4-thiadiazolium Salts (2a, b, c) with Diethyl Benzoylphosphonate (1)——A solution of 10 mmol of DBU in 6 ml of triethylamine at −20° was added dropwise to a suspension of 10 mmol of 2-methyl-1,3,4-thiadiazolium salt (**2a, b, c**) and 12 or 24 mmol of diethyl benzoylphosphonate (**1**) in 20 ml of dry DMF under a nitrogen atmosphere. The mixture was stirred at −20° for 2 hr, and at room temperature for 3 hr, then it was allowed to stand overnight at room temperature. The solvent was removed *in vacuo* at 60°, and water was added to the residue. This was then extracted with chloroform (when a precipitate formed during extraction, it was collected by filtration and the crystals were mixed with the chloroform extract). 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 eluates were evaporated to dryness, and the residue was recrystallized from ethyl acetate for **3a**, ethylacetate-ether for **9**, ethanol-chloroform for **6**, ethanol for **7** and dimethyl sulfoxide for **3b** and **8**. Analytical data, UV and NMR spectra are listed in Tables I, II and III, respectively.

5-Acetamido-2,3-dimethyl-1,3,4-thiadiazolium Iodide (2b)——A solution of 7 g of 2-acetamido-5-methyl-1,3,4-thiadiazole (**4**)[9] in 150 ml of DMF was treated with 30 ml of methyl iodide and the solution was stirred for 24 hr at 50° under a nitrogen atmosphere. Removal of DMF *in vacuo*, followed by recrystallization from ethanol gave 5.2 g (39%), mp 249—251°, of **2b**. From the mother liquor, a small amount of crystals, mp 198—200°, was obtained. **2b**: *Anal.* Calcd for $C_6H_{10}IN_3OS$: C, 24.09; H, 3.37; I, 42.42. N, 14.05; S, 10.72; Found: C, 24.05; H, 3.26; N, 14.09; S, 10.61; I, 42.18.

6) A. Takamizawa, H. Harada, H. Sato, and Y. Hamashima, *Heterocycles*, **2**, 521 (1974).
7) H. Spiesecke and W.G. Schneider, *J. Chem. Phys.*, **35**, 722 (1961).
8) All melting points are uncorrected. Proton and carbon magnetic resonance spectra were taken using Varian T-60 and XL-100A-12 spectrometers, respectively, with tetramethylsilane (TMS) as an internal standard. Signal multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), b (broad), m (multiplet) and dd (double doublet). Chemical shifts are given in δ values and coupling constants in Hz.
9) M. Ohta and T. Higashijima, *Yakugaku Zasshi*, **72**, 376 (1952).

Table I. Analytical Data for Acylation Reaction Products

No.	mp	Formula	Calcd				Found			
			C	H	N	S	C	H	N	S
3a	123—124°	$C_{12}H_{12}N_2OS$	62.04	5.21	12.06	13.80	62.00	4.92	11.83	13.96
3b	330—340°	$C_{13}H_{13}N_3O_2S$	56.70	4.76	15.26	11.64	56.29	4.88	14.84	11.78
6	250—252° (dec.)	$C_{11}H_{11}N_3OS$	56.63	4.75	18.01	13.74	56.48	4.72	17.95	13.73
7	266—267°	$C_{11}H_{11}N_3OS$	56.63	4.75	18.01	13.74	56.23	4.72	17.54	13.61
8	306°	$C_{18}H_{15}N_3O_2S \cdot 3/4DMSO$	59.15	4.96	10.61	14.17	58.93	5.07	10.37	14.14
9	235—236°	$C_{18}H_{15}N_3OS$	67.27	4.70	13.07	9.98	67.01	4.81	12.74	10.09

Table II. Ultraviclet Spectra of the Acylation Reaction Products in EtOH

No.	Peak wavelength, nm (ε)
3a	248.0 (10830), 278^{sh} (2300), 367 (24400)
3b	246.5 (11160), 294 (4120), 378 (24640)
6	237.0 (10540), 273.5 (7550), 315.0 (14820)
7	245.0 (11940), 382 (22350)
8	243.0 (21490), 382 (24410)
9	237.5 (22280), 297.5 (16620), 388 (27700)

Table III. Proton Magnetic Resonance Spectra of the Acylation Reaction Products in a Dimethyl Sulfoxide-d_6 Solution

No.	Chemical shifts, δ in ppm
3a[a]	2.45^s (3H, 5-Me), 3.75^s (3H, NMe), 6.30^b (1H, =–H), 7.28—8.13^m (5H, Ph)
3b	2.15^s (3H, COMe), 3.78^s (3H, NMe), 6.58^s (1H, =–H), 7.30—8.38^m (5H, Ph), 11.98^{bs} (1H, NH)
6	2.76^s (3H, 5-Me), 4.02^s (3H, NMe), 7.27—8.33^m (5H, Ph)
7	3.63^s (3H, NMe), 6.37^s (1H, =–H), 6.81^{bs} (2H, NH_2), 7.30—8.08^m (5H, Ph)
8	3.93^s (3H, NMe), 6.73^s (1H, =–H), 7.33—8.35^m (10H, 2×Ph), 12.36^{bs} (1H, NH)
9	4.23^s (3H, NMe), 7.33—8.41^m (12H, 2×Ph+2×=–H)

a) The spectrum of **3a** was taken in $CDCl_3$ solution. Ph=phenyl.

5-Amino-2,3-dimethyl-1,3,4-thiadiazolium Iodide (2c)——A mixture of 3 g of 5-acetamido-2,3-dimethyl-1,3,4-thiadiazolium iodide (**2b**) and 10 ml of 20% hydroiodic acid was refluxed for 2 hr, then concentrated *in vacuo*. Recrystallization from ethanol gave 2.4 g of **2c**, mp 239—240°. *Anal.* Calcd for $C_4H_8IN_3S$: C, 18.69; H, 3.14; I, 49.36. N, 16.34; S, 12.47; Found: C, 18.78; H, 3.04; N, 16.45; S, 12.00; I, 49.20. NMR δ ppm (DMSO-d_6): 2.83^s (3H, 2-Me), 3.93^s (3H, NMe), 8.20^{bs} (2H, NH_2).

Reaction of 5-Acetamido-2,3-dimethyl-1,3,4-thiadiazolium Hydroxide Inner Salt (6) with Diethyl Benzoylphosphonate (1)——a) A mixture of 116 mg of **6**, 130 mg of **1** and 1.2 ml of DMF was treated with a mixture of 75 mg of DBU and 0.3 ml of triethylamine as described in the general procedure. Separation by silica gel column chromatography, eluting with ethyl acetate, gave 33 mg (20%) of yellow crystals, which were identical with **8** obtained by the reaction of **2c** with **1**.

b) A mixture of 2.3 g of **6**, 5.2 g of **1** and 10 ml of DMF was treated with a mixture of 1.5 g of DBU and 6 ml of triethylamine as described in the general procedure. A crude mixture of **8** and **9** was dissolved in a large amount of chloroform and subjected to silica gel column chromatography. The large volumes of ether and ethyl acetate eluates gave 1.75 g (50%) of **8** and 0.84 g (25%) of **9**, respectively. Both compounds were identical with the products obtained by the reaction of **2c** with **1**.

Reaction of 2-(5-Amino-3-methyl-1,3,4-thiadiazolin-2-ylidene)acetophenone (7) with Diethyl Benzoylphosphonate (1)——A mixture of 50 mg of **7**, 51.8 mg of **1** and 1 ml of DMF was treated with a mixture of 32.3 mg of DBU and 0.13 ml of triethylamine as described in the general procedure. Separation by silica gel column chromatography, eluting with chloroform-ethyl acetate, gave 23 mg (33%) of yellow crystals, which

were identical with **8** obtained by the reaction of **2c** with **1**. The starting material (**7**) was also recovered, 17 mg (34%).

5-Benzoylamido-2,3-dimethyl-1,3,4-thiadiazolium Iodide (12)——A mixture of 100 mg of 5-benzoylamido-2,3-dimethyl-1,3,4-thiadiazolium hydroxide inner salt (**6**) and 3 ml of 20% hydroiodic acid was refluxed for 5 min, then cooled on an ice bath. Precipitated crystals were collected by filtration and recrystallized from ethanol to give 125 mg (81%) of the iodide (**12**), mp 227—228° (dec.). *Anal.* Calcd for $C_{11}H_{12}IN_3OS \cdot H_2O$: C, 34.84; H, 3.70; I, 33.46. N, 11.08; S, 8.45; Found: C, 35.01; H, 3.54; N, 11.11; S, 8.44; I, 33.35. IR ν_{max}^{Nujol} cm^{-1}: 3400, 3360, 1670, 1340, 1280. NMR δ ppm (DMSO-d_6): 3.03^s (3H, 2-Me), 4.22^s (3H, NMe), 7.43—8.25^m (5H, Ph).

5-Benzoylamido-2,3-dimethyl-1,3,4-thiadiazolium Hydroxide Inner Salt (6)——A solution of 6.32 g of benzoyl chloride in 50 ml of abs. acetonitrile was treated with 4.37 g of potassium thiocyanate and the mixture was refluxed for an hour. Precipitates were removed by filtration, then 4.7 g of N′-methyl thioacetohydrazide[10] was added to the filtrate and the solution was refluxed for 15 hr. After cooling, the precipitates were collected by filtration, the filtrate was concentrated *in vacuo* and the further precipitates were collected. The precipitates were combined and recrystallized from chloroform–ethanol to give 8.3 g (79%) of pale yellow crystals, mp 250—252°, which were identical with the product obtained by the reaction of **2c** with **1**.

5-Benzoylamido-3-methyl-2-(2-styryl)-1,3,4-thiadiazolium Hydroxide Inner Salt (9)——A mixture of 100 mg of 5-benzoylamido-2,3-dimethyl-1,3,4-thiadiazolium hydroxide inner salt (**6**), 200 mg of benzaldehyde and 35 mg of anhydrous zinc chloride was heated at 180° for one hour with stirring. The mixture was extracted with chloroform, and the chloroform solution was washed with water, dried and concentrated *in vacuo*. The residue was chromatographed on a silica gel column, and elution with ethyl acetate gave 89 mg (63.6%) of yellow crystals, mp 235—236°, which were identical with **9** obtained by the reaction of **2c** with **1**.

5-Benzoylamido-3-methyl-2-(2-phenethyl)-1,3,4-thiadiazolium Hydroxide Inner Salt (13)——A solution of 100 mg of 2-styryl derivative (**9**) in 25 ml of methanol was hydrogenated over 1.5 ml of Raney nickel catalyst for 8 hr. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in chloroform, washed, dried and concentrated. Recrystallization from ether gave 50 mg (50%) of colorless crystals, mp 202—204°. *Anal.* Calcd for $C_{18}H_{17}N_3OS$: C, 66.85; H, 5.30; N, 12.99; S, 9.91. Found: C, 67.27; H, 5.24; N, 12.37; S, 10.20. NMR δ ppm ($CDCl_3$): 2.83—3.43^m (4H, $2 \times CH_2$), 3.60^s (3H, NMe), 6.90—7.57^m and 8.17—8.40^m (8H and 2H, $2 \times$ Ph).

10) K.A. Jensen, H.R. Baccaro, O. Buchardt, G. E. Olsen, C. Pedersen, and J. Toft, *Acta Chem. Scand.*, **15**, 1109 (1961).