SOME CYCLIZATION REACTIONS OF ω-CHLORO-ω-ACYLAMIDOACETOPHENONES

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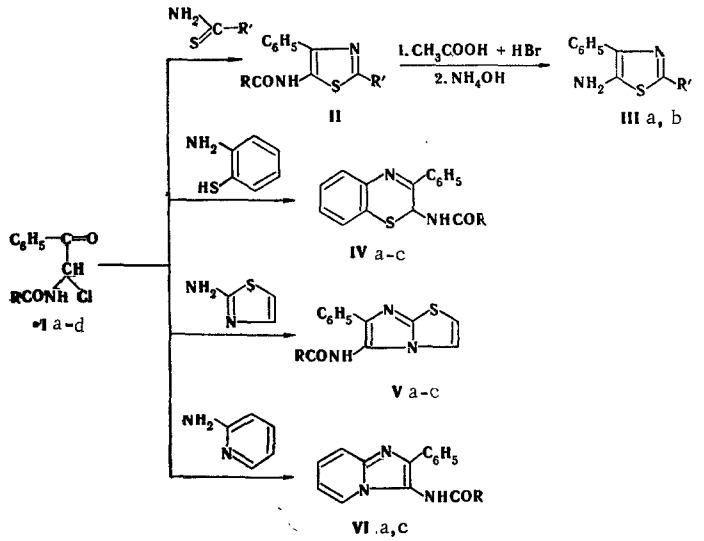
Substituted thiazoles, 1,4-benzothiazines, imidazo[2,1-b]thiazoles, and imidazo[1,2-a]pyridines containing acylamide residues as substituents were obtained by reaction of ω-chloro-ω-acylaminoacetophenones with thioamides, o-aminothiophenol, 2-aminothiazole, and 2-aminopyridine. Some of these substances can be used for the synthesis of heterocyclic bases with an unsubstituted amino group.

The products of condensation of phenylglyoxal with acid amides [1, 2] react with thionyl chloride or phosphorus pentachloride to give high yields of ω-chloro-ω-acylamidoacetophenones (I), which are extremely reactive and readily react with diverse substances containing a labile hydrogen atom [1, 3, 4]. We recently found that I condensed with thioacetamide under very mild conditions via the general scheme of the synthesis of thiazoles [2]. In a continuation of this research we have investigated the condensations of I with thioformamide, thiobenzamide, thiourea, methyl dithiocarbamate, o-aminothiophenol, 2-aminothiazole, and 2-aminopyridine (see the scheme below).



I, IV—VI a R=CH_3; b R=C_6H_5; c R=CH_3O; d R=$C_6H_5CH_2O$; III a R′=CH_3; b R′=C_6H_5

In all cases, the reaction of thioamides gave substituted thiazoles (II) containing acylamide residues in the 5 position. There is no doubt about the structures of these compounds because some of them were previously synthesized by other methods. For example, the product of condensation of ω-chloro-ω-acetamidoacetophenone (Ia) with thioformamide is undoubtedly 4-phenyl-5-acetamidothiazole (see Table 1), inasmuch

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TABLE 1. Acyl Derivatives of 2-R'-4-Phenyl-5-aminothiazoles (II)

R	R'	mp, °C (crystallization solvent)	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	S	C	H	S	
CH_3	H	145—146 (benzene)*	$C_{11}H_{10}N_2OS$	60,6	4,6	—	60,5	4,6	—	70
CH_3	C_6H_5	181—182 (benzene)	$C_{17}H_{14}N_2OS$	—	—	10,9	—	—	10,9	77
CH_3	CH_3S	166—167 (benzene)†	$C_{12}H_{12}N_2OS_2$	—	—	23,9	—	—	24,3	80
CH_3	NH_2	217—220 (methanol)‡	$C_{11}H_{11}N_3OS$	56,6	4,8	—	56,6	4,8	—	60
CH_3O	C_6H_5	163—164 (benzene)	$C_{17}H_{14}N_2O_2S$	—	—	10,6	—	—	10,3	64
CH_3O	CH_3S	78—80(benzene+hexane)	$C_{12}H_{12}N_2O_2S_2$	—	—	22,6	—	—	22,9	65
C_6H_5	NH_2	175—176 (methanol)‡	$C_{16}H_{13}N_3OS$	64,7	4,6	—	65,1	4,4	—	71
$C_6H_5CH_2O$	CH_3	107—108 (cyclohexane)	$C_{18}H_{16}N_2O_2S$	66,8	5,0	—	66.6	5,0	—	80
$C_6H_5CH_2O$	C_6H_5	134—135 (cyclohexane)	$C_{23}H_{18}N_2O_2S$	71,2	4,7	—	71,5	4,7	—	94

*In conformity with the literature data [5].
†According to [6], this compound has mp 168°.
‡This is the decomposition temperature.

TABLE 2. Heterocyclic Bases III-VI

Compound	mp, °C (crystallization solvent)	Empirical formula	Found, %	Calc., %	Yield, %
IIIa	122—124 (cyclohexane)	$C_{10}H_{10}N_2S$	C 63,1 H 5,3	C 63,1 H 5,3	90
IIIb	107—110 (cyclohexane)	$C_{15}H_{12}N_2S$	C 71,6 H 5,0	C 71,4 H 4,8	87
IVa	142—145 (benzene)	$C_{16}H_{14}N_2OS$	S 11,2	S 11,4	60
IVb	143—144 (benzene+cyclohexane)	$C_{21}H_{16}N_2OS$	S 9,3	S 9,3	86
IVc	183—184 (benzene)	$C_{16}H_{14}N_2O_2S$	S 10,7	S 10,7	67
Va	167—168 (benzene)	$C_{13}H_{11}N_3OS$	S 12,4	S 12,5	55
Vc	175—180*(ethyl acetate)	$C_{13}H_{11}N_3O_2S$	S 11,7	S 11,7	62
VIa	208—209*(ethyl acetate)	$C_{15}H_{13}N_3O$	N 16,6	N 16,7	60
VIc	177—178 (acetone)	$C_{15}H_{13}N_3O_2$	N 15,5	N 15,7	68

*This is the decomposition temperature.

as it is identical to the product of the reaction of acetic anhydride with 4-phenyl-5-aminothiazole [5]. 2-Methylmercapto-4-phenyl-5-acetamidothiazole [6], which proved to be identical to the product of condensation of Ia with methyl dithiocarbamate, was also similarly synthesized.

The direction of the condensations of I with aminothiophenol, 2-aminothioazole, and 2-aminopyridine does not raise any special doubts and was not specially proved. Evidently, these condensations, like the reactions with thioamides, proceed via a general scheme that is characteristic for many α-halocarbonyl compounds [7]. As a result, 2-acylamido-3-phenylbenzo-1,4-thiazines (IV), 5-acylamido-6-phenylimidazo-[2,1-b]thiazoles (V), and 2-phenyl-3-acylamidoimidazo[1,2-a]pyridines (VI), respectively, were obtained.

A simple synthesis of acyl derivatives of various heterocyclic amines from readily accessible I is of preparative interest because the corresponding primary amines, from which such acyl derivatives might have been obtained, are difficult to obtain or are unknown. The products of condensation of ω-chloro-ω-carbobenzoxyamidoacetophenone with thioamides are especially interesting, inasmuch as these substances readily split out the protective group from the nitrogen atom and give 2-alkyl(aryl)-4-phenyl-5-aminothiazoles (III) in good yields. This method for the preparation of 5-aminothiazole homologs is more convenient than the literature method for their synthesis by condensation of α-aminonitriles with esters or salts of dithiocarboxylic acids [5, 6].

The previously unknown ω-chloro-ω-carbobenzoxyamidoacetophenone (Id) is readily obtained from the product of the condensation of phenylglyoxal with benzylurethane.

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EXPERIMENTAL

ω-Chloro-ω-acylamidoacetophenones (Ia-c). These compounds were obtained by the action of thionyl chloride on the products of condensation of phenylglyoxal with acid amides as previously described in [1-4].

For the preparation of Id, 0.03 mole of benzylurethane was added to a solution of 0.03 mole of freshly distilled phenylglyoxal in 20 ml of tetrahydrofuran (THF), and the mixture was refluxed for 4 h. The THF was then vacuum evaporated, and the residual ω-hydroxy-ω-carbobenzoxyamidoacetophenone was washed with ether and crystallized from acetone to give a product with mp 133-134° in 77% yield. Found: C 67.5; H 5.3%. $C_{16}H_{15}NO_4$. Calculated: C 67.4; H 5.3%. Treatment of a suspension of 0.01 mole of this compound in 20 ml of anhydrous THF with 2 ml of thionyl chloride for 24 h gave Id, with mp 91-92° (from cyclohexane), in almost quantitative yield. Found: Cl 11.4%. $C_{16}H_{14}ClNO_3$. Calculated: Cl 11.7%.

Acyl Derivatives of Heterocyclic Amines (II, IV-VI). A saturated solution of 0.01 mole of the appropriate thioamide, o-aminothiophenol, 2-aminothiazole, or 2-aminopyridine in THF was added to a solution of 0.01 mole of freshly prepared I in 10-15 ml of THF, and the mixture was allowed to stand for 24 h. The THF was vacuum evaporated, and the residue was mixed with 20 ml of absolute methanol. The mixture was refluxed for 1 h, the methanol was vacuum evaporated, and the residue was treated with 30 ml of a saturated aqueous solution of sodium bicarbonate. The resulting precipitated bases (II, IV, or V) were removed by filtration, dried in a vacuum desiccator over phosphorus pentoxide, and crystallized from a suitable solvent. Ammonium hydroxide (10%) was used to isolate VI.

2-Amino-4-phenyl-5-benzamidothiazole, which was obtained from Ib and thiourea, was dried with great difficulty, inasmuch as a hydrate is formed [8]. The anhydrous base was obtained after drying this hydrate for a week in a vacuum desiccator over fresh portions of phosphorus pentoxide.

2-Alkyl(aryl)-4-phenyl-5-aminothiazoles (III). A 0.003-mole sample of the product of condensation of Id with the appropriate thioamide was mixed with 4 ml of a saturated solution of hydrogen bromide in glacial acetic acid by the method in [9]. After 3-4 h, at which point carbon dioxide evolution had ceased, 30 ml of absolute ether was added to the mixture, and the resulting precipitate was removed by filtration, vacuum dried, and treated with 20 ml of 10% ammonium hydroxide. Bases III precipitated initially as oils that gradually crystallized. The crystalline masses were removed by filtration, dried in a vacuum desiccator over alkali, and purified by recrystallization from cyclohexane.

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