

A P P E N D I X . I

Synthetic Studies in Carbocyclic Systems : Part I -- A new
Synthesis of Nopinone.

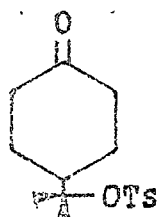
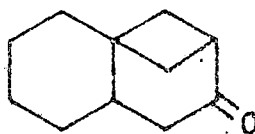
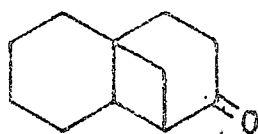
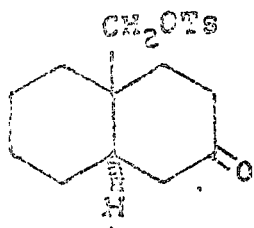
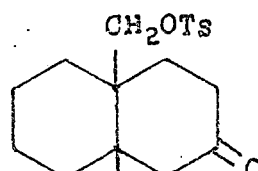
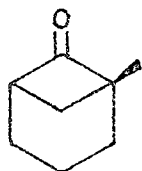
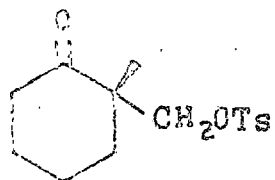
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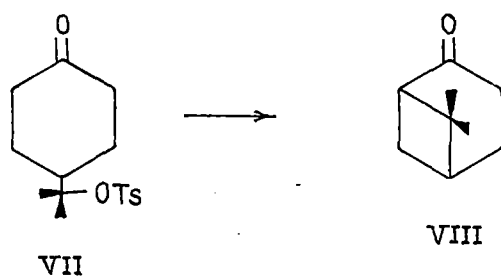
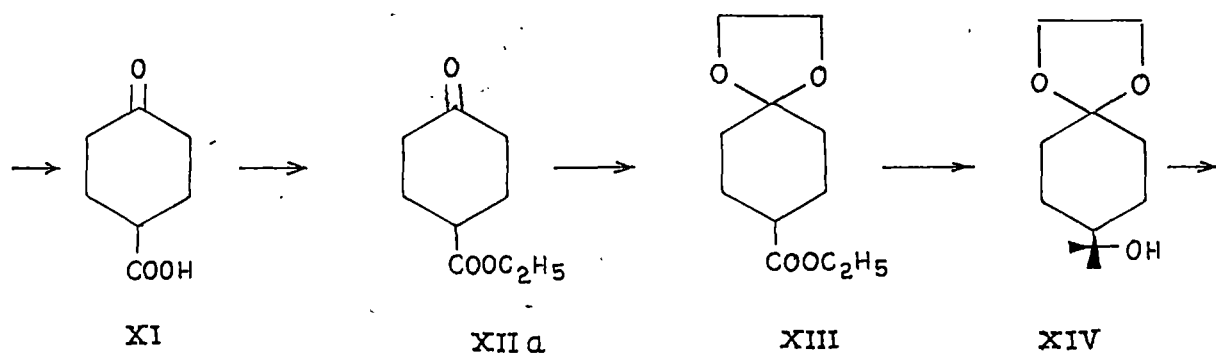
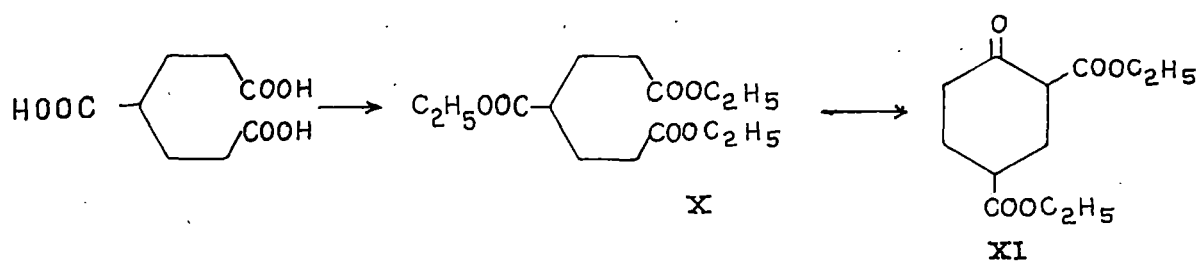
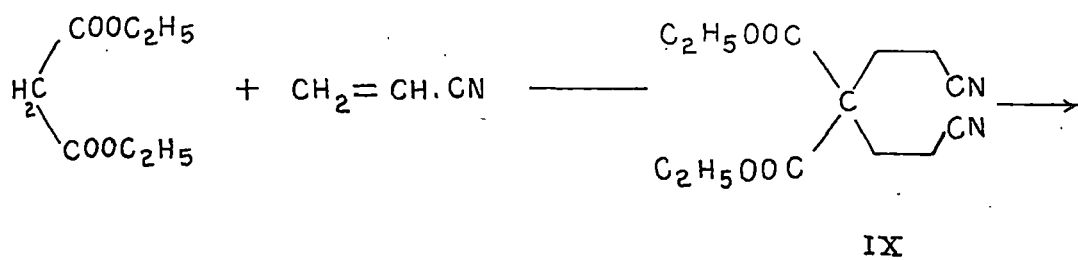
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Base-induced intramolecular nucleophilic displacement of the tosyloxy group of 4-isopropyl-7-tosyloxycyclohexanone affords nopinone, identical with an authentic specimen.

The formation of cyclobutane derivatives by base-induced intramolecular nucleophilic displacement of the tosyloxy groups in oppositely substituted ketotosylates has been reported in the literature. Wenkert and Strike¹ reported the formation of 1-methylbicyclo [3.1.1] heptan-6-one (II) by the action of a base on 2-methyl-2-tosyloxymethyl-cyclohexanone (I). By treating cis- and trans-10 tosyloxymethyl-2-decalones (III) and (IV) with base Mukharji and coworkers^{2,3} prepared the tricyclic ketones (V) and (VI). It was therefore felt that 4-isopropyl-7-tosyloxycyclohexanone (VII) will undergo base-induced intramolecular nucleophilic displacement reaction to give nopinone (VIII) as one of the products. This compound has previously been synthesized by Kulkarni and





Bhattacharjee⁴.

Cyclohexane-4-carboxylic acid (XII), a key intermediate, was synthesized by a different route.

Michael addition of acrylonitrile to diethyl malonate furnished the dinitrile (IX)⁶ which on hydrolysis, decarboxylation and esterification gave diethyl γ -carboethoxypimelate (X). Dieckmann cyclization of the pimelate followed by hydrolysis and decarboxylation of cyclohexanone- β , δ -dicarboxylic ester (XI) gave XII. Grignard reaction with excess of methylmagnesium iodide on the derived ketal ester (XIII) gave the tertiary alcohol (XIV) which was converted to the ketosylate (VII) by treating with *p*-toluenesulphonyl chloride in benzene at room temperature. The crude tosylate was treated with one equivalent of methanolic potassium hydroxide and the product on chromatography and fractional distillation afforded nopinone (VIII) which was identified by comparing some of its derivatives with those prepared from an authentic sample.

E X P E R I M E N T A L

Melting points and boiling points are uncorrected. All organic extracts were dried over anhydrous sodium sulphate. Alumina (S. Merck) was used for column chromatography. Infrared spectra were recorded on Beckman-20 IR spectrophotometer and PMR spectrum of nopinone was recorded on a Varian A-60 90 Mhz spectrometer.

Diethyl γ -carboethoxypimelate (X) — To a stirred solution of diethyl malonate (160 g) and 20% methanolic potassium hydroxide (15 ml) in *t*-butanol (150 ml) was added dropwise freshly distilled acrylonitrile at 5-10°. After the addition the reaction mixture was stirred for a further 3 hr. The dinitrile (IX) which separated as a white crystalline solid (250 g) was filtered and hydrolysed with hydrochloric acid (500 ml) for 90 hr. Evaporation

of the reaction mixture gave the crude acid which was esterified by alcohol-sulphuric acid method to give X after usual work-up, b.p. 195°/15 mm (69 g).

Ethyl cyclohexanone - 4 - carboxylate (XIIa) — The triester (X, 86.4 g) was refluxed with sodium dust (6.8 g) in anhydrous benzene (500 ml) until the sodium particles disappeared (14 hr). Decomposition of the enolate with cold dil. acid and usual work-up furnished the β -ketoester (XI) which was hydrolysed with a mixture of sulphuric acid (10 ml), phosphoric acid (5 ml) and water (100 ml) for 6 hr. The reaction mixture was extracted with chloroform. Evaporation of the solvent furnished cyclohexanone-4-carboxylic acid (XII) which crystallized from benzene-pet, ether, m.p. 67° (lit.⁶ 67-68°); oxime 147° (lit.⁶ 147°); semicarbazone 200° (lit.⁶ 200°); ester (XIIa) (alcohol-H₂SO₄ method), b.p. 185°/15 mm (15 g).

4-Isopropyl-7-tosyloxy-cyclohexanone (VII) — The keto-ester, (XII a, 10.2 g) and ethanediol (7.5 g) in anhydrous benzene (150 ml) containing *p*-toluenesulphonic acid (0.1 g) was heated under reflux until the calculated amount of water separated. Usual work-up gave the ketal ester (XIII), b.p. 180°/10 mm (11g) which was used as such in the next step.

XIII in dry ether (50 ml) was added dropwise to a stirred solution of excess of methylmagnesium iodide in dry ether (100 ml) during 2 hr and the mixture refluxed for a further period of 2 hr and

Usual work-up gave the tertiary alcohol (XIV) (8 g) as a very viscous oil which was used as such in the next step.

The crude XIV (6 g) in anhydrous benzene was treated with freshly distilled *p*-toluenesulphonyl chloride (6.5 g) in dry benzene (100 ml), left overnight, then refluxed for 2 hr, cooled, washed with water, dried and concentrated. The tosylate (VII) was obtained as a gummy mass and could not be crystallized (9 g). It was used as such in the next step.

Nopinone (VIII) — A solution of crude VII (8 g) in methanol (50 ml) was refluxed with 3% methanolic potassium hydroxide solution (100 ml) for 6 hr. The initial pH of 12-13 dropped to about 9.5 in 5 hr. There was no further drop even on refluxing. The reaction mixture was cooled and thoroughly extracted with pet. ether, the extract washed with water, dried and concentrated. The residual oil was adsorbed on a column of alumina (30 g) and eluted with pet. ether (60-80°). Further purification was done by fractional distillation under reduced pressure. Nopinone was obtained as an oil (3 g) b.p. 115-16°/9 mm (TLC single spot); hydrate, m.p. 48° (lit.^{7,9} 42-43°); semicarbazone, m.p. 187° (lit.^{7,9} 187°);

IR : 1709, 1408, 1368, 1346, 1311, 1280, 1250, 1096, 1070,
1030, 960, 940, 915, 880 and 752 cm^{-1} , PMR : 2.41 (2H,t),
1.73(2H,d), 1.26 (1H,d), 1.51 (q,2H), 2.06 (1H,t),
1.1 (3H,s) and 1.2 (3H,s).

The derivatives did not show any depression in melting points on admixture with those prepared from an authentic sample of nopinone.

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