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THIOPEGAN DERIVATIVES—XXI

A MECHANISM FOR THE FORMATION OF 9:10 AND 10:11 THIOPEGAN DERIVATIVES

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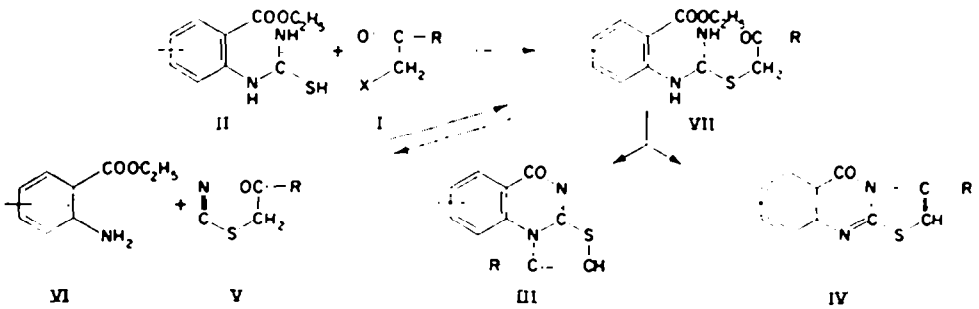
Abstract—Reactions between α-haloketones and *o*-carbethoxy phenyl thiourea have been discussed; a mechanism for the observed exclusive formation of 9:10-thiopega-2:10-diene-4-ones in the case of α-haloalkaryl ketones has been advanced and a number of intermediates isolated in case of chloro acetone.

NARANG *et al.* have shown that interaction of α-haloketone (I) with *o*-carbethoxy-phenylthiourea (II) in general leads to the formation of 9:10-thiopegan derivatives (III). The only exception observed was that of chloroacetone which in addition to yielding the corresponding 9:10-thiopegan derivatives (III, R = CH_3) gave appreciable amounts of the 10:11-isomer (IV, R = CH_3).[2,3] It was further observed that if this reaction between the haloketones and the thiourea was stopped after a few minutes heating in ethanol, α-thiocyano ketone (V) corresponding to the α-haloketone (I) employed, could be isolated from the reaction mixture while the thiourea (II) was found to have retrograded to anthranilic ester (VI).[1] The authors thus postulated that the first reaction product can be VII which could cyclize to the thiopegan derivatives both with linear (10:11; IV) or angular (9:10; III) annulation. The thiourea adduct (VII) could also account for the observed formation of the α-thiocyanoketones and anthranilic ester as shown; the retrogression being:



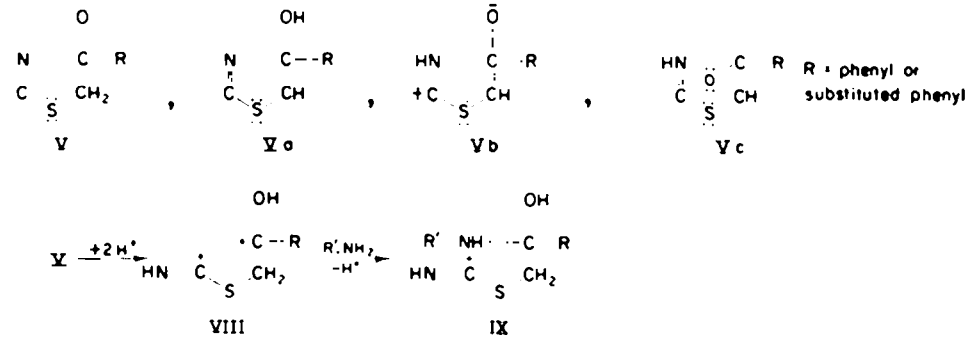
facilitated by the presence of COOH or $COOC_2H_5$ groups.

The above mechanism was further elaborated by these authors[4,5] in view of a

[1] D. S. Bariana, M. S. Dhatt, H. S. Sachdev and K. S. Narang, *J. Ind. Chem. Soc.* **32**, 848 (1954).
[2] G. M. Sharma, I. S. Gupta and K. S. Narang, *J. Ind. Chem. Soc.* **32**, 959 (1955).
[3] H. S. Sachdev and K. S. Narang, *J. Ind. Chem. Soc.* **32**, 427 (1955).
[4] S. Gurjit, H. S. Sachdev and K. S. Narang, *J. Sci. Ind. Res.* **16B**, 359 (1957).
[5] H. S. Sachdev, K. S. Dhami and K. S. Narang, *J. Sci. Ind. Res.* **19C**, 11 (1960).

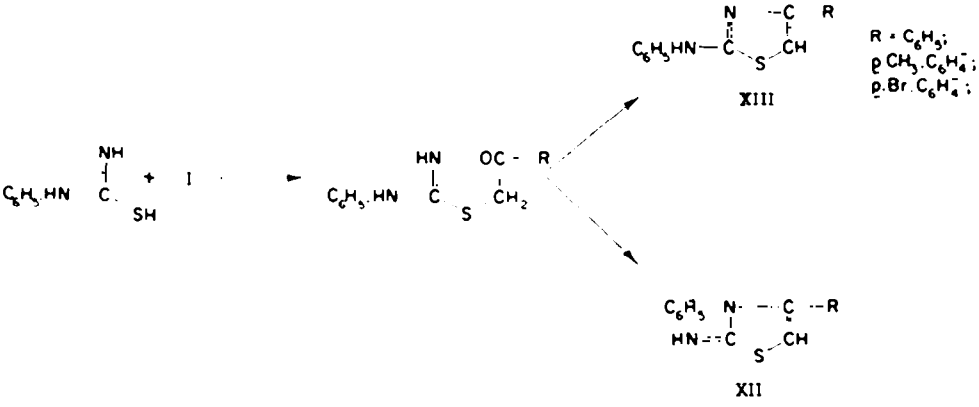
subsequent finding that the same 9:10-thiopegan derivatives (III) could be obtained in the same facile manner by the interaction of α-thiocyanoalkaryl ketones (corresponding to the α-haloalkarylketones previously used) and anthranilic acid or ester in presence of acid catalysts. This mechanism, however, again visualized the thiourea adduct VII as being the precursor for the formation of 9:10-thiopegans.[4]

It is considered likely that α-thiocyanoalkarylketones which can exist in various tautomeric forms V, Va, Vb, Vc could react with an amino group in two ways depending upon whether the C of the carbonyl group or that of the thiocyano group is first attacked. The former course shall give rise to an intermediate (IX) which will exclusively lead to the formation of 9:10-thiopegans (*vide infra*) while the latter would give

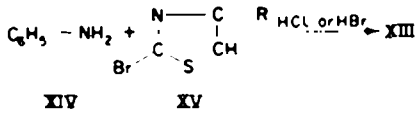


rise to the thiourea adduct (VII) which now could afford both varieties of the thiopegans.

Therefore, to further understand the mechanism of thiopegan formation it was considered desirable to study the reaction between an α-haloketone and a substituted thiourea where the factors leading to the retrogression of the intermediate adduct were precluded. Consequently a few condensations between phenylthiourea and some α-haloalkarylketones have been carried out. The intermediate adduct (X) which could again be considered capable of giving two types of products XII and XIII would not be expected to retrograde because of the absence of carboxy or carbethoxy groups on its N-phenyl part. In these reactions, only one type of product could be isolated for which 2-anilino-4-arylthiazole structure (XIII) has been confirmed through an



unambiguous synthetic route involving the interaction of aniline (XIV) with a requisite 2-bromo-4-arylthiazoles (XV) as shown:

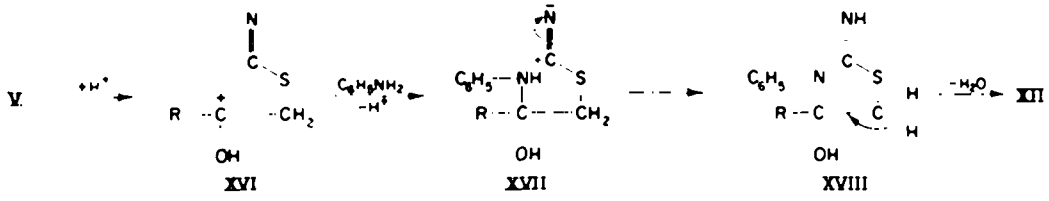


XIV XV

Excellent yields of the thiazole derivatives (XIII) were realized by carrying out these condensations in phenol solution in presence of catalytic amounts of hydrobromic acid or hydrochloric acid in contrast to the basic catalysts employed by some previous workers who recorded lower yields.[6-8]

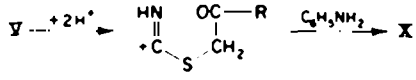
However, when α-thiocyanoalkarylketones corresponding to the α-haloalkarylketones, employed in the above set of condensations, were reacted with aniline in presence of mineral acid catalyst, a different series of thiazole derivatives were obtained to which the 2-amino-thiazoline-4-structure (XII) can be assigned with a reasonable certainty. The mechanistic trend of the reaction can be depicted as under:

An alternative reaction course visualizing an initial nucleophilic attack at the C



XVI XVII XVIII

of the thiocyano group as shown below, is discounted as that would give rise to the thiourea intermediate (X) which should furnish XII as well as XIII but only one product (XIII) has been isolated from the cyclization of the thiourea (X).

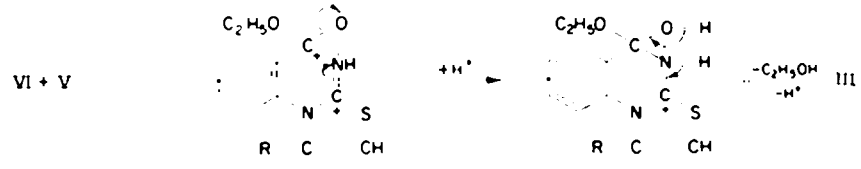


In the above reaction if the addition of one H^+ to V could be assumed to take place in the initial stage, it should preferably add to C=O with the formation of XVI and if addition of 2H could be presumed leading to the formation of VIII it is evident that the electrophilic activity on $-\underset{\underset{OH}{|}}{C^+}-$ is stronger than on $-S-C^{\cdot}=NH$; presence of sulphur with unshared electrons possibly reduces the electrophilicity of carbon in $S-C^{\cdot}=NH$.

In none of these reactions the formation of two products could be detected. The 2-imino-thiazolines-4 (XII) and 1-anilino-4-arylthiazoles (XIII) could be regarded as prototypes of 9:10-(III) and 10:11-(IV) thiopegans respectively. The foregoing observations suggest that the reaction between *o*-carbethoxyphenylthiourea (II) and α-haloalkarylketones (I) is equivalent to that between an α-thiocyanoalkarylketone and anthranilic ester and apparently in the former case the intermediate adduct (VII) undergoes complete retrogression to the products of the latter reaction, which then

[6] I. A. Kaye and C. L. Parris, *J. Amer. Chem. Soc.* **74**, 6921 (1952).
[7] J. N. Ashley and J. F. Grove, *J. Amer. Chem. Soc.* **67**, 768 (1945).
[8] Elderfield, *Heterocyclic Compounds* Vol. V, p. 610. John Wiley, New York (1957).

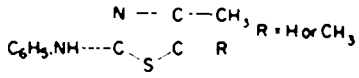
interact in a manner similar to that of the reaction between aniline and α-thiocyanoketones. An imino-thiazoline-4-derivative (XIX) would be expected to be the precursor of the 9:10-thiopegans (III) as indicated (first few steps similar to these in structures (XVI XVIII) have been omitted).



XIX

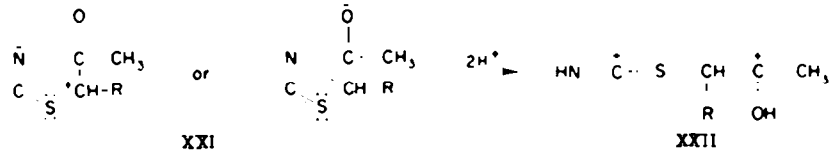
From the foregoing it could be concluded that in the formation of linear thiopegans, the precursor would essentially be thiourea derivatives of the type X while the angular thiopegans are formed from the intermediates of the type XVII.

There seems to be a divergence from the above generalization in the case of aliphatic α-thiocyanoketones. Both the thiocyanoacetone and α-thiocyanoethylmethyl-ketone exclusively give 2-anilinothiazoles (XX) and not the corresponding 2-iminothiazolines, when reacted with aniline in the presence or absence of protonic reagents, the reaction is, however, slow in the absence of protonic catalysts. The identity of 2-anilino-4-methylthiazole and 2-anilino-4:5-dimethylthiazole[10] has been confirmed through their unambiguous syntheses involving the reaction between aniline and corresponding 2-chlorothiazoles. Since the thiocyanoacetone and α-



XX

thiocyanoethylmethyl-ketone give only 2-anilinothiazoles, it indicates that aliphatic α-thiocyanoketones can, partly acquire structure XXI in addition to those already postulated for the α-thiocyanoacetophenones.

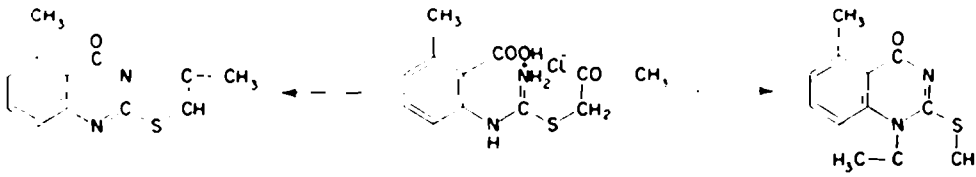


XXI XXII

It is, evident that in the structure XXII which XXI acquires by taking two H^+, it is the —S ·C· NH, which reacts with the amino group while the C of the carbonyl is lacking the requisite + ve charge to undergo such reaction.

Again when, reviving the reactions between thiocyanoacetone and various anthranilic acids, it was possible in the case of 6-methylanthranilic acid, to isolate and purify the intermediate (XXIII), which furnishes 9:10-thiopegan (XXIV) on dry heating and 10:11-thiopegan (XXV) on refluxing in alcohol.

[9] W. Traube, *Ber. Dtsch. Chem. bes.* **32**, 3156 (1899).
[10] R. A. Mathes, *J. Amer. Chem. Soc.* **74**, 1719 (1952).



XXV XXIII XXIV

The intermediate (XXIII) is assigned the thioureanium salt structure on the basis of its elemental analysis and its flexibility to cyclize in either fashion under two different sets of conditions.

Further work on various aspects of the mechanism of the reactions involved and the peculiar behaviour of the aliphatic and aromatic thiocyano ketone is in hand.

EXPERIMENTAL

Condensation of phenyl thiourea with ω-bromoacetophenones

Formation of 2-anilino-4-aryl thiazoles (XIII). Equivalent quantities of the requisite ω-bromoacetophenone and phenylthiourea, dissolved in minimum amount of absolute ethanol were refluxed for 4–5 hr on a water bath with separation of a white solid. The solvent was removed under red. press. and the residue basified with sodium hydroxide, washed with water and crystallized from a suitable solvent (Table 1).

Interaction of 2-bromo-4-arylthiazoles with aniline hydrobromide

Direct synthesis of 2-anilino-4-aryl thiazoles (XIII). 2-Bromo-4-arylthiazoles were obtained from the corresponding α-thiocyanoketones by treatment with dry hydrobromic acid gas.[11,12]

Equivalent amounts of the requisite 2-bromo-4-arylthiazoles and aniline hydrobromide were taken in phenol (2 ml per gramme of the reactant) and heated in an oil bath at 130–140° for about 6–7 hr. After this the reaction mixture was cooled and basified with sodium hydroxide to remove phenol and washed with water. The solid product was crystallized from a suitable solvent (Table 1). The identity of these products was confirmed by mixed m.p. determination with the corresponding products obtained above.

Interaction of ω-thiocyanoacetophenones with aniline hydrobromide

Synthesis of 2-imino-3-phenyl-4-substituted phenylthiazoles (XII). Equimolecular amounts of the requisite ω-thiocyanoacetophenone and aniline hydrobromide were dissolved in a minimum amount of dry ethanol and the mixture heated under reflux for 5–6 hr with separation of a white solid. The solvent was removed by distillation on a water bath and the residue basified with sodium hydroxide, washed with water and crystallized from suitable solvent (Table 2).

In the case of 2-imino-3,4-diphenyl- and 2-imino-3-phenyl-4-bromophenyl-thiazoline-4, their hydrobromides were also isolated which were analysed after crystallization from glacial acetic acid (Table II).

R = H (XX). A solution of aniline hydrochloride (1·3 g; 1·0 mole) in absolute alcohol (15 ml) was added to thiocyanoacetone (1·2 g; 1·0 mole) taken in the same solvent. After keeping the mixture at room temp. for 20 hr it was basified with sodium hydroxide solution. The product was crystallized from ethanol, m.p. 117°; yield 0·8 g (42·1%) and confirmed as 2-anilino 4-methyl-thiazole.[9]

R = CH_3 (XX). 2-Chloro-4:5-dimethyl thiazole[13] (1·5 g; 1·0 mole) was mixed with aniline hydrochloride (1·3 g; 1 mole) and phenol (7 ml). The mixture was heated at 130–140° for 2 hr, cooled, basified with 2% sodium hydroxide and the residual solid crystallized from dil. ethanol, m.p. 105°, yield 1·5 g. It was identical with the product obtained by Mathes[10] by the interaction of α-thiocyanoethylmethylketone and aniline hydrochloride.

[11] D. S. Bariana, H. S. Sachdev and K. S. Narang, *J. Ind. Chem. Soc.* **32**, 427 (1955).
[12] N. K. Ralhan, K. Gurmit, H. S. Sachdev and K. S. Narang, In press.
[13] K. Ganpathi and A. Venkataraman, *Proc. Ind. Acad. Sci.* **32**, 374 (1945).
[14] H. S. Sachdev, N. K. Ralhan, M. S. Atwal, H. S. Garg and K. S. Narang, *J. Sci. Ind. Res.* **19B**, 217 (1960).

TABLE 1. 2-ANILINO-4-ARYL THIAZOLES (XIII)*

S. No.	Reactants	Product	Solvent of crystallization	Yield %	m.p. and mixed m.p.	M.F.	Analysis Found %	Analysis Required %
1a	Phenylthiourea and ω-bromoacetophenone	2-anilino-4-phenylthiazole	pet ether (80°–100°)	70	136°	$C_{15}H_{12}N_2S$	N, 11·6	N, 11·11
1b	Aniline hydrochlofide and 2-bromo-4-phenylthiazole	2-anilino-4-phenylthiazole	pet ether (80°–100°)	60	136°			
2a	Phenyl thiourea and ω-bromo-p-methylacetophenone	2-anilino-4-(p-tolyl)thiazole	pet ether (80°–100°)	72	92–100°	$C_{16}H_{14}N_2S$	N, 10·10	N, 10·52
2b	Aniline hydrobromide and 2-bromo-4-(p-tolyl)thiazole	2-anilino-4-(p-tolyl)thiazole	pet ether (80°–100°)	67	92–100°			
3a	Phenylthiourea and ω-p-dibromoacetophenone	2-anilino-4-(p-bromophenyl)thiazole	pet ether (80°–100°)	65	145°	$C_{15}H_{10}N_2SBr$	C, 54·50 H, 3·33 N, 8·5	C, 43·38 H, 3·32 N, 8·45
3b	Aniline hydrobromide and 2-bromo-4-(p-bromophenyl)thiazole	2-anilino-4-(p-bromophenyl)thiazole	pet ether (80°–100°)	66	145°			

* Note: Table 1 hydrobromides of S. No. 1, 2 and 3 have m.p. 185°, 209° and 218° respectively and crystallize from g. acetic acid.

TABLE 2. 2-IMINO-3-PHENYL-4-SUBSTITUTED PHENYL THIAZOLINE-4 (XII)

S. No.	Reactants	Product	Solvent of crystallization	Yield %	m.p. and mixed m.p.	M.F.	Analysis Found %	Analysis Required %
1.	Aniline hydrobromide and ω-thiocyanoacetophenone	2-amino-3:4-diphenyl-thiazoline-4 (hydro-bromide	glacial acetic acid	71	300°	$C_{15}H_{13}N_2SBr$	N, 7·9	N, 8·4
		base)	pet-ether (80–100°)	84	84°	$C_{15}H_{12}N_2S$	C, 71·23 H, 5·05 N, 10·77	C, 71·42 H, 4·78 N, 11·11
2.	Aniline hydrobromide ω-thiocyano p-methyl-acetophenone	2-imino-3-phenyl-4-(p-tolyl)thiazoline-4 (hydrobromide	glacial acetic acid	61	309°			
		base)	pet-ether (80–100°)	93		$C_{16}H_{14}N_2S$	N, 10·29	N, 10·53
3.	Aniline hydrobromide ω-thiocyano-p-bromo-phenylacetophenone	2-imino-3-phenyl-4-2-bromophenyl-thiazolin-4 (hydro-bromide	glacial acetic acid	84	377°	$C_{15}H_{12}N_2SBr$	Br, 39·07	Br, 38·83
		base)	pet-ether (80–100°)		122°			

(b) A mixture of α-thiocyanoethylmethylketone (1·3 g) and aniline (0·9 g) in absolute ethanol (25 ml) after refluxing for 8 hr furnished 0·8 g of XX (R = CH_3).

Isolation of XXIII. Thiocyanoacetone (0·57 g; 1·0 mole) taken in absolute ethanol (5 ml) was added to a solution of 6-methylanthranilic acid hydrochloride (0·9 g, 1·0 mole) in the same solvent (15 ml). In about 10 min at room temp. fine needles separated. The product was collected and repeatedly washed with absolute ethanol, yield 0·75 g. This product first melts at 187°, solidifies and again melts at 247°. It could not be recrystallized and a sample prepared from very pure raw materials was analysed. (Found: C, 49·46; H, 4·45; N, 9·25; S, 11·0; Cl, 11·74 $C_{12}H_{11}O_2N_2SCl$ requires: C, 49·60; H, 4·96; N, 9·26; S, 10·6; Cl, 11·73%).

XXV. A mixture of 2-chloro-4-methyl thiazole (0·67 g, 1·0 mole) and 6-methylanthanilic acid (0·75 g; 1·0 mole) in phenol (5 ml) was heated in an oil bath, the temperature of which was raised to 180° during half an hour. It was further heated for 2 hr cooled and basified with sodium hydroxide solution. The solid collected, washed free of alkali and crystallized from ethanol as white needles m.p. 225°, yield 0·45 g (41%).

Formation of XXV *from* XXIII. The intermediate XXVII (R = H, R_1 = CH_3) on refluxing in alcohol for about 6 hr and subsequent removal of the solvent furnish a compound, m.p. 225° which is identical with the product obtained above.

Formation of XXV *from* XXIII. The intermediate was heated in an oil bath at 180–190° for about 2 hr and then crystallized from ethanol as white needles, m.p. 247. (Found: S, 13·76; N, 12·20; $C_{12}H_{10}N_2OS$ requires: S, 13·91; N, 12·20%).