A STUDY OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

XV*. THE REACTION OF 3-AMINO-2-MERCAPTO-5,6-DIPHENYLPYRAZINE WITH α-HALOGENO KETONES

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UDC 547.86 :543.422.4

The reaction of 3-amino-2-mercapto-5,6-diphenylpyrazine I with phenyl halides in ethanol in the presence of an equimolecular amount of alkali has given 3-amino-2-phenacylthio-5,6-diphenylpyrazines (II-VII), while the reaction of I with chloroacetone or 1,3-dichloroacetone at 0°C has given 6-alkyl-6-hydroxy-5,6-dihydropyrazino[2,3-b]-[1,4]-thiazines (VIII and IX). The 6-aryl-2,3-diphenylpyrazino[2,3-b]-[1,4]-thiazines (X-XIV) have been synthesized by heating the 3-amino-2-phenacylthio-5,6-diphenylpyrazines (II-VI) with acetic anhydride.

In a preceding communication [1] it was shown that the reaction of 3-amino-2-mercapto-5,6-dimethylpyrazines with α-halogeno ketones forms unstable 2-acylmethylthio-3-amino-5,6-dimethylpyrazines, which change into 2,3-dimethylpyrazino[2,3-b]-[1,4]-thiazines. In development of this work [1], we have studied the reaction of 3-amino-2-mercapto-5,6-diphenylpyrazine (I) with various phenacyl halides and also with chloroacetone and 1,3-dichloroacetone. It has been found that the reaction of I with phenacyl bromide and its 4-bromo, 2,5-dichloro, 3-nitro, 4-nitro, and 4-methoxy derivatives in ethanol in the presence of 1 mole of alkali at 18-20°C forms the 3-amino-2-phenacylthio-5,6-diphenylpyrazines II-VII (Table 1).

Under similar conditions, but at 0°C, compound I with chloroacetone and 1,3-dichloroacetone has given the 6-alkyl-6-hydroxy-5,6-dihydropyrazino[2,3-b]-[1,4]-thiazines VIII and IX.

The structures of II-VIII were confirmed by the presence in their IR spectra of the absorption band of a ketonic CO (1680-1715 cm^{-1}) and that of a primary amino group (1628-1640 cm^{-1}). The PMR spectrum of VII (in pyridine) exhibits the signal of the protons of a CH_3O group and a signal of four proton units with a chemical shift of 4.92 ppm corresponding to the protons of CH_2 and NH_2 groups

The IR spectra show that VIII and IX exist in the solid state in the form of cyclic hydroxy compounds [1] and not as 2-acylthio-3-amino derivatives. Thus, the spectra lack the absorption band of a CO group, and in the high frequency region there is the absorption of NH and OH groups: for VIII at 3390 and 3420 cm^{-1} and for IX at 3260 and 3380 cm^{-1}.

As was to be assumed, the introduction into the pyrazine nucleus of two electrophilic groups leads to a still greater deficit of electron density in the pyrazine nucleus [2] and to a decrease in the nucleophilicity of the amino group in position 3. Because of this, the 3-amino-2-phenacylthio-5,6-diphenylpyrazines II-VII are more stable substances than their 5,6-dimethyl analogs: they undergo no change on being heated with polar solvents and form 2,4-dinitrophenylhydrazones. For example, when II is treated with 2,4-dinitrophenylhydrazine in hydrochloric acid, the corresponding hydrazone separates out quantitatively.

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*For Communication XIV, see [4].

Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, Vol. 6, No. 8, 1101-1103, August, 1970. Original article submitted October 14, 1968.

TABLE 1. Characteristics of the Compounds Obtained

Compound	R	mp °C [a,b]	Empirical formula[c,d]	Found, %					Calculated, %					Yield, %
				C	H	N	S	Br/Cl	C	H	N	S	Br/Cl	
II	C_6H_5	124—125	$C_{24}H_{19}N_3OS$	72,29	4,71	10,42	7,91	—	72,51	4,82	10,58	8,07	—	89,3
III	p- BrC_6H_4	152—153	$C_{24}H_{18}BrN_3OS$	60,16	3,83	8,76	6,61	16,95	60,50	3,81	8,82	6,73	16,78	85,7
IV	m, o-$Cl_2C_6H_3$	111—112	$C_{24}H_{17}Cl_2N_3OS$	61,75	3,82	9,20	6,91	15,26	61,72	3,67	9,01	6,87	15,23	94,5
V	m-O_2N-C_6H_4	151	$C_{24}H_{18}N_4O_3S$	65,10	4,22	12,90	7,34	—	65,14	4,10	12,66	7,25	—	90,8
VI	p- O_2N-C_6H_4	152—153	$C_{24}H_{18}N_4O_3S$	65,05	4,00	12,80	7,27	—	65,14	4,10	12,66	7,25	—	70,2
VII	p-CH_3O-C_6H_4	159	$C_{25}H_{21}N_4O_2S$	70,19	5,00	10,01	7,66	—	70,23	4,96	9,83	7,50	—	89,3
VIII	H	120—121	$C_{19}H_{17}N_3OS$	68,08	5,30	12,47	9,43	—	68,03	5,11	12,53	9,56	—	77,3
IX	Cl	101—102	$C_{19}H_{16}ClN_3OS$	61,48	4,23	10,97	8,77	9,39	61,69	4,36	11,36	8,67	9,60	53,5
X	C_6H_5	266	$C_{24}H_{17}N_3S$	75,67	4,51	11,02	8,06	—	75,96	4,52	11,07	8,45	—	42,5
XI	p- BrC_6H_4	246—247	$C_{24}H_{16}BrN_3S$	62,60	3,50	8,82	6,71	17,61	62,88	3,52	9,17	7,00	17,43	66,3
XII	m, o-Cl_2-C_6H_3	294—298	$C_{24}H_{15}Cl_2N_3S$	64,05	3,07	9,36	6,89	16,02	64,27	3,37	9,38	7,15	15,83	53,8
XIII	m, O_2N-C_6H_4	222—224	$C_{24}H_{16}N_4O_2S$	67,75	4,06	—	7,74	—	67,90	3,80	13,20	7,56	—	75,7
XIV	p-O_2N-C_6H_4	301—303	$C_{24}H_{16}N_4O_2S$	67,84	3,70	13,19	7,49	—	67,90	3,80	13,20	7,56	—	73,6

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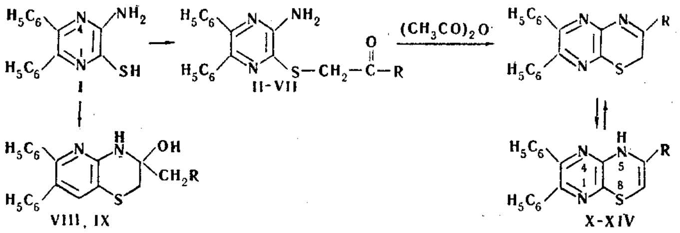
[a] For analysis, the compounds were purified by crystallization: IV and VII from methanol, II and VIII from ethanol, III from isopropanol, X from ether, V and VI from benzene, XIV from toluene, and XIII from dimethylformamide–water (2:1); IX was purified by reprecipitation from benzene with petroleum ether, and XI and XII by being boiled in ethanol. [b] Compounds VIII and IX were colorless; II-IV and VII light yellow; V, VI, and XI-XIV yellow; and X red. [c] The IR spectra were obtained on a UR-10 instrument in paraffin oil. For compounds II-VII the frequencies of the vibrations of the amide C = O and the NH_2 group are given, for VIII and IX those of the NH and OH groups, and for X-XIV those of the NH groups, cm^{-1}: II – 1710, 1638, 3210, 3320, 3490; III – 1705, 1638, 3310, 3480; IV – 1715, 1638, 3300, 3380, 3480; V – 1700, 1639, 3310, 3480; VI – 1705, 1625, 3300, 3490; VII – 1680, 1628, 3280, 3450; VIII – 3390, 3420; IX – 3260, 3380; XIV – 3410. [d] The PMR spectra (obtained on a JNM-4H-100 instrument at 100 MHz with TMS in pyridine as internal standard) are given in ppm on the δ scale: VII – 4.92 (2H, $-CH_2$ singlet); 3.60 (OCH_3); XIV – 5.17 (H, 7-H, singlet).



In compounds II-VI, the amino group is so strongly passivated that in spite of the presence of electron-accepting groups suppressing the electrophilicity of the carbonyl carbon in the ketonic part of the molecule, the cylization of II-VI to the corresponding pyrazinothiazines takes place under the action of water-abstracting substances. Thus, when II-VI are heated with acetic anhydride at 90-100°C the pyrazinothiazines X-XIV are obtained. The IR spectra of the 6-aryl-2,3-diphenylpyrazino[2,3-b]-[1,4]-thiazines, with the exception of XIV, lack the absorption of a NH group, which confirms their structure as 7H derivatives. The IR spectrum and PMR spectrum of XIV show that this substance, like the 6-aryl-2,3-dimethylpyrazino[2,3-b]-[1,4]-thiazines [1], exists in the form of the 5H derivative. Thus, the IR spectrum of XIV has the band of a NH group (3410 cm^{-1}, and in the PMR spectrum there is the isolated signal of an olefinic proton with a chemical shift of 5.17 ppm.

EXPERIMENTAL

3-Amino-2-mercapto-5,6-diphenylpyrazine (I) was obtained as described previously [3], yield 75.7%, mp 259-261°C.

3-Amino-2-phenacylthio-5,6-diphenylpyrazine (II). At 20-22°C, an ethanolic solution of 0.46 g (2.3 mmoles) of phenacyl bromide was added dropwise to a solution of 0.7 g (2.5 mmoles) of I in 20 ml of ethanol containing 0.14 g of KOH. After three hours' stirring, the precipitate was separated off and was washed with 5-10% aqueous alkali and water. Yield 0.82 g (89.3%), mp 147-151°C; it was recrystallized from ethanol. Compounds III-VII were obtained similarly.

2,4-Dinitrophenylhydrazone of II. Yellow crystals, mp 236-237°C (from ethanol). Found, %: C 62.38; H 3.80; N 17.04; S 5.34. Calculated for $C_{30}H_{23}N_4O_4S$, %: C 62.38; H 4.01; N 16.98; S 5.55.

6-Hydroxy-6-methyl-2,3-diphenyl-5,6-dihydropyrazino[2,3-b]-[1,4]-thiazine (VIII). At 0 to -5°C, an ethanolic solution of 0.28 g (3 mmoles) of chloroacetone was added to a solution of 1.0 g (3.6 mmoles) of I in 35 ml of methanol containing 0.2 g of KOH, the mixture was stirred for 3 hr, the sodium chloride was filtered off, the filtrate was evaporated, the residue was triturated with ether, and the solid matter was filtered off. Yield 0.8 g (77.3%), mp 103°C. It was recrystallized from ether. Compound IX was obtained similarly.

2,3,6-Triphenylpyrazino[2,3-b]-[1,4]-thiazine (X). A mixture of 0.37 g of II and 7 ml of acetic anhydride was heated at 90-95°C for 2 hr and cooled to 18-20°C, after which the precipitate was filtered off and washed with water. Yield 0.15 g (42.5%). It was purified by two recrystallizations from ether. Compounds XI-XIV were synthesized similarly.

LITERATURE CITED

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