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THIOPEGAN DERIVATIVES—XVI

SYNTHESIS OF 10:11-THIOPEGAN DERIVATIVES CONTAINING A SATURATED THIAZOLE MOIETY AND OF THEIR RELATED COMPOUNDS

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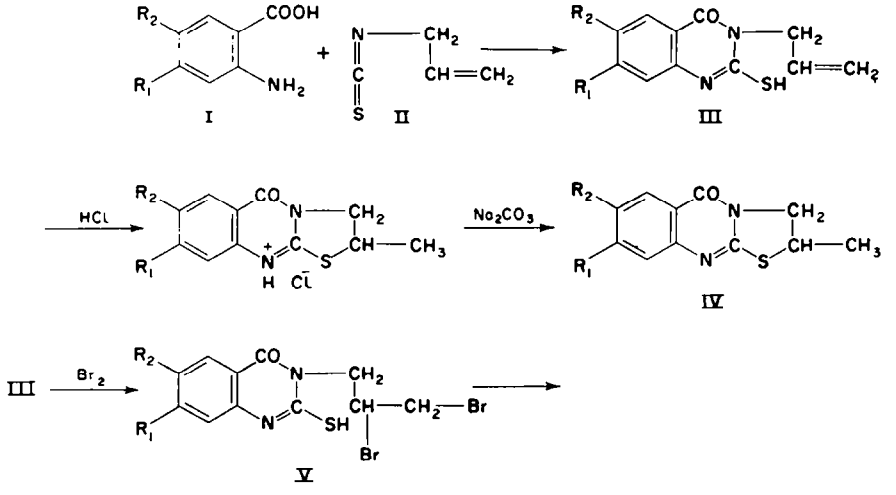
Abstract—2-Methyl-6-chloro-10:11-thiopegene-9:4-one, 2:7-dimethyl-10:11-thiopegene-9:4-one and the corresponding methylene bases have been synthesized. These methylene thiopegans furnish corresponding isomeric 2-methyl derivatives on acid treatment. 2-Bromomethyl-7-methyl-10:11-thiopega-2:9-diene-4-one has been condensed with piperidine and diethylamine to incorporate the therapeutically important basic moiety in these compounds. New routes to the synthesis of various substituted 2-methyl-10:11-thiopegans and 2-bromomethyl-10:11-thiopega-2:9-diene-4-ones have been developed with a view to improve their yields.

THIS paperconstitutes an extension and continuation of the previous work.[1,2] 6-Chloro and 7-methyl thiopegan derivatives containing saturated thiazole moiety and their related compounds have been synthesized with a view to study the effect of the chloro and methyl groups in these positions on the biological properties of the thiopegan ring system. The initiating reaction employs the condensation between allyl isothiocyanate and the requisite anthranilic acid followed by a series of operations, sequentially represented as under:



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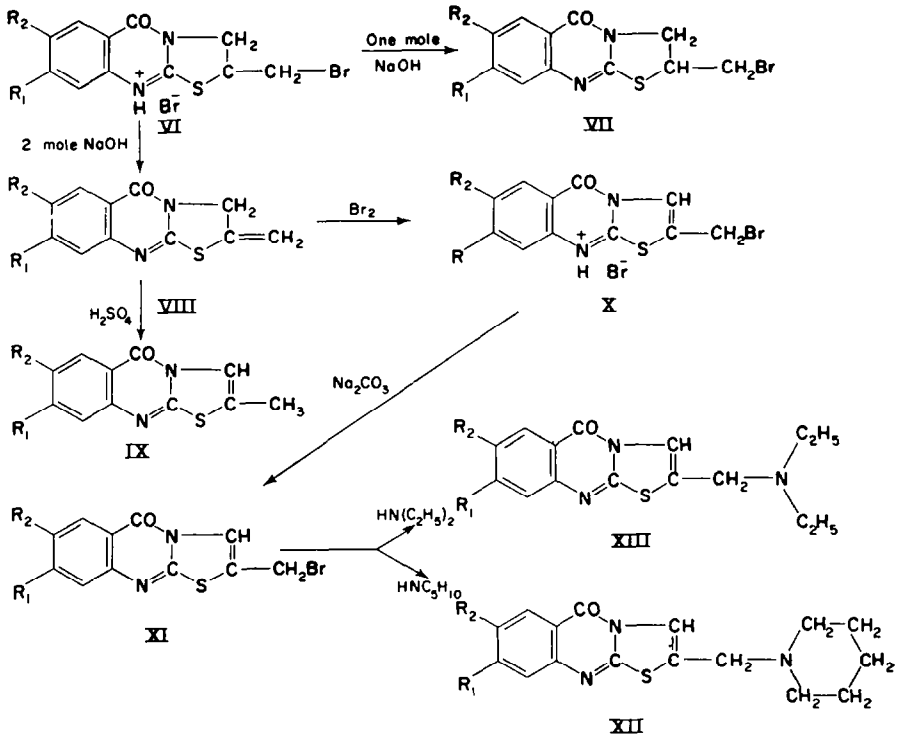
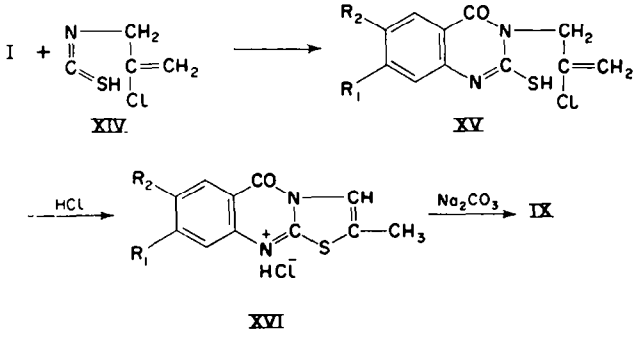
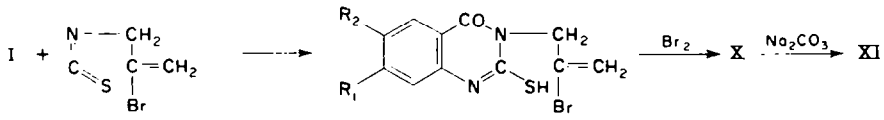
[1] K. S. Dhami *et al.*, *J. Sci. and Ind. Res.* **15**, 690 (1956).
[2] K. S. Dhami *et al.*, *J. Sci. and Ind. Res.* **16**, 311 (1957).



A simpler and superior pathway for the synthesis of 2-methyl-10:11-thiopegans (IX) was eventually developed which completes the synthetic scheme in fewer steps and better overall yield. The initiating reaction employs a new variant i.e. β-chloro-allyl-isothiocyanate (XIV) in the aforementioned condensation with anthranilic acid. The resulting 3-(2-chloroallyl)-4-keto-2-mercapto-tetrahydroquinazolines (XV) underwent smooth cyclization to 2-methyl-10:11-thiopegan derivatives (XVI) with dry hydrochloric acid gas in boiling acetic acid solution. The direct ring closure involving dehydrochlorination of the intermediate (XV) was not observed in the initiating stage which apparently is due to the restricted mobility of the chlorine atom. The following explain the reaction sequence:



2-Bromomethyl-10:11-thiopega-2:9-diene-4-one reported earlier (X, $R_1 = R_2 =$ H) has been prepared in 28 per cent yield which is better than that obtained by the previous route (14·1 per cent), by a variation involving the condensation between β-bromoallyl isothiocyanate (XVII) with anthranilic acid (I) followed by the bromination of the intermediate tetrahydro derivative (XVIII) and subsequent basification of the bromo-compound (X) thus obtained; the course of various reactions is represented as follows:



XVIII

EXPERIMENTAL PROCEDURE

5-Chloroanthranilic-Acid Series

3-Allyl-6-chloro-4-keto-2-thio-tetrahydroquinazoline (III, $R_1 = H$, $R_2 = Cl$)

A mixture of 5-chloroanthranilic acid (33 g) and allyl-isothiocyanate (17·5 g) (prepared by refluxing 22 g allyl bromide and 19·5 g potassium thiocyanate in 10 ml ethanol for 30 min) was heated in an oil bath. A vigorous reaction ensued at 100°C and the reaction mixture was kept at this temperature for about 30 minutes when it began to solidify. It was then maintained at 110–115°C for 6 hr when practically all of it became solid. Crystallization from acetic acid (norit) furnished light pale rectangular needles, m.p. 237°C (18 g, 40%). (Found: S, 12·7. $C_{11}H_9ON_2SCl$ requires: S, 12·67%).

6-Chloro-2-methyl-10:11-thiopegene-9,4-one (IV; R_1—H; R_2—Cl)

Dry hydrochloric acid was passed through are fluxing solution of (III, $R_1 = H$; $R_2 = Cl$) (5 g) in glacial acetic acid (75 ml) for 6 hr. The residue obtained after evaporating off the solvent, was basified with sodium carbonate solution. After collecting and washing with water, the product was crystallized from alcohol (norit) in fine colourless rectangular plates, m.p. 146° (3 g, 60%). (Found: S, 12·38; $C_{11}H_9ON_2SCl$ requires: S, 12·67%).

Hydrochloride of the above base was obtained by saturating a solution of the substance in ethylmethyl ketone with dry hydrochloric acid gas. The product was crystallized from ethylmethyl ketone in fine colourless needles, m.p. 228° (74%). (Found: N, 9·40. $C_{11}H_{10}ON_2SCl_2$ requires: N, 9·68%).

2-Bromomethyl-6-chloro-10-11-thiopegene·9:4-one-hydrobromide (VI; $R_1 = H$; $R_2 = Cl$) *and the free base* (VII; $R_1 = H$; $R_2 = Cl$)

Bromine (3 ml) dissolved in glacial acetic acid (15 ml) was slowly added to a solution of (III; $R_1 = H$; $R_2 = Cl$) (15 g) in acetic acid (170 ml) at 45°, accompanied with thorough shaking of the reaction mixture. A fine pale yellow solid separated out instantaneously on the addition of the bromine solution. The reaction mixture was cooled and the product was collected under suction which on crystallization from glacial acetic acid furnished colourless compound, m.p. 288°, yield being 17·5 g (73%) (Found: S, 7·57. $C_{11}H_9ON_2SBr_2Cl$ requires: S, 17·7%).

Sodium hydroxide (1%) (0·0044 mole, 17·6 ml) was added to a solution of the above hydrobromide (0·0044 mole, 1·8 g) in 60% ethanol (40 ml) at 40°. The low melting solid obtained on cooling, was crystallized from dilute ethanol (norit) in white rectangular plates (0·82 g), m.p. 144°. (Found: N, 8·45. · $C_{11}H_8ON_2SBrCl$ requires: N, 8·5%).

6-Chloro-2-methylene-10:11-thiopegene-9:4-one (VIII; $R_1 = R_2 = Cl$)

The hydrobromide (VI; $R_1 = H$; $R_2 = Cl$) (20 g, 0·06 mole) was dissolved in 70% ethanol (350 ml) and to this was added 2% sodium hydroxide solution (240 ml) (0·12 mole) at 45°. A white flocculent precipitate separated out instantaneously. This was collected after cooling and crystallized

from 60% ethanol as long rectangular needles, m.p. 193° (9 g, 70%). (Found: N, 11·2. $C_{11}H_7ON_2SCl$ requires: N, 11·15%).

Isomerization of (VIII, $R_1 = H$; $R_2 = Cl$) *to 6-chloro-2-methyl-10:11-thiopega-2:9-diene-4-one* (IX: $R_1 = H$; $R_2 = Cl$). Methylene base (1 g) was dissolved in concentrated sulphuric acid (25 ml) at 8°. After about 5 min it was poured into crushed ice when a white solid separated out. It was collected after 30 min and washed with water. Crystallization from dilute ethanol furnished colourless slender needles, m.p. 206° (0·67 g, 67%). (Found: N, 10·6. $C_{11}H_7ON_2SCl$ requires: N, 11·1%).

Bromination of (VIII; $R_1 = H$; $R_2 = Cl$)-*2-Bromomethyl-6-chloro-10:11-thiopega-2:9-diene-4-one hydrobromide* (X; $R_1 = H$; $R_2 = Cl$)

Bromine (1 ml) dissolved in glacial acetic acid (7 ml) was added during 25 min to a solution of the methylene base (5 g) in acetic acid (95 ml) at 55°. A fine orange coloured solid (6·5 g) obtained on keeping was crystallized from glacial acetic acid (norit) as colourless product which melted at 272° with decomposition. (Found: N, 7·05, S, 7·85. $C_{11}H_8ON_2SBr_2Cl$ requires: N, 7·0; S, 8·0%).

6-Chloro-2-piperidinemethyl-10:11-thiopega-2:9-diene-4-one (XII; $R_1 = H$; $R_2 = Cl$)

A solution of (XI; $R_1 = H$; $R_2 = Cl$) (0·002 mole, 0·75 g) in ethanol (45 ml) and piperidine (0·004 mole; 0·405 ml) was refluxed for 3 hr. The residue obtained after the distillation of the solvent was crystallized from ethanol as light pale needles, m.p. 193° (0·43 g, 44%). (Found: S, 9·55. $C_{16}H_{16}ON_3SCl$ requires: S, 9·6%).

2-Bromomethyl-6-chloro-10:11-thiopega-2:9-diene-4-one (XI; $R_1 = H$; $R_2 = Cl$)

The above hydrobromide (3 g) was thoroughly triturated with sodium carbonate solution. The pale yellow product was collected and washed with water. Crystallization from dilute ethanol furnished fine pale yellow needles (1·6 g, 66·3%) m.p. 202°. (Found: N, 8·16. $C_{11}H_6ON_2SBrCl$ requires: N, 8·5%).

6-Chloro-2-diethylaminomethyl-10:11-thiopega-2:9-diene-4-one (XIII, $R_1 = H$, $R_2 = Cl$)

A solution of the bromobase (XI; $R_1 = H$; $R_2 = Cl$) (1 g, 0·003 mole) in ethanol (60 ml) and diethylamine (0·006 mole, 0·61 ml) was refluxed for 4 hr. The solvent was distilled off and the residue crystallized from 90% ethanol which deposited (0·55 g, 46%) white rectangular needles, m.p. 136°. (Found: N, 13·0. $C_{16}H_{16}ON_3SCl$ requires: N, 13·04%).

4-Methyl Anthranilic Acid Series

The experimental conditions employed are almost the same as in the case of 5-chloroanthranilic acid series.

3-Allyl-4-keto-7-methyl-2-thio-tetrahydroquinazoline (III; $R_1 = CH_3$; $R_2 = H$)

Crystallized from glacial acetic acid in colourless rectangular plates m.p. 233° (44%). (Found: N, 11·91. $C_{12}H_{12}ON_2S$ requires: N, 12·06%).

2:7-Dimethyl-10:11-thiopegene-9,4-one (IV; $R_1 = CH_3$; $R_2 = H$)

Crystallized from dilute ethanol (norit) in fine colourless rectangular plates, m.p. 144° (50%). (Found: N, 11·9; S, 13·68. $C_{12}H_{12}ON_2S$ requires: N, 12·1; S, 13·9%).

Hydrochloride of the base was obtained in 90% yield from glacial acetic acid as a colourless product melting at 264°. (Found, N, 10·2, S, 11·8. $C_{12}H_{12}ON_2SCl$ requires: N, 10·4; S, 11·9%).

2-Bromomethyl-7-methyl-10:11-thiopegene-9:4-one-hydrobromide (VI; $R_1 = CH_3$; $R_2 = H$)

Crystallized from glacial acetic acid (norit) as a colourless product m.p. 320° (d) (55%). (Found: N, 6·96; Br, 38,75. $C_{12}H_{12}ON_2SBr_2$ requires: N, 7·14; Br, 40·0%)

2-Bromomethyl-7-methyl-10:11-thiopegene-9:4-one (VII; $R_1 = CH_3$; $R_2 = H$)

Crystallized from dilute ethanol (norit) in white needles, m.p. 125° (80%). (Found: Br, 25·85. $C_{12}H_{11}ON_2SBr$ requires: Br, 25·72%).

2-Methylene-7-methyl-10:11-thiopegene-9:4-one (VII; $R_1 = CH_3$; $R_2 = H$)

Crystallized from dilute ethanol (norit) in long rectangular plates m.p. 189° (70%). (Found: N, 12·0. S, 13·95; $C_{12}H_{10}ON_2S$ requires: N, 12·17; S, 13·91%).

2:7-Dimethyl-10:11-thiopegene-2:9-diene-4-one (IX; $R_1 = CH_3$; $R_2 = H$)

Crystallized from dilute ethanol in long slender needles m.p. 200° (75%) (Found: N, 12·1, S, 13·47. $C_{13}H_{11}ON_2S$ requires: N, 12·17; S, 13·9%).

Bromination of (VIII; $R_1 = CH_3$; $R_2 = H$); *2-bromomethyl-7-methyl-10:11-thiopega-2:9-diene-4-one hydrobromide* (X; $R_1 = CH_3$; $R_2 = H$)

Crystallization from glacial acetic acid furnished colourless solid melting at 311–312° (d) (73%). (Found: N, 6·94; Br, 40·8. $C_{13}H_{10}ON_2SBr_2Cl$ requires: N, 7·2; Br, 41·0%).

2-Bromomethyl-7-methyl-10:11-thiopega-2:9-diene-4-one (XI; $R_1 = CH_3$; $R_2 = H$)

Crystallized from ethanol in light yellow needles, m.p. 210° (83%). (Found: N, 8·57. $C_{12}H_9ON_2SBr$ requires: N, 9·0%).

2-Diethylaminomethyl-7-methyl-10:11-thiopega-2:9-diene-4-one (XIII; $R_1 = CH_3$; $R_2 = H$)

Crystallized from dilute ethanol (norit) in colourless needles, m.p. 125° (50%). (Found: N, 14·2, $C_{16}H_{19}ON_2S$ requires: N, 13·95%).

Synthesis of various 2-methyl-10:11-thiopega-2:9-diene-4-ones by the alternate route

The initial reaction between β-chloroallyl isothiocyanate and various anthranilic acids was carried out under conditions identical with those for allyl isothiocyanate.

3-(2′-Choroallyl)-2-mercapto-4-keto-tetrahydroquinazoline (XV, $R_1 = R_2 = H$)

Crystallized from ethanol in fine needles, m.p. 191° (27%). (Found: N, 11·1; Cl, 13·8 $C_{11}H_9ON_2SCl$ requires: N, 11·1; Cl, 14·1%).

2-Methyl-10:11-thiopega-2:9-diene-4-one (IX; $R_1 = R_2 = H$)

Crystallized from ethanol as a colourless compound m.p. 183° (25%). Mixed m.p. with (IX; $R_1 = R_2 = H$) as obtained by the isomerization of 2-methylene-10:11-thiopegene-9,4-one.[1] (XIII, $R_1 = R_2 = H$) gave no depression.

3-(2′-Chloroallyl)-2-mercapto-4-keto-6-methyl tetrahydroquinazoline (XV; $R_1 = H$; $R_2 = CH_3$)

Crystallization from glacial acetic acid furnished rectangular needles, m.p. 228° (32%). (Found: N, 10·8, Cl, 13·6. $C_{12}H_{11}ON_2SCl$ requires: N, 10·9; Cl, 13·7%).

2:6-Dimethyl-10:11-thiopega-2:9-diene-4-one (IX; $R_1 = H$; $R_2 = CH_3$)

Crystallized from dilute ethanol in fine colourless slender needles m.p. 168° (40%). This was identical with the compound obtained by the isomerization of 2-methylene-6-methyl-10:11-thiopegene-9,4-one[2] (VIII; $R_1 = H$; $R_1 = CH_3$) as confirmed through undepressed m.m.p.

6-Chloro-3-(2′-chloroallyl)-2-mercapto-4-keto-tetrahydroquinazoline (XV; $R_1 = H$; $R_2 = Cl$)

Crystallization from glacial acetic acid furnished sulphur yellow product m.p. 222° (27%). (Found: N, 9·7; Cl, 24·8. $C_{11}H_8ON_2SCl_2$ requires: N, 9·76; Cl, 25·5%).

6-Chloro-2-methyl-10:11-thiopega-2:9-diene-4-one (IX; $R_1 = H$; $R_2 = Cl$)

Crystallized from dilute ethanol (norit) in long rectangular needles m.p. 206° (69%). This was found to be identical with (IX; $R_1 = H$; $R_2 = Cl$) obtained earlier through undepressed mixture m.p.

3-(2′-Bromoallyl)-2-mercapto-4-keto-tetrahydroquinazoline (XVIII; $R_1 = R_2 = H$)

Crystallized from alcohol in colourless light yellow needles m.p. 198° (50%). (Found: S, 11·0; Br, 26·9. $C_{11}H_9ON_2SBr$ requires: S, 10·79; Br, 26·9%).

2-*Bromomethyl*-10:11-*thiopega*-2:9-*diene*-4-*one hydrobromide* (X; $R_1 = R_2 = H$)

Crystallized from glacial acetic acid as a colourless product m.p. 295° (84%). (Found: S, 8·61; Br, 42·8. $C_{11}H_8ON_2SBr_2$ requires: S, 8·0; Br, 42·5%).

2-*Bromomethyl*-10:11-*thiopega*-2:9-*diene*-4-*one* (X, $R_1 = R_2 = H$)

The above hydrobromide was triturated with sodium carbonate solution. The residue was crystallized from alcohol as colourless solid m.p. 210° (30%). Mixed m.p. determination proved its identity with 2-bromomethyl-10:11-thiopega-2:9-diene-4-one obtained earlier.[1]

3-Allyl-6-chloro-4-keto-2-thio-tetrahydroquinazoline, 2-methyl-6-chloro-10:11-thiopegene-9;4-one-hydrochloride, 2-Methylene-6-chloro-10:11-thiopegene-9;4-one and 2-methyl-6-chloro-10:11-thiopega-2:9-diene-4-one were found active against St. haemolyticus at a dilution of 1:1000, 1:5000, 1:1000 and 1:1000 respectively.

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