ISOTHIOCYANATES AND THEIR SYNTHETIC PRODUCERS. X.*

SYNTHESIS OF 3-SUBSTITUTED 2-THIOXO-4-OXO-3,4-DIHYDRO-2H-1,3-BENZOXAZINES

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A new method for preparation of N-aryl-substituted 2-thioxo-4-oxo-3,4-dihydro-2*H*-1,3-benzoxazines is described, using methyl salicylate as starting material. The salicylate is converted by thiophosgene into the chlorothioformate which is then condensed with an appropriate aromatic amine. The cyclization is carried out in glacial acetic acid saturated with dry hydrogen chloride. This method is not suitable for preparation of N-alkylated benzoxazine derivatives.

Within the framework of systematic study of the synthesis, structure and properties of precursors of isothiocyanates in the present work we have centered on the new type of these compounds, 3-substituted 2-thioxo-4-oxo-3,4-dihydro-2*H*-1,3-benzoxazines, the skeleton of which contains the —N—C=S grouping.

The marked antimicrobial action of benzoxazines[1-6] could make these compounds useful as medicaments. In this connection we have been interested in biological activity of the title compounds. The active part of these compounds in biological medium is the isothiocyanate formed by their cleavage. Our experience gained by long-standing study of isothiocyanates led us to the preparation of N-substituted derivatives with aromatic substituents. The synthesis and properties of these compounds have not yet been reported.

Unlike other benzoxazine derivatives, which were thoroughly studied, the only prepared 2-thioxo-4-oxobenzoxazines were the parent compound[7], 3-methyl derivative[7] and 3-(tetra-O-acetyl-β-D-glucosyl)-2-thioxo-4-oxo-3,4-dihydro-2*H*-1,3-benzoxazine[8]. Wagner and Richter[9] described alkaline decomposition of the 3-phenyl-2-thioxo-4-oxo derivative, without reporting however its preparation.** Capuano and Zander[10] has worked out the method consisting of the action of isothiocyanate on methyl salicylate in the presence of benzene-diazo compounds as catalysts. By this way the already known 3-methyl-2-thioxo-4-oxo-3,4-dihydro-2*H*-1,3-benzoxazine was synthesized. We have tried to apply this simple method in preparing new aromatic and aliphatic N-substituted derivatives, but without success.

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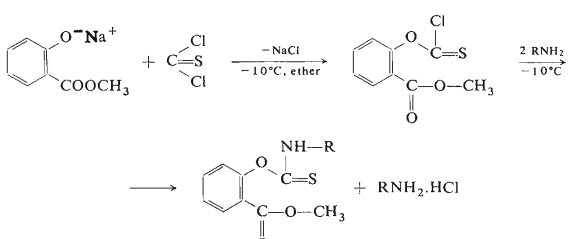
** The authors communicated to us that the N-phenyl derivative was prepared from salicylanilide by the action of thiophosgene in the presence of trimethylamine. The disadvantage of this method lies in that the corresponding salicylanilide is not easily available.

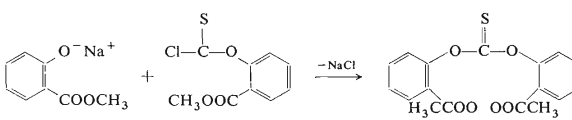
We have therefore attempted to work out a new, general method for preparing N-substituted 2-thioxo-4-oxo-3,4-dihydro-2*H*-benzoxazines. As starting compounds for the preparation of the 3-substituted derivatives we have used N-substituted O-(2-methoxycarbonyl)phenyl monothiourethanes, which were prepared by the reaction of thiophosgene with sodium salt of methyl salicylate, followed by treatment of the formed (**2-**methoxycarbonyl)phenyl chlorothioformate (Eq. (*A*)) with a primary amine.



(*A*)

The preparation of the chlorothioformate by the method of direct action of thiophosgene on phenol[11] has failed with methyl salicylate. When the sodium salt of methyl salicylate was used, reaction proceeded smoothly. The phenolate anion of this compound is sufficiently strong nucleophile to react with thiophosgene. In fact, the reactivity of this derivative was so high that it had to be added to thiophosgene with efficient cooling the reaction mixture.

If thiophosgene is added to the sodium salt, the reaction leads to the formation of corresponding ester of thiocarbonic acid (Eq. (*B*)); yellow crystals m.p. 113–115°C (chloroform–light petroleum); for $C_{17}H_{14}O_6S$ (346·4) calculated: 59·9% C, 4·12% H; 9·33% S; found: 59·01% C, 4·14% H, 9·21% S.



(*B*)

Chlorothioformate *I* is a relatively stable, yelowish oily liquid which can be distilled at reduced pressure without decomposition. By the action of 2 mol of an appropriate amine on 1 mol of chlorothioformate *I* we have obtained N-substituted O-(2-methoxycarbonylphenyl) monothiourethanes *II*–*XVI*. Dry ether was used as solvent and the reaction was carried out with efficient cooling the reaction mixture. The change in the order of the added reactants results in ammonolysis of the formed monothiourethane, yielding corresponding disubstituted thiourea, the identity of

TABLE I
Properties and Analyses of N-Substituted O-(2-Methoxycarbonylphenyl) monothiourethanes

Derivative	Yield, % m.p., °C	Formula m.w.	Calculated/Found % N	Calculated/Found % S	λ_{max}[a], nm log ε		$\tilde{\nu}$(N—H)[b]	$\tilde{\nu}$(C=O)[b]	$\tilde{\nu}$(C—O—C)[b]	$\tilde{\nu}$(NH—C=S)[b]
Phenyl (*II*)	75 112—114[d]	$C_{15}H_{13}NO_3S$ (287·3)	4·87 5·02	11·16 10·99	281 4·30	—	3 420 3 398	1 725	1 303 1 165	1 530 1 385 1 365
4-Tolyl (*III*)	67 141—143[e]	$C_{16}H_{15}NO_3S$ (301·4)	4·64 4·41	10·64 10·48	283 4·25	—	3 420 3 398	1 726	1 302 1 160	1 530 1 380 1 368[e]
4-Methoxyphenyl (*IV*)	62 114—115[d]	$C_{16}H_{15}NO_4S$ (317·4)	4·41 4·29	10·10 10·17	285 4·27	—	3 423 3 399	1 732	1 306 1 162	1 530 1 388 1 372[e]
4-Dimethylaminophenyl (*V*)	65 110—111[d]	$C_{17}H_{18}N_2O_3S$ (330·4)	8·48 8·38	9·71 9·58	300 4·25	—	3 423 3 398	1 730	1 305 1 160	1 536 1 385[e] 1 358
4-Diphenylyl (*VI*)	68 139—141[d]	$C_{21}H_{17}NO_3S$ (363·4)	3·85 3·87	8·82 8·21	300 4·48	—	3 420 3 395	1 720	1 305 1 166	1 532 1 388 1 370[e]
4-Bromophenyl (*VII*)	78 145—147[e]	$C_{15}H_{12}BrNO_3S$ (366·2)	3·82 3·73	8·76 8·53	288 4·33	—	3 415 3 399	1 724	1 302 1 164	1 520 1 379 1 358[e]
4-Methoxycarbonylphenyl (*VIII*)	71 148—149[d]	$C_{17}H_{15}NO_5S$ (345·4)	4·08 4·18	9·28 9·17	302 4·33	—	3·420 3 396	1 731	1 290 1 170	1 536 1 378
4-Nitrophenyl (*IX*)	43 138—139[d]	$C_{15}H_{12}N_2O_5S$ (332·3)	8·43 8·30	9·65 9·76	329 4·25	—	3 420 3 392	1 735	1 308 1 172	1 548 1 378
1-Naphthyl (*X*)	65 119—120[d]	$C_{19}H_{15}NO_3S$ (337·4)	4·15 4·10	9·50 9·60	297 4·01	325 3·79	3 415 3 390	1 729	1 306 1 168	1 520[e] 1 385 1 352
2-Naphthyl (*XI*)	64 106—108[f]	$C_{19}H_{15}NO_3S$ (337·4)	4·15 4·23	9·50 9·53	274 4·49	302 4·30	3 420 3 398	1 725	1 302 1 162	1 539 1 390 1 355
Butyl (*XII*)	84 90—92[f]	$C_{13}H_{17}NO_3S$ (267)	5·26 5·45	11·99 11·84	248 4·04	— —	3 415	1 732	1 308 1 167	1 545 1 420 1 412[e]
Octyl (*XIII*)	75 63—65[f]	$C_{17}H_{25}NO_3S$ (323·4)	4·33 4·28	9·91 10·00	248 4·10	— —	3 410	1 728	1 300 1 168	1 536 1 415

Cyclohexyl (*XIV*)	64 132–133[d]	$C_{15}H_{19}NO_3S$ (293·4)	4·77 4·75	10·92 10·71	250 4·11	— —	3 402	1 726	1 301 1 161	1 522 1 390[e] 1 412
Benzyl (*XV*)	63 80–82[d]	$C_{16}H_{15}NO_3S$ (301·4)	4·65 4·80	10·64 10·48	250 4·11	—	3 410	1 727	1 302 1 142	1 528 1 408 1 390[e]
Furylmethyl (*XVI*)	81 68–70[f]	$C_{14}H_{13}NO_4S$ (291·3)	4·81 4·84	11·01 10·84	250 4·28	— —	3 415	1 729	1 304 1 150	1 528 1 410 1 385[e]

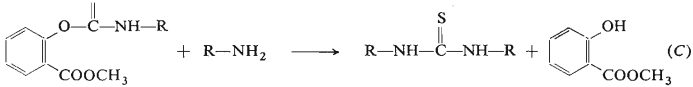
[a] In dioxane. [b] In chloroform (cm^{-1}). [c] Shoulder. [d] Chloroform–light petroleum. [e] Chloroform–n-heptane. [f] Diethyl ether–n-heptane.

TABLE II
Properties and Analyses of 3-Substituted 2-Thioxo-4-oxo-3,4-dihydro-2*H*-1,3-benzoxazines

Derivative	Yield, % m.p., °C	Formula m.w.	Calculated/Found % N	% S	λ_{max}[a], log ε	nm	$\tilde{\nu}$(C=O)[b]	$\tilde{\nu}$(C—O—C)[b]	$\tilde{\nu}$(N—C=S)[b]
Phenyl (*XVII*)	65 218·5[c]	$C_{14}H_9NO_2S$ (255·3)	5·49 5·52	12·56 16·60	276 4·35	300 3·75	1 724	1 184	1 300
4-Tolyl (*XVIII*)	58 247–248[c]	$C_{15}H_{11}NO_2S$ (269·3)	5·20 5·32	11·91 11·81	276 4·36	300 3·77	1 720	1 172	1 300
4-Methoxyphenyl (*XIX*)	59 204–205[c]	$C_{15}H_{11}NO_3S$ (282·3)	4·91 4·83	11·24 11·18	275 4·21	300 3·62	1 730	1 172	1 306
4-Dimethylaminophenyl (*XX*)	63 283–284[c]	$C_{16}H_{14}N_2O_2S$ (298·3)	9·32 9·48	10·75 10·87	267 4·61	300 4·01	1 730	1 160	1 307
4-Diphenyl (*XXI*)	71 256–257[c]	$C_{20}H_{13}NO_2S$ (331·4)	4·23 4·25	9·68 9·81	270 4·59	302 3·88	1 731	1 185	1 302
4-Bromophenyl (*XXII*)	65 263–264[c]	$C_{14}H_8BrNO_2S$ (334·2)	4·19 4·03	9·59 9·61	275 4·40	300 3·81	1 724	1 182	1 300
4-Methoxycarbonylphenyl (*XXIII*)	64 247–248[d]	$C_{16}H_{11}NO_4S$ (313·3)	4·47 4·51	10·23 10·28	275 4·37	303 3·78	1 731	1 188	1 305
4-Nitrophenyl (*XXIV*)	70 279–280[d]	$C_{14}H_8N_2O_4S$ (300·3)	9·37 9·44	10·68 10·76	274 4·41	303 4·02	1 738	1 190	1 295
1-Naphthyl (*XXV*)	67 240–241[d]	$C_{18}H_{11}NO_2S$ (305·3)	4·59 4·60	10·50 10·58	275 4·50	297 4·13	1 720	1 171	1 306
2-Naphthyl (*XXVI*)	68 254–255[c]	$C_{18}H_{11}NO_2S$ (305·3)	4·59 4·45	10·50 10·41	275 4·48	304 3·88	1 725	1 164	1 300

[a] In dioxane. [b] In chloroform (cm^{-1}). [c] Glacial acetic acid. [d] Glacial acetic acid–diethyl ether.

which was confirmed by elemental analysis and by comparison of physico-chemical properties of the isolated compound with those reported in literature (Eq. (*C*)).



(*C*)

Cyclisation of N-aryl monothiourethanes *II*—*XI* to corresponding 3-substituted 2-thioxo-4-oxo-3,4-dihydro-2*H*-1,3-benzoxazines *XVII*—*XXVI* can be achieved by dry hydrogen chloride in glacial acetic acid. At room temperature the reaction proceeds several days. Because of the low solubility of cyclisation products in the reaction medium, they precipitate out during the reaction, which favourably affects their yields. In this way we have prepared 10 new benzoxazine derivatives. The above cyclisation does not take place with N-alkylsubstituted monothiourethanes *XII*—*XVI*, not even in the presence of a strong base such as potassium tert-butylate or phenyldiazomethane.

EXPERIMENTAL

The analytical samples were dried at 50°C *in vacuo* above P_2O_5. The UV spectra were recorded with Perkin-Elmer 402 instrument. The IR spectra were measured on Zeiss, Model UR-20, spectrophotometer (Zeiss, Jena). The elemental analyses were carried out in the Analytical Department, Slovak Academy of Sciences, Bratislava.

(2-Methoxycarbonyl)phenyl chlorothioformate (*I*)

To an ether solution of 86·5 g (0·75 mol) of thiophosgene were added in portions 87·07 g (0·5 mol) of powdered sodium methyl salicylate with stirring. The reaction temperature was maintained at −10°C. After the reaction was complete, the precipitate of sodium chloride was separated by filtration and the filtrate was freed from the solvent by evaporation on a rotatory evaporator. The remaining oily liquid was distilled under reduced pressure, the fraction of b.p. 130—136°C : : 5 Torr being collected. The yield of the product was 67·8 g (58%). The IR spectrum (in chloroform): C=O 1684; ester C—O 1308; ether C—O 1160 cm^{-1}. For $C_9H_7ClO_3S$ (230·7) calculated: 46·85% C, 3·06% H, 13·90% S, 15·35% Cl; found: 46·91% C, 3·10% H, 13·81% S, 15·25% Cl.

Synthesis of N-Substituted O-(2-Methoxycarbonylphenyl) monothiourethanes *II*—*XVI*

In a three-necked flask equipped with a mechanical stirrer and a dropping funnel were placed 4·35 mmol of chlorothioformate *I* dissolved in 25 ml of dry ether. The content of the flask was cooled to −10°C and then an ethereal solution of 8·7 mmol of an appropriate amine was gradually added, while stirring and maintaining the temperature. During the reaction the formed amine hydrochloride precipitates out, which indicates the progress of the reaction. After the addition was complete, the reaction mixture was allowed to stir for another 15 min, then the hydrochloride was separated by filtration with suction. The filtrate was freed from the solvent by evaporation on a rotatory evaporator and the remainder of the liquid was washed by 20 ml of light petroleum to remove the unreacted chlorothioformate. The impure product was then recrystallized from the appropriate solvent. The compounds so prepared are characterized in Table I.

Synthesis of 3-Substituted 2-Thioxo-4-oxo-3,4-dihydro-2*H*-1,3-benzoxazines *XVII*–*XXVI*

A solution of 1 g of N-substituted O-(2-methoxycarbonylphenyl) monothiourethane in the least amount of glacial acetic acid saturated by dry hydrogen chloride was allowed to stand at room temperature for several days. The colourless crystals, separated from the reaction mixture by filtration, were washed with acetic acid and dried in air. Further portion of the product can be obtained by concentration of the mother liquor. The compounds so prepared are characterized in Table II.

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