INVESTIGATIONS IN THE SYNTHESIS OF PRECURSORS AND FRAGMENTS OF ANTIBIOTICS

XII. NEW DERIVATIVES OF THIOGLYCOLIC ACID

N. M. Ryabova and M. S. Rabinovich

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This work is a continuation of our investigations in the synthesis of various sulfur-containing carboxylic acids [1, 2] obtained for the purpose of acylating 6-aminopenicillanic acid with them and studying the connection between the chemical structure of the starting carboxylic acids and the biological properties of the penicillins obtained.

The synthesis of the following series of mercaptoacetic acid derivatives with the general formula $RCOSCH_2COOH$ is described in this article: benzoylthioglycolic acid (I), its ethyl ester (II), and its acid chloride (III), phenoxyacetylthioglycolic acid (IV), its ethyl ester (V), and amide (VI), phenacetylthioglycolic acid (VII) and its ethyl ester (VIII), α-bromophenacetylthioglycolic acid (IX) and its ethyl ester (X), α-aminophenacetylthioglycolic acid (XI) and its ethyl ester hydrochloride (XII), and N-phthalyl-α-aminophenacetylthioglycolic acid (XIII):

$RCOSCH_2COOH$

(I) $R = C_6H_5-$

(IV) $R = C_6H_5OCH_2-$

(VII) $R = C_6H_5CH_2-$

(IX) $R = C_6H_5\underset{\displaystyle Br}{\underset{|}{C}}H-$

(XI) $R = C_6H_5CH(NH_2)-$

(XIII) $R = C_6H_5\underset{\displaystyle N(CO)_2C_6H_4}{\underset{|}{C}}H-$

Acids I, IV, VII, and VIII were synthesized by the method described for preparing some acyl derivatives of sulfur-containing carboxylic acids [3], which is brought about by reacting the appropriate acid chlorides with thioglycolic acid in an aqueous alkaline solution.

We failed to obtain acid IX in the same way because the very active bromine atom in the α-bromophenylacetic acid molecule is partially hydrolyzed in a sodium hydroxide solution forming a mixture of reaction products; the acid was obtained by the direct reaction of thioglycolic acid and α-bromophenylacetyl chloride without using alkali.

The ethyl esters of V and X were indirectly prepared from phenoxyacetyl and α-bromophenylacetyl chlorides and ethyl thioglycolate. The ethyl esters II and VIII were synthesized from the corresponding acids by the usual esterification in the presence of catalytic amounts of concentrated sulfuric acid.

Attempts to prepare acid XI from the acid chloride of C-phenylglycine hydrochloride and thioglycolic acid and also by treating acid IX with ammonia were not successful. The synthesis of acid XI was successfully brought about starting with thioglycolic and N-substituted α-aminophenylacetic acids by the combined anhydrides method. Acetoacetic ester [4] was used to shield the amino group. The combined anhydride, which was further acylated with thioglycolic acid, was prepared from potassium N-(1-methyl-2-ethoxycarbonylvinyl)-α-aminophenylacetate and ethyl chlorocarbonate in the presence of N,N-dimethylbenzylamine as the catalyst [5] (scheme on the following page).

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TABLE 1. Acylthioglycolic Acids $RCOSCH_2COOH$

Compound	Formula of starting acid chloride RCOCl	Yield (in %)	Melting point (in deg)	Found (in %)				Empirical formula	Calculated (in %)			
				C	H	S	N		C	H	S	N
I	C_6H_5COCl	69.4	105-6[1]	55.31	4.43	16.08	–	$C_9H_8O_3S$	55.12	4.11	16.31	–
IV	$C_6H_5OCH_2COCl$ [7]	69.2	72-5[2]	53.21	4.62	14.03	–	$C_{10}H_{10}O_4S$	53.07	4.45	14.17	–
VII	$C_6H_5CH_2COCl$	88.0	89-91[3]	57.21	4.80	15.87	–	$C_{10}H_{10}O_3S$	57.14	4.76	15.23	–
XIII	$C_6H_5CHCOCL$ $\vert$ $N(CO)_2C_6H_4$	57.0	185-7[4]	60.78	3.79	8.69	4.07	$C_{18}H_{13}O_5NS$	60.84	3.69	9.02	3.94

[1]IR spectrum: 1710 cm^{-1} (COOH), 1667 cm^{-1} (C = O), 1595, 1490, 1240, 795, 733 cm^{-1} (C_6H_5), 1450, 1210 cm^{-1} (– CH_2 –), 925 cm^{-1} (C – S).

UV spectrum: λ_1 237.5 mμ (ε ~ 11,100), λ_1 265 mμ (ε ~ 7500); pK_a = 3.77.

[2]IR spectrum: 1704 cm^{-1} (COOH), 1683 cm^{-1} (C = O), 1597, 1505, 1200, 760, 732 cm^{-1} (C_6H_5), 1490, 1380 cm^{-1} (–CH_2–), 1232 cm^{-1} (– O – CH_2 –), 920 cm^{-1} (C – S).

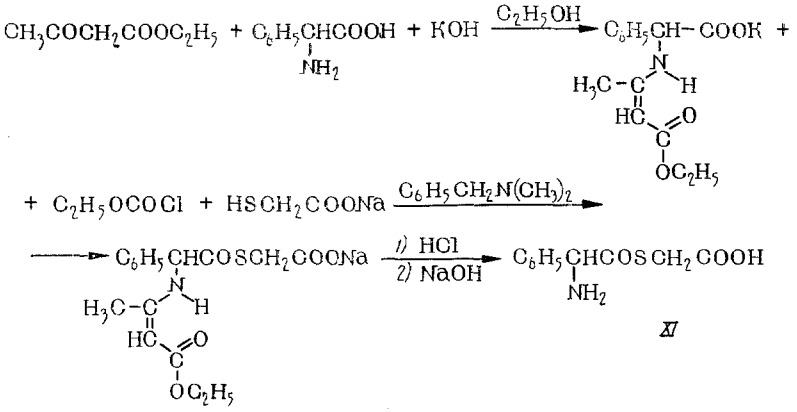
UV spectrum: λ_1 264.5 mμ (ε ~ 1100), λ_2 270.5 mμ (ε ~ 1400), λ_3 277 mμ (ε ~ 1200); pK_a = 3.585.

[3]IR spectrum: 1710 cm^{-1} (COOH), 1683 cm^{-1} (C = O), 1605, 1500, 1425, 1207, 760, 725 cm^{-1} (C_6H_5), 1320, 790, 770 cm^{-1} (–CH_2–), 915 cm^{-1} (C – S).

UV spectrum: λ_1 212.5 mμ (ε ~ 9300), λ_2 264 mμ (ε ~ 420); pK_a = 4.18

[4]IR spectrum: 2700, 2570 cm^{-1} (–CH_2 –), 1770 cm^{-1} (COOH), 1670 cm^{-1} (C = O), 1620, 1500, 1217, 750, 725 cm^{-1} (C_6H_5), 1617, 1440, 870, 850 cm^{-1} (C_6H_4), 1385 cm^{-1} (–CH_2–), 920 cm^{-1} (C – S).

UV spectrum: λ_1 295 mμ (ε ~ 2000); pK_a = 4.42.



Ethyl α-aminophenacetylthioglycolate hydrochloride (XII) was obtained by passing dry hydrogen chloride through a mixture of XI and ethyl alcohol.

The acid chlorides of phenacetyl- (XIV), phenoxacetyl- (XV), benzoyl- (III), and α-bromophenacetylthioglycolic (XIV) acids were synthesized by the usual method of reacting them with a two-fold excess of thionyl chloride in the presence of catalytic amounts of dimethylformamide.

The pKa [6] were also determined and the UV and IR spectra of all the new thioglycolic acid derivatives obtained were run.

EXPERIMENTAL

Benzoyl- (I), Phenoxyacetyl- (IV), Phenacetyl- (VIII), and N-phthalyl-α-aminophenacetylthioglycolic (XIII) Acids were prepared by a single general method. An equimolar amount of the appropriate acid chloride (for compound XIII the crystalline acid chloride (XVII) was dissolved in acetone in a 1 : 7.5 ratio) was added with agitation over a period of 1.5 to 2 h to a solution of 4.6 g of thioglycolic acid in 100 ml of 1 N sodium hydroxide, which had been cooled to 0 to 3°. The reaction was carried out at a temperature not higher than 10°, so that the medium would remain alkaline (pH 8.0-8.5) during the reaction. Then the reaction solution was extracted with ether which removes the acid chloride that did not react, the aqueous layer was acidified with 15% hydrochloric acid to pH 1.0, and extracted with ether three times. The combined ether extracts were washed with water, dried over magnesium sulfate, the ether was distilled off, and the

remaining oily substance gradually crystallized. After treating it with petroleum ether, the residue was filtered off, and dried over phosphorus pentoxide and paraffin. The yields and the constants of the compound obtained are presented in Table 1.

Phthalyl-C-phenylglycine was obtained by a typical method [8] with a 75% yield, mp 167-168.5° [9].

Phthalyl-C-phenylglycine Acid Chloride (XVII) was synthesized by heating phthalyl-C-phenylglycine with a two-fold excess of thionyl chloride in a benzene solution. After recrystallizing it from a 1 : 1 benzene-petroleum ether mixture, the acid chloride yield was 63%, mp 144-145°. Found %: C 63.64; H 3.81; Cl 11.63. $C_{10}H_{10}ClNO_3$. Calculated %: C 63.92; H 4.02; Cl 11.8.

α-Bromophenacetylthioglycolic Acid (IX). Thioglycolic acid, 4.6 g, and α-bromophenylacetyl chloride, 11.7 g [10], were mixed together, and the mixture was kept at room temperature for 12 h. After the gaseous hydrogen chloride ceased evolving, the reaction mixture was treated with a mixture of ethyl ether and petroleum ether (1 : 1), the residue was filtered and dried. A white crystalline substance, 10.4 g (72%) mp 87-89°, was obtained. Found %: C 41.76; H 3.42. $C_{10}H_9BrO_3S$. Calculated %: C 41.5; H 3.14. pK_a = 3.67. UV spectrum: λ_1 212 mμ (ε ~ 1800), λ_2 237 mμ (ε ~ 1500), λ_3 257 mμ (ε ~ 1000).

IR spectrum: 2700, 2590 cm^{-1} (−CH−), 1722 cm^{-1} (COOH), 1695 cm^{-1} (C = O), 1490, 1420, 1205, 760, 720 cm^{-1} (C_6H_5), 1370 cm^{-1} (− CH_2 −), 925 cm^{-1} (C − S), 707 cm^{-1} (C − Br).

Potassium N-(1-methyl-2-ethoxycarbonylvinyl)-D(−)-α-aminophenylacetate. A suspension of 6.04 g of D(−)-α-aminophenylacetic acid and 5.08 ml of acetoacetic ester in 37.5 ml of absolute ethyl alcohol was heated to 75-80°, and while agitating, 25 ml of a 10% potassium hydroxide solution in absolute ethyl alcohol was added dropwise so that the pH of the reaction solution was maintained at 8.0-8.5. The addition was continued for 15-20 min, then the entire suspension went into solution. After distilling 20 ml of the alcohol off, the precipitate remaining was filtered off, washed twice with absolute alcohol (2 × 5 ml), and dried. A total of 9.74 g (81%) of the dry preparation was obtained. $[\alpha]_D$ + 272° (concn. 0.5; absolute alcohol). The mp was 229-231°. Found %: C 56.13; H 5.31; N 4.65. $C_{14}H_{16}KNO_4$. Calculated %: C 55.18; H 5.50; N 4.82.

α-Aminophenacetylthioglycolic Acid (XI). Methyl chlorocarbonate, 3.4 ml, and 1.1 ml of a 1% N,N-dimethylbenzoylamine solution in acetone were added with agitation to a solution of 13.2 g of potassium N-(1-methyl-2-ethoxycarbonylvinyl)-D(−)-α-aminophenylacetate in 140 ml of acetone which had been cooled to −7 to −9°, within 20 min, a solution of 4 g of thioglycolic acid in 40 ml of 1 N sodium hydroxide and 40 ml of acetone, which was prepared earlier and cooled to −8°, was added with vigorous agitation. The acylation was continued for 4 h at a temperature not higher than 5° and at a pH of 6.0-6.5, after which, in order to remove the N-shielding group, the reaction mixture was filtered, the filtrate was acidified with 20% hydrochloric acid to a pH of 3.3 and it was stirred at room temperature for 1.5 h. At the end of the hydrolysis and after distilling the acetone off, the aqueous solution was washed with ether and acidified with 20% hydrochloric acid to pH 1.5. Upon bringing the pH up to 3.0-4.0 (with NaOH), a precipitate began crystallizing out of the aqueous layer, it was filtered, washed with water and acetone, and dried in a vacuum desiccator over phosphorus pentoxide. A total of 2 g of α-aminophenacetylthioglycolic acid (XI), mp 142-144°, was obtained. Another 2 g of acid (XI), mp 142-144°, was obtained when the aqueous mother liquor was evaporated further. The overall yield was 40%. $[\alpha]_D$ −5.8° (concn. 1.5; 1 N HCl); pK_1 = 3.47, pK_2 = 6.94. Found %: C 53.25; H 5.00; S 14.16; N 6.46. $C_{10}H_{11}NO_3S$. Calculated %: C 53.3; H 4.8; S 14.2; N 6.22.

IR spectrum: 3100 cm^{-1} (NH_3^+), 2730, 2650 cm^{-1} (−CH−), 1863 cm^{-1} (C = O), 1615, 1520, 1200, 760, 730 cm^{-1} (C_6H_5), 1397 cm^{-1} (− CH_2 −), 1220 cm^{-1} (COO^-), 930 cm^{-1} (C − S), 697 cm^{-1} (NH_3^+).

UV spectrum: λ_{max} 267 mμ (ε ~ 250).

Ethyl Phenoxyacetylthioglycolate (V) and Ethyl α-Bromophenacetylthioglycolate (X) were obtained by reacting equimolar amounts of the appropriate acid chlorides and ethyl thioglycolate at room temperature. When gaseous hydrogen chloride ceased evolving, the reaction mixture was treated with a 3% sodium bicarbonate solution (pH 6.0-6.5), extracted with methylene chloride, the extracts were washed with water, dried with magnesium sulfate, and the solvent was distilled off. The oily substance obtained was vacuum distilled several times (Table 2).

Ethyl Phenacetylthioglycolate (VIII) and Ethyl Benzoylthioglycolate (II) were obtained after boiling 0.05 g-mole of acids (VII) and (I) with ten times the volume of anhydrous ethyl alcohol for 3-4 h in the

TABLE 2. Ethyl Acylthioglycolates $RCOSCH_2COOC_2H_5$

Compound	Bp (in deg), pressure in parentheses (mm of Hg)	n_D	Found (%)			Empirical formula	Calculated (%)		
			C	H	S		C	H	S
V	178—180 (3)	1,5365 (21)	56,71	5,73	12,34	$C_{12}H_{14}O_4S$	56,67	5,55	12,61
X	173—175 (3)	1,5680 (22)	45,55	4,39	—	$C_{12}H_{13}BrO_3S$	45,42	4,13	—
VIII	147—148 (2,5)	1,5354 (22)	60,36	6,20	13,76	$C_{12}H_{14}O_3S$	60,46	5,92	13,45
II	155—157 (4)	1,5553 (20)	58,89	5,40	14,3	$C_{11}H_{12}O_3S$	58,74	5.55	14,36

TABLE 3. Acylthioglycolyl Chlorides $RCOSCH_2COCl$

Compound	Yield (%)	Found (%)				Empirical formula	Calculated (%)				Purity of preparation (%)
		C	H	Cl	Cl + Br		C	H	Cl	Cl + Br	
III*	71	50,35	3,29	14,93	—	$C_9H_7ClO_2S$	50,49	3,71	16,51	—	90,4
XIV	63,5	—	—	13,49	—	$C_{10}H_9ClO_2S$	—	—	15,50	—	88
XV	95,9	—	—	14,40	—	$C_{10}H_9ClO_3S$	—	—	14,49	—	96,7
XVI †	95,5	—	—	—	33,06	$C_{10}H_8BrClO_3S$	—	—	—	37,36	88,5

* The mp of III was 40-41° (petroleum ether).

† The total Cl + Br was determined in substance XVI.

presence of catalytic amounts of concentrated sulfuric acid (0.25 ml). At the end of the reaction, the alcohol was distilled off, the remainder was dissolved in methylene chloride, the solution was washed with a 3% sodium bicarbonate solution (pH 6.0-6.5), then with water, dried over magnesium sulfate, the methylene chloride was distilled off, and the remainder was distilled several times (see Table 2).

Ethyl α-Aminophenacetylthioglycolate Hydrochloride (XIII). Dry hydrogen chloride was passed through a suspension of 3.15 g of acid (XI) in 50 ml of absolute ethyl alcohol. During the dissolution of the acid suspension, the reaction mixture was cooled with an ice-water mixture and hydrogen chloride continued to be passed through until saturation was achieved. The alcohol was evaporated in vacuo and the remainder was treated with dry acetone. A white crystalline substance (XII), 3 g (74%) mp 158.5-160°, was obtained. Found %: C 50.12; H 5.95; N 4.73. $C_{12}H_{16}ClNO_3S$. Calculated %: C 49.73; H 5.57; N 4.83.

Phenacetyl- (XIV), Phenoxyacetyl- (XV), Benzoyl- (III), and α-Bromophenacetylthioglycolyl Chlorides. A 0.01 g-mole sample of the appropriate acid in 15-20 ml of dry benzene was heated with a two-fold excess of thionyl chloride in the presence of catalytic amounts (1-2 drops) of dimethylformamide over a 4 h period. The excess thionyl chloride was removed by vacuum distillation after a three-fold addition of dry benzene was made; the percent halide was determined by a Volhard titration. The characteristics of the acid chlorides obtained are presented in Table 3.

Phenoxyacetylthioglycolamide (VI) was obtained by reacting 2.4 g of acid chloride (XV) with 2.5 ml of concentrated aqueous ammonia over a 12 h period. After recrystallizing the precipitate from alcohol three times, the mp was 143.5-145°. Found %: C 53.68; N 5.26; S 14.44; N 6.04; $C_{10}H_{11}NO_3S$. Calculated %: C 53.60; H 4.92; S 14.23; N 6.22.

CONCLUSIONS

1. The following new S-acyl mercaptoacetic acids were obtained: phenoxyacetyl, phenacetyl, α-bromophenacetyl-, α-aminophenacetyl-, and N-phthalyl-α-aminophenacetylthioglycolic acids and some of their derivatives.

2. Phenoxacetyl-, phenacetyl-, α-bromophenacetyl-, and N-phthalyl-α-aminophenacetylthioglycolic acids were synthesized by reacting the appropriate acid chlorides with thioglycolic acid in an aqueous alkaline or neutral solution.

3. α-Aminophenacetylthioglycolic acid was obtained by acylating thioglycolic acid with N-substituted α-aminophenylacetic acid by the combined anhydrides method.

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