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APPLICATION OF A BIOGENETIC-TYPE SCHEME FOR RESORCINOL AMINO DERIVATIVE SYNTHESIS

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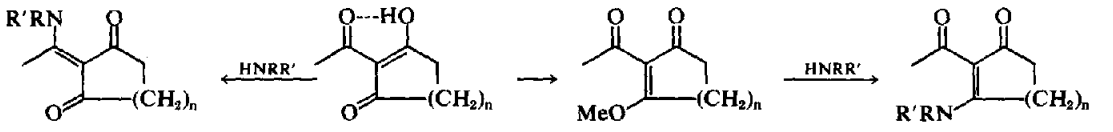
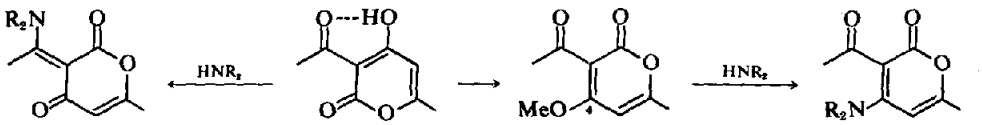
Abstract—Secondary amines react with methyl dehydroacetate (7) and with the γ-amino-α-pyrones (8) to give symm-tolylenediamines (14)—nitrogeneous derivatives of orcinol (15). Diazaresorcinols (25 and 28) have also been prepared by the same route. The reactions studied resemble those postulated in the biosynthesis of a number of natural phenolic compounds and reveal the interesting possibility of biogenetic-type synthesis of some modified acetogenins.

Recent studies[1] have shown that vinylic substitution of various amines in the alycyclic vinylogous esters series (3) produces enaminodiketones (4); the latter compounds being isomeric with vinylogous amides (1), which in some cases can be formed by direct enamination of β-triketones (2). It has been found that the heterocyclic triacylmethane—dehydroacetic acid (6)—as well as its methyl ester (7) reacts with amines in a similar way, yielding the isomeric amino derivatives 5 and 8 respectively.[2,3] When secondary amines were used, in addition to 4-amino-2-pyrones 8 generated evidently by C_4-O bond cleavage in 7, no oxygen containing products were isolated. The formation of these compounds implies dramatic transformation of the parent pyrone (7) under comparatively mild conditions and which is assumed to proceed through the opening of the pyrone ring by the C_6-O bond cleavage in either molecule 7 or 8. Ring opening of this type is a characteristic feature of 2-pyrones.[4] For instance the dehydroacetic acid (6) with secondary amines taken in excess is readily converted *via* liable intermediate acids (9) into fairly stable bis-enaminoketones (10).[5] Similar transformations of the methyl dehydroacetate (7) should afford 11 and 12, and the latter substance is expected to be more reactive than its structural isomer 10. As shown in the present work, in this case the reaction results in the tolylenediamines 14. This reaction is of biosynthetic interest because of its similarity to some processes including polyketides and leading to naturally occurring phenolic products of the orcinol group (15).

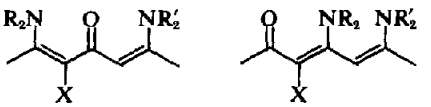


1 2 3 4

n = 1, 2, with various substs in nuclei



5 6 7 8



9: X = CO_2H
10: X = H

11: X = CO_2H
12: X = H

Heating of pyrrolidino-pyrone (**8a**) or piperidino-pyrone (**8b**) with the corresponding amine in an inert medium yields (70–80%) bases of general formula $C_{15}H_{22}N_2$ and $C_{17}H_{26}N_2$ respectively, in accordance with elemental analysis and mass spectral data. When the methyl dehydroacetate (**7**) was treated with an excess of the aforementioned amines the same products were obtained. A similar compound was also isolated when the morpholine and pyrones **7** or **8c** were allowed to react. The proposed structure of these previously unknown substances was definitely proved by NMR data. Thus methyl resonance of the tolylic type ($\delta \sim 2{\cdot}2$ ppm) in addition to methylene peaks of amino residues with usual chemical shifts are present in the NMR spectra of all these compounds. There are also signals of three aromatic protons at 5–6 ppm which are best resolved in the spectrum of the pyrrolidine derivative (Fig 1). Therefore all products have the structure of symmetrically substituted aminotoluidines (**14**) explaining the strong diamagnetic shift of aromatic resonances.[6] This agrees also with the IR and UV spectra which exhibit characteristic aromatic absorbtion.

The formation of phenylenediamines (**14**) from methyl dehydroacetate (**7**) is in accordance with the following scheme. The reaction of **7** with different amines proceeds through several stages including amino-pyrones (**8**) as the necessary intermediates.[2,3] As stated, when treated with an amine these pyrones can undergo ring opening to give the unsaturated aminoketo acids (**11**). A series of transformations can be postulated for this polyfunctional system, leading to loss of all three O atoms in the starting molecule (**8**), decarboxylation and/or dehydration being the most reasonable among such conversions. In fact compound **11** could be regarded as both a β-keto acid and its enamino derivative. It is this particular property which makes similar systems very unstable owing to a tendency to decarboxylate,[7] which is well documented by quite a few examples in dehydroacetic acid chemistry.[5,8] Decarboxylation and intramolecular cyclization of the bis-enaminoketo acid (**11**) may proceed through the intermediate bis-enamine **13** (or its mesomer). To date the behaviour of these polyfunctional compounds is not understood completely though its terminal methylene group is known[9] to be highly reactive towards electron deficient centers. As a consequence, the bis-enamine (**13**) could undergo in addition an intramolecular aldol type condensation to afford the symmetrical tolylenediamine (**14**) at the final stage in the chain of the methoxy-pyrone (**7**) transformations.

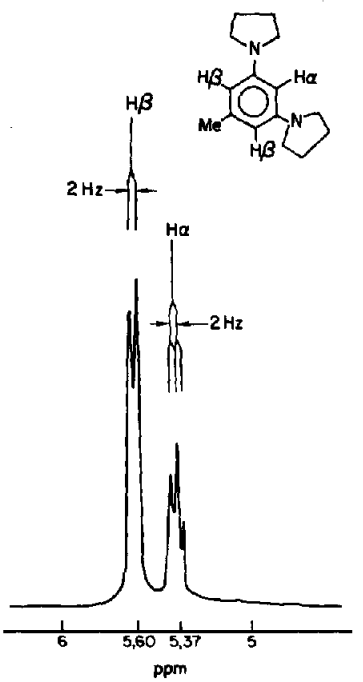
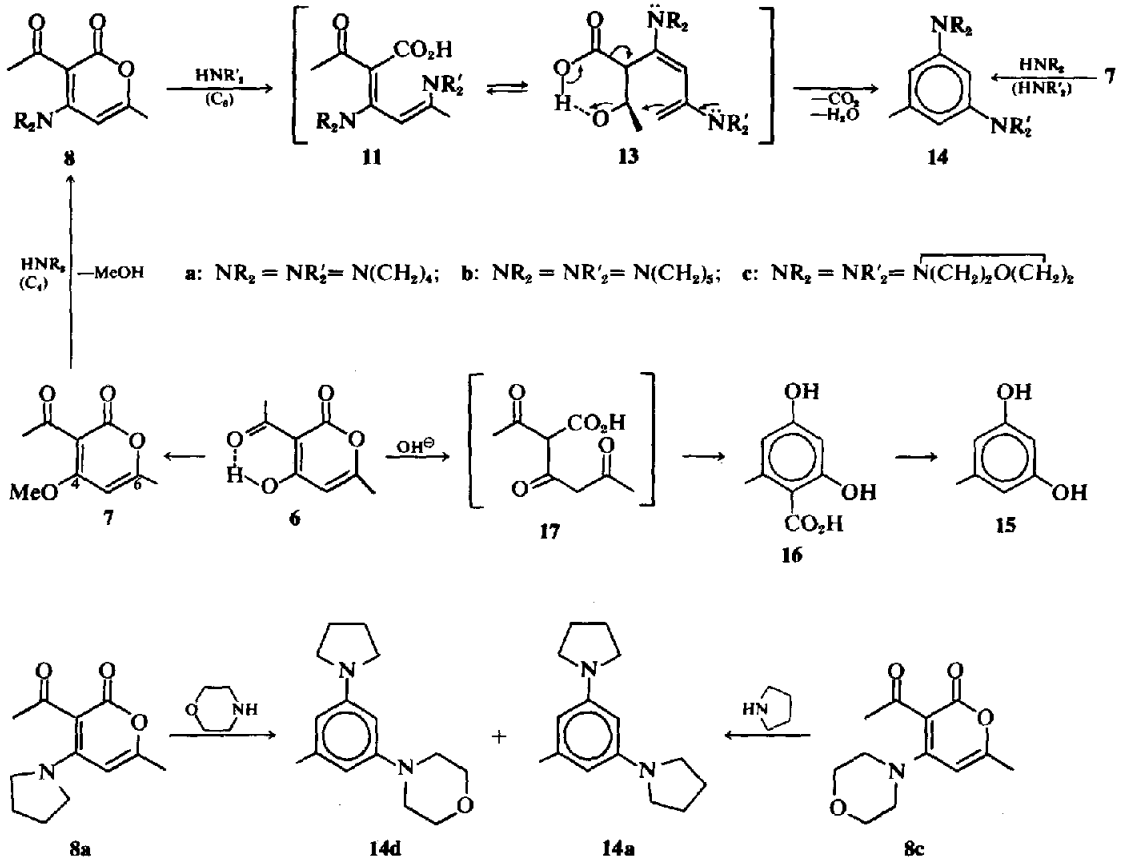


Fig 1. Aromatic portion of the 60 MHz spectrum of bis-pyrrolidino toluene **14a** in CCl_4 solution.

If the proposed scheme is correct, one could predict *a priori* that the introduction of different secondary amines at the steps **7** → **8** and **8** → **14** should result in "mixed" bases **14**.* As was expected, treatment of the pyrrolidino-pyrone (**8a**) by morpholine, or, *vice versa* of morpholino-pyrone (**8c**) by pyrrolidine yielded the related to diamines (**14a–c**) tolylenediamine (**14d**). Its structure was proved by spectral data and elemental analysis. In both cases the base (**14a**) was also isolated in moderate yield presumably due to re-enamination at one of the stages influenced by the more active pyrrolidine.

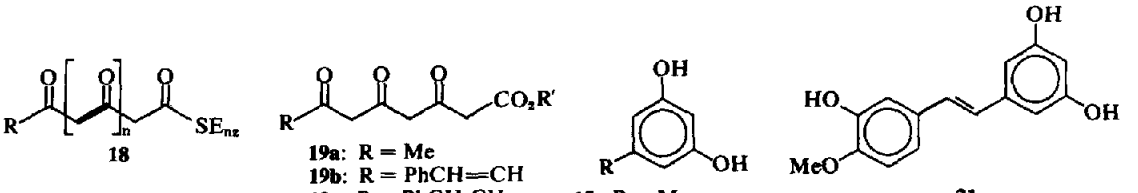
The formation of diamines (**14**) from the methyl dehydroacetate (**7**) and ultimately from dehydroacetic acid (**6**) may provide a particular biosynthetic interest. Indeed a certain parallel exists between this reaction and the conversion of the acid **6** into orcinol **15**, orsellinic acid **16** and some other products of natural type under alkaline conditions, as was demonstrated by Collie[10] as early as in the beginning of the century. The relative facility of such conversions for the substances with regularly alternating acetate moieties enabled Collie to suggest that similar processes occur in living systems. According to the modern viewpoint[11–14] the biogenesis of many secondary phenolic metabolites and of a number of phenols from higher plants can be satisfactorily rationalized on the basis of enzyme-bound poly-β-keto thiolester progenitor **18** ($n = 2-8$). In order

*The discussed route **7** → **14** was only realised in presence of *secondary* amines. When *primary* amines or *secondary* pyrono amines were used the reaction appeared to terminate at the step **11**[3].



to verify this hypothesis a particular case (**18**; n = 2) has been studied[15–18] *in vitro* starting from the keto esters of type **19** related to oligo-β-ketides. Under certain conditions an internal basic aldolization of such compounds results in resorcinols (**20**) including orcinol (**15**) as the simplest acetogenin of the series. Transformation **6** → **15** *via* triketo acid **17**, only slightly differing from hypothetical tetraketide **19a**, has been considered, *cf*,[15] as a biogenetic-like synthesis. Therefore it seems logical to describe the observed transformation of the methoxy **7** and amino **8** pyrones under the action of secondary amines as a biogenetic-type synthesis of nitrogeneous derivatives of orcinol **15**—*diazaorcinols* **14**. Such consideration is favoured by both a similarity in chemical behaviour and the structural resemblance of corresponding probable intermediates, **17** and **11**.

It appeared reasonable to apply the same approach to the synthesis of more complicated resorcinols, for example stilbenes of the type **21**. The known[19] dehydroacetic acid derivatives (**22** and **26**) were chosen as the starting materials for this purpose. The treatment of corresponding methoxy pyrones (**23** and **27**) with secondary amines was believed to afford, as in the case of methyl dehydroacetate **7**, intermediate bis-enaminoketo acids (for instance **24**) related to bis-enamines (**11**). By the same reasoning, the acid **24** could be considered as a nitrogeneous analog of

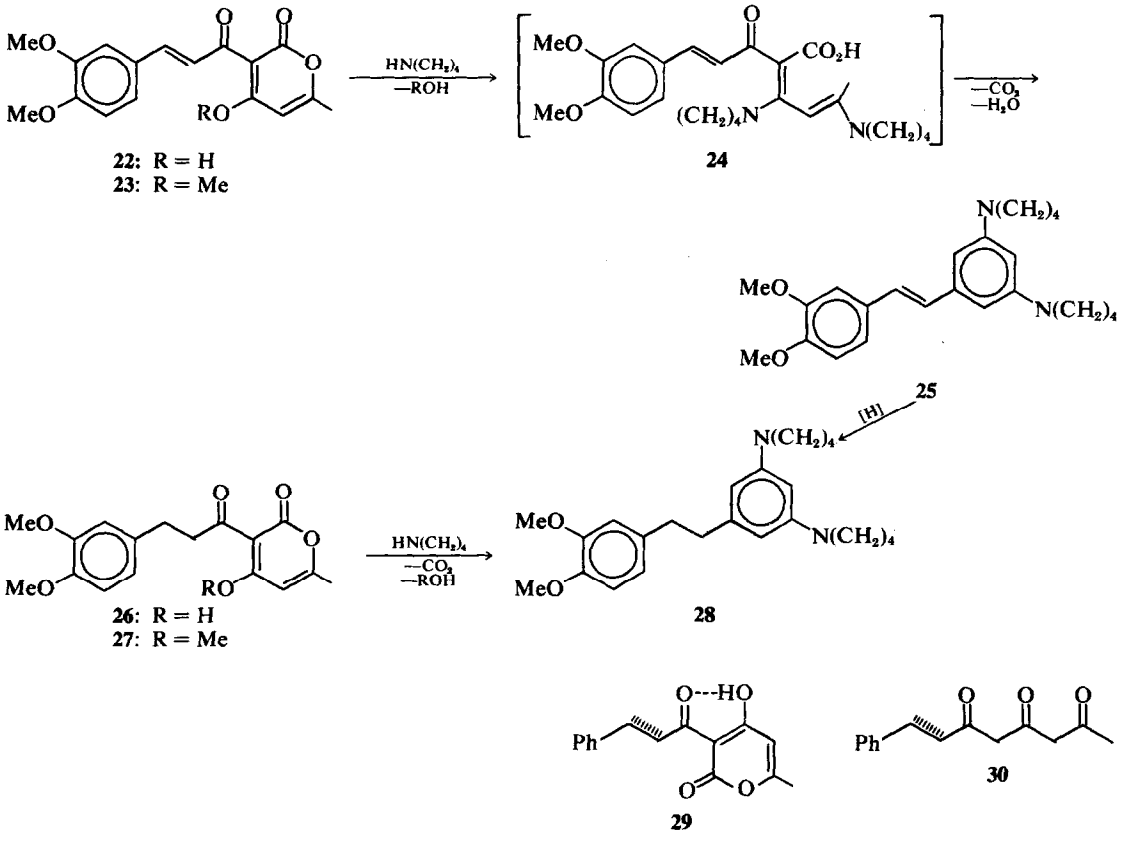


"mixed" acetate-shikimate tetraketide (**19b**) postulated,[11,14,15,20] as well as its dihydro derivative (**19c**) in the biosynthesis of stilbenes (**20a**, **21**) and dihydrostilbenes of type **20b**, respectively. It should be noted that Birch *et al.*[15] and later Crombie and James[21] attempted to realise the biogenetic-like synthesis of these phenols starting from the (hydrogenated) cynnamoyl pyrone (**29**). They considered the intermediate (unsaturated) triketone (**30**) which should arise from **29** under basic conditions as a fairly good model of postulated tetraketide (**19b**, **c**). However, the saturated pyrone (**29**) was only converted into the dihydropinosylvin (**20b**) in low yield.[15]

In our case, as was expected, O-methylation of the γ-hydroxy-pyrone (**22**) by diazomethane followed by treatment of the resulting[22] methoxy derivative **23** (without further purification) with excess of pyrrolidine and chromatography of the complex reaction mixture gave the rhapontigenin (**21**)[20] analog, stilbene **25**.* The structure of this rather unstable compound was based on physical and chemical evidence. Thus in the NMR spectrum signals at *ca* 5·5 ppm of the *m*-protons of aromatic cycle bearing the pyrrolidine substituents are very close to those observed in the spectrum of the tolylenediamine **14a** (Fig 1). This spectrum contains also the AB-quartet of the stilbene protons centered at 6·77 ppm, the value of $J_{AB} = 14$ Hz implying[23] *trans*-configuration of the olefine **25**. Its hydrogenation gives a compound which exhibits no olefinic resonances in the NMR but contains a broadened singlet at 2·80 ppm. Since all other elements of the spectrum are practically identical with those of **25** the structure of the bibenzyl (**28**) was assigned to the hydrogenated product which was confirmed by IR and UV data as well as by independent synthesis. All operations described for the cynnamoyl-pyrone (**22**) were repeated for its dihydro derivative (**26**) and the bibenzyl (**28**) identical with that formed from the stilbene (**25**) was prepared in satisfactory yield.

Thus the conversion of the γ-hydroxy-α-pyrones (**6**, **22**, **26**) into respective phenylenediamines (**14**, **25**, **28**) involves the formation of intermediates of type **11** related to oligoketide amino derivatives and resembles some reactions postulated in the

*Both the TLC analysis (on alumina or silicic acid) and preparative isolation of the stilbene **25** was greatly facilitated by a characteristic blue-violet colouring of this substance (as well as tolylenediamines **14**) which rapidly developed on the exposure of chromatograms to the open air.



biosynthesis of a number of phenols from fungi and higher plants. Therefore, γ-hydroxy-α-pyrones, or better γ-amino-α-pyrones of type **8** may be successfully applied to a biogenetic-like synthesis of some nitrogen containing acetogenins which hitherto have not been found in Nature.

EXPERIMENTAL

All m.ps are uncorrected. The IR spectra were taken in KBr pellets with a UR-10 spectrometer. UV spectra were taken in EtOH soln on a Unicam SP-700 double beam recording spectrophotometer. NMR spectra were measured on a Varian DA-60-IL spectrometer and chemical shifts are represented in δ values (TMS).

Preparations of 4-*amino*-3-*acetyl*-6-*methyl*-2-*pyrones* **8a–c**

(a) A soln of **7**[22] (1·0 g) and pyrrolidine (0·39 g) in toluene (200 ml) was kept at 0–5° for 3 hr and then evaporated. The residue was crystallized from THF-hexane to give **8a** (1·0 g, 80%), m.p. 141–142°; IR ν_{max} 1694, 1660, 1642, 1520, 1470 cm^{-1}; UV λ_{max} 246 nm (ε 17,800), 283 (5700), 325 (7700). (Found: C, 65·14; H, 6·85; N, 6·28. $C_{12}H_{15}NO_3$ requires: C, 65·14; H, 6·83; N, 6·33%).

(b) The reaction was performed as above for 3 days using 0·5 g of **7** and 0·23 g of piperidine. The dry residue was refluxed in toluene until the colour faded. Evaporation and crystallization of the resulting solid from THF-hexane afforded **8b** (0·5 g, 70%), m.p. 131–132°; IR ν_{max} 1685, 1660, 1640, 1523, 1475 cm^{-1}; UV λ_{max} 247 nm (ε 19,700), 288 (7700), 333 (7500). (Found: C, 65·98; H, 7·23; N, 6·11. $C_{13}H_{17}NO_3$ requires: C, 66·36; H, 7·28; N, 5·95%).

(c) The reaction was performed as above for 3 hr using 0·9 g of **7** and 0·43 g of morpholine. The colourless product was crystallized from THF-hexane to give **8c** (0·6 g, 50%), m.p. 150–151°; IR ν_{max} 1695, 1660, 1640, 1510, 1477 cm^{-1}; UV λ_{max} 247 nm (ε 18,900), 290 (7300), 339 (8400). (Found: C, 60·45; H, 6·49; N, 6·02. $C_{12}H_{15}NO_4$ requires: C, 60·75; H, 6·37; N, 5·90%).

Preparation of tolylenediamines **14a–d** *– Reaction of methyl dehydroacetate* **7** *and amino pyrones* **8** *with excess of secondary amines*

(a) A soln of **7** (1·0 g) and pyrrolidine (0·5 g) in benzene (100 ml) was refluxed for 4·5 hr and then evaporated. The residue was crystallized from ether-hexane to give **14a** (0·8 g, 60%), m.p. 96–97°; UV λ_{max} 241 nm (ε 40,500), 310 (6000). (Found: C, 77·94; H, 9·45; N, 12·49. $C_{15}H_{22}N_2$ requires: C, 78·21; H, 9·63; N, 12·16%).

The reaction was performed similarly for 4·5 hr using 110 mg of **8a** and 1 ml of pyrrolidine. Crystallization from hexane gave **14a** (90 mg, 80%), m.p. 95–97°, identical in all respects with the sample of **14a** prepared as above.

(b) A soln of **7** (1·3 g) and piperidine (1·9 g) in toluene (150 ml) was refluxed for 7 hr and then evaporated. The oily residue solidified on treatment with dry HCl in ether to give **14b** as dihydrochloride (0·6 g, 25%), m.p. 165–175° (dec) from MeOH-ether. (Found: C, 62·05; H, 8·52; N, 8·56; Cl, 21·22. $C_{17}H_{28}N_2Cl_2$ requires: C, 61·82; H, 8·52; N, 8·46; Cl, 21·40%).

The reaction was performed similarly for 12 hr using 0·18 g of **8b** and 0·33 g of piperidine to give the dihydrochloride of **14b** (0·18 g, 70%), m.p. 165–175° (dec), identical in all respects with the above specimen.

(c) A soln of **7** (1·0 g) and morpholine (0·3 g) in benzene (100 ml) was refluxed for 2 hr, then evaporated and the residue was chromatographed on silicic acid (75 g; 18% H_2O; 250–300 mesh) under N_2. Elution with acetone-hexane (1:2) gave **14c** (0·9 g, 60%), m.p. 94–95° from ether-hexane. (Found: C, 68·65; H, 8·49; N, 10·79. $C_{15}H_{22}N_2O_2$ requires: C, 68·67; H, 8·45; N, 10·68%).

(d) A soln of **8a** (1·0 g) and morpholine (2·8 g) in benzene (100 ml) was refluxed for 20 hr, then evaporated *in vacuo* to dryness and the residue was crystallized from THF-hexane to give 0·3 g of the starting amino pyrone **8a**, m.p. 140–142°. The concentrated mother liquor (*ca* 0·8 g) was subjected to preparative TLC on neutral alumina (grade II, nonbound layer) using the acetone-heptane (1:5) solvent mixture. From the zone with R_f *ca* 0·7 was obtained **14a** (60 mg), m.p. 95–97°, identical (m.m.p., IR) with the authentic sample of **14a**. The zone with R_f *ca* 0·5 afforded **14d** (120 mg, 15%), m.p. 56–57° from hexane. (Found: C, 73·22; H, 9·06; N, 11·56. $C_{15}H_{22}N_2O$ requires: C, 73·13; H, 9·00; N, 11·37%).

A soln of **8c** (0·5 g) and pyrrolidine (0·6 g) in toluene (100 ml) was refluxed for 5 hr, then evaporated *in vacuo* and the oily residue was subjected to preparative TLC under the same conditions as above. From the zone with R_f *ca* 0·7, **14a** (40 mg) was isolated, m.p. 94–96°, and from the zone with R_f *ca* 0·5 the "mixed" diamine **14d** (0·2 g, 40%) was isolated, m.p. 56–57°.

Preparation of 3,4-*dimethoxy*-3',5'-*dipyrrolidinostilbene* **25**

To a soln of **22**[18] (0·5 g) in THF (80 ml) an ethereal soln of diazomethane (prepared from 5 g of nitrosomethylurea), was added and the mixture was kept at room temp for 1·5 hr and evaporated. The residue was dissolved in toluene (100 ml) containing pyrrolidine (2·0 g), refluxed for 6 hr, then evaporated and the resulting mixture was chromatographed on silicic acid (60 g) under N_2. Elution with hexane gave **25** (50 mg, 8% based on the starting pyrone **22**) as the fine yellowish needles, m.p. 115–116° (from ether); UV λ_{max} 241 nm (ε 37,000), 285 (20,400), 298 (19,400), 330 (22,600). (Found: N, 7·49; M^+ 378. $C_{24}H_{30}N_2O_2$ requires: N, 7·40%; mol.w. 378·5).

Preparation of 3,4-*dimethoxy*-3',5'-*dipyrrolidinobibenzyl* **28**

To a soln of **26**[19] (1·2 g) in THF (100 ml) an ethereal soln of diazomethane (prepared from 5 g of nitrosomethylurea), was added and the mixture kept at room temp for 3 hr and evaporated. The residue was dissolved in toluene (100 ml) containing pyrrolidine (2·5 g), refluxed for 20 hr, then evaporated and the resulting mixture was chromatographed on silicic acid (60 g) under N_2. Elution with ether-hexane (1:3) gave **28** (0·2 g, *ca* 15% based on the starting pyrone **26**), m.p. 118–122° (from ether-isopentane). An analytical sample had m.p. 122–124°; UV λ_{max} 242 nm (ε 40,800), 272 (12,700), 289 (4300), 315 (4800). (Found: C, 75·65; H, 8·39; N, 7·37; M^+ 380. $C_{24}H_{32}N_2O_2$ requires: C, 75·75; H, 8·48; N, 7·36%; mol.w. 380·5).

The stilbene **25** (40 mg) in EtOH (20 ml) was hydrogenated at room temp in the presence of 30% Pd/$SrCO_3$ (10 mg) to give 15 mg of **28**, m.p. 122–124° (from ether-isopentane), identical (m.m.p., IR) with the above sample of **28**.

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