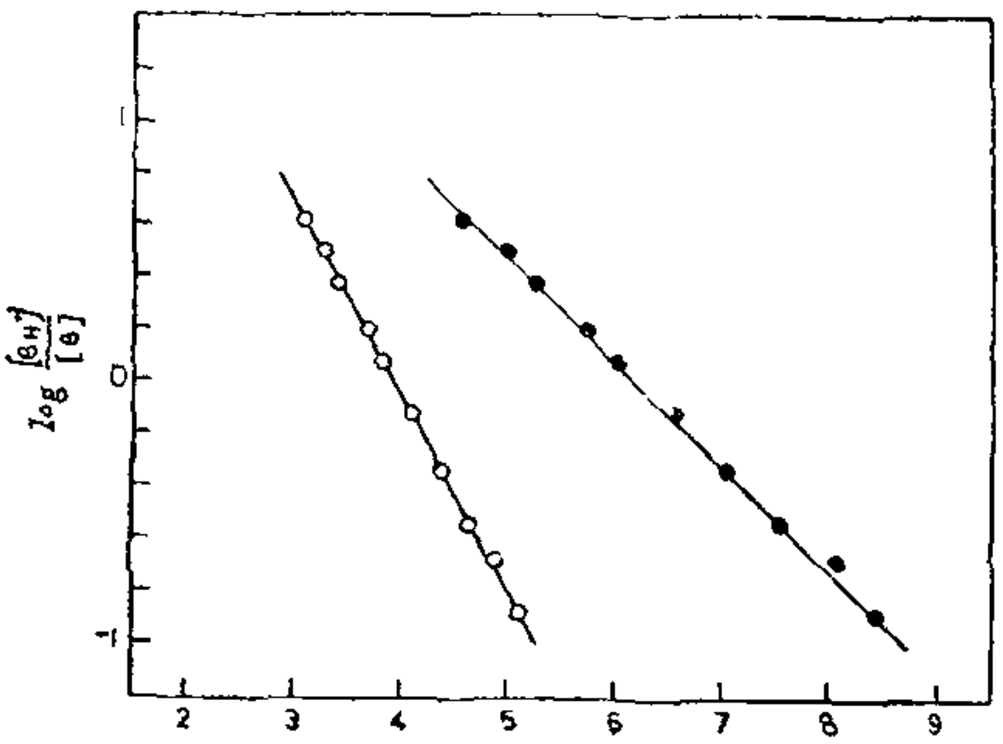

FIG. 2. Plot of log $[BH^+]/[B]$ *vs.* acidity of protonated 3,3-dimethyl-1-cyclobutene carboxylic acid.
O represent H_A and represent H_o.

3,3-dimethyl-1-cyclobutene carboxylic acid for comparison of acidities. The extra methyl groups at 3-position are unlikely to cause any changes in the conjugative ability of the double bond and, therefore, we have measured the acid strength of protonated 3,3-dimethyl-1-cyclobutene carboxylic acid which is quite stable in sulphuric acid solution.

The absorption maxima of IV*a* shifts from 254 to 214 nm, when the medium is altered from 95·32% sulphuric acid to water. The pKa value was found to be −4·10 and the acid IV seems to be stronger than the other protonated cyclic acids namely, cyclopentene, cyclohexene and cycloheptene carboxylic acids, whose pKa values are −4·05, −3·88 and −3·84 respectively. Other factors like solvation and the inductive effect of alkyl groups should have decreasing effect on the acid strength of the protonated species. Therefore, the increase in acidity in this system suggests that the conjugative effect of the double bond is less in the four-membered ring system, compared to other cyclic systems. The protonated form (IV) is destabilized with respect to the free base (IV*a*), thereby shifting the equilibrium towards right IV $\rightleftharpoons$ IV*a*. It appears, therefore, that the endo-double bond is preferred in the cyclobutene system and the acidity of the protonated cyclic *a*, *β*-unsaturated cyclic acids can be arranged in terms of their ring size as $4 > 5 > 6 \sim 7$.

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A NEW METHOD FOR THE TOTAL SYNTHESIS OF 1-OXO-3-THIA-10-PHENYL-9-METHYL-9-AZA-1,2,3,4,9,10-HEXAHYDROPHENANTHRENE

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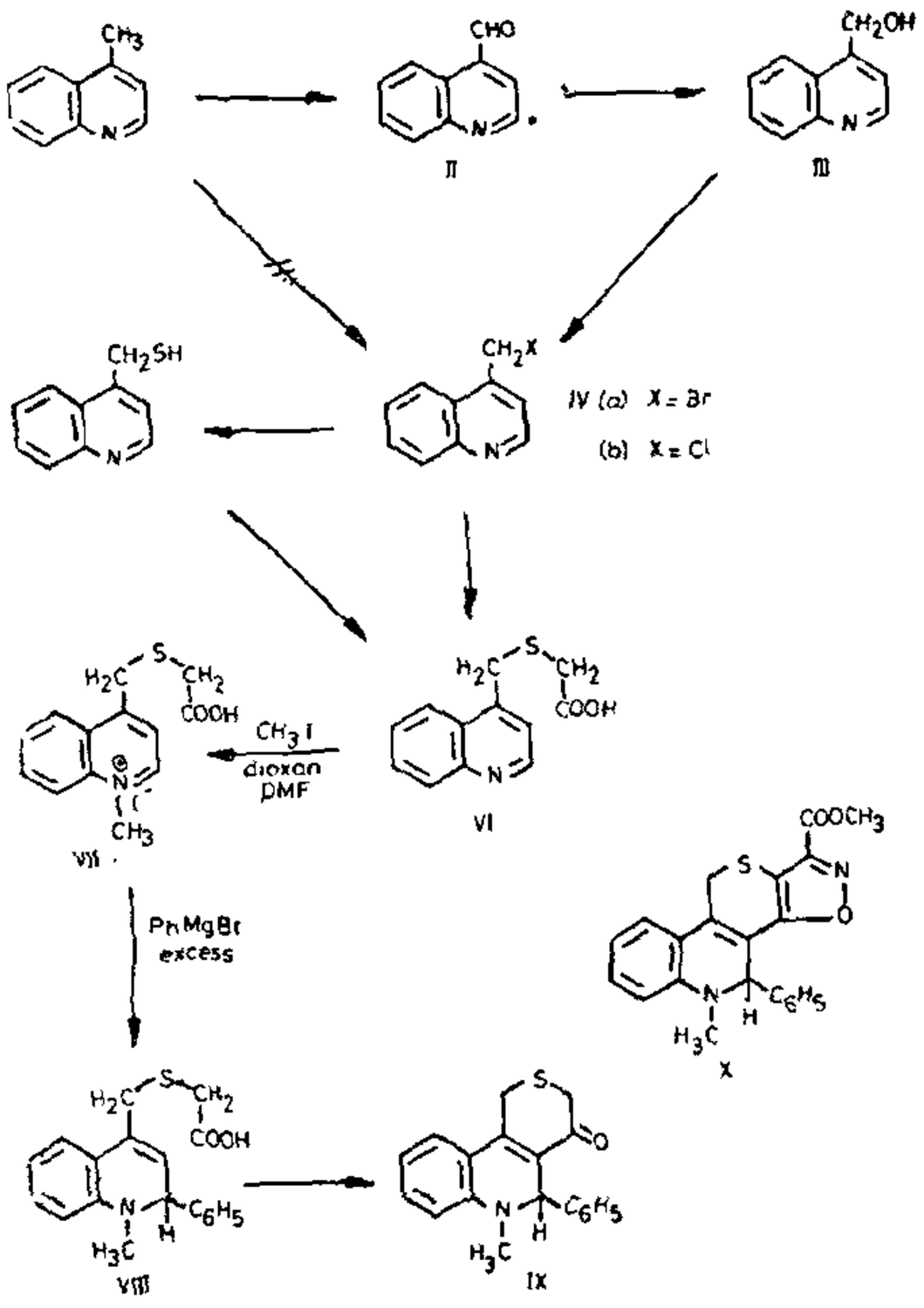
ABSTRACT

The synthesis of the tricyclic ketone, 1-oxo-3-thia-10-phenyl-9-methyl-9-aza-1,2,3,4,9,10-hexahydrophenanthrene (IX), starting with lepidine, is described, as a key intermediate for the total synthesis of the unknown 1-carbomethoxy-4-phenyl-5-methyl-4H, 5H, 10H-isoxazolo-[4,5-*b*] thiopyrano [4,3-*c*] quinoline (X).

INTRODUCTION

RECENT publications[1–4] point out that several steroidal analogues with replacement of D-ring of the normal steroid by an isoxazole or pyrazole ring exhibit interesting biological properties. Encouraged by these findings, the total synthesis of the hitherto unknown tricyclic ketone (IX) was achieved with a view to converting it into the desired isoxazole derivative (X).

CHART 1



The envisaged steps for the synthesis of the key intermediate, *i.e.*, the tricyclic ketone (IX), starting with the easily available lepidine are depicted in Chart I.

It is well known that lepidine reacts with NBS[5] to furnish the unstable 4-bromomethylquinoline (IV*a*). Following the specifications of Campbell & coworkers[5], a high melting deep red solid was isolated in all attempts, instead of the desired 4-bromomethylquinoline as claimed[5]. This necessitated us to undertake an involved procedure to convert lepidine into the relatively more stable 4-chloromethylquinoline as detailed below.

Oxidation of lipidine with freshly prepared and sublimed selenium dioxide (from metal selenium and conc. nitric acid) afforded the known quinoline-4-carboxaldehyde (II) as a white crystalline solid, m.p. 51–53° C, in 60% yield adopting a reported[6] procedure. Borohydride reduction of the aldehyde (II) gave the known 4-hydroxymethylquinoline (III) as a white crystalline solid, m.p. 96–97°, in 95% yield, while Brown and coworkers[7] obtained the alcohol (III) in 87% yield by a crossed Cannizzaro reaction of the aldehyde (II). The alcohol (III) failed to furnish the expected 4-bromomethylquinoline (IV*a*) by reaction with PBr_3. However, treatment of the alcohol (III) with thionylchloride initially at 0° C and later at room temperature gave the known 4-chloromethylquinoline (IV*b*) as white crystalline needles, m.p. 55–57°, in 90% yield, though Ochiai and coworkers[8] obtained (IV*b*) in 50% yield from lepidine-1-oxide, tosylchloride and BF_3 in DMF.

Treatment of 4-chloromethylquinoline (IV*b*) with thiourea in DMSO followed by treatment with 10% alkali gave the unknown mercaptan (V) in a single pot reaction adopting the general procedure of Hsi-Lung Pan and Fletcher[9].

The structure assigned to this mercaptan (V) was evident from its spectral and analytical data. IR spectrum ($CHCl_3$) indicated bands at 2540 (w, SH stretching), 1590, 1500 cm^{-1} (aromatic C=C); ^1H NMR ($CDCl_3$) δ 3·85 (s, 2H, –S–CH_2) and δ 7–9 (m, 7H, aromatic protons and SH proton). The signal due to SH proton disappeared on exchange with deuterium. Conversion of the aforesaid mercaptan to 12-thia-6-aza-equilenin is currently in progress.

On treatment with chloroacetic acid in 10% aqueous potassium hydroxide, the mercaptan (V) gave the thioacetic acid derivative (VI). The structure assigned to this thioacetic acid was evident from its spectral and analytical data as detailed below.

The IR spectrum (KBr) of (VI) indicated bands at 3300–3100 (–OH, broad) 1690 (acid carbonyl), 1590, 1500 cm^{-1} (aromatic C=C). The ^1H NMR spectrum (DMSO-d_6) indicated signals at δ 3·35 (s, 2H, –S–CH_2–COOH), 4·4 (s, 2H, Ar–CH_2–S), 7·4–7·9 (m, 6H, aromatic protons). Alternatively, the desired thioacetic acid derivative (VI) was obtained in a superior yield by treating 4-chloromethylquinoline (IV*b*) directly with thioglycolic acid (99%) in presence of 10% aqueous sodium hydroxide. By this procedure the yield of the thioacetic acid derivative (VI) was raised to 85%.

The thioacetic acid derivative (VI) on treatment with methyl iodide, in a mixture of ether and DMF at room temperature under stirring, furnished the corresponding quaternary iodide (VII), which on further treatment with phenylmagnesium bromide gave the anticipated (1-methyl-2-phenyl-4-methylthio-1,2-dihydroquinoline) acetic acid (VIII) as a gummy solid, in 20% yield. This was further purified to furnish almost pure sample of (VIII). The ^1H NMR spectrum of (VIII) ($CDCl_3$) indicated signals at δ 1·3 (s, 3H, CH_3), 4·8 (d, 1H, methine proton at 2), 3·35 (s, 2H, –S–CH_2 COOH), 3·8 (m, 2H, Ar–CH_2–S) and 6·7–7·8 (m, 10 H, aromatic and olefinic). Though it failed to solidify, it indicated a single spot in TLC [benzene and ethyl acetate (4 : 1)]. Attempted cyclodehydration of (VIII) with trifluoroacetic acid and acetic anhydride under dry nitrogen atmosphere at 100° C for 4 hr gave the anticipated tricyclic ketone as a thick gum in extremely poor yield (10%). Purification of the gum by column chromatography over

neutral alumina gave from benzene eluates an analytical sample of the tricyclic ketone (IX) as a thick yellow gum which also defied all attempts towards solidification. The assigned structure for (IX) was based on the following spectral data. The ^1H NMR spectrum ($CDCl_3$) indicated signals at δ 1·3 (s, 3H, N–CH_3), 3·5 (s, 2H, S–CH_2–C–), δ 4·25 (q, 2H, Ar–CH_2–S), 4 8 (d, 1H, methine proton at 2) and 7–8 (m, 9H, aromatic protons).

Experimental

All melting points reported herein are uncorrected. Petroleum ether refers to petrol in the boiling range of 40–60° only. Infrared spectra were recorded using Perkin–Elmer grating infrared spectrophetometer, Model 257. ^1H NMR spectra were recorded on XL-100 Spectrometer using TMS as the internal standard. The chemical shifts are reported in 'δ'. Mass spectra were taken using Varian MAT CH-7 spectrometer.

Microanalyses were carried out at the Departments of Organic Chemistry, IISc., Bangalore and Institute für Organische Chemie, Universitat Karlsruhe, Karlsruhe (West Germany). TLC plates were coated with silica gel-G (0–25 mm thickness) and plates were developed with iodine vapour. Silica gel (BDH) (60–120 mesh) was used for column chromatography. Anhydrous sodium sulphate was used for drying the organic extracts.

Quinoline-4-carboxaldehyde (*II*): Oxidation of lepidine (Aldrich) (40 g) with freshly prepared selenium dioxide (45 g), adopting the procedure reported by Mac Donald[6] gave the expected (II) in good yield (24 g, 60%).

4-Hydroxymethylquinoline (*III*): Sodium borohydride (1·95 g; 0·05 mole) was added to quinoline-4-carboxaldehyde (II) (15·7 g; 0·1 mole) in methanol (70 ml) at 0–5° C under stirring. After stirring the solution for 6 hr, methanol was evaporated and the residue was dissolved in water (30 ml). The resulting aqueous solution was extracted with chloroform (3 × 25 ml). The organic extract was washed with water (2 × 20 ml), dried and evaporated to yield the crude alcohol as a brown solid which, on recrystallization from benzene, gave a very pure sample of 4-hydroxymethylquinoline (III) as a white crystalline solid, m.p. 96–97 (15·1 g; 95% yield), (reported[7], m.p. 96–97°; yield 87%).

4-Chloromethylquinoline (*IVb*): Freshly distilled thionyl chloride (8·85 g; 0·75 mole) in dry ether (15 ml) was added dropwise to a stirred solution of 4-hydroxymethylquinoline (III), (11·9 g; 0 075 mole) in dry ether (200 ml) cooled to 0–5° C. Later, the contents were stirred at room temperature for 7 more hours. The hydrochloride of the product separated out as a white precipitate as reaction progressed. The resulting mixture was treated with aqueous ammonia (30%) until it became alkaline. The liberated free base went into solution in ether. The ethereal solution was separated, washed with water (2 × 20 ml), dried and evaporated. The residual solid was treated with petrol and evaporation of petrol afforded 4-chloromethylquinoline (IV*b*) as white crystalline needles, m.p. 55–57° (11·5 g; 90% yield) (reported[8], m p. 56–57° in 50% yield).

4-Mercaptomethylquinoline (*V*): A mixture of 4-chloromethylquinoline (IV*b*) (17·7 g; 0·1 mole), thiourea (8·36 g; 0·11 mole) and DMSO (300 ml) was stirred at room temperature for 12 hours. At the end of this period, aqueous sodium hydroxide (10%) (45 ml) was added to the reaction mixture and the resulting mixture was stirred for 30 min. It was neutralised with ice-cold 1 : 1 hydrochloric acid and extracted with chloroform (3 × 50 ml). The organic layer was washed with water (2 × 25 ml), dried and evaporated to yield the crude mercaptan as brown gummy solid, which, on repeated recrystallization from benzene, afforded the analytically pure sample of 4-mercaptomethylquinoline (V) as a brownish white crystalline solid, m.p. 162–164°, (9·6 g; 55% yield).

Mass spectrum indicated peaks at m/z 175 (M^+, 17%), m/z 174 (10%), m/z 173 (22%), m/z 172 (14%), m/z 143 (52%), m/z 142 (100%), m/z 114 (61%).

Found: C, 68·53; H, 5·18; N, 7·99; $C_{10}H_9NS$ requires C, 68·89; H, 4·65; N, 7·95%).

(4-Quinolinomethylthio) acetic acid (*VI*)

Method A: 4-Mercaptomethylquinoline (V) (4·4 g; 0–025 mole) dissolved in 14 ml of 10% KOH and 50 ml of ethanol was treated with chloroacetic acid (2·4 g; 0·025 mole) and solid potassium carbonate (3·5 g). The resulting mixture was refluxed for 3 hr. Ethanol was evaporated and water was added. The resulting aqueous solution was acidified to pH 4–5 with ice-cold 1 : 1 hydrochloric acid. The precipitated solid was filtered, dried and recrystallized from methanol to afford pure (4-quinolinomethylthio) acetic acid (VI) as shining pale pinkish white crystals, m.p. 195–6° C (4·3 g; 75% yield). Mass spectrum showed peaks at m/z 233 (M^+; 60%) m/z 174 (59%), m/z 173 (23%), m/z 143 (27%), m/z 142 (100%), m/z 114 (42%).

Found: C, 61·91; H, 5·02; N, 6·17, $C_{12}H_{11}NO_2S$ requires C, 61·79; H, 4·75; N, 6·01%.

Method B: A solution of 4-chloromethylquinoline (IV*b*) (4·4 g; 0·025 mole) in acetone (15 ml) was added dropwise to a well-cooled solution of thioglycolic acid (2·3 g; 0·025 mole) in 2N NaOH (15 ml) for a period of 3 hr with vigorous stirring. Stirring of the resulting mixture was continued for a further period of 24 hr at room temperature. It was diluted with water (100 ml) and the resulting aqueous solution was

extracted with chloroform (1 × 30 ml) to remove unreacted 4-chloromethylquinoline. The clear aqueous solution, on acidification as described above in Method 'A', gave the pure sample of (VI) (4·9 g; 85% yield).

N-Methiodide of (*4-quinolinomethylthio*) *acetic acid* (*VII*): The thioacetic acid derivative (VI) (5·8 g; 0·025 mole) dissolved in a mixture of dry ether (50 ml) and DMF (10 ml) was cooled to 0° C. Excess of freshly distilled methyliodide (15 ml) was added in one lot to the above solution at 0° C. The resulting mixture was stirred at room temperature for 6 hr. Ether and DMF were evaporated under vacuo to furnish the expected quaternary iodide (VII) as a brownish gummy solid in almost quantitative yield.

(*1-Methyl-2-phenyl-4-methylthio-1, 2-dihydro-quinolino*) *acetic acid* (*VIII*): To phenylmagnesium bromide [prepared from bromobenzene (40 g; 0·25 mole) and magnesium turnings (6 g) in dry ether under dry nitrogen atmosphere was added a solution of the methiodide of the acid (VII) (9·3 g; 0·025 mole) in dry monoglyme (10 ml)] dropwise under stirring over a period of 15 minutes. The resulting mixture was stirred overnight. It was decomposed with ice-cold 15% acetic acid. The aqueous layer was extracted with chloroform (3 × 25 ml). The combined organic extract was thoroughly washed with water (2 × 25 ml), dried and evaporated. The crude residual solid was once redissolved in chloroform (50 ml) and washed with a saturated solution of sodium bicarbonate (3 × 50 ml). The combined bicarbonate layers were acidified carefully at ice temperature with 1 : 1 hydrochloric acid. The resulting mixture was extracted with chloroform (2 × 30 ml). The chloroform layer was washed with water (2 × 20 ml), dried and evaporated to give the analytically pure sample of (VIII) (1·6 g; 20% yield) as a pale yellow gummy solid. All attempts towards its solidification failed.

1-Oxo-3-thia-10-phenyl-9-methy-l9-aza-1,2,3,4,9,10-hexahydrophenanthrene (*IX*): A solution of the above-mentioned acid (VIII) (1·6 g), in acetic anhydride (4 ml) and trifluoroacetic acid (0·5 ml) was heated on steam bath for 4 hr under nitrogen atmosphere and under anhydrous conditions. Acetic anhydride and trifluoroacetic acid were removed under reduced pressure. The residue was treated with water (50 ml) and extracted with ether (3 × 25 ml). The ethereal layer was washed with a saturated solution of sodium bicarbonate (3 × 30 ml), and dried. Evaporation of the dried ether extract gave the product as a gum (0·8 g), which on column chromatography over neutral alumina gave from benzene eluates, the analytical sample of the tricyclic ketone (IX) as a thick yellow gum. It resisted all attempts towards solidification.

Found: C, 73·99, H, 5·20; N, 4·60; $C_{19}H_{17}NSO$ requires C, 74·26; H, 5·53; N, 4·56%.

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