SYNTHESIS AND REACTIONS OF β-LACTONES

XV.* REACTION OF β-TRICHLOROMETHYL-β-PROPIOLACTONE WITH α-AMINO HETEROCYCLIC NITROGEN COMPOUNDS

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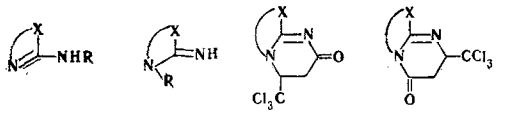
In contrast to β-propiolactone and diketene, β-trichloromethyl-β-propiolactone generally reacts with α-amino heterocyclic nitrogen compounds to give amides of 3-hydroxy-4,4,4-trichlorobutyric acid (with the participation of the exocyclic and endocyclic nitrogen atoms of the reagents) rather than condensed heterocycles (pyrimidine derivatives). The reasons for the difference in the reactivities of the indicated β-lactones are discussed.

In a continuation of our study of the properties of β-trichloromethyl-β-propiolactone (I) in comparison with β-propiolactone (II) and β-methylene-β-propiolactone (diketene), we became interested in the reaction of I with α-amino heterocyclic nitrogen compounds (AHNC), considering it to be a potential route to condensed systems containing a pyrimidine ring [1, 2]. The selection of β-lactones was made from the point of view of ascertaining the role of substitution and the character of the substituent attached to the β-carbon atom of the ring – one of its two reaction centers.

Although the aminolysis and alcoholysis of I [3, 4], in contrast to the analogous transformations of II, are accompanied by cleavage of exclusively the O–acyl bond of the lactone, one still cannot exclude the probability of alkylation of AHNC by the lactone. In addition to the possible products of the acylation and alkylation by the lactone of the exocyclic and endocyclic nitrogen atoms of AHNC (structures A-D), one might also expect the formation of condensed compounds of the E and F types.



A, B C, D E F

X=C, N, S; R=$COCH_2CH(OH)CCl_3$; $CH(CCl_3)CH_2COOH$

Except for the product of the reaction with 3-amino-5-phenylpyrazole, the IR spectra of the products of the reaction of I with AHNC (Table 1) contain intense absorption at 3000-3600 cm^{-1}, which is evidence that these compounds are affiliated with structures A-D.

In contrast to II [5] and like diketene [6, 7], I acts only as an acylating agent on reaction with 2-aminopyridine and 2-aminothiazole. Products of the acylation by the lactone are formed exclusively in the reaction with 2-aminopyridine in benzene, acetone, dioxane, and CCl_4 or by fusion. The exo-N-acyl derivative (III, $\nu_{C=O}$ 1675 cm^{-1}) was isolated, while the endo-N-acyl derivative (IV), because of difficulties involved in its crystallization, was identified from the characteristic absorption of the heterylamide carbonyl group [8] in the IR spectrum (1733 cm^{-1}). The UV spectrum of III contains two absorption maxima (236 and 277 nm), which confirm [9] the retention of the pyridine ring with an N-acylamino substituent (in

* See [1] for communication XIV.

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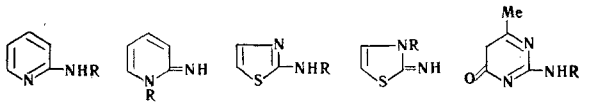
TABLE 1. Products of the Reaction of β-Trichloromethyl-β-propiolactone with α-Amino Nitrogen Heterocycles*

Compound	Name	Mp, °C (crystallization solvent)	Empirical formula	Found, %		Calc., %		Yield, %
				N	Cl	N	Cl	
III	2-(3-Hydroxy-4,4,4-trichlorobutyryl-amino)pyridine	193—195 (dioxane + CCl_4)	$C_9H_9Cl_3N_2O_2$	10,1	—	9,8	—	8,1
V	2-(3-Hydroxy-4,4,4-trichlorobutyryl-amino)thiazole	198—200 (alcohol + ether)	$C_7H_7Cl_3N_2O_2S$	9,6	S 10,8	9,8	S 11,0	19,8
VI	1-(3-Hydroxy-4,4,4-trichlorobutyryl)-2-iminothiazole	53—54 (alcohol)	$C_7H_7Cl_3N_2O_2S$	—	37,2	—	36,85	64,8
VII	2-(3-Hydroxy-4,4,4-trichlorobutyryl-amino)-4-methyl-6-oxopyrimidine	205—207 (sublimation, dimethylformamide	$C_9H_{10}Cl_3N_3O_3$	13,7	—	13,3	—	56
VIII	3-(3-Hydroxy-4,4,4-trichlorobutyryl-amino)-5-phenylpyrazole	270—273 (alcohol)	$C_{13}H_{12}Cl_3N_3O_2$	12,2	—	12,5	—	43
IX	2-Oxo-4-trichloromethyl-7-phenyl-3,4-dihydro-6H-pyrazolo[3,2-b]pyrimidine	148—150 (alcohol)	$C_{13}H_{10}Cl_3N_3O$	12,1	—	12,7	—	48,5
X	1-Phenyl-2-(3-hydroxy-4,4,4-trichlorobutyryl)-3-imino-Δ^2-pyrazoline	96—98 (alcohol)	$C_{13}H_{14}Cl_3N_3O_2$	—	31,0	—	30,5	97
XI	2-(3-Hydroxy-4,4,4-trichlorobutyryl-amino)-1,3,4-thiadiazole	197—200 (alcohol + ether)	$C_6H_6Cl_3N_3O_2S$	—	36,7	—	36,6	31
XII	2-(3-Hydroxy-4,4,4-trichlorobutryl-amino)-3-(3-hydroxy-4,4,4-trichlorobutyryl)-1,3,4-thiadiazole	88—90 (CCl_4 + heptane)	$C_{10}H_9Cl_6N_3O_4S$	—	43,8	—	44,4	40,2
XIII	2-(3-Hydroxy-4,4,4-trichlorobutyryl-amino)-5-ethyl-1,3,4-thiadiazole	190—193 (CCl_4 + heptane)	$C_8H_{10}Cl_3N_3O_2S$	12,8	—	13,2	—	93
XIV	2-(3-Hydroxy-4,4,4-trichlorobutyryl-amino)-3-acetyl-5-ethyl-1,3,4-thiadazole	143—145 (acetic acid + water)	$C_{10}H_{12}Cl_3N_3O_3S$	11,8	—	11,7	—	80
XV	1-(3-Hydroxy-4,4,4-trichlorobutyryl)-3-amino-1,2,4-triazole	250—253 (alcohol + ether)	$C_6H_7Cl_3N_4O_2$	—	38,4	—	38,7	35
XVI	2,4-Bis(3-hydroxy-4,4,4-trichlorobutyryl)-3-imino-1,2,4-triazole	75—76 (alcohol + ether)	$C_{10}H_{10}Cl_6N_4O_4$	—	44,5	—	45,5	45,3
XVII	1,3,5-Tris(3-hydroxy-4,4,4-trichlorobutyryl)-2,4,6-triimino-1,3,5-triazine	113—114 (CCl_4 + heptane)	$C_{15}H_{15}Cl_9N_6O_6$	—	45.3	—	45,2	88,5

* Compound III was obtained by refluxing a solution of the reagents in CCl_4 for 1 h, VII was obtained by refluxing a solution in dimethylformamide for 15 min, XIII was obtained by heating at 130° for 5 min, and XV and XVI were obtained by heating at 100° for 40 min. Compound XIV was obtained by refluxing a solution of XIII in acetic anhydride.

contrast to N-alkylated structures of the B and D types [5, 10]). In contrast to diketene [6, 7], cyclization to pyridopyrimidine does not occur in the reaction of 2-aminopyridine with I.



III IV V VI VII

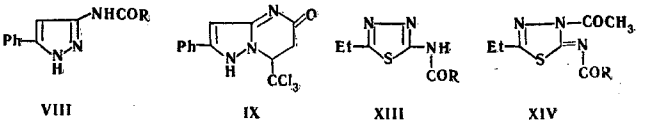
R=$COCH_2CH(OH)CCl_3$

Compound I reacts similarly with 2-aminothiazole to give V and VI, which are readily separated through their different solubilities in ether. The structure of V is confirmed by the characteristic absorption in the IR spectrum ($\nu_{C=O}$ 1675 cm^{-1}) and UV spectrum (λ_{max} 266 nm) peculiar to exo-N-acylaminothiazoles (in the acylamino rather than in the acylimino form) [11]. Isomer VI, which is lower-melting and more soluble in ether, is characterized by a carbonyl group vibration (1750 cm^{-1}) that corresponds to endo-N-acylation of the heterocycle [12].

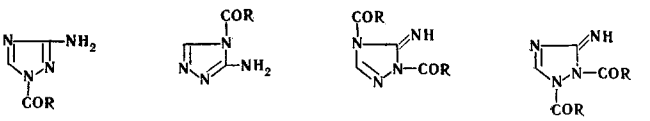
The reaction of I with 2-amino-4-methyl-6-hydroxypyrimidine gives VII, in which, judging from the absence in the IR spectrum of carbonyl group vibrational bands characteristic for ester or carboxyl functions, alkylation or acylation of the hydroxyl group of the molecule by lactone is excluded. The spectrum of VII contains an intense broad absorption band at 1660 cm^{-1} and an extremely weakened (in comparison with the spectrum of the starting AHNC) absorption of a free hydroxyl group at 3300-3600 cm^{-1}. While retaining the long-wave maximum of the starting AHNC (284 nm), the UV spectrum of VII is characterized by a bathochromic shift of the low-wave maximum (237 nm as compared with 226 nm). The set of spectral data make it possible to assume that adduct VII has the structure indicated here with predominance of the 6-oxo form in the solid phase.

In contrast to diketene, which acylates 1-substituted 3-amino-5-pyrazolones at the exo-N-atom to give the corresponding pyrazolopyrimidines [13], I does not react with them on refluxing in acetonitrile, dioxane, or xylene or on fusion. We obtained two compounds, which were separable through their different solubilities in alcohol, from the reaction of I with 3-amino-5-phenylpyrazole. Judging from the IR and UV absorption, they are, respectively, the exo-N-acylated adduct (VIII) and the product of its subsequent cyclization (IX). The vibrational frequencies of the carbonyl groups in the spectra of these compounds are 1680 and 1690 cm^{-1}, respectively; the spectrum of IX at 3000-3700 cm^{-1} contains a weak band of a free NH group (3393 cm^{-1}), while, as in the spectrum of VIII, there is intense absorption over a broad range at 3100-3300 cm^{-1} (with maxima at 3140, 3246, and 3310 cm^{-1}). The UV spectra of VIII and IX are characterized by a slight bathochromic shift of the maximum for the latter (248 and 255 nm).

We carried out the reaction of I with 1-phenyl-3-amino-2-pyrazoline in both water and in an organic solvent. In this case, only the endo-N-acylation product (X, Table 1) with $\nu_{C=O}$ 1750 cm^{-1} is formed.



VIII IX XIII XIV



XVa XVb XVIa XVIb

R=$CH_2CH(OH)CCl_3$

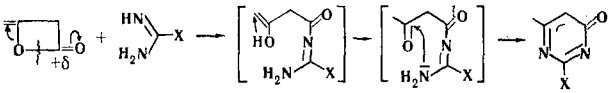
When 2-amino-1,3,4-thiadiazole is fused with a threefold excess of I, the exo-N and $N_{(3)}$ atoms of the reagent undergo mono- and diacylation. The different solubilities in ether make it possible to readily separate the compounds (XI and XII), the structures of which are confirmed by the characteristic $\nu_{C=O}$ absorption in the IR spectrum (1700 cm^{-1} for XI, and 1700 and 1765 cm^{-1} for XII). In contrast to 2-aminothiadiazole, only the exo-N-acyl derivative (XIII) is formed in the reaction of I with 5-ethyl-2-amino-1,3,4-thiadiazole in alcohol, dioxane, and acetonitrile or on fusion. An attempt to cyclize it by refluxing in acetic anhydride led only to acetylation of the nitrogen atom of the heterocycle. The structures of XIII and XIV were confirmed by the $\nu_{C=O}$ frequencies in the IR spectra at 1664, 1692, and 1760 cm^{-1}, respectively.

The latter make it possible to reject the structures of the isomeric exo-N [14] and exo-O-acetyl [15] derivatives of XIII, as well as the endo-N-acetyl structure, for which $\nu_{C=O}$ should range from 1700 to 1710 cm^{-1}.

In addition to the 1-(or 4)-N-acyl adduct (XVa or b), which has $\nu_{C=O}$ of 1715 cm^{-1} in its IR spectrum, I also reacts with 3-amino-1,2,4-triazole to give a diacyl derivative in which both acyl fragments, judging from the IR characteristics ($\nu_{C=O}$ 1720 and 1750 cm^{-1}), are connected to the ring heteroatoms [16-18] (structures XVIa or XVIb).*

Judging from the literature [19], sym-triamino-1,3,5-triazine (melamine) is smoothly acylated by acid anhydrides at the amino groups, but the structure of the products has not been proved. The reaction of I with melamine in a melt containing excess I leads to the formation of a 3 : 1 adduct (XVI), the IR spectrum of which contains three very intense vibrational bands at 1765, 1675, and 1630 cm^{-1}, which are related, respectively, to the C=O stretching vibrations, the exo-C=N stretching vibrations, and the deformation vibrations of the N–H bond. The presence also of intense absorption at 3070-3388 cm^{-1} ($\nu_{OH,NH}$) confirms the absence of cyclization to the tris)pyrimido)triazine. The spectral data are evidence for the formation of 2,4,6-triimino-1,3,5-(3-hydroxy-4,4,4-trichlorobutyryl)-1,3,5-triazine (XVII).

Thus, except for one case, the investigated reactions of I with AHNC form heterylamides of 3-hydroxy-4,4,4-trichlorobutyric acid that do not cyclize to condensed pyrimidine derivatives. The differences in reactivity with respect to the AHNC and I, II, and diketene are based on the peculiarities of the structures of these β-lactones. Compound II is a pronouncedly difunctional electrophilic compound with a strained ring in which both reaction centers are accessible to attack by even a weakly nucleophilic reagent. If the latter is in turn a difunctional compound (for example, amidines, thioureas, etc.), closure of the pyrimidine ring can occur. Although diketene is also potentially a difunctional compound, because of stabilization of the O–alkyl bond by the mesomeric effect of the adjacent exo-methylene group, it acts only as an acylating agent in nucleophilic addition. The intermediate α-hydroxyvinyl derivative formed in the process, by isomerizing to an acetoacetyl derivative, is subsequently comparatively readily cyclized.



In contrast to II and diketene, I has an O–alkyl bond that is reinforced as a consequence of the strong effect of the CCl_3 group, which also creates steric hindrance to nucleophilic attack of the β-carbon atom of the lactone. In this case, the acyclic product obtained by acylation of the $HN{=}C(-NH_2)-$ fragment by the lactone is completely stable. Its subsequent cyclization with dehydration is hindered, apparently not only because of the increased strength of the O–alkyl bond, but also as a result of steric shielding of the β-carbon atom by the bulky substituent. In the case of the weakly nucleophilic reagents of the type that we used, attack of the β-carbon atom by the free imino group of the acyclic adduct is therefore, as a rule, impossible.

EXPERIMENTAL

The compounds obtained are presented in Table 1. The reagents were introduced into reaction in equimolar ratios except when I was also the solvent. Examples of the synthesis are presented below. The IR spectra of mineral oil suspensions were recorded with an IKS-14A spectrometer. The UV spectra of alcohol solutions were recorded with an SF-4 spectrometer.

Reaction of I with 2-Aminothiazole. A mixture of 380 mg of I and 200 mg of 2-aminothiazole (2 mmole each) was heated at 100°C for 7-10 min and cooled. The melt was ground and washed with ether to give 115 mg of V. UV spectrum: λ_{max} 266 nm (log ε 3.04). IR spectrum: 3100-3300, 1695, 1575, 1340, 1290, 1200, 1180, 1125 cm^{-1}. Removal of the solvent from the ether solution gave 375 mg of VI. IR spectrum: 3020-3310, 1760, 1680, 1626, 1563, 1325, 1277, 1161, 1074, 1040 cm^{-1}.

Reaction of I with 3-Amino-5-phenylpyrazole. A mixture of 190 mg of I and 146 mg of 3-amino-5-phenylpyrazole (1 mmole each) was refluxed for 1 h in 1.5 ml of dioxane, and the mixture was cooled and filtered to give 140 mg of VIII. IR spectrum: 3310, 3246, 3140, 1680, 1552 cm^{-1}. The mother liquor was diluted with water and cooled. The resulting oil crystallized after 24 h to give 156 mg of IX. IR spectrum:

*It is not yet possible to distinguish between XVIa and XVIb.

3343, 1690, 1620, 1580 cm^{-1}. When equimolecular amounts of the reagents were fused at 100° for 15 min with subsequent treatment of the cooled melt with carbon tetrachloride and separation of the products with respect to their different solubilities in alcohol, the yields of VIII and IX were 19.5 and 57.5%, respectively.

3-(3-Hydroxy-4,4,4-trichlorobutyryl)amino-1-phenylpyrazole (X). A mixture of 190 mg of I and 161 mg of 3-amino-1-phenylpyrazoline (1 mmole each) was heated with 3 ml of water until the solids dissolved, and the solution was cooled immediately (the solution darkens when it is heated beyond this point, and the product partially resinifies.) The water was decanted, and three extractions of the oily residue with ether gave 40 mg of the starting pyrazoline with mp 162-165°. The residue from the extraction was treated with cold water until it crystallized to give 255 mg (97% based on the pyrazoline recovered) of X. IR spectrum: 3080-3300, 1750, 1650-1660, 1595, 1150, and 1020 cm^{-1}.

Reaction of I with 2-Amino-1,3,4-thiadiazole. A mixture of 570 mg (3 mmole) of I and 101 mg (1 mmole) of 2-amino-1,3,4-thiadiazole was fused at 100° for 2 h and cooled. The melt was ground and treated with ether. The insoluble XI (70 mg) was removed by filtration, and the mother liquor was vacuum evaporated. The residue was refluxed with heptane, and the insoluble oil was then dissolved in ether. Removal of the ether by vacuum distillation gave 400 mg of a solid with mp 75-80°. Treatment of the solid with boiling benzene or carbon tetrachloride gave 20 mg of insoluble XI. The overall yield of XI was 90 mg. IR spectrum: 3370, 3100-3160, 1700, 1670-1675, 1575 cm^{-1}. Dilution of the benzene (or CCl_4) solution with heptane precipitated 200 mg of XII. IR spectrum: 3200-3400, 3185, 1765, 1702, 1550-1564, 1325, 1280, 1235, 1170 cm^{-1}.

Reaction of I with Melamine. A mixture of 630 mg (3.3 mmole) of I and 126 mg (1 mmole) of melamine was fused at 100° for 3 h and cooled. The melt was ground and treated with 5 ml of alcohol, and the insoluble residue (64 mg, mp above 350°, not analyzed) was removed by filtration. Evaporation of the alcohol solution to dryness in vacuo gave 678 mg of XVII. IR spectrum: 3388, 3310, 3192, 3108, 1765, 1675, 1630, 1550, 1535, 1337, 1275, 1238, 1160, 1098, 1062, 1025 cm^{-1}.

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