Synthesis Using Allylidenedihydropyridines. VIII.[1] Facile Preparation of 2-Alkylthio-3-vinylpyrazolo[1,5-*a*]pyridines

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Synopsis. Reactions of 1-[bis(alkylthio)methyleneamino]-2-methylpyridinium iodides with activated ethoxymethylene compounds in the presence of alkali gave the corresponding 1-[bis(alkylthio)methyleneamino]-2-allylidene-1,2-dihydropyridines in considerable yields, and their thermolyses in benzene afforded 2-alkylthio-3-vinylpyrazolo[1,5-*a*]pyridine derivatives.

In a previous paper a report was given on a simple preparation method of 2-alkylthio-1-vinylindolizine derivatives from the corresponding pyridinium 1-[(alkylthio)thiocarbonyl]methylides.[2] The extension of this route for synthesizing its azaanalogue, 2-alkylthio-3-vinylpyrazolo[1,5-*a*]pyridine, should be possible if an appropriate starting material such as pyridinium 1-[(alkylthio)thiocarbonyl]aminide is available.[3] In contrast with pyridinium 1-[(alkylthio)thiocarbonyl]-methylide,[4] however, such type of pyridinium 1-aminide has not been reported. In this paper we wish to report the syntheses of pyridinium 1-[(alkylthio)thiocarbonyl]-aminides and of the title compounds using them.

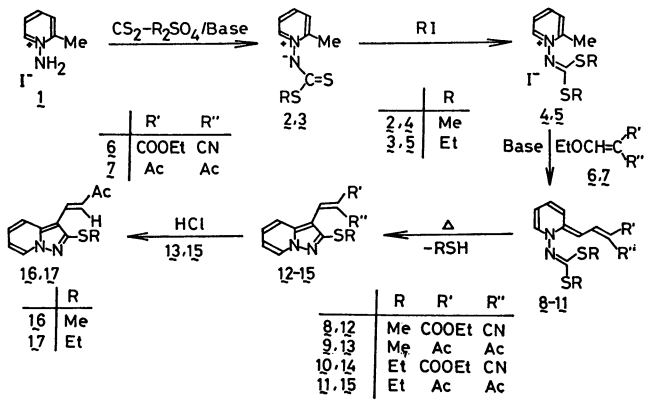
Since the smooth formation of *S*-involving pyridinium betaines from the reactions of various pyridinium 1-methylides with carbon disulfide are well known,[4] the preparation of pyridinium 1-[(alkylthio)thiocarbonyl]aminide by a similar procedure was attempted and accomplished well when the reaction of pyridinium 1-aminide with carbon disulfide was carried out in the presence of a certain alkylating agent: When a mixture of 1-amino-2-methylpyridinium iodide (**1**), carbon disulfide, and dimethyl or diethyl sulfate was treated with potassium hydroxide in ethanol, the expected 2-methylpyridinium 1-[(methylthio)- (**2**) or 1-[(ethylthio)-thiocarbonyl]aminide (**3**) was obtained in 59 or 65% yield. The respective reactions of **2** and **3** with methyl and ethyl iodide gave the *S*-alkylated products, 1-[bis(methylthio)- (**4**) and 1-[bis(ethylthio)-methyleneamino]-2-methylpyridinium iodide (**5**), in quantitative yields. The reactions of the pyridinium salts (**4** and **5**) with ethyl (ethoxymethylene)cyanoacetate (**6**) and 3-(ethoxymethylene)pentane-2,4-dione (**7**) in the presence of potassium carbonate afforded the corresponding 1-[bis(alkylthio)methyleneamino]-2-allylidene-1,2-dihydropyridine derivatives (**8**—**11**) in 47—56% yields. These compounds (**8**—**11**) were then thermolysed smoothly in refluxing benzene to give 2-alkylthio-3-vinylpyrazolo[1,5-*a*]pyridines (**12**—**15**) with the elimination of methanethiol or ethanethiol. Interestingly, pyrazolopyridines (**12**—**15**) were very stable and unchanged even in dilute hydrochloric acid or aqueous sodium hydroxide. However, **13** and **15** were decomposed by the treatments of conc. hydrochloric acid to yield products (**16** and **17**), and **12** and **14** under similar conditions gave only intractable tarry substances. These results are summarized in the following Scheme.

The structures of these compounds (**2** and **3**, **4** and **5**, **8**—**11**, and **12**—**15**) were determined by their physical and spectral analyses and by comparisons with spectral data of known pyridinium 1-aminides, pyridinium salts, 2-allylidene-1,2-dihydropyridines, and 3-vinylpyrazolo-[1,5-*a*]pyridines, respectively.[3] On the other hand, those of **16** and **17** were concluded to be the monodeacetylated compounds of starting pyrazolopyridines (**13** and **15**), because their NMR spectra exhibited a characteristic AB quartet signal coupled with 16.0 Hz at δ 7.89, 7.62, 6.78, and 6.50 (**16**) or at δ 7.90, 7.82, 6.79, and 6.51 (**17**) and only one acetyl singlet at δ 2.35

TABLE 1. IR SPECTRAL DATA AND ELEMENTARY ANALYSES

Compd No.	Formula	Calcd (%)			Found (%)			ν^{KBr} (cm^{-1})	
		C	H	N	C	H	N		
2	$C_8H_{10}N_2S_2$	48.45	5.08	14.13	48.21	5.04	14.40	1399	971
3	$C_9H_{12}N_2S_2$	50.91	5.70	13.20	51.02	5.68	13.07	1392	978
4	$C_9H_{13}IN_2S_2$	31.77	3.85	8.23	31.65	3.87	8.35	1476	1235
5	$C_{11}H_{17}IN_2S_2$	35.87	4.65	7.45	36.02	4.61	7.45	1470	1230
8	$C_{15}H_{17}N_3O_2S_2$	53.70	5.11	12.53	53.81	5.15	12.47	2210	1668
9	$C_{15}H_{18}N_2O_2S_2$	55.86	5.63	8.69	55.87	5.92	8.40	1583	1506
10	$C_{17}H_{21}N_3O_2S_2$	56.19	5.83	11.57	56.10	5.93	11.59	2215	1667
11	$C_{17}H_{22}N_2O_2S_2$	58.25	6.33	7.99	58.29	6.39	7.89	1590	1505
12	$C_{14}H_{13}N_3O_2S$	58.52	4.56	14.63	58.28	4.59	14.52	2215	1721
13	$C_{14}H_{14}N_2O_2S$	61.29	5.14	10.21	61.00	5.11	10.21	1674	1492
14	$C_{15}H_{15}N_3O_2S$	59.78	5.02	13.94	59.85	5.05	13.92	2210	1718
15	$C_{15}H_{16}N_2O_2S$	Oil						1679	1500[a]
16	$C_{12}H_{12}N_2OS$	62.04	5.21	12.06	62.02	5.18	12.11	1603	1259
17	$C_{13}H_{14}N_2OS$	63.91	5.78	11.47	63.80	5.78	11.49	1602	1252

a) Neat.



(**16**) or 2.37 (**17**) due to the protons of the 3-vinyl moiety.[5] Furthermore, the configuration of the 3-vinyl group was determined to be *trans* by the large coupling constant (16.0 Hz) between the olefinic protons.

Experimental

Melting points were measured with a Yanagimoto micro-melting point apparatus and are uncorrected. Microanalyses and IR spectra were measured with a Perkin-Elmer 240 Elemental Analyzer and a Hitachi 260-10 Infrared Spectrophotometer, respectively, and are listed in the Table. The NMR spectra were determined with a Varian EM360A Spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. The chemical shifts are expressed in δ values.[6]

Preparations of 2-Methylpyridinium 1-[(Alkylthio)thiocarbonyl]-aminides (2 and 3). To an ethanolic solution (50 ml) of 1-amino-2-methylpyridinium iodide (**1**, 4 mmol), carbon disulfide (6 mmol), and dimethyl or diethyl sulfate (6 mmol) aqueous potassium hydroxide (9 mmol in 5 ml of water) was added dropwise under stirring at room temperature. After the addition the mixture was stirred for additional 1 h, and then poured into ice–water (200 ml). The resulting solution was extracted two times with chloroform (100 ml) and the combined extract was washed with water, dried over anhydrous sodium sulfate, and concentrated at reduced pressure. Column separation (alumina) of the residue and recrystallization from chloroform–hexane gave **2**, 59%, mp 128—129 °C, δ 2.57 (3H, s, SMe), and 2.64 (3H, s, C_2–Me), and **3**, 65%, mp 113—115 °C, δ 1.37 (3H, t, J=7.0 Hz, $SCH_2\underline{CH_3}$), 2.62 (3H, s, C_2–Me), and 3.13 (2H, q, J=7.0 Hz, $S\underline{CH_2}CH_3$), as colorless crystals.

Preparations of 2-Alkylthio-3-vinylpyrazolo[1,5-a]pyridine Derivatives (12—15). To a chloroform solution (30 ml) of **2** or **3** (2 mmol) methyl or ethyl iodide (2 ml) was added at room temperature and the solution was allowed to stand for 20 min. The reaction mixture was then concentrated and the residue was recrystallized from chloroform–ether to give **4**, mp 134—136 °C, and **5**, mp 131—132 °C, as slightly brown crystals in almostly quantitative yields. The mixture of salt (**4** or **5**, 2 mmol) and ethoxymethylene compound (**6** or **7**, 2 mmol) was treated with potassium carbonate (5 g) in chloroform (50 ml) at room temperature for 3 d and, then, the reaction solution was filtered to remove insoluble substances. The filtrate was concentrated at reduced pressure and the residue was separated by column chromatography (alumina) using ether and then chloroform as eluents. Recrystallizations from chloroform–hexane of the crude products gave **8**, 50%, mp 116—117 °C, δ 1.30 (3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 2.57 and 2.73 (each 3H, s, SMe), 4.22 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 5.57 (1H, d, J=14.0 Hz, vinyl-H), and 8.19 (1H, d, J=14.0 Hz, vinyl-H), **9**, 47%, mp 93—95 °C, δ 2.40 (6H, s, 2×COMe), 2.56 and 2.80 (each 3H, s, SMe), 6.85 (1H, d, J=14.0 Hz, vinyl-H), and 7.98 (1H, d, J=14.0 Hz, vinyl-H), **10**, 51%, mp 108—109 °C, δ 1.28, 1.32, and 1.49 (each 3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$ and 2×$SCH_2\underline{CH_3}$), 3.10 and 3.33 (each 2H, q, J=7.0 Hz, $S\underline{CH_2}CH_3$), 4.51 (2H, q, J=7.0 Hz, $OCH_2\underline{CH_3}$), 5.53 (1H, d, J=14.0 Hz, vinyl-H), and 8.18 (1H, d, J=14.0 Hz, vinyl-H), and **11**, 56%, mp 101—102 °C, δ 1.30 and 1.49 (each 3H, t, J=7.0 Hz, $SCH_2\underline{CH_3}$), 2.33 (6H, s, 2×COMe), 3.10 and 3.39 (each 2H, q, J=7.0 Hz, $S\underline{CH_2}CH_3$), 6.73 (1H, d, J=14.0 Hz, vinyl-H), and 8.01 (1H, d, J=14.0 Hz, vinyl-H). A benzene solution (30 ml) of 2-allylidene-1,2-dihydropyridine (1 mmol) was heated under reflux until the TLC spot of the material disappeared (about 3—6 h). The reaction mixture was then concentrated and separated by column chromatography (alumina) using ether. Recrystallizations from ether–hexane afforded 2-alkylthio-3-vinylpyrazolopyridines (**12**—**15**) as yellow needles: **12**, 57%, mp 169—170 °C, δ 1.39 (3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 2.70 (3H, s, SMe), 4.37 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), and 8.34 (1H, s, vinyl-H), **13**, 43%, mp 104—105 °C, δ 2.29 and 2.42 (each 3H, s, COMe), 2.68 (3H, s, SMe), and 7.73 (1H, s, vinyl-H), **14**, 55%, mp 143—144 °C, δ 1.40 and 1.43 (each 3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$ and $SCH_2\underline{CH_3}$), 3.27 (2H, q, J=7.0 Hz, $SCH_2\underline{CH_3}$), 4.38 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), and 8.39 (1H, s, vinyl-H), **15**, 53%, oil, δ 1.44 (3H, t, J=7.0 Hz, $SCH_2\underline{CH_3}$), 2.31 and 2.47 (each 3H, s, COMe), 3.29 (2H, q, J=7.0 Hz, $S\underline{CH_2}CH_3$), and 7.88 (1H, s, vinyl-H).

Acid Hydrolyses of 13 and 15. Pyrazolopyridines (**13** or **15**, 100 mg) was dissolved in 10 ml of concd hydrochloric acid and kept for 3 h at room temperature. The solution was concentrated to dryness at reduced pressure and the residual oil was separated by column chromatography (alumina) using ether and then chloroform as eluents. Recrystallizations of the crude products from chloroform–hexane gave 2-methylthio-(**16**), 65%, mp 142—144 °C, and 2-ethylthio-3-(3-oxo-1-butenyl)pyrazolo[1,5-*a*]pyridine (**17**), 79%, mp 107—109 °C, as pale yellow needles. On the other hand, similar treatments of **12** and **14** gave only tarry substances and the separation of any significant products from them was unsuccessful.

References

1) For part 7 of this series, see A. Kakehi, S. Ito, K. Watanabe, T. Ono, and T. Miyazima, *J. Chem. Res.*, (*S*), 18 (1980), (*M*), 401—425 (1980).

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4) a) F. Kröhnke and K. Gerlach, *Chem. Ber.*, **95**, 1108 (1962); b) F. Kröhnke, K. Gerlach, and K.-K. Schnalke, *Chem. Ber.*, **95**, 1118 (1962); c) Y. Tominaga, Y. Miyake, H. Fujito, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **97**, 927 (1977).

5) The facile elimination of an acetyl substituent on the carbon-carbon double bond is very interesting.

6) The proton signals on the pyridine ring appeared at δ 7.5—8.5 (**2** and **3**), 8.1—9.3 (**4** and **5**), 6.4—7.7 (**8**—**11**), 6.8—8.6 (**12**—**15**), and 6.8—8.4 (**16** and **17**), respectively.