

## HETEROCYCLIC COMPOUNDS.

### Part II. The Synthesis of Cyclopenteno-(1' : 2' : 4 : 3)-carbostyryl Derivatives.

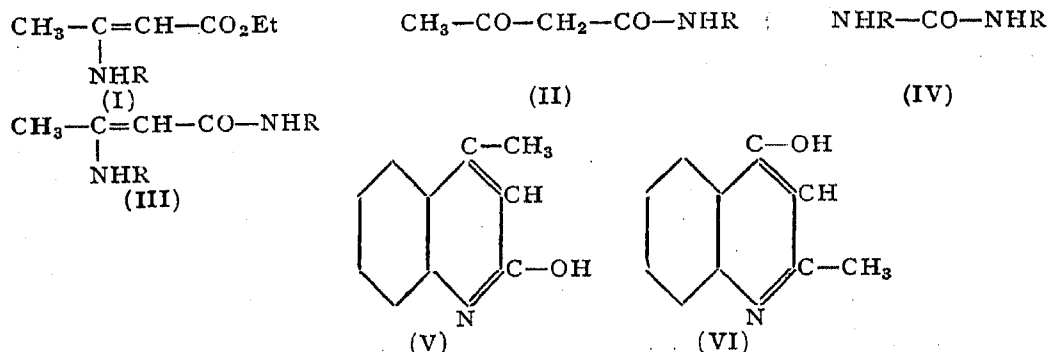
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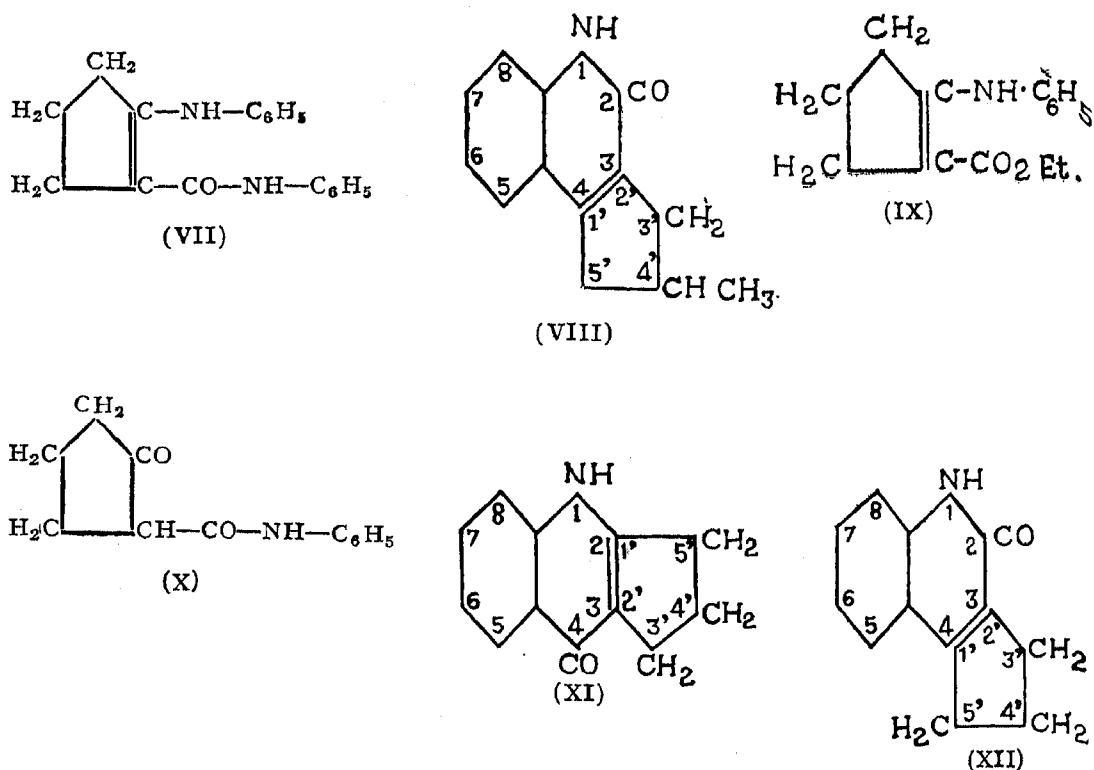
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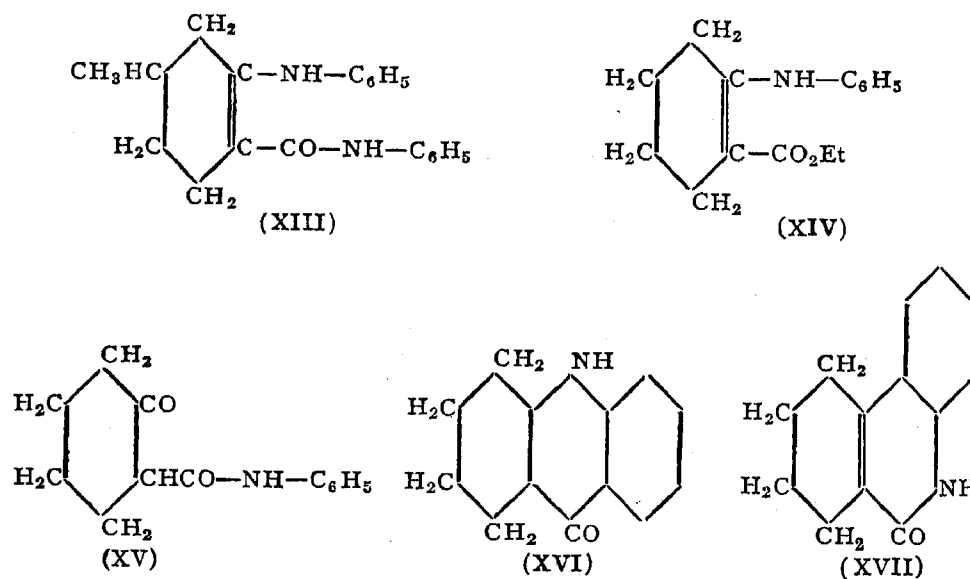
THE condensation of arylamines with open-chain  $\beta$ -ketonic esters has been the subject of an extensive study by various investigators.<sup>1</sup> The reaction is an exceedingly complex one, but the following six types of compounds have been definitely isolated according to the experimental conditions. Thus ethyl acetoacetate and a primary arylamine give ethyl  $\beta$ -arylamino-crotonate (I), acetoacetarylamide (II),  $\beta$ -arylamino-crotonoarylamide (III), Sym-diarylurea (IV), substituted 2-hydroxy-lepidine (V), and substituted 4-hydroxy-quinaldine (VI).



On the other hand, the work on the condensation of these amines with cyclic  $\beta$ -ketonic esters is very meagre. Dieckmann<sup>2</sup> has studied the action of aniline on 4-methylcyclopentanone-2-carboxylate, obtaining 1-anilino- $\Delta$  1 : 2-4-methylcyclopentene-2-carboxyanilide (VII) which was cyclised to 4'-methylcyclopenteno-(1' : 2' : 4 : 3)-carbostyryl (VIII). Blount, Perkin and Plant<sup>3</sup> succeeded in condensing cyclopentanone-2-carboxylate with aniline with the formation of 1-anilino- $\Delta$  1 : 2-cyclopentene-2-carboxylate (IX) and cyclopentanone-2-carboxyanilide (X) which were easily cyclised to 4-keto-1 : 4 dihydro-cyclopenteno-(1' : 2' : 2 : 3)-quinoline (XI) and cyclopenteno-(1' : 2' : 4 : 3)-carbostyryl or 2-keto-1 : 2 dihydro-cyclopenteno-(1' : 2' : 4 : 3)-quinoline (XII) respectively.



Kötz and Merkel<sup>4</sup> obtained 1-anilino- $\Delta$  1:2-5-methyl-cyclohexene-2-carboxyanilide (XIII) from aniline and 5-methylcyclohexanone-2-carboxylate, while Sen and Basu<sup>5</sup> have studied the condensation of cyclohexanone-2-carboxylate with various aromatic amines isolating 1-anilino- $\Delta$  1:2-cyclohexene-2-carboxylate (XIV) and cyclohexanone-2-carboxyanilide (XV), and Sym-diarylureas (IV). They also succeeded in cyclising (XIV) and (XV) into their respective tetra-hydro-acridones (XVI) and tetra-hydro-phenanthridones (XVII).

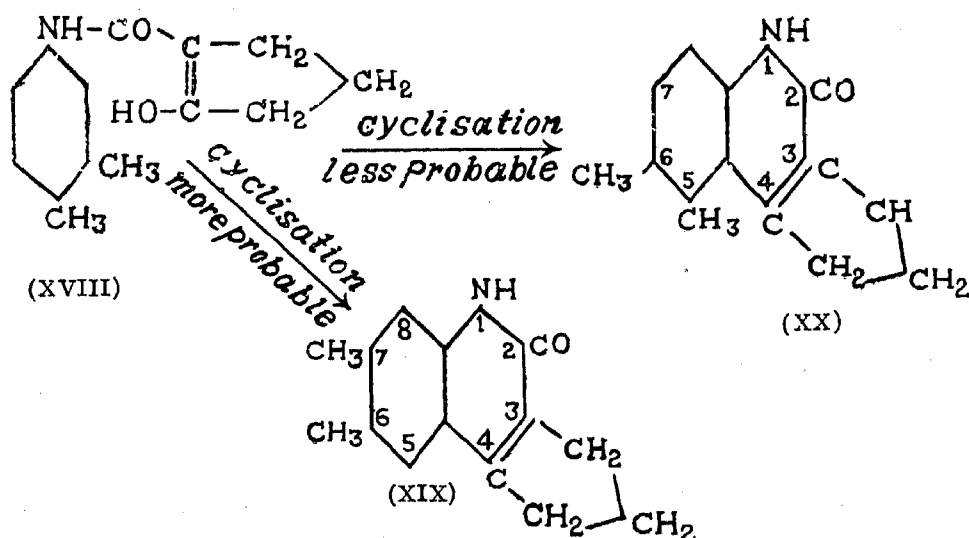


There being a considerable lacuna in the work on the condensation of aromatic amines with cyclopentanone-2-carboxylate, we studied the action of aniline, *p*-toluidine, 1:3:4-xylidine,  $\alpha$ -naphthylamine,  $\beta$ -naphthylamine, *p*-chloraniline, *p*-bromaniline, and *o*-anisidine on this ester by heating at 170–180° for a period varying from two to five minutes using equimolecular quantities. The first three amines gave a mixture, separable into products of type (X) and (VII) while others gave compounds exclusively of the type (VII). The arylamides of type (X) were smoothly cyclised into the carbostyryl derivatives of type (XII) by concentrated sulphuric acid, while contrary to the observation of Dieckmann (*loc. cit.*), the compounds of the type (VII) could not be cyclised.

4-Methylcyclopentanone-2-carboxylate was condensed with aniline, *p*-toluidine, 1:3:4-xylidine, *p*-chloraniline, and *p*-bromaniline under identical conditions. Aniline and *p*-toluidine gave compounds of type (X) but although pure, crystalline products could not be isolated, the crude products were smoothly converted into carbostyryl derivatives. 1:3:4-xylidine gave a separable mixture of products of types (X and VII) while *p*-chloraniline and *p*-bromaniline gave products of type (VII) only.

The 1:3:4-xylidides (XVIII) obtained from the two esters may cyclise giving either, 6:7-dimethyl- (IXX) or 5:6-dimethyl-derivative (XX) of carbostyryl, but as the possibility for the former is much greater, we have assumed that they are 6:7-dimethyl-derivatives (IXX).

When the reaction was carried out at the boiling point of the mixture, only Sym-diarylureas could be isolated in a pure condition, showing that compounds of types (VII) and (X) underwent decomposition to Sym-diarylureas. We are busy studying the action of arylamines on these as well as



other cyclic  $\beta$ -ketonic esters to standardise conditions for the individual isolation of compounds of type (VII, IX and X) in each reaction.

*Experimental.*

*Cyclopentanone-2-carboxyanilide (type X).*—A mixture of cyclopentanone-2-carboxylate (1.5 g.) and aniline (1.5 g.) was heated at 155–160° in an oil-bath for five minutes. The solid that separated out after 24 hours was collected, washed with petrol (b.p. 60–80°) and crystallised from alcohol, when colourless needles, m.p. 105–106°, were obtained. Its alcoholic solution gave a dark green colour with ferric chloride. On heating it with concentrated sulphuric acid on a water-bath for 15–20 minutes, and pouring the cooled mixture into water, a solid was formed which crystallised from dilute acetic acid in colourless plates, m.p. 256°. This was, therefore, *cyclopenteno-(1' : 2' : 4 : 3)-carbostyryl* (XII) [cf. Blount, Perkin and Plant (*loc. cit.*)].

*Cyclopentanone-2-carboxy-p-toluidide (type X).*—A mixture of the ester (2.5 g.) and *p*-toluidine (1.7 g.) was heated in an oil-bath at 180° for two minutes. The solid (m.p. 105–110°) which separated on rubbing the cold mixture with petrol (b.p. 60–80°), was separated, washed, and treated with cold alcohol, which dissolved only a part of the solid. On concentration, the alcoholic solution gave colourless needles, m.p. 130°. Its alcoholic solution gave violet colour with ferric chloride. (Found: C, 72.0; H, 7.3;  $C_{13}H_{15}O_2N$  requires C, 71.9; H, 6.9 per cent.)

*1-p-Tolylamino- $\Delta$  1 : 2-cyclopentene-2-carboxy-p-toluidide (type VII).*—The residue insoluble in cold alcohol dissolved on warming, and crystallised on cooling in colourless needles, m.p. 143°. Its alcoholic solution did not give any colour with ferric chloride. (Found: C, 78.9; H, 7.5;  $C_{20}H_{22}ON_2$  requires C, 78.4; H, 7.2 per cent.) Its solution in concentrated sulphuric acid did not cyclise on warming.

*6-Methyl-2-keto-1 : 2-dihydro-cyclopenteno-(1' : 2' : 4 : 3)-quinoline (type XII).*—The solution of cyclopentanone-2-carboxy-*p*-toluidide (0.5 g.) in concentrated sulphuric acid (10 c.c.) was heated on a water-bath for 15 minutes. The solid which was obtained on pouring the cooled mixture into water was collected, washed and crystallised from alcohol when colourless needles, m.p. 295°, were obtained. (Found: C, 78.3; H, 6.8;  $C_{13}H_{13}ON$  requires C, 78.4; H, 6.5 per cent.)

*Cyclopentanone-2-carboxy-(1 : 3 : 4)-xylidide.*—A mixture of the ester (2 g.) and 1 : 3 : 4-xylidine (1.6 g.) is heated in an oil-bath at 180–185° for three minutes. The solid that separated out by rubbing the cooled mixture with petrol (b.p. 60–80°) was filtered off, and washed with the same solvent.

The residue (m.p. 110–150°) was treated with cold alcohol, and on concentration, a solid was obtained. This crystallised from petrol in needles or from dilute alcohol in plates, m.p. 107–108°. Its alcoholic solution gave a dark-green colour with ferric chloride. (Found: C, 72.4; H, 7.3;  $C_{14}H_{17}O_2N$  requires C, 72.7; H, 7.4 per cent.)

*1-Xylidino-(1:3:4)- $\Delta$ 1:2-cyclopentene-2-carboxy-(1:3:4)-xylidide.*—The residue insoluble in alcohol dissolved on warming, and crystallised from the same solvent on cooling in colourless needles, m.p. 184°. Its alcoholic solution did not give any colouration with ferric chloride, nor did it undergo cyclisation on heating with concentrated sulphuric acid. (Found: C, 78.9; H, 8.0;  $C_{22}H_{26}ON_2$  requires C, 79.0; H, 7.8 per cent.)

*6:7-Dimethyl-2-keto-1:2-dihydro-cyclopenteno-(1':2':4:3)-quinoline.*—The solution of cyclopentanone-2-carboxy-(1:3:4)-xylidide (0.5 g.) in concentrated sulphuric acid (10 c.c.) was heated in a boiling water-bath for 15 minutes. The flocculent precipitate obtained by pouring into a large volume of water, was filtered, washed and crystallised from methyl alcohol, when colourless needles, m.p. 280°, were obtained. (Found: C, 78.6; H, 7.0;  $C_{14}H_{15}ON$  requires C, 78.9; H, 7.0 per cent.)

*1-p-Chloranilino- $\Delta$ 1:2-cyclopentene-2-carboxy-p-chloranilide.*—The mixture of the ester (2.5 g.) and *p*-chloranilide (2.2 g.) was heated in an oil-bath at 180–185° for three minutes. After treating the cooled mass with petrol, the residue was crystallised from warm alcohol, when colourless needles, m.p. 173–174°, were obtained. Its alcoholic solution did not give any colour with ferric chloride, and the substance could not be cyclised by the usual method. (Found: Cl, 20.3;  $C_{18}H_{16}N_2OCl_2$  requires Cl, 20.5 per cent.)

*1-p-Bromanilino- $\Delta$ 1:2-cyclopentene-2-carboxy-p-bromanilide.*—This was similarly prepared from the ester (2 g.) and *p*-bromaniline (1.8 g.) and crystallised from dilute, warm alcohol in colourless needles, m.p. 179°. It resembled the chloro-analogue in its chemical properties. (Found: Br, 36.4;  $C_{18}H_{16}ON_2Br_2$  requires Br, 36.7 per cent.)

*1-o-Anisidino- $\Delta$ 1:2-cyclopentene-2-carboxy-o-anisidide.*—A mixture of *o*-anisidine (2 g.) and the ester (2 g.) was heated for 5 minutes at 150°. After washing the solid with petrol, the residue crystallised from warm, dilute alcohol in colourless plates m.p. 130–131°. Its alcoholic solution gave no colour with ferric chloride, and no cyclisation was possible by warming it with concentrated sulphuric acid. (Found: C, 70.8; H, 6.4;  $C_{20}H_{22}O_3N_2$  requires C, 71.0; H, 6.5 per cent.)

*1- $\alpha$ -Naphthylamino- $\Delta$ 1:2-cyclopentene-2-carboxy- $\alpha$ -naphthalide.*—The mixture of  $\alpha$ -naphthylamine (1.5 g.) and the ester (1.5 g.) was heated in

an oil-bath at 100–105° for three hours. The solid left after triturating with petrol, crystallised from warm, dilute alcohol in colourless needles, m.p. 164°. It gave negative reaction with ferric chloride and concentrated sulphuric acid. (Found: C, 82.2; H, 6.0;  $C_{26}H_{22}ON_2$  requires C, 82.5; H, 5.8 per cent.)

1- $\beta$ -Naphthylamino- $\Delta$  1 : 2-cyclopentene-2-carboxy- $\beta$ -naphthalide.—The mixture of the ester (2 g.) and  $\beta$ -naphthylamine (1.8 g.) was heated for three minutes at 180–185° and the cooled mixture was washed with ether. The residue crystallised from warm alcohol in colourless needles, m.p. 184°; and resembled the  $\alpha$ -isomer in chemical properties. (Found: C, 82.5; H, 5.8;  $C_{26}H_{22}ON_2$  requires C, 82.5; H, 5.8 per cent.)

*Condensation of 4-Methylcyclopentanone-2-carboxylate with Arylamines.*

2-Keto-1 : 2-dihydro-4'-methylcyclopenteno-(1' : 2' : 4 : 3)-quinoline.—A mixture of 4-methylcyclopentanone 2-carboxylate (3.5 g.) and aniline (2 g.) was heated for four minutes at 145–150°. As attempts to isolate the condensation product in a state of purity failed, the cooled mass was treated with concentrated sulphuric acid (20 c.c.) and warmed for 15 minutes. The solid obtained by pouring the mixture into water crystallised from methyl alcohol in colourless plates, m.p. 249°. (Found: C, 78.4; H, 6.7;  $C_{13}H_{13}ON$  requires C, 78.4; H, 6.5 per cent.)

6-Methyl-2-keto-1 : 2-dihydro-4'-methylcyclopenteno-(1' : 2' : 4 : 3)-quinoline.—The mixture of the ester (2.5 g.) and *p*-toluidine (1.3 g.) was heated at 180 for two minutes. As no pure solid could be obtained, concentrated sulphuric acid (15 c.c.) was added to the cooled mixture, and warmed on a water-bath for 20 minutes. The solid obtained by pouring the mixture on ice was washed and crystallised from alcohol when needles, m.p. 230–231° were obtained. (Found: C, 78.5; H, 6.7;  $C_{14}H_{15}ON$  requires C, 78.8; H, 7.0 per cent.)

4-Methylcyclopentanone-2-carboxy-(1 : 3 : 4)-xylidide.—A mixture of (1 : 3 : 4)-xylidine (2.5 g.) and the ester (3 g.) was heated at 180° for three minutes. The mixture gave, on rubbing with petrol (b.p. 40–60°), a solid which was removed and washed with the same solvent. A part of the solid dissolved in cold methyl alcohol, and the solution, on concentration, gave white, silky needles, m.p. 114°. Its alcoholic solution gave dark-green colour with ferric chloride. (Found: C, 73.8; H, 7.8;  $C_{15}H_{19}O_2N$  requires C, 73.5; H, 7.8 per cent.)

1-Xylidylamino- $\Delta$  1 : 2-4-methylcyclopentene-2-carboxy (1 : 3 : 4)-xylidide.—The solid insoluble in cold alcohol was soluble in the same solvent on warming, and crystallised in colourless needles, m.p. 180°. It gave negative

tests with ferric chloride and concentrated sulphuric acid. (Found : C, 79.4 ; H, 8.0 ;  $C_{23}H_{28}ON_2$  requires C, 79.3 ; H, 8.0 per cent.)

6 : 7-Dimethyl-2-keto-1 : 2-dihydro-4'-methylcyclopenteno-(1' : 2' : 4 : 3)-quinoline.—A solution of 4-methylcyclopentanone-2-carboxy-(1 : 3 : 4)-xylylidide (0.5 g.) in concentrated sulphuric acid (10 c.c.) was heated on a water-bath for 15 minutes, and poured into water, after cooling. The solid crystallised from methyl alcohol in colourless plates, m.p. 215°C. (Found : C, 79.1 ; H, 7.5 ;  $C_{15}H_{17}ON$  requires C, 79.3 ; H, 7.5 per cent.)

1-p-Chloramino- $\Delta$  1 : 2-4-methylcyclopentene-2-carboxy-p-chloranilide.—A mixture of the ester (2.5 g.) and *p*-chloraniline (2 g.) was heated at 170° for four minutes. After triturating the viscous mass with petrol, the solid was crystallised from alcohol when colourless needles, m.p. 167–168°, were obtained. (Found : Cl, 19.4 ;  $C_{19}H_{18}ON_2Cl_2$  requires Cl, 19.7 per cent.) It gave negative tests with ferric chloride solution and concentrated sulphuric acid.

1-p-Bromanilino- $\Delta$  1 : 2-4-methylcyclopentene-2-carboxy-p-bromanilide.—A mixture of the ester (2.5 g.) and *p*-bromaniline (2.5 g.) was heated at 130–135° for 5 minutes. The reaction was vigorous and the cooled mass was triturated with petrol. The solid crystallised from alcohol in colourless needles, m.p. 185°, and gave negative tests with ferric chloride and concentrated sulphuric acid. (Found : Br, 35.5 ;  $C_{19}H_{18}ON_2Br_2$  requires Br, 35.6 per cent.)

Condensation of the esters with arylamine at higher temperatures.—A mixture of the ester (2 g.) and aniline (2 g.) was rapidly heated to its boiling point in a hard-glass boiling tube and maintained at this temperature for 5 minutes. The reaction was vigorous, and the mixture became viscous on cooling. On rubbing with dilute alcohol, there resulted a solid which, on recrystallisation, gave prismatic needles, m.p. 235° and was identified as Sym-diphenylurea by mixed melting point with an authentic specimen. Other arylamines behaved similarly with this ester as well as its homologue.

We have great pleasure in tendering our thanks to Dr. R. F. Hunter for his kind interest in this work.

#### Summary of Part II.

The action of various aromatic amines on cyclopentanone-2-carboxylate and 4-methylcyclopentanone-2-carboxylate has been studied, and it has been observed that it is possible to prepare the arylamides and arylimino-amides. The former can be cyclised to carbostyryl derivatives.

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