Tetrahedron. Vol. 27, pp 5031 to 5047. Pergamon Press 1971 Printed in Great Britain

NENITZESCU SYNTHESIS OF 5-HYDROXYINDOLES—II*

5,6,7-TRIMETHOXYINDOLES AND CYCLIZATION OF ENAMINO HYDROQUINONES, -QUINONES AND INTERMEDIATE IMINO DERIVATIVES

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(*Received in the UK* 20 *May* 1971; *Accepted for publication* 8 *June* 1971)

Abstract—The Nenitzescu reaction between 2,3-dimethoxyquinone and β-aminocrotonic ester gave an appreciable yield of the hydroquinone derivative **16** which was cyclized to the planar lactone **19** and oxidized to quinone **27**. The same reaction applied to the α-methyl-β-aminocrotonic ester afforded a dihydrobenzofuranol (*trans*- and *cis* **25**) which is considered as evidence for the formation of an imino derivative (**3**) as transient intermediate of the title reaction. The double cyclization of the *bis*-enaminoquinone **28** resulted in the formation of two benzo[1.2-b; 4.5-b']dipyrrole derivatives **33** and **34**. The assumed primary cyclization product is the *S*-1,5-diazaindacene **32**, which stabilizes itself by addition of acetic acid to **33** and **34**. This finding is in favour of a quinoneimine structure (**12**) of the immediate precursor of the formation of 5-hydroxyindoles by the Nenitzescu reaction.

IN THE previous paper of this series[1] a mechanism of the Nenitzescu reaction was described based on experimental evidence, namely the isolation of several intermediates and by-products as well as their behaviour in various reactions. The main steps of this mechanism are (Chart I): a 1.4-addition of an activated enamine (**1**) to 1.4-benzoquinone, the formation of an imino compound (**3**), its isomerization to an enamino derivative of hydroquinone (*cis*-**4**), subsequent oxidation to the corresponding quinone (*cis*-**5**) by the initial still unreacted quinone or by **6**, cyclization to a carbinolamine (**6**) and formation of the 5-hydroxyindole **7** by water elimination and concomitant reduction at the expense either of *cis*-**4** or of the hydroquinone resulting from reduction of the initial 1.4-benzoquinone.

The experimental evidence was based on the isolation as main product of a hydroquinone derivative (*trans*-**4**; R = Ph) which could not be made to cyclize to the indole **7** (R = Ph) except in AcOH and the presence of a catalytic amount of 1.4-benzoquinone. In the absence of the latter the corresponding benzofuran (**9**) was formed. The acid medium is necessary to induce a *trans-cis* isomerization through the intermediate of the immonium ion **8** (Chart 1). Further evidence was furnished by the reaction between 1.4-benzoquinone and the αmethyl-β-aminocrotonic ester which leads to a compound whose molecular formula corresponds to an imino derivative of type **3**. This reaction was described in 1953.[2]

In 1966 Allen jr and Weiss[3] independently proposed a mechanism also based on

* Part I. see ref. 1

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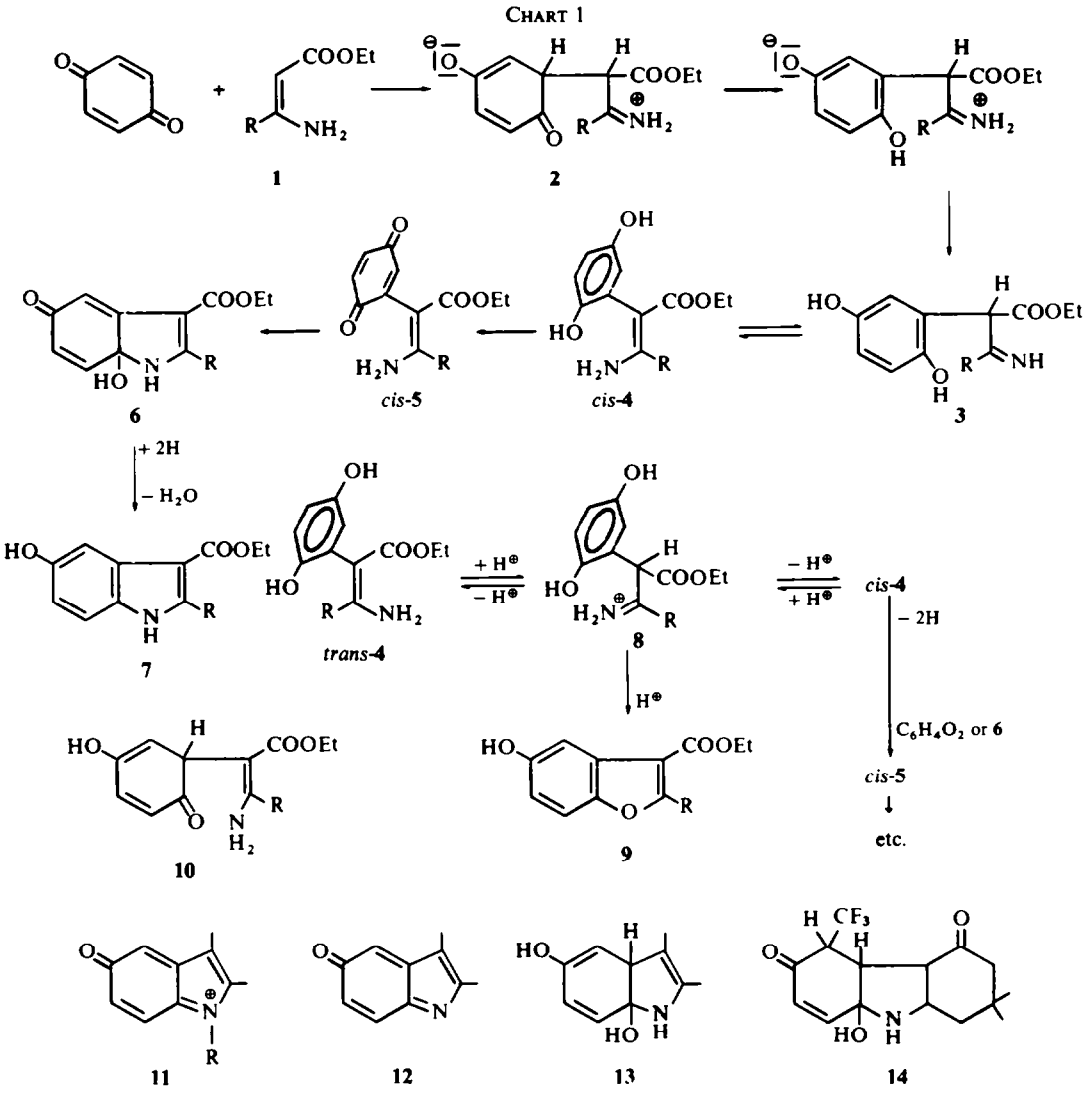
CHART 1



experimental evidence, essentially the same as that described by us. Using as starting materials monoalkylated 1,4-benzoquinones and β-aminocrotonic esters they succeeded in isolating in small amounts (0·3—15%) as by-products. hydroquinone derivatives of type *trans*-**4** (R = alkyl). Geometrical isomers of compounds of the type *trans*-**4** or *trans*-**5** were considered as intermediates of the reaction. Actually both the enamino hydroquinones and -quinones could be cyclized to indoles in the presence of small amounts of their conjugate acids and of either 1,4-benzoquinone or sodium hydrosulfite respectively. However these authors do not consider the imino derivative (**3**) as an intermediate, the hydroquinone adduct in their opinion being formed from the zwitterionic dienone **2** which is transformed into an enamino dienone **10**. By aromatization of the latter the substituted hydroquinone **4** is formed directly. An

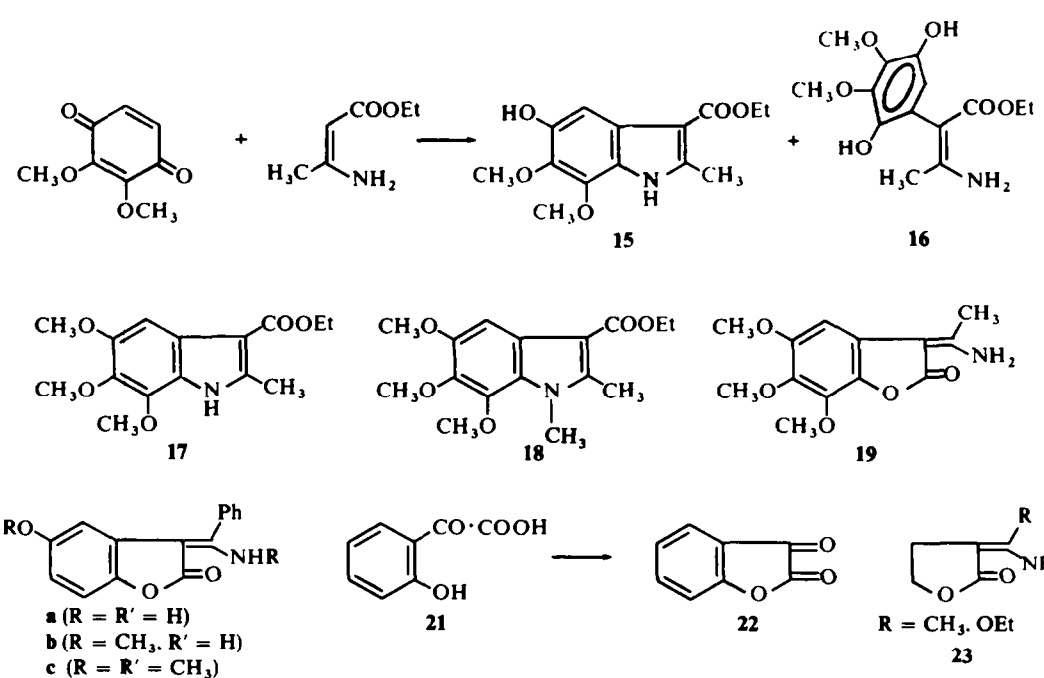
interesting feature was the formulation of the carbinolamine **6** as a quinoneimmonium ion (**11**).

The afore mentioned mechanism[1,3] was confirmed by Monti[4] who added new experimental evidence to its support. Also in 1966 Domschke[5] sustained, only on theoretical grounds, that the key intermediate should be the zwitterion **2** which by direct ring closure affords the carbinolamine **13** without an intermediate aromatization. A compound of this type (**14**), was recently isolated by Allen jr.[6] and was proved to be not a true intermediate of the reaction. Carbinolamine **14** could be converted to the corresponding indole only by the prior opening of the ring with intermediate formation of the corresponding hydroquinone derivative. All attempts to eliminate a molecule of water from compound **14** in order to obtain the corresponding indole failed. Neither were attempts at dehydrogenation to the corresponding dienonic carbinolamine of type **6** successful.

5,6,7-*Trimethoxyindoles*

The aim of the work described in the present paper was to find a Nenitzescu reaction in the crotonic series which would afford acceptable yields of hydroquinone derivatives or of enamino quinones of similar type to the supposed intermcdiates of the title reaction. It was found that the reaction between 2,3-dimethoxy-1,4-benzoquinone (Chart 2) and the β-aminocrotonic ester fulfills the former requirement: from the mixture the hydroquinone derivative **16** was readily isolated in yields of about 24–28% besides the corresponding indole **15** obtainecl in yields of 23–36%.

CHART 2



These derivatives also present psychopharmacological interest for the synthesis of analogs of serotonine and mezcaline. The parent compounds of this series were synthesized quite recently[7]; the 5,6,7-trimethoxyindole by reduction of the corresponding *oω*-dinitrostyrene (another Nenitzescu indole synthesis[8]) and the 4,5,6-trimethoxyindole by reduction of the corresponding isatin.

The 2-methyl-3-carbethoxy-5-hydroxy-6,7-dimethoxyindole (**15**) was methylated to the corresponding 5,6,7-trimethoxyindole **17**. Changing the molar ratio between indole, methyl sulfate and NaOH from 1:1·1:1·1 to 1:4:4 resulted unexpectedly in the exclusive formation of the N-methylated indole **18** (81%). A mixture of 40% **17** and 60% **18** (indicated by NMR) was obtained when the ratio was 1:2:2. This methylation takes place very smoothly at room temperature and preliminary experiments showed it to be applicable also in other cases although indole itself failed to react. This fact deserves attention since N-alkylation of indoles usually require much more drastic conditions (Na and liquid NH_3)[9,10] and only a few cases are known by relatively mild conditions (e.g. with *p*-toluenesulfonic esters at temperatures over 100°).[10,11] Our results in this respect will be published in a separate paper.

The indole structures are confirmed by their spectra. UV absorptions indicate in all cases the existence of the indole chromophore and only small differences are registered from one compound to the other. IR spectra exhibit for **15** the existence of group OH and NH for **17** the existence of only the group NH and complete absence of any absorption in this region for **18**. Taking into account the NMR chemical shifts of the α-CH_3 and N-CH_3 groups in **18**, an indolenine structure can easily be excluded unequivocally. Mention is deserved by the fact that trimethoxyindole **17** in CCl_4 solution shows association through hydrogen bonds in the IR spectra. The intensity of the band decreases on dilution without change in its position which indicates bimolecular association.

Enamino hydroquinones

The *trans-cinnamic* configuration of the hydroquinone derivative *trans*-**4** (R = Ph) as well as the non-coplanarity of the hydroquinone moiety with the rest of the molecule was previously discussed by us.[1] It is worthy of mention that since in all cases when UV, IR and NMR spectra were recorded[3,4] no imino-enamine tautomerism could be detected nor could an equilibrium between *cis* and *trans* isomers. The sole observed isomer was the one derived from the β-amino-*trans*-crotonic acid and characterized by the low IR frequency of the chelated carbonyl (for **16**: ν_{CO} = 1658 cm^{-1}) and a normal value of the NMR chemical shift of the Me group attached to the double bond (δ_{CH_3} = 1·74 ppm). For the corresponding *cis* derivatives values should fall downfield about δ = 2·5 ppm.[12,*] The non-coplanarity of the hydroquinone moiety with the rest of the molecule can also be observed in the crotonic series by comparing the UV spectra of enamino hydroquinones to the corresponding β-aminocrotonic esters (for **16** and β-amino- or β-N,N-dimethylaminocrotonic ester see the Table).

* In the cinnamic series there is no Me group attached to the double bond so that the NMR measurements somewhat lose their reliability as based only upon a secondary splitting of the Et triplet and quartet. In order to obtain sharper signals the methanesulfonic diester of the hydroquinone *trans*-**4** (R = Ph) was also prepared and neither in that case could any splitting of the Me or Et groups be observed. The OH groups being protected so as to make impossible a cyclization to benzofuran, addition of a small amount of TFA resulted in partial decomposition so that no conclusion could be drawn.

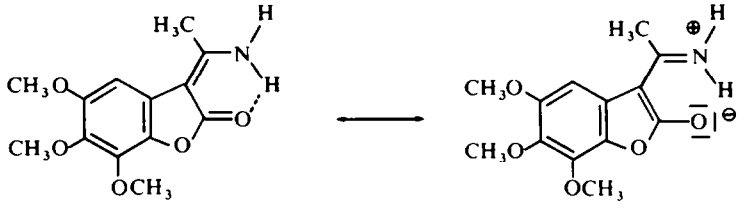
Lactonization products of enamino hydroquinones

The satisfactory yields and easy isolation of the hydroquinone derivative **16** made possible a closer examination of its behaviour. On treatment with methyl sulfate in alkaline a cyclization product was formed, a coplanar lactone **19** of type previously described by us in the cinnamic series.[1] As the latter compounds had not been closer examined at the time we considered it useful to draw a parallel between the two series: esters and lactones. On ring closure the hydroquinone derivatives are forced to adopt a planar configuration and this fact is made obvious by a dramatic shift of the absorption bands in the electronic spectra toward visible or even beyond. In the case of compound **16** on lactonization the longest wavelength UV maximum was shifted by 49 mμ while in the cinnamic series (**20**) the corresponding band was shifted by 51·5–58·5 mμ (see Table). Absorption in the cinnamic series is extended beyond the limit of the visible region. a fact which explains the yellow color of the Ph derivatives.

This strong bathochromic effect is not even partly due. as one may suspect. to formation of a chromophore of the isatin type whose extreme maximum of weak intensity (log ε = 2·5–3) lies beyond 400 mμ.[14] In fact it can be seen from literature data.[15] that there is almost no difference between the UV spectra of the *o*-hydroxyphenylglyoxylic acid (**21**) [$\lambda_{max}^{E\,OH}$ (log ε) = 291 mμ (4·071)] and the corresponding lactone. the coumarandione-2.3 (**22**) [$\lambda_{max}^{E\,OH}$ (log ε) = 292 mμ (4·083)]. Hence there is no analogy with the isatin case. The theoretical explanation of this phenomenon may probably be found in the hybridization of the heteroatoms as well as in their electronegativity. The nitrogen conserves its sp^2 hybridization as in indole while the oxygen has its unshared pairs of electrons in 2*p* orbitals possessing also a certain amount of *s* character owing to the deformation of the valence angle. Even a sp^3 hybridization may not be excluded. On the other hand the stronger electronegativity of oxygen weakens the mobility of the unshared electrons.*

The IR spectra of these lactones exhibit as it can be seen from the Table very low carbonyl absorptions as compared to literature data[17] which indicate a frequency range between 1740–1800 cm^{-1}. This appreciable frequency decrease shows the existence of a hydrogen bond to the amino group. therefore a *trans*-crotonic or -cinnamic configuration. similar to that of the corresponding hydroquinone derivative. Some saturated enamino lactones are known[18] (**23**) which show still lower values for the carbonyl absorption (ν_{CO} = 1675–1690 cm^{-1}) owing to the absence of the aromatic double bond. The lack of any higher absorption in this region removes the possibility of a detectable *trans–cis* equilibrium or of imino–enamine tautomerism.

The NMR spectrum of the trimethoxylactone **19** shows an interesting phenomenon. namely the resonance between two canonical forms. which confer on the C—N



bond a partially double-bond character,† hindering the free rotation and resulting in the non-equivalence of the two protons of the amino group. In fact they actually

* Sulfur which is less electronegative than both oxygen and nitrogen confers on the isatin analog in this series. the thianaphthenequinone. only a yellow color as compared to the colorless *o*-mercaptophenylglyoxylic acid.[16] Therefore it may be concluded that both hybridization of the heteroatom and electronegativity play an important part in this phenomenon.

† This is also reflected in the UV spectra and contributes. in part and together with the supplementary conjugation from coplanarity of the benzene nucleus. to the large bathochromic effect observed.

TABLE 1. CHARACTERISTIC UV and IR ABSORPTIONS OF ENAMINO ESTERS, -HYDROQUINONES, -QUINONES AND -γ-LACTONES

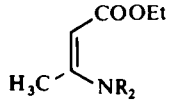
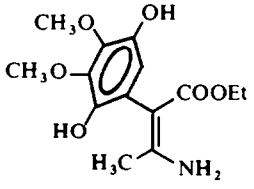
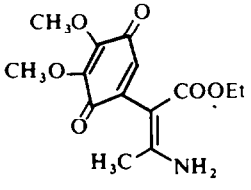
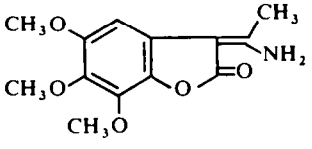
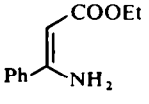
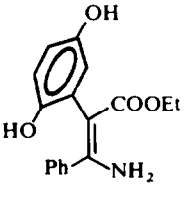
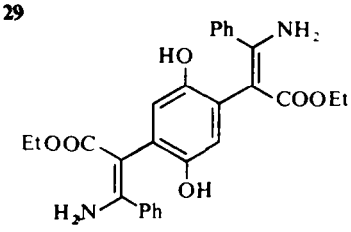
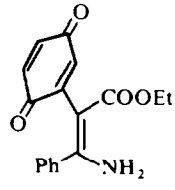
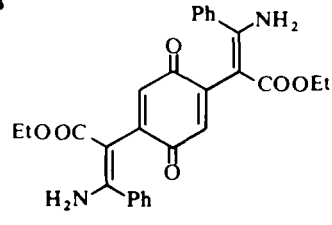
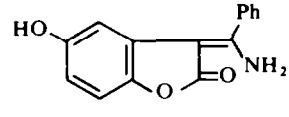
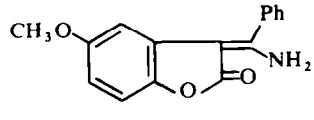
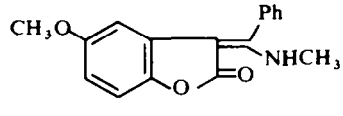
Compound	UV: $\lambda_{max}^{E\,OH}$ mμ (log ε)		IR: ν_{max} cm^{-1} [a]
	Enamine band	Other bands	
	(R = H): 274 (4·31)[13] (R = CH_3): 284 (4·51)[13]	—	1665 (CO)[19] 1677 (CO)[19]
16 	286 (4·22)	—	3540 (OH). 3510 and 3328 (NH_2). 1658 (CO)
27 	276 (4·29)[b]	370 (3·416). 470 (3·047)	(CCl_4): 3505 and 3310 (NH_2). 1667 (CO)
19 	335 (4·17)	218 (4·32). 257 (4·17)	3496 and 3305 (NH_2). 1712 (CO)
	302·5 (4·14)[1] ε = 13.800	—	(CCl_4): 1670 (CO)
trans-**4** (R = Ph) 	298·5 (4·16)[1]	—	3550 (OH). 3496 and 3320 (NH_2). 1659 (CO)[c]

TABLE 1—*Continued*

Compound	UV: $\lambda_{max}^{E\,OH}$ mμ (log ε)		IR: ν_{max} cm^{-1} [a]
	Enamine band	Other bands	
29 	295 (4·35) ε = 22,180	—	3546 (OH). 3496 and 3323 (NH_2) 1658 (CO)
26 	290 (4·11)[b] ε = 12.980	236 (4·29). 470 (3·23)	(KBr): 3546 and 3324 (NH_2). 1662 (CO)
28 	290 (4·36)[b] ε = 22.750	230 (4·35). 410–420 (3·86). 480 (2·34) (sh)	1662 (CO)[1]
20a 	357 (4·06)	214 (4·39). 270 (4·00)	($C_2Cl_2H_4$): 3570 (OH). 3475 and 3308 (NH_2). 1713 (CO)
20b 	350 (4·05)	206 (4·43). 268 (4·00)	3487 and 3303 (NH_2). 1705 (CO)
20c 	355 (4·13)	206 (4·41) 268 (4·06)	(KBr): 3260 (NH). 1713 (CO)

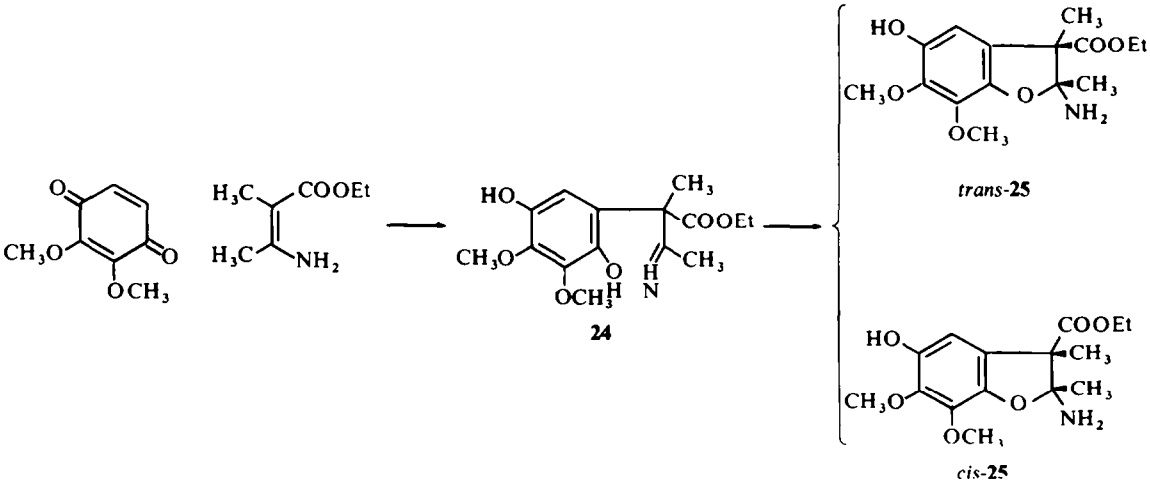
[a] in $CHCl_3$ if not otherwise stated: [b] in dioxane: [c] new corrected values

show different chemical shifts arising as broadened bands at $\delta = 7{\cdot}58$ ppm and $\delta = 8{\cdot}84$ ppm, the latter value corresponding to the chelated hydrogen. The phenomenon is reproducible in the cinnamic series although less obviously, one of the amino proton absorptions being overlapped by that of the Ph group. This type of non-equivalence has been described for formamide by Sunners *et al.*,[19] who worked with $DCO^{15}NH_2$.

It is also of interest to mention the chemical shift of the allylic Me group which is exposed to through space deshielding by the benzene nucleus of the molecule forced now to coplanarity, which was not the case for the uncyclized product **16**.

2,3-Dihydrobenzofuranol-5 derivatives as cyclization products of intermediate imino compounds

Another reaction studied is between the 2,3-dimethoxy-1,4-benzoquinone and α-methyl-β-aminocrotonic ester. This was expected to give **24** a product of the type isolated by Beer *et al.*[2] whose molecular formulae corresponded to imino derivatives. The quinone-enamine adduct initially formed cannot isomerize to an enamino compound in this case. The above authors made no spectral measurements and no other structural proof was brought in favour of the supposed structures. This has been done now for the dimethoxy derivative which was obtained from the above reaction (46%) and whose analysis fitted the molecular formula of the imino compound **24**. Its IR spectrum however indicates the presence of an NH_2 group (in CCl_4: $\nu_{NH_2} = 3415$ and 3343; $\nu_{OH} = 3545$ cm^{-1}). Therefore it was concluded that the real structure corresponds to a cyclization product, namely a stereoisomeric dihydrobenzofuran (*cis*- and *trans*-**25**) which may be considered as strong evidence in favour of the existence of **24** as transient intermediate.



Derivatives of this kind have been obtained from enamines derived from unconjugated aldehydes or ketones and 1,4-benzoquinone by Domschke[20] and Brannock *et al.*[21] but no stereoisomers were detected.

In our case the existence of two stereoisomers was deduced from examination of the NMR spectra. The two Me groups of **25** in positions 2 and 3 may be *trans* or *cis*

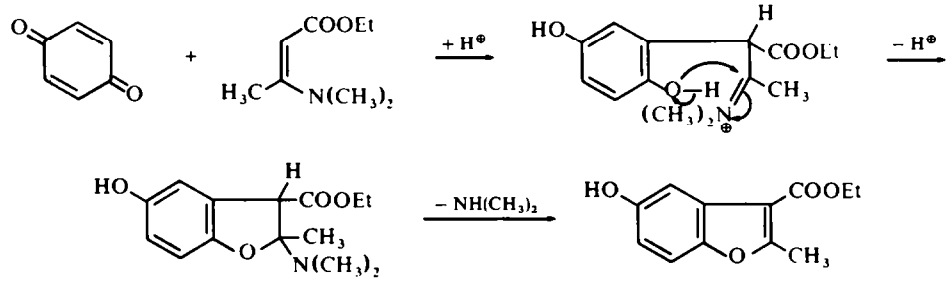
to each other and the two stereoisomers actually represent approximately 78% and 22% of the reaction product respectively. The NMR measurements were made in several solvents ($CDCl_3$, CCl_4, CCl_4 + 15% benzene, benzene and hexamethylphosphoramide) and the proportion of the two stereoisomers remained unchanged throughout. This shows that an equilibrium mixture can be excluded as well as 'ring-chain tautomerism' which could make possible such an equilibrium.

$$cis\text{-}\mathbf{25} \rightleftharpoons \mathbf{24} \rightleftharpoons trans\text{-}\mathbf{25}$$

Supplementary evidence in favour of structure **25** lies in the fact that no color was obtained on treatment with $FeCl_3$, characteristic for hydroquinone derivatives.

The identification of the stereoisomers was done on basis of the chemical shifts of the Me groups in positions 2 and 3 which when *cis* to each other have very similar environments (92 and 94 cps), when *trans* the carbethoxy group exerts a paramagnetic through space shielding effect on the 2-Me group (100 and 88 cps).

The existence of an imino derivative as transient intermediate is also supported by the numerous unsuccessful attempts to obtain an adduct between 1,4-benzoquinone and the β-N,N-dimethylaminocrotonic ester in the normal conditions of the Nenitzescu reaction. Both reagents were consumed during the reaction but no products could be isolated.[22] From the zwitterionic immonium ion of dienone **2** as a key intermediate.[1, 3, 5] the hydroquinone derivative should have been easily formed as well as the corresponding benzofuran, in case the reaction had taken place directly rather than through formation of an imino derivative. Actually benzofuran derivatives were formed but in the presence of AcOH which stabilizes the zwitterion **2** by giving up a proton and leading thus by cyclization to benzofuran which does not occur in its absence.



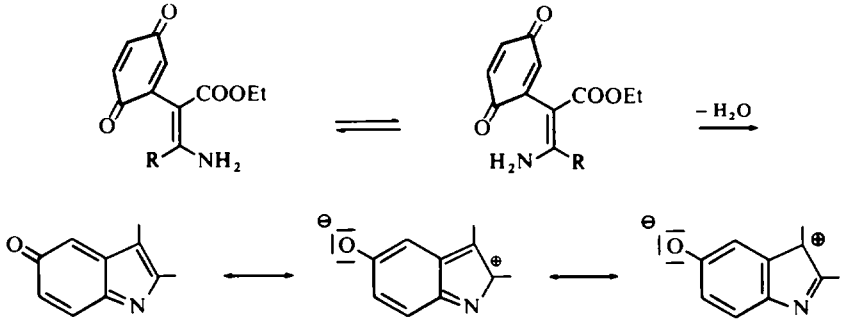
The α-methyl-β-amino-*trans*-cinnamic ester when reacted with 2,3-dimethoxy-1,4-benzoquinone gave no product, as was the case with 1,4-benzoquinone in several solvents ($CHCl_3$, benzene, EtOH, nitromethane and AcOH).

Cyclization of enamino quinones

Another problem which draw our attention was the structure of the immediate precursor of the indole, which until now has been formulated as a carbinolamine (**6**).[1] a quinoneimine (**12**) or as a quinoneimmonium ion (**11**).[3] Among these possibilities the first and last also explain the formation of N-alkylindoles. No such compounds have been isolated as yet. In the first place several attempts were made to cyclize the enaminoquinones **26** and **27** (Chart 4) obtained by silver oxide oxidation of the corresponding hydroquinones *trans*-**4** (R = Ph) and **16**. The NMR and IR spectra

of both enaminoquinones show the existence of one isomer. namely the *trans*. In both cases. the quinone moiety shows no coplanarity with the rest of the molecule. The enamine UV-absorption band exhibits only small changes as a function of the α-crotonic or α cinnamic substituents and its molar absorptivity is increased almost two times when two unconjugated (because of non-coplanarity) enamino groups are introduced in the molecule (see Table).

The quinones **26** and **27** when dissolved in AcOH or EtOH lose their characteristic red color after several hours. It seems quite probable that in these solvents an equilibrium exists between the *cis* and *trans*. The former being very reactive. a ring closure takes place and a quinoneimine type of compound is formed. very unstable because of its strongly unsaturated character. and which in the absence of a reductive reagent converts to indefinitive products. In fact this is what was obtained after removing



the solvents from the discolored solutions. These amorphous products could not be purified and on reduction with sodium hydrosulfite gave no indole but only tars.

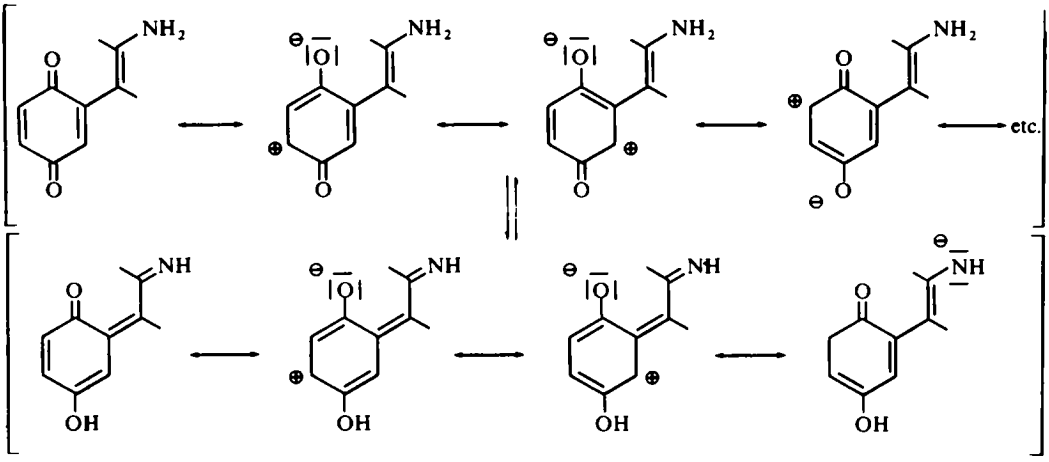
It seemed worthwhile to try the same reaction on the disubstituted quinone **28** previously obtained by us as a by-product.[1] A more stable product would be expected to result by cyclization which could throw light on the problem of the immediate precursor for 5-hydroxyindole formation. At first it was necessary to ascertain the assigned structure of **28**. namely the positions of the side-chains.

2.5-Substitution. as initially suggested by us. seems reasonable in the case of nucleophilic attack on a quinone carrying an electron-donating substituent and supposing a mechanism with intermediate formation of the monosubstituted quinone **26** which could further react with a second molecule of enamine. Although the electronic effect of the quinone substituents does influence the isomer distribution in a predictable manner. mixtures of isomers are frequently encountered.[3, 23] On the other hand tautomerism with an *ortho*-quinoid form can not be excluded and in that case the following reactive possibilities may be envisaged as shown in Chart 3.

To our surprise in the usual conditions of the Nenitzescu reaction quinone **26** did not react with the β-aminocinnamic ester and the starting material was recovered unchanged.

A comparative examination of the NMR spectra of the mono- and disubstituted quinones (**26** and **28**) was expected to furnish convincing evidence in this respect. However this was not feasible. quinone **28** being practically insoluble in ordinary deuterated solvents except DMSO and pyridine when decomposition occurred. The corresponding hydroquinones. *trans*-**4** (R = Ph) and **29** turned out to be more suitable

CHART 3



to this purpose. The latter was obtained by reduction of **28** with sodium hydrosulfite. Both *trans*-**4** (R = Ph) and **29** being sparingly soluble in ordinary solvents. in the first instance a 15% solution in MeCN was used. Unfortunately in this solvent the three aromatic protons of *trans*-**4** (R = Ph) exhibit an ABC system difficultly resolvable. However it was found that in hexamethylphosphoramide chemical shifts were affected in a favourable way so that the three aromatic protons did form an ABX system from which the ν_x value could be easily picked out. The concentrations of the solutions being the same. identical values were found for the chemical shifts of the aromatic protons of the hydroquinone nucleus situated in the *ortho* position relative to the enamino side-chains: ν_{3-H} (*trans*-**4**; R = Ph) = ν_{3-H} (**29**) = ν_{6-H} (**29**) = 372·5 cps (the solvent signal: ν = 158·5 cps. as internal standard) (Fig. 1).

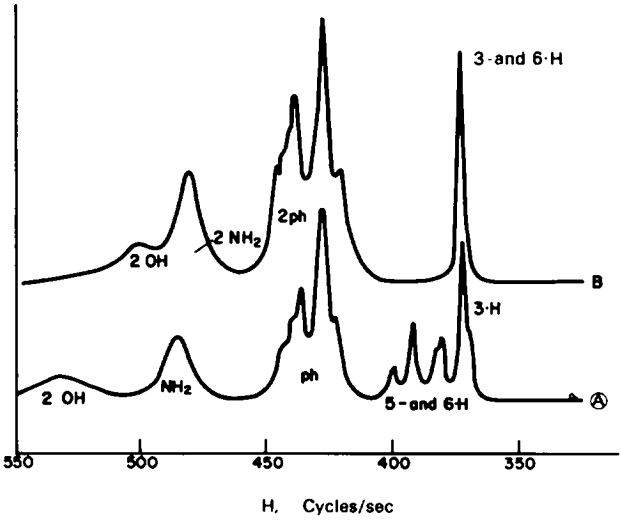
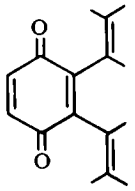
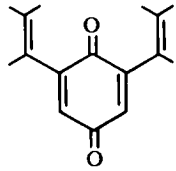


FIG 1. The region 350–550 cps of the NMR spectra (60 Mc/s) of *trans*-**4** (R = Ph) (A) and **29** (B) in hexamethylphosphoramide

Therefore it can be concluded that the two quinone protons in **28** are *ortho* to the enamino side-chains. However among the three possibilities. **28**, **30** and **31**. only **30** can be excluded as possessing no quinoid proton *ortho* to the side chain. Evidence to rule out structure **31** will be furnished by the cyclization reaction itself.



30



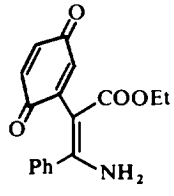
31

The side-chain configuration of **28** and **29** are *trans*-cinnamic as shown by their carbonyl absorptions and non-coplanarity with the rest of the molecule can be deduced from UV spectra (see Table). It can be concluded that this non-coplanarity is a common feature to all enamino-hydroquinones and -quinones mono- and disubstituted in both the cinnamic and crotonic series.

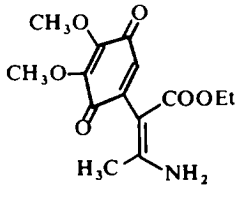
The cyclization of quinone **28** was carried out in AcOH by gentle warming. the reaction being completed in a few minutes.

Two products were obtained. **33** and **34**. 48% and 21% respectively. The

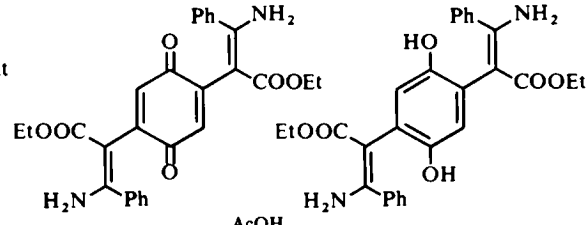
CHART 4



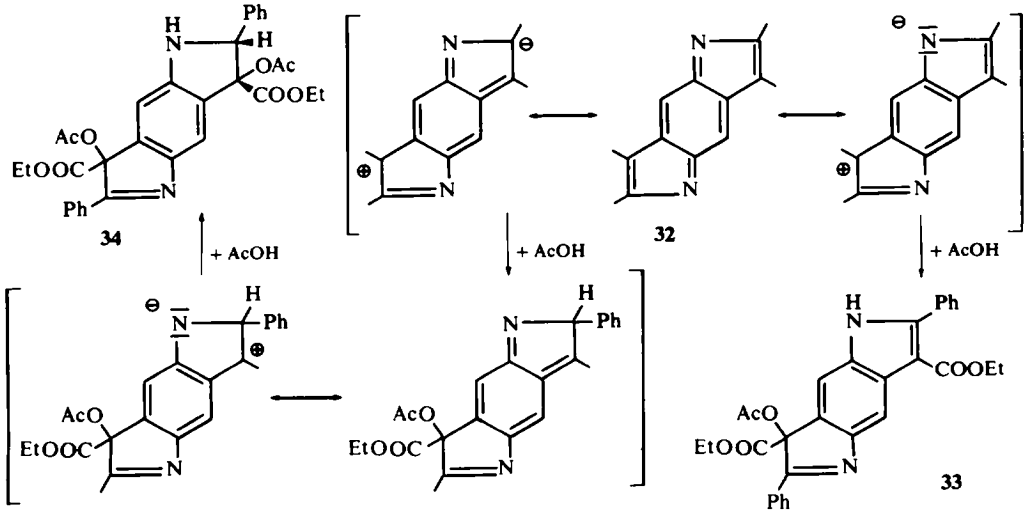
26



27



28 **29**



34 **32** **33**

assigned structures are based on spectral data and mechanistic considerations. For **34** the UV spectrum indicates the existence of an indolenine chromophore [λ_{max}^{EtOH} (log ε) = 306 mμ (4·278)] closely resembling that of the 2-phenyl-3,3-dimethylindolenine[24] [λ_{max}^{EtOH} (log ε) = 306 mμ (4·18)]. The following characteristic IR absorptions have been recorded (in $CHBr_3$): ν_{NH} (indoline nucleus) = 3425, ν_{CO} (saturated ester = 1731 and $\nu_{C=N}$ = 1670 cm^{-1}. The NMR spectrum is also in accordance with the proposed structure, nevertheless attention must be drawn to the characteristic coupling between the indoline NH and the α-H of the same nucleus. the value is in good agreement with literature data.[25] On double irradiation the splitting of the doublet of α-H coalesces as it does on deuteration. when the NH-doublet completely disappears. Taking into account the strong deshielding of the α-H it can be inferred that the corresponding configuration implies the α-H and the carbethoxy group to be *cis*. the latter exerting a deshielding effect through space which at the same time corresponds to a less hindered structure.

To compound **33** the structure of a pyrroloindolenine was assigned. The UV spectrum shows the three maxima of the indole cromophore. A slight bathochromic effect can be observed owing to supplementary conjugation with the indolenine double bond [λ_{max}^{EtOH} (ε) = 315 (18840), 254 (27800) and 230 mμ (31750); for 2-phenyl-3-carbethoxy-5-hydroxyindole: λ_{max}^{EtOH} (ε) = 308 (17100), 249 (21300) and 221 mμ (29250)]. The IR spectrum (KBr pellet) indicates the presence of a saturated ester carbonyl group (1740 cm^{-1}). aromatic ester carbonyl group (1704 cm^{-1}). indolenine C=N double bond (1660 cm^{-1}) and in $CHCl_3$, of the indole-NH (3455 cm^{-1}).

The NMR data are in accordance with the assigned structure.

In our view the mechanism of the formation of these two compounds seems to occur by the addition of one or two molecules of AcOH to a three-ring system of the type. *s*-1.5-diazaindacene (**32**) which is formed as an unstable intermediate and which possesses a strong unsaturated character. Depending on which of the mesomeric structures is implied either one or another of compounds **33** and **34** is formed (Chart 4). and this is suggestively reflected in the respective proportions (70% and 30%) explained by the smaller contribution of the *o*- quinoid canonical form.

The formation of these two compounds furnishes complementary evidence for the structure of the initial quinone **28**. Structure **31** can be easily excluded since it does not allow a double cyclization with formation of a median aromatic nucleus. As a result of the cyclization and of the AcOH addition. the two protons of the quinone nucleus become non-equivalent. in the case of structure **28** being practically uncoupled and strongly coupled in the case of **30**. as *ortho* to each other. In the NMR spectra no *AB* quartet could be observed. possibly hidden by the rest of the aromatic protons in the molecule. Nevertheless in the case of **34**. between the two aromatic heaps. a sharp singlet corresponding to an uncoupled proton does appear.

The described mechanism which explains the formation of the two cyclization products **33** and **34** seems to support the existence of the quinoneimine structure of the immediate precursor of 5-hydroxyindole formation from the corresponding enaminoquinone. at least in the case of non-alkylated primary enamino groups.

EXPERIMENTAL

M.ps were taken in unsealed capillaries unless otherwise stated and are uncorrected. NMR spectra were measured with a Varian A 60-A instrument. TMS as internal standard. UV spectra were determined with

a Specord Carl Zeiss-Jena spectrometer and IR spectra with UR-20 Carl Zeiss-Jena and Perkin-Elmer 621 spectrometers.

2.3-*Dimethoxy*-1.4-*aminophenol.* 2.3-Dimethoxyphenol was used as a starting material obtained from pyrogallol by a Kolbe reaction.[26] dimethylation of the pyrogallolcarboxylic acid[27,28] and decarboxylation of the corresponding dimethylether.[28,29]

2.3-Dimethoxyphenol (51 g) were dissolved in a solution of NaOH (43 g) in water (260 ml). Separately sulfanilic acid (75 g) were diazotized in Na_2CO_3 (31 g) in 500 ml of water by addition of $NaNO_2$ (30 g) in water (80 ml) and the whole poured immediately into a mixture of 600 g of ice and 100 ml of 35% HCl. temperature below 15°. After 30 min the solution of the diazonium salt was introduced with good stirring to the initial solution of 2.3-dimethoxyphenol. The mixture was left at room temp. overnight. Sodium hydrosulfite (250 g) were added and the mixture heated with stirring on a water bath for two hr. The red color of the intermed azoderivative suddenly disappeared. The mixture was extracted four times with $CHCl_3$. Removal of solvent gave 2.3-dimethoxy-1.4-aminophenol (26 g). (46%). m.p. 116°. Recrystallization from CCl_4. m.p. 119 . (Found: C. 57·07; H. 6·62; N. 8·58. Calcd. for $C_8H_{11}NO_3$: C. 56·79: H. 6·55: N. 8·28%).

2.3-*Dimethoxy*-1.4-*benzoquinone.* Oxidation of crude 2.3-dimethoxy-1.4-aminophenol (10 g) was carried out in water (167 ml) with 100 g of $Fe_2(SO_4)_3$ in 334 ml of water. After several extractions with $CHCl_3$. drying and removal of the solvent. 0·75 g of 2.3-dimethoxyquinone (68%) were obtained. m.p. 65–67° (lit.[29] m.p. 66–67°).

2-*Methyl*-3-*carbethoxy*-5-*hydroxy*-6.7-*dimethoxyindole* (**15**) *and ethyl* α-(2.5-*dihydroxy*-3.4-*dimethoxyphenyl*)-β-*amino*-trans-*crotonate* (**16**). In 40 ml $CHCl_3$ were introduced 4 g of each 2.3-dimethoxyquinone and β-aminocrotonic ester. The mixture was refluxed for 30 min and another portion of $CHCl_3$ (40 ml) added. The reflux condenser was removed and 60 ml $CHCl_3$ distilled over 1 hour to remove the water formed. The rest of the solvent was evaporated in vacuum and the residue treated with 40 ml benzene. After concentration to one half it was left overnight in the refrigerator. After filtration and drying 2·7 g crude product were obtained. By refluxing in 50 ml of ether. a small amount of insoluble **16** (0·25 g) was separated. Removal of the ether afforded 2·4 g of **15** (36%) m.p. 162–163°. Analysis sample from benzene. m.p. 164°. (Found: C. 60·47; H. 6·32; N. 5·27. Calcd. for $C_{14}H_{17}NO_5$: C. 60·20; H. 6·32: N. 5·27%) UV λ_{max}^{EtOH} (log ε); 290 (4·078). 242 (4·274) and 216 mμ (4·548); IR cm^{-1} ($CHCl_3$); 3540 (OH). 3464 (NH). 1692 (CO); NMR δ ($CDCl_3$): 1·48 (t. 3. $CH_2C\underline{H}_3$). 2·78 (s. 3 α-CH_3). 4·02 and 4·10 (singlets. 6. OCH_3). 4·45 (2. 2. $OC\underline{H}_2CH_3$). 5·84 (s. 1. OH) 7·49 (s. 1. aromatic proton). 8·90 (broad s. 1. NH).

The volume of the benzene filtrate was reduced to one third and after addition of a small amount of ether and keeping over night in refrigerator 1·25 g of **16** were isolated. The filtrate was evaporated and the residue on treatment with ether afforded another 0·2 g of **16**. The combined crops gave overall yield of 1·7 g of **16** (24%). m.p. 162° (dec.). Analysis sample from ether. m.p. 168° (dec.). An EtOH solution of **16** on treatment with a few drops of $FeCl_3$ aq produced an intense red color. (Found: C. 56·80; H. 6·72; 4·72. Calcd. for $C_{14}H_{19}NO_6$: C. 56·55; H. 6·44; N. 4·71%). IR cm^{-1} ($CHCl_3$); 3540 (OH). 3510 and 3328 (NH_2). 1658 (CO); NMR δ (CD_3COCD_3): 1· 7 (t. 3. $CH_2C\underline{H}_3$). 1·74 (s. 3. α-CH_3). 3·86 and 3·88 (singlets. 6. OCH_3). 4·00 (q. 2. $OC\underline{H}_2CH_3$). 6·34 (s. 1. aromatic proton). 6·60 (s. 1. OH). 7·05 (s. 1. OH). 7·33 (broad s. 2. NH_2).

2-*Methyl*-3-*carbethoxy*-5.6.7-*trimethoxyindole* (**17**) *and* 1.2-*dimethyl*-3-*carbethoxy*-5.6.7-*trimethoxyindole* (**18**). In a mixture of 6 ml of dioxane and 5 ml of 2 N NaOH (10 mmoles). 1·4 g (5 mmoles) of **15** were dissolved and 1·26 g (10 mmoles) of methyl sulfate added. The mixture was shaken 1 hr and subsequently diluted with water when an oil separated which crystallized on standing (1·20 g). The supernatant aqueous layer was diluted with water and extracted several times with ether. After drying the combined ether layers and removal of solvent. a second crop (0·25 g) crude product were obtained. The combined crops which represent a mixture of **17** and **18** were chromatographed on a Brockman alumina column with CCl_4 as eluent. First fraction afforded 0·6 g of **18**. sufficiently pure for analysis. m.p. = 99°. yield 39%. (Found: C. 62·65; H. 7·15; N. 4·47. Calcd for $C_{16}H_{21}NO_5$: C. 62·52; H. 6·88; N. 4·55%). UV λ_{max}^{EtOH} mμ (log ε): 294 (4·075). 244 (4·328). 220 (4·500); IR cm^{-1} (CCl_4): 1690 (CO); NMR δ (CCl_4): 1·43 (t. 3. $CH_2C\underline{H}_3$). 2·67 (s. 3. α-CH_3). 3·88 (s. 3. NCH_3). 3·93. 3·97 and 4·02 (singlets. 9. OCH_3). 4·40 (q. 2. $OC\underline{H}_2CH_3$). 7·50 (s. 1. aromatic proton).

A second fraction gave after removal of solvent 0·65 g of **17**. yield 44%. m.p. = 114. Analysis sample from 40% EtOH. m.p. = 119–120°. (Found: C. 61·67; H. 6·58; N. 4·82. Calcd for $C_{15}H_{19}NO_5$: C. 61·42: H. 6·52; N. 4·78%). UV λ_{max}^{EtOH} mμ (log ε): 290 (4·060). 242 (4·313). 215 (4·504); IR cm^{-1} (CCl_4): 3472 (NH). 3322 (associated NH). 1700 (CO); NMR δ ($CDCl_3$): 1·43 (t. 3. $CH_2C\underline{H}_3$). 2·70 (s. 3. α-CH_3). 3·95 (s. 6. OCH_3). 4·05 (s. 3. OCH_3). 4·42 (q. 2. $OC\underline{H}_2CH_3$). 7·45 (s. 1/ aromatic proton). 9·27 (s. 1. NH).

2-*Methyl*-3-*carbethoxy*-5.6.7-*trimethoxyindole* (**17**). In a mixture of 2 ml of dioxane and 1 ml of 2 N NaOH (2 mmoles), 0·5 g of indole **15** (1·8 mmoles) were dissolved. After homogeneization 0·25 g of methyl sulfate (2 mmoles), freshly distilled were added. Manual shaking was applied intermittently for 1 hr. Then the mixture was diluted with 15 ml water and three times extracted with 10 ml portions of ether. The ether layer after drying was evaporated and an oily residue crystallized. The crude solid obtained was triturated with 10 ml of CCl_4 and filtered when a first crop of **17** was obtained. 0·3 g. The filtrate was chromatographed on neutral alumina with $CHCl_3$ as eluent. A second crop of 0·16 g of **17** was obtained after removal of the solvent. Overall yield 83%. After recrystallization from 40% EtOH. m.p. = 119°. The m.m.p. with a sample obtained by the preceding method showed no depression.

1.2-*Dimethyl*-3-*carbethoxy*-5.6.7-*trimethoxyindole* (**18**). In a mixture of 8·7 ml of dioxane and 6·4 ml of 2 N NaOH (13 mmoles), 0·9 g (3·2 mmoles) of **15** were dissolved and 1·64 g (13 mmoles) of methyl sulfate added. Method as above. On dilution with water indole **18** separated as white crystals. 0·8 g (yield 81%). m.p. = 99°.

2-*Oxo*-3-(α-*aminoethylidene*)-5.6.7-*trimethoxycoumaran* (**19**). In a mixture of 8·6 ml of dioxane and 7·2 ml of 2 N NaOH. 2 g of the hydroquinone derivative **16** were dissolved and 1·37 ml of methyl sulfate added. The mixture was shaken for 1 hr. diluted with 10 ml of water and left overnight in the refrigerator. Crystallization occurred and after filtration 0·75 g of **19**. m.p. = 134° were isolated. The filtrate was diluted with 10 ml of water and extracted with ether to give a second crop. 0·5 g of of **19**. Overall 1·25 g (69%). Analysis sample from benzene. m.p. = 138°. (Found: C. 58·74; H. 5·82; N. 5·36. Calcd for $C_{13}H_{15}NO_5$: C. 58·86; H. 5·70; N. 5·28%). NMR δ (CD_3COCD_3): 2·35 (s. 3. C═C—CH_3). 3·83. 3·92 and 4·06 (singlets. 9. OCH_3). 6·78 (s. 1. aromatic proton). 7·58 and 8·84 (broad singlets. 2. NH_2).

2-*Amino*-2.3-*dimethyl*-3-*carbethoxy*-6.7-*dimethoxy*-2.3-*dihydrobenzofuranol*-5 (cis- *and* trans-**25**). α-Methyl-β-aminocrotonic ester.[30] 1 g., and 2.3-dimethoxyquinone. 1 g. were refluxed for 2·5 hours in 7 ml of $CHCl_3$. After removal of solvent the residue was further refluxed with CCl_4. After cooling the supernatant solvent layer was decanted. evaporated and the residue triturated with a small volume of ether to give after filtration and washing with another portion of ether 0·6 g of **25**. m.p. 122–3°. On further work-up of the insoluble residue by repeating the described procedure a second crop of **25** was obtained. 0·25 g. The overall yield 46%. After recrystallization from benzene-petroleum ether (b.p. = 30–40°). m.p. 124–5°. (Found: C. 58·02; H. 6·92; N. 4·61. Calcd for $C_{15}H_{21}NO_6$: C. 57·86; H. 6·80; N. 4·50%). IR cm^{-1} (CCl_4): 1738 (CO-saturated ester); NMR δ ($CDCl_3$): 1·30 (t. 3. CH_2—$C\underline{H}_3$). 1·47. 1·53. 1·57 and 1·67 (singlets. 6. 2- and 3-CH_3). 2·53 (broad s. 3. OH and NH_2). 4·00 and 4·05 (singlets. 6. OCH_3). 4·33 (q. 2. $OC\underline{H}_2CH_3$). 6·76 (s. 1. aromatic proton).

Ethyl α-*methyl*-β-*amino*-trans-*cinnamate*. In a suspension of 2·5 g of powdered Na in 30 ml of dry ether. 20 g of β-aminocinnamic ester diluted with 20 ml of dry ether were introduced in three portions. External cooling was necessary. the reaction being appreciably exothermic. The sodium derivative of the ester is soluble in the mixture but several hours may be needed for the Na to go completely into solution. At the end of this period 7·3 ml MeI in a small volume of dry ether was added. Refluxing took place and a bulky precipitate was formed until the contents of the flask became a slurry. After addition of the MeI heating at 50–55) was applied for 5 hr. The cooled mixture was decomposed with ice-water and the ether layer separated. The aqueous layer was extracted with ether and the combined ether layers washed with water. After drying ($MgSO_4$) and removal of ether the residue was distilled and the fraction boiling at 129–130°/3 mm collected. Yield 13 g (61%). n_D^{20} = 1·5657. (Found: C. 70·33: H. 7·32; N. 7·09. Calcd for $C_{12}H_{15}NO_2$: C. 70·22; H. 7·36; N. 6·82%). IR cm^{-1} (CCl_4): 3498 and 3320 (NH_2). 1666 (CO); NMR δ (CCl_4): 1·25 (t. 3. $CH_2C\underline{H}_3$). 1·58. (s. 3. C═C—CH_3). 4·09 (q. 2. $OC\underline{H}_2CH_3$). 6·38 (s. 2. NH_2). 7·30 (s. 5. Ph).

Ethyl-α-(2.5-*dimesylphenyl*)-β-*amino*-trans-*cinnamate* [trans-**4** (R = Ph) *dimesylate*]. Methanesulfonic acid chloride was prepared in almost quantitative yield from methyl sulfocyanide.[31] To a solution of 4 g of *trans*-**4** (R = Ph)[1] in 28 ml pyridine. 4·75 g of mesyl chloride were added and the mixture left overnight. 55 ml $CHCl_3$ were added to the mixture and the pyridine removed by extraction with 7% HCl. The $CHCl_3$ layer was washed with water and dried ($MgSO_4$). After filtration the volume of the solution was reduced to a quarter and ether added until a faint opalescence appeared. Left overnight in the refrigerator crystallization of the dimesylate occurred and after filtration and thorough washing with ether to remove traces of acid chloride. 5 g of dimesylate of *trans*-**4** (R = Ph) were obtained. m.p. = 158° (82%). On recrystallization from $CHCl_3$-ether. m.p. = 160°. (Found: C. 50·20; H. 4·77; N. 3·17; S. 13·75. Calcd for $C_{19}H_{21}NO_8S_2$: C. 50·10; H. 4·65; N. 3·07; S. 14·07%). UV $\lambda_{max}^{E\ OH}$ mμ (log ε): 300 (4·08); IR cm^{-1} ($CHCl_3$): 3493 and 3320 (NH_2). 1659 (CO). 1372 and 1144 (SO_2); NMR δ ($CDCl_3$): 1·18 (t. 3. $CH_2C\underline{H}_3$). 2·85 and 3·07 (singlets. 6. CH_3SO_3). 4·15 (q. 2. $OC\underline{H}_2CH_3$). 7·06 and 7·12 (multiplets. 3. aromatic ABC). 7·23 (s. 5. Ph) and δ_{NH_2} very broadened in the aromatic region.

Ethyl α(α-*aminobenzylidene*)-3,6-*dioxo*-1,4-*cyclohexadieneacetate* (**26**). In 40 ml of dry THF 3·5 g of hydroquinone derivative *trans*-**4** (R = Ph) were dissolved and 8·75 g of AgO added. The mixture was shaken for ten min and after another ten min the insolubles removed by filtration and the THF evaporated. The residue was treated with enough benzene for complete solution to occur. By precipitation with cyclohexane 3 g of **26** (86%) were obtained. m.p. = 145°. Supplementary recrystallization from benzene-cyclohexane gave m.p. = 147°. (Found: C, 68·72; H, 5·20; N, 4·89. Calcd for $C_{17}H_{15}NO_4$: C, 68·67; H, 5·08; N, 4·71%). NMR δ ($CDCl_3$): 1·18 (t, 3, $CH_2C\underline{H}_3$), 4·12 (q, 2, $OC\underline{H}_2CH_3$), 6·16 and 6·58 (multiplets, 3, quinoid ABC), 7·26 (s, 5, Ph) and δ_{NH_2} very broadened in the aromatic region.

Ethyl α-(α-*aminoethylidene*)-4,5-*dimethoxy*-3,6-*dioxo*-1,4-*cyclohexadieneacetate* (**27**). In 15 ml THF 1·2 g hydroquinone derivative **16** were dissolved and 3·3 g of AgO added. After working-up described in the preceding paragraph the residue was repeatedly extracted with hot cyclohexane. On cooling a viscous oil separated which crystallized after decanting the supernatant cyclohexane and addition of a small amount of ether. Yield 0·9 g of **27** (75%), m.p. = 89–90°. On recrystallization from ether m.p. = 91°. (Found: C, 57·02; H, 6·02; N, 4·89. Calcd for $C_{14}H_{17}NO_6$: C, 56·95; H, 5·81; N, 4·74%. NMR δ ($CDCl_3$): 1·17 (t, 3, $CH_2C\underline{H}_3$), 1·93 (s, 3, C═C—CH_3), 4·02 and 4·08 (singlets, 6, OCH_3), 4·08 (q, 2, $OC\underline{H}_2CH_3$), 5·52 (s, 1, quinoid proton) and δ_{NH_2} very broadened in the aromatic region.

Ethyl-α,α′-*bis*-(α-*aminobenzylidene*)-2,5-*dihydroxy*-*benzene*-1,4-*diacetate* (**29**). In 30 ml of hexamethylphosphoramide 1·5 g of quinone **28** were dissolved with gentle heating and left to cool to room temp. To it a solution of 3 g of hydrosulfite in water (60 ml) were added as fast as possible with good stirring. An almost instantaneous loss of color occurred. Stirring was continued for 30 min and the separated white precipitate was filtrated and washed with distilled water. Yield 3 g of **29** (86%), m.p. = 216–218° (dec.). After recrystallization from EtOH m.p. = 220° (dec.). (Found: C, 68·65; H, 5·98; N, 5·97. Calcd for $C_{28}H_{28}N_2O_6$: C, 68·84; H, 5·78; N, 5·74%). NMR δ (CH_3CN): 4·07 (q, 4, $OC\underline{H}_2CH_3$), 5·63 (s, 2, OH), 6·10 (s, 2, aromatic protons) 7·22 (s, 10, Ph) and δ_{NH_2} very broadened in the aromatic region.

Ethyl 3-*acetoxy*-3,5-*hydro*-2,6-*diphenylbenzo*[1·2-b; 4·5-b′]*dipyrrole*-3,7-*dicarboxylate* (**33**) *and ethyl* 3,7-*diacetoxy*-1,2,3,7-*tetrahydro*-2,6-*diphenylbenzo*[1·2-b; 4·5-b′] *dipyrrole*-3,7-*dicarboxylate* (**34**). In 15 ml of glacial AcOH, 1 g of quinone **28** ground in a mortar was suspended and gentle heating was started with manual stirring. Before the b.p. of the AcOH was reached, complete dissolution occurred and at the same time the quinone red color disappeared. The clear solution thus formed was left to cool and evaporated after treatment with active charcoal and filtration. The residue was treated with ether when crystallization occurred. 0·75 g of crude product were obtained, consisting of a mixture of **33** and **34** (m.p. 234°). By refluxing in 20 ml of dioxane and allowing to cool at room temperature overnight, 0·25 g of **34** were obtained. m.p. = 286–287° (dec.). 21%. After recrystallization from dioxane, m.p. 290° (dec.) (Boetius microplate). (Found: C, 67·52; H, 5·48; N, 5·19. Calcd for $C_{32}H_{30}N_2O_8$: C, 67·35; H, 5·30; N, 4·91%. NMR δ (DMSO): 1·10 and 1·22 (triplets, 6, —$CH_2C\underline{H}_3$), 4·10 and 4·27 (quartets, 4, $OC\underline{H}_2CH_3$), 5·88 (d, 1, 2-H, J = 7·5 cps), coalesces to a singlet on double irradiation, Δ = − 176 cps, or deuteration, 7·73 (m, 9, aromatic protons), 8·04 (s, 1, aromatic proton), 8·28 (m, 2, aromatic protons), 8·82 (d, 1, NH, J = 7·5 cps, disappears on deuteration). DMSO signal taken as internal reference. The region 1·42–3·67 ppm being obstructed by the solvent the two remaining Me groups could be observed in quinoline as a solvent: 2·00 and 2·09 (singlets, 6, CH_3COO).

The solvent was removed from the dioxane filtrate when 0·5 g of **33** were obtained, m.p. = 254° (yield 48%). By recrystallization from nitromethane, m.p. = 263° (Boetius microplate). (Found: C, 70·54; H, 5·42; N, 5·68. Calcd for $C_{30}H_{26}N_2O_6$: C, 70·58; H, 5·12; N, 5·49%). NMR δ (DMSO): 0·73 and 1·30 (triplets, 6, $CH_2C\underline{H}_3$), 3·71 and 4·30 (quartets, 4, $OC\underline{H}_2CH_3$), 7·45 (s, 5, Ph), 7·62 (m, 7, aromatic protons), 12·27 (s, 1, NH). DMSO signal taken as internal reference. The region 1·42–3·67 ppm being obstructed by the solvent the remaining Me group could be observed in PhCN: 2·12 (s, 3, CH_3COO).

Acknowledgements—Thanks are due to F. Chiraleu for NMR measurements, to C. Drăghici for UV measurements and to Miss E. Sliam and Mrs V. Daniel for microanalyses.

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