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Stereochemistry of some thioether ketoximes (Part II)[1])

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In a former study (1) one of us (*V.*) has shown that the phenyl-(phenylthiomethyl)ketoxime (IV, R = R' = H) has the *anti*-phenyl configuration if the *Beckmann* rearrangement of this oxime follows the *Meisenheimer* rule (2).

The object of this work was (i) to study the influence of substituents on the contifiguration of aryl (arylthiomethyl) ketoximes (IV. or. V.), and (ii) to obtain in this way the other stereoisomer oxime (V.).

$$\underset{\text{(R; R'; SH=4; 3; 1)}}{\underset{\text{I.}}{R_2C_6H_3 . SH}} + \underset{\text{(R'; R'; BrCH}_2\text{.CO=4'; 3'; 1')}}{\underset{\text{II.}}{BrCH_2 . CO . C_6H_3R'_2}} \longrightarrow \underset{\text{III.}}{R_2C_6H_3S . CH_2 . CO . C_6H_3R'_2}$$

$$\longrightarrow \underset{\text{IV.}}{R_2C_6H_3S . CH_2 . C(=N . OH) . C_6H_3R'_2} \quad \text{or} \quad \underset{\text{V.}}{R_2C_6H_3S . CH_2 . C(=N . OH) . C_6H_3R'_2}$$

This oxime —the syn-phenyl — by a *Beckmann* rearrangement should give an acylamine (IX.), which may be transformed by cyclisation into benzometathiazione derivatives (X.) (3.).

$$\underset{\text{V.}}{\xrightarrow{PCl_5}} R_2C_6H_3 . S . CH_2 . \underset{\text{IX.}}{NH . CO . C_6H_3R'_2} \xrightarrow[-H_2O]{} \underset{\text{X.}}{R_2C_6H_2 \begin{cases} S \text{———} CH_2 \\ C(C_6H_3R'_2) : N \end{cases}}$$

In order to study the first problem we have chosen the methoxyl group, because from analogous cases (3) we could suppose, that its presence will facilitate the cyclisation of the acylamines (IX.). We have built up by action of phenacylbromide derivatives (II) on sodium salts of thiophenol derivatives (I.) the corresponding di- resp. tetramethoxy ketones (III.).

The transformation of these ketones (III.) into ketoximes (IV. or V.) was carried out essentially with the method of *K. v. Auwers* (4) i. e. the alcoholic solution or suspension of the ketone and hydroxylamine salt was treated with a solution of sodiumhydroxide. The resulting oximes appear all quite homogenous.

In order to study the stereochemistry of these ketoximes (IV. or V.) we undertook with them a *Beckmann* rearrangement. This was carried out in one case with benzene sulfonyl chloride and in all other cases with phosphorus pentachloride. All three oximes gave substituted phenylthioglycolic acid anilides (VI.).

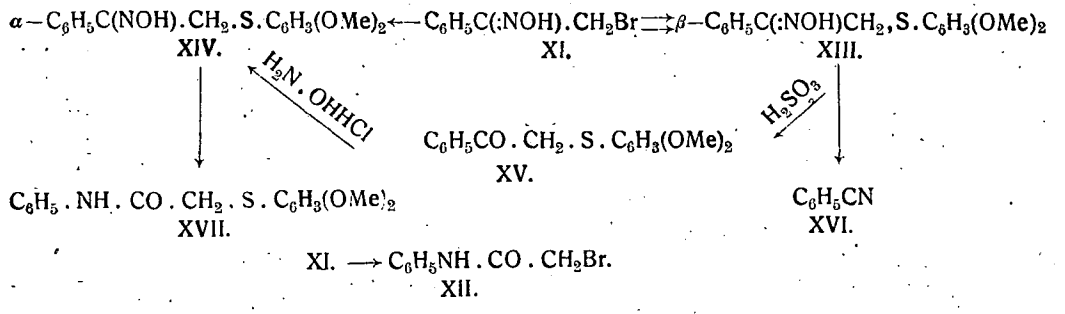
$$\underset{\text{IV.}}{\xrightarrow{PCl_5}} \underset{\text{VI.}}{R_2C_6H_3 . S . CH_2 . CO . NH . C_6H_3R'_2} \leftarrow \underset{\text{VII.}}{R_2C_6H_3 . S . CH_2 . COCl} + \underset{\text{VIII.}}{H_2N . C_6H_3R'_2}$$

If we suppose, that the *Meisenheimer* rule is valid in all three cases it follows, that they will have the *anti*-phenyl resp. *anti*-3,4-dimethoxyphenyl configuration (IV.).

The constitution of these anilides (VI.) is confirmed by their synthesis. They could be obtained by action of arylthioglycolic acid chlorides (VII.) on substituted aromatic amines (VIII.).

It is obvious that the methoxyl groups have no influence on the configuration of the oximes (IV.). We have established different isomerisation experiments in order to obtain the *syn*-aryl isomers (V.). All oximes (IV.) have shown a great stability. We have found that these oximes can be heated in a sealed tube 15—20° over their melting points, furthermore hydrochloric acid and alcalic solutions were found to be without any effect. Under energetic conditions the reaction led to thiophenols.

At last we could synthetise the other — labile — isomer oxime by the reaction of the lower melting i. e. (β)-ω-bromoacetophenone oxime (XI.) described by *Korten* and *Scholl* (5) with the sodium salt of dimethoxythiophenol (I., R = OMe). In the following we designate the higher melting oxime (α)-oxime, the lower melting isomer (β)-oxime. If we consider that the (β)-ω-bromoacetophenone oxime (XI.) of the named authors is formed in an acid solution in a good yield and by the *Beckmann* rearrangement they obtained from it bromoacetanilide (XII.) the compound would be according to the *Meisenheimer* rule the *anti*-phenil isomer. *Korten* and *Scholl* (5) describe this oxime on the basis of the earlier *Hantzsch* concept (2) of the *Beckmann* reaction as a *syn*-phenyl isomer. By this reaction we obtained a mixture of the two thioetheroximes (IV. and V.). The labile lower melting, (β)-oxime (XIII.) was present in a much greater amount. This (β)-oxime (XIII.) could be transformed into the stable (α)-isomer (XIV.) thermically and by the action of hydroxylamine hydrochloride.



The two oximes have different crystallform. We could suppose that they are not different compounds, but polymorph modifications of the same substance. But we could exclude this possibility because the mixture of the two oximes gave a meltingpoint depression. Moreover the oximes give by *Beckmann* rearrangement two different compounds. The (α)-oxime (XIV.) gave with benzene sulfonyl chloride in pyridine solution 3,4-dimethoxyphenylthioglycolic acid anilide (XVII.), the (β)-oxime (XIII.) under the same conditions suffered a *Beckmann* rearrangement of second order (6) and led to benzonitril (XVI.). Finally the same constitution of the both oximes could be supported by sulfurous acid hydrolysis. We obtained from the (β)-oxime (XIII.) phenyl-(3,4-dimethoxyphenylthiomethyl)ketone (XV.).

In the above reaction of (α)-Br-acetophenone oxime (XI.) the *Meisenheimer* rule predicts the formation of the (α)-oxime only. The experi-

mental facts presented above, led us to consider the following two alternatives:

(i.) If we suppose that the *Beckmann* rearrangement happens by *both* oximes (XI. and XIV.) according to the *Meisenheimer* rule, then the two oximes have *indentical* configuration. The formation of the (β)-thioetheroxime (XIII.) is possible only by a change of the configuration during the reaction. In this case the stable oxime should partly isomerise in to the labile one. We arrive to the same result if we apply Hantzsch's concept on the course of the reaction.

(ii.) Let us suppose that the *Beckmann* reaction of either the (β)-ω-Br-acetophenone oximes (XI.) or of the (α)-thioether oximes (XIV.) does not follow the *Meisenheimer* rule. In this case the configuration of the two oximes is *different*. Thus the (β)-ω-Br-acetophenone oxime (XI.) and the (β)-phenyl-(3,4-dimethoxyphenylthiomethyl)ketoxime (XIII.) would have identical configuration. In this case the reaction would lead to the labile oxime (XIII.) and this would partly isomerise to the stable one (XIV.).

From the two alternatives the latter one is more plausible, because here we would obtain from the labile configuration a stable one. There are some cases known (7) in wich the stable compound is transformed into the labile one, and these might be cited in favour of the first alternative.

The question of which of the two alternatives is right remains unanswered. Therefore it is not possible to assigne the correct configuration to the two oximes. This will be part of a following work.

Experimental.

3,4-dimethoxyphenyl-(phenylthiomethyl) ketone. (III, R = H, R' = OMe). A suspension of ω-Br-acetoveratrone (8) (13 g) in alcohol (65 ccm) was mixed gradually — under chilling — with a concd. aqueous solution of thiophenole (6 ccm) and potassium hydroxide (5,6 g). After a few hours the compound was precipitated by aqueous dilution as an oil, which crystallises after standing. Yield 72%. It was recrystallised from aqueous methanol. Colorless radial needles. M. p. 75—76°.

Anal: Calcd. for $C_{16}H_{16}O_3S$: C, 66,62; H, 5,59.
Found: C, 66,39; H, 5,38.

Phenyl-(3,4 dimethoxyphenylthiomethyl)ketone. (III, R = OMe, R' = H). A solution of 3,4 dimethoxythiophenole (9) (10,2 g) in alcohol (100 ccm) was neutralised with alcoholic potassium hydroxide. (Phenolphtaleine). After gradually mixing this solution with a suspension of phenacylbromide (10 g) in alcohol (50 ccm) it was refluxed for 15 minutes. We precipitated the compound by aqueous dilution. Yield 79%. It was recrystallised from alcohol. Long colorless prisms. Mp. 72°.

Anal. Calcd. for $C_{16}H_{16}O_3S$: C, 66,62; H, 5,59. Found: C, 66,42; H, 5,86.

3,4 dimethoxyphenyl-(3,4-dimethoxyphenylthiomethyl)ketone. (III, R = R' = = OMe). To a solution of sodium methoxyde, — prepared from sodium (0,58 g) and abs. alcohol (30 ccm) — was added dimethoxythiophenole (9) (4,25 g). After 10 minutes we precipitated the mercaptide as a white powder, filtered and washed with ether. It was quickly dried *in vacuo* at room temperature. The mercaptide was gradually added to a solution of ω-Br-acetoveratrone (8) (6,5 g) in abs. alcohol (45 ccm) under chilling with ice. It was refluxed for 10 minutes. The ketone was precipitated by dilution with water. Yield 82%. It was recrystallised from alcohol. Colorless needles M. p. 139°.

Anal. Calcd. for $C_{18}H_{20}O_5S$: C, 62,05; H, 5,79. Found: C, 62,24; H, 5,98.

Anti-aryl-(arylthiomethyl)ketoximes (IV.). The oximes of the three ketones (III.) we have prepared as follows: A suspension of the ketone (0,01 mole) and powdered hydroxylamine hydrochloride (0,02 mole) in alcohol (see table I.) was treated gradually with a concd. aqueous solution of sodium hydroxide (0,02 mole). The mixture was allowed to stand at room temperature and it was mechanically shaken during intervals. (See table I.) The solution was then neutralised with dilute hydrochloric acid. We obtained the oximes by gradual adition of water. The compounds were recrystallised from aqueous alcohol.

Anal. Calcd. for $C_{16}H_{17}O_3NS$ (IV, R = H, R' = OMe): C, 63,32; H, 5,65. Found: C, 63,17; H, 5,55. Calcd. for $C_{16}H_{17}O_3NS$ (IV, R = OMe, R' = H): C, 63,32; H, 5,65. Found: C, 63,10; H, 5,41. Calcd. for $C_{18}H_{21}O_5NS$ (IV, R = = R' = OMe): C, 59,49; H, 5,83. Found: C, 59,25; H, 5,66.

Table I.

IV.	Standing. Days.	Shaking. Hours.	Alkohol ccm.	Yield.	M. p.	
R=H, R'=OMe.	1	5	50	72%	98°	Colorles needles.
R=OMe, R'=H.	5	12	50	88%	112°	Colorles prisms.
R=R'=OMe.	4	20	60	68%	114°	Colorles needles.

The *Beckmann rearrangement* of the three oximes (IV.) *with* PCl_5 was carried out as follows: The oxime (see table II.) was dissolved in ether (table II.) and under chilling with ice was treated in several portions, under shaking, with finely powdered PCl_5 (table II.). After standing at room temperature (table II.), the ethereal solution was decanted from the dark gums into ice. The ethereal layer was washed with water and dried with sodium sulfate. Evaporation of the solvent left the crude amide (VI.) back. These could be purified by recrystallisation (table II.). All three compounds yield colourless needles.

Table II.

VI.	Oxime IV.	g	PCl_5 g	Ether ccm	Standing. Hours.	Yield.	Recryst.	M. p.
R=H, R'=OMe.	R=H, R'=OMe.	2	3,5	50	3	60%	Aqu. MeOH	104°
R=OMe, R'=H.	R=OMe, R'=H	1,7	2,2	50	1/2	70%	Aqu. MeOH	101°
R=R'=OMe.	R=R'=OMe.	1	2	200	1/2	55%	C_6H_6	146°

These amides gave no m. p. depression with those obtained by acylation of amines.

Anal. Calcd. for $C_{16}H_{17}O_3NS$ (VI, R = H, R' = OMe): C, 63,32; H, 5,65, Found: C, 63,39; H, 5,83.

Beckmann rearrangement with benzene sulfonyl chloride. To a solution of the oxime (IV, R = OMe, R' = H) (0,9 g.) in dry pyridine (8 ccm) benzene sulfonyl chloride (0,5 g) was added dropwise. After standing at room temperature for five hours, the solution was poured into dilute sulfuric acid. The mixture was extracted with ether. The ethereal layer was washed with

water and dried with sodium sulfate. Evaporation of the solvent left the crude amide (VI, R = OMe, R' = H) back, which was — after drying over sulfuric acid *in vacuo* — recrystallised from aqueous methanol. Yield 44%. The compound is identical with the with PCl_5 obtained amide.

Phenylthioglycolic acid 3,4-dimethoxyanilide (VI. R = H, R' = OMe). To 4-aminoveratrole (9) (1.6 g) phenylthioglycolic acid chloride (10) (1,9 g) was added dropwise. It developed heat. It was heated slowly during one hour at 120°. After standing at room temperature for twelve hours the mass was dissolved in hot benzene and filtered. From this solution the crude acylamine crystallises on cooling. It was treated with diluted alkali, diluted hydrochloric acid and water. Yield 74%. The compound was recrystallised from benzene. M. p. 104°.

3,4 dimethoxyphenylthioglycolic acid chloride (VII. R = OMe). Dimethoxyphenylthioglycolic acid (11) (7,5 g) was treated with PCl_3. (1,6 g) at 85—90° for one hour. The mixture melts with the formation of hydrochloric acid. After standing a few hours at room temperature the chloride was extracted with abs. ether. After filtration the solvent was evaporated *in vacuo*. The residue is a yellowish viscous oil, which could not be distilled without decomposition. Yield 86%.

3,4-dimethoxyphenylthiomethylglycolic acid anilide (VI. R = OMe, R' = H). A mixture of acidchloride (VII, R = OMe) (2 g) and aniline (4 g) was slowly heated to boiling. It was refluxed for 15 minutes. The cold mixture was treated with dilute alkali and extracted with ether. By treating the ethereal layer with hydrochloric acid crystalls appeared, which were dissolved by the addition of chloroform. The clear solution was washed with water, dried with calcium chloride and evaporated *in vacuo*. The resulting crystalls were recrystallised from aqueous methanol. Yield 75%. M. p. 101°.

Anal. Calcd. for $C_{16}H_{17}O_3NS$: C, 63,32; H, 5,65. Found: C, 62,97; H, 5,74.

3,4-dimethoxyphenylthioglycolic acid 3,4-dimethoxyanilide (VI, R = R' = = OMe). To a solution of 4-aminoveratrole (9) (0,9 g) in dry pyridine (5 ccm) was gradually added 3,4-dimethoxyphenylthiomethylglycolic acid chloride (10) (VII. R = OMe) (1,5 g). After standing for one day at room temperature the solution was treated with dilute hydrochloric acid and water. It was dried with sodium sulfate and evaporated *in vacuo*. The residue oil was recrystallysed with benzene. M. p. 146°.

Anal. Calcd. for $C_{18}H_{21}O_5NS$: C, 59,49; H, 5,83. Found: 59,37; H, 5,70.

(β)-phenyl-(3,4-dimethoxyphenylthiomethyl)ketoxime (XIII.). a) *Preparation.* A solution of mercaptide prepared from sodium and 3,4-dimethoxythiophenole (9) (0,85 g) in abs. alcohol (10 ccm) was added gradually to a solution of (β)-Br-acetophenone oxime (5) (1,1 g) in abs. alcohol (5 ccm). After standing for three hours at room temperature the mixture was gradually diluted with water. The (β)-oxime appears in long colorless needles. After a few hours they have been filtered. Yield 47%. The crystalls were several times dissolved in alcohol, reprecipitated with water, m. p. 111°.

Anal. Calcd. for $C_{16}H_{17}O_3NS$: C, 63,32; H, 5,65; N, 4,62. Found: C, 62,93; H, 5,59; N, 4,97.

By the further addition of water to the mother liquor of the (β)-oxime we obtained prisms of the (α)-oxime (XIV.). Yield 28%.

It occur sometimes that cyrstalls of the (β)-oxime appear before the addition of water. In that case we must add slowly about two volumes of water and filter. We could always easily separate the two oximes in this way.

b) *Isomerisation.* α). 0,3 g of (β)-oxime (XIII.) was heated in a sealed tube for one and a half hours at 113—115°. After one day the yellow product was dissolved in alcohol and cautiously precipitated with water. The crystalls (0,25 g) show under the microscope the characteristic prisms of the (α)-oxime (XIV.) and the long, thin needles of the unchanged (β)-oxime (XIII.). The product obtained has no sharp melting point when mixed with the (α)-oxime a m. p.-elevation was observed.

β) A mixture of (β)-oxime (XIII.) (0,5 g) and of hydroxylamine hydrochloride (0,1 g) in aqueous alcohol (50%) (10 ccm) was refluxed for four hours. After cooling a colorless oil separates which crystallises on rubbing. The compound is identical with the (α)-oxime and gave no m. p.-depression with an authentic sample of ketoxime (IV, R = OMe, R' = H).

c) *Hydrolysis.* A solution of (β)-oxime (XIII.) (0,5 g) in cold saturated aqueous solution of sulfurous acid (200 ccm) was heated under shaking on steam bath for one hour and a half. A yellowish oil separated, which crystallises when seeded with the ketone (XV.). It was recrystallised from alcohol. Yield 0,36 g. The compound gave no m. p. depression with the ketone (III, R = H, R' = OMe).

d) *Beckmann rearrangement.* To a solution of the (β)-oxime (XIII.) (0,9 g) in dry pyridine (32 ccm) was added dropwise, under chilling with ice, benzene sulfonyl chloride (3,4 g). After standing at room temperature for four hours the solution was poured into an excess of sulfuric acid. A dark oil separated, which was extracted with water, dried with sodium sulfate and evaporated *in vacuo*. The resulting darkbrown viscous bitter-almond smelling oil was treated with kerosene. The residue was a dark gum and the solution after evaporation of the solvent left back a pale-yellow oil (0,7 g). It proved to be benzonitril, as it yielded benzoic acid by boiling with an excess of methanolic sodium hydroxide (10%) for one day.

We came to the same result if the (β)-oxime was treated with phosphorus pentachloride in ether.

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