CYCLIZATION OF ARYLTHIOHYDRAZIDES OF CARBOXYLIC ACIDS UNDER THE INFLUENCE OF PHOSPHORUS HALIDES

A. N. Kost, G. A. Golubeva, and A. G. Popova

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It is shown that arylthiohydrazides of carboxylic acids undergo cyclization to give both bis(1-methyl-2-indolyl) disulfides and salts of the corresponding 1-methyl-2-aminoindole under the influence of phosphorus halides ($POCl_3$ or PCl_3).

A comparison of the reactivities of oxygen- and sulfur-containing compounds makes it possible to assume that a 2-aminoindole (as observed in the case of N'-arylhydrazides [1]) or a benzothiazole (as is known for thiosemicarbazides, which undergo cyclization under the influence of polyphosphoric acid [2]) may be formed by the action of phosphorus halides on N'-arylthiohydrazides of carboxylic acids. The sulfur atom is more nucleophilic than the oxygen atom, but the presence of several reactive centers in the thiohydrazide molecule creates a situation in which a priori there is an almost equal chance of attack on the sulfur atom and the nitrogen atom [3]. One must simultaneously take into account the reaction to give thiadiazoles, which has even been used in preparative syntheses [4]; in addition, one could not exclude cleavage of the N–N bond, splitting out of a thioacyl residue [2], and more complex processes that take place with the participation of two thiohydrazide molecules [5, 6].

We have observed that N'-methyl-N'-arylthiohydrazides of carboxylic acids (I) undergo cyclization under the influence of phoshporus oxychloride or PCl_3 to give bis(1-methyl-2-indolyl) disulfides (II) containing a small amount of a 2-iminoindoline salt (III), i.e., a protonated 2-aminoindole. The process is more complex for hydrazides of aliphatic acids (Ia-c), since the formation of II and III is accompanied by even more pronounced resinification. We were unable to, in general, obtain individual compounds from the products of the conversion of phenoxyacetic acid N'-methyl-N'-phenylthiohydrazide because of complete resinification of the entire reaction mass. Preparative yields of disulfides II were obtained only from phenylacetic acid thiohydrazides (Id-g).

In the synthesis of starting thiohydrazides I we observed that not only partial formation of thiohydrazides [7] but also simultaneous cyclization to disulfides (II) took place in the reaction of phosphorus pentasulfide with our hydrazides. Moreover, by treatment of N'-methyl-N'-phenyl-N-phenacetylhydrazine in absolute ether (in an argon atmosphere) with a threefold excess of phosphorus pentasulfide we obtained, in addition to thiohydrazide Id and disulfide IId [determined in solution by thin-layer chromatography (TLC)], 1-methyl-3-phenyl-2-iminoindoline salt III, from which the rather stable free base (IIIa) was isolated by alkalization with aqueous sodium hydroxide solution, although such amines are easily oxidized [8]. On the basis of the spectral data, it may be assumed that IIIa exists in the 2-aminoindoline form, since the absorption band of an NH group at 3310 cm^{-1} is observed in the IR spectrum (in CCl_4). Signals of a β proton at 2.93 ppm (s, 1H), protons of an $N-CH_3$ group at 3.47 ppm (s, 3H), and a multiplet of aromatic protons, which includes the signal of the proton of an imine nitrogen atom at 6.84-7.5 ppm (10H), are observed in the PMR spectrum (in CCl_4). It is possible that the partial liberation of hydrogen sulfide in the reaction and the formation of a sulfite (a reductive medium) protect IIIa from rapid oxidation. When IIIa is stored in air, TLC reveals the appearance of a new spot with R_f 0.38 (in contrast to R_f 0.48 for 2-iminoindoline), which corresponds to the oxidation product. We were unable to isolate 2-aminoindoles from the other thiohydrazides. The presence of their hydrochlorides in the reaction mixtures was established by chromatography.

We subsequently used a method for the preparation of thiohydrazides involving the action of phosphorus pentasulfide on hydrazides [7]; however, we did not isolate them (their presence was determined by TLC) but

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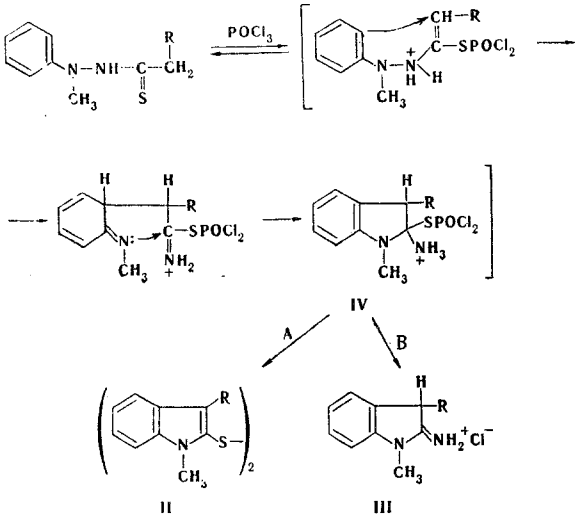
immediately treated the reaction mixtures with phosphorus halides ($POCl_3$ or PCl_3). The resulting disulfides (IIa,d-f) were identified with respect to the previously described constants [9]. The desulfuration of IId over Raney nickel leads to the known 1-methyl-3-phenylindole [10].

During a study of rearrangement of carboxylic acid hydrazides to 2-aminoindoles [1] it was assumed that the reaction proceeds through the formation of an intermediate complex, which can undergo decomposition via two pathways. Correspondingly, the cyclization of sulfur analogs of hydrazides evidently leads to the analogous IV complex, the possible decomposition of which via pathway A or B leads to either disulfide II or to 2-iminoindoline III, depending on the strength of the C–N, C–S, and S–P bonds. The cyclization



probably proceeds as ordinary electrophilic attack by the protonated form of the thiohydrazide on the aromatic ring. Let us note that salt III is not converted to disulfide II by the action of phosphorus pentasulfide (although Hino and Nakagawa used the reverse reaction of 2-indolyl thiones with amines for the preparation of 2-aminoindoles [9]). This constitutes evidence that the reaction proceeds through complex IV. The pathway by which the disulfide is formed is not clear. It would be logical to assume the formation of the S–S bond as a secondary process involving oxidation of the 2-indolyl thione. However, we carried out this reaction in an inert atmosphere (argon) and detected the disulfide rather than the 2-indolyl thione by TLC after the addition of phosphorus halide to the thiohydrazide. It is possible that the formation of the disulfide proceeds as an oxidative process with the reduction of phosphorus to trivalent phosphorus or that cleavage of the S–P bond occurs homolytically with subsequent coupling of the radicals; however, we do not have experimental data. The introduction of substituents in the para position of the phenyl ring of the hydrazine or acid fragment did not have a substantial effect on the course of the reaction.

According to the data of Bobkova and Chepunova (department of lower plants of the biology faculty of Moscow State University), thiohydrazides I (R = H, C_6H_5, OC_6H_5), phenoxyacetic acid N'-methyl-N'-phenylhydrazide, and disulfides IId,e in alcohol solution (1 mg/ml) do not suppress the growth of Aspergillus niger, Aspergillus terreus, and Penicillium cyclopium and do not affect the growth of Staphylococcus aureus, Bacillus substilis, Microbacterium lacticola, and Escherichia coli. Only Ie (R = C_6H_5) displayed a weak suppressive effect on the growth of Gram-positive bacteria in the form of an alcohol solution (1 mg/ml) in an agar-agar medium; however, it did not have this effect in experiments in a liquid medium.

The constants and yields of disulfides II are presented in Table 1.

EXPERIMENTAL

The UV spectra of the compounds were recorded with Cary and Specord spectrophotometers. The PMR spectra of solutions of the compounds in CF_3COOH [with hexamethyldisiloxane (HMDS) as the external standard] and other solvents (with HMDS as the internal standard) were recorded with a Varian T-60 spectrometer. Thin-layer chromatography on a fixed layer of kiesel gel H with rhodamine 6Zh as the indicator in a hexane–acetone–benzene system (2 : 1 : 1) was used to estimate the individuality of the compounds. The synthesis and characteristics of the thiohydrazides were described in [7].

Method A. A 0.6-ml (6 mmole) sample of phosphorous oxychloride was added to a solution of 0.51 g (2 mmole) of phenylacetic acid N',-methyl-N'-phenylthiohydrazide (Id) in 10 ml of absolute toluene, and the mix-

TABLE 1. Bis(1-methyl-2-indolyl) Disulfides II

Compound	R	mp, °C	UV spectrum, λmax, nm (log ε)	PMR spectrum, ppm	Found, % C	Found, % H	Empirical formula	Calc., % C	Calc., % H	Yield, %
IIa	CH_3	120—122[g]	228 (3,29)[a] 320 (2,93)	1,76 (s, 3H), 3,43 (s, 3H) 7,2—7,5 (m, 4H)[b]	—	—	—		—	22
IIb	C_2H_5	82—84	236 (3,21)[a] 310 (1,32)	1,32 (t, 3H), 1,53 (q, 2H)[c] 3,16 (s, 3H), 6,5—7,5 (4H)	70,1	6,5	$C_{22}H_{24}N_2S_2$	69,4	6,3	8
IIc	n-C_3H_7	65—67	230 (3,05)[a] 310 (1,7)	1,0 (t, 3H), 1,7 (m, 2H)[d] 2,63 (t, 2H), 2,99 (s, 3H) 6,9—7,5 (m, 4H)	70,6	6,2	$C_{24}H_{28}N_2S_2$	70,6	6,4	6
IId	C_6H_5	142—143[g]	227, 258[a] 360 (4,14)[e]	3,5 (s, 3H), 6,5—7,5 (m, 9H)[c]	—	—	—	—	—	45
IIe	p-CH_3O—C_6H_5	171—173[g]	230, 260[a] 355 (4,14)[e]	3,56 (s, 3H), 3,73 (s, 3H) 6,4—6,9 (m, 4H), 7,1—7,6 (m, 4H)[d]	—	—	—	—	—	62
IIf	p-NO_2—C_6H_5	276—278[g]	238, 280[a] 427 (4,39)[e]	3,56 (s, 3H), 7,26—7.4 (m, 4H), 8,2—8,33 (m, 4H)[b]	—	—	—	—	—	78
IIg	o-CH_3—C_6H_5	143—145	228, 285[a] 355 (4,00)[e]	2,5 (s, 3H), 3,33 (s, 3H) 6,7—7,3 (m, 9H)[d]	76,3	5,6	$C_{32}H_{28}N_2S_2$	76,19	5,6	43

a) In methanol. b) In trifluoroacetic acid. c) In carbon tetrachloride. d) In carbon disulfide. e) In dioxane.

ture was refluxed for 6 h. The solvent was then removed by evaporation, and the residue was dissolved in ether. The insoluble residue was removed by filtration, and the filtrate was washed successively with 10% sodium hydroxide solution and water (until the wash waters were neutral). The ether was removed by evaporation, and the solid residue was refluxed for 10 min in ethanol containing activated charcoal. The hot mixture was then filtered, and the filtrate was cooled. The precipitated crystals were separated and recrystallized from absolute ethanol to give 0.28 g (58%) of bis(1-methyl-3-phenyl-2-indolyl) disulfide (IId).

Method B. A 0.41-g (3 mmole) sample of phosphorus trichloride was added to a solution of 0.256 g (1 mmole) of thiohydrazide Id in 5 ml of absolute toluene, and the mixture was refluxed for 6 h. The solvent was then removed by evaporation, and the residue was worked up as in method A to give 0.12 g (50%) of disulfide IId.

Method C. A 0.3-g (1.5 mmole) sample of phosphorus pentasulfide was added with stirring to a solution of 1.02 g (4 mmole) of phenylacetic acid N'-methyl-N'-phenylhydrazide in 20 ml of dioxane, and the mixture was refluxed for 1 h. A 1.1-ml (12 mmole) sample of phosphorus oxychloride was added, and the mixture was refluxed for 2 h. At the end of the reaction (as monitored by TLC) the solution was subjected to evaporation, the residue (salt IIId containing phosphorus compounds) was washed with water, and the wash waters were extracted twice with benzene, which was added to the bulk of the reaction product. The benzene was removed by evaporation, and the residue was purified by means of activated charcoal and recrystallization from absolute ethanol to give 0.48 g (46%) of bis(1-methyl-3-phenyl-2-indolyl) disulfide (IId). The R_f value of the starting hydrazide was 0.35, and the R_f value of disulfide IId was 0.60. Compounds IIe-g were similarly obtained.

Method D. A 0.28-g (1.25 mmole) sample of phosphorus pentasulfide was added in 20-mg portions with stirring in the course of an hour to a solution of 1.27 g (5 mmole) of p-methoxyphenylacetic acid N'-methyl-N'-phenylhydrazide in 25 ml of methylene chloride, and the solution was refluxed for 1 h. A 1.32-ml (15 mmole) sample of phosphorus oxychloride was added, and the mixture was refluxed for 4 h. Precipitated salt III containing phosphorus compounds was removed by filtration, and washed twice with methylene chloride. The combined filtrate and wash solutions were evaporated to dryness, and the residue was dissolved in benzene. The benzene solution was washed successively with 10% sodium hydroxide solution and water, the benzene was removed by distillation, and the residue was recrystallized from absolute ethanol to give 0.78 g (63%) of bis[1-methyl-3-(p-methoxyphenyl)-2-indolyl] disulfide (IIe). The R_f value of the starting hydrazide was 0.38, and the R_f value of disulfide IIe was 0.65. Compounds IIa-c were similarly obtained.

1-Methyl-3-Phenylindole. A mixture of 0.5 g (1.1 mmole) of disulfide IId in 20 ml of absolute ethanol and 1 g of Raney nickel was refluxed until the starting compound vanished (according to TLC) (~8 h). The

solution was evaporated, and the residue was dissolved in benzene and passed through a column filled with silica gel (100/160 μ) with elution by chloroform. The solvent was removed from the eluate by evaporation to give 0.1 g (20%) of 1-methyl-3-phenylindole with mp 63-65 deg C. Mass spectrum: [M^+] 207. The product had R_f 0.52. According to the data in [10], this compound has mp 65 deg C.

1-Methyl-3-phenyl-2-iminoindoline (IIIa). A 1.7-g (0.075 mole) sample of phosphorus pentasulfide was added to a solution of 2.4 g (0.1 mole) of phenylacetic acid N'-methyl-N'-phenylhydrazide in 24 ml of absolute ether, and the mixture was refluxed in a stream of argon for 8 h. Complete disappearance of the starting hydrazide was observed by TLC after 1 h. The mixture was then cooled, and the resulting precipitate was removed by filtration, washed twice with dioxane and ether, and dried to give 1.7 g (66%) of crude salt III with mp 172-210 deg C. The precipitate was made alkaline with 1 N sodium hydroxide solution, and the mixture was refluxed for 5 min. The insoluble material [0.98 g (45%)] was removed by filtration, washed twice with water, and dissolved completely in acetone. The product was precipitated by the addition of water, and the precipitate was refluxed for 10 min in 50% ethanol containing activated charcoal. The hot ethanol solution was filtered, and the filtrate was cooled. The resulting crystals were separated and recrystallized from absolute ethanol to give 280 mg of 1-methyl-3-phenyl-2-iminoindoline with mp 110-112 deg C. Mass spectrum: [M^+] 222. Found: N 12.2%. Calculated N 12.6%. UV spectrum (in methanol), λ_{max}(log ε): 272 (3.89) and 300 nm (3.84).

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SYNTHESIS OF ARYL β-HETERYLETHYL KETONES

G. V. Grigoryan and S. G. Agbalyan

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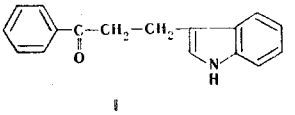
The decarboxylation of β-aroyl-α-heterylpropionic acids in vacuo leads to the formation of the corresponding ketones.

To solve the problem of the direction of nucleophilic attack by enamines of the indole and pyrrole type at the ethylene bond of β-aroylacrylic acids we have previously accomplished the decarboxylation of β-benzoyl-α-(3-indolyl)propionic acid [1]. The structure of the resulting ketone could be represented by the following formulas, depending on the structure of the starting acid:



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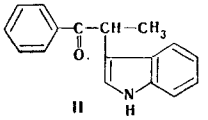

II

The PMR signals of the $-CH_2-CH_2-$ or $CH-CH_3$ fragments constitute a criterion for the identification of the two alternative structures. On the basis of the spectra obtained (from the absence of signals of a CH_3

Institute of Organic Chemistry, Academy of Sciences of the Armenian SSR, Yerevan 375052.

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