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DOUBLE CYCLISATION OF PHENYLGLYCINE-*o*-CARBOXYLIC ACIDS—I†

NEW STABLE MESOIONIC OXAZOLONES[1]

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Abstract—Remarkably stable mesoionic oxazolones possessing an oxazolo[3,2-a]quinolinium structure (**5a–b**, **8**, **16**, **17**) were obtained by the double cyclisation of phenylglycine-*o*-carboxylic acids (**3a–c**) in refluxing acetic anhydride or in benzoic anhydride at 140°. The *O*-Ac group was eliminated to give the corresponding lactones (**6a–b**) or replaced by *O*-Ts (**7**). IR stretching vibrations of the *endo*-carbonyl were in the range 1710–1768 cm^{-1}, while $\nu_{1\text{-}CH}$ exhibited unusually high values (3159–3194 cm^{-1}). 1-Acyl derivatives could be obtained only with TFAA (**23–24**), although easy deuteration of the same position took place in the presence of traces of trifluoroacetic acid. Hydrolysis of **5b** led to the α-quinolone-N-acetic acid **27a**. In the case of **5a**, hydrolysis was accompanied by self-acylation of the nucleophilic site at C-4 with formation of a dimeric acid **28a**. The presence of an additional Me group in phenylalanine-*o*-carboxylic acid (**36**) activates the corresponding mesoionic oxazolone **37** so that 1-acylation becomes possible with formation of the fused oxazole **38** by the Dakin–West reaction. Temperature dependent magnetic non-equivalence of methylene protons has been observed in acids **3b–d** and **f** and also in the 7-membered anhydride **48b**.

During the last decade a new impulse has been given to research in the field of mesoionic compounds[2] when it was found that their 1,3-dipoler cycloadditions to various reagents[3], provide a new synthetic tool for a variety of heterocyclic compounds. Huisgen *et al.*[4] described in an exhaustive manner the "münchnones", unstable mesoionic oxazolones of type **1** with azomethine ylide structure and their reactions which closely parallel those of the related sydnones. MO calculations have been applied[5] and the crystal structure of 4-acylated münchnone determined.[6] The attempts to obtain fused mesoionic oxazolones with an oxazolo[3,2-a]pyridinium skeleton led invariably to 4-acylated products like **2a**[7] and **2b**.[8] The corresponding non-acylated compound **2c** could be obtained only in solution by deprotonation of the perchlorate salt with Et_3N and could be kept only for a short period.[8] Other attempts to prepare analogous quinoline derivatives failed: the 2-quinolone did not react with chloroacetic acid and refluxing of phenylglycine-*o*-carboxylic acid (**3a**) in acetic anhydride in the presence of 3-picoline was reported to give only small amounts of N,O-diacetylindoxyl (**4a**).[7,9]

Mesoionic quinolinooxazolones. The present work describes a new type of mesoionic oxazolones of remarkable stability with an oxazolo[3,2-a]quinolinium skeleton. The parent compound **5a** was obtained in appreciable yields (62%) by the double cyclisation in refluxing acetic anhydride of N-acetylphenylglycine-*o*-carboxylic acid (**3b**). Although the condensed heterocyclic system of oxazolo[3,2-a]quinolinium was described in 1967,[10] the cyclisation of **3a** and its N-acetylated derivative **3b** has been known since the end of the last century to yield N,O-diacetylindoxyl (**4a**).[11]

The product of the title reaction (**5a**), straw-white crystals, m.p. 131°, could be kept for several months without alteration. Unstable in benzene and dioxane solution, the new mesoionic compound remained unchanged after several weeks in acetone and acetonitrile, while a moderate stability in chloroform, ethanol and pyridine permitted measurements of spectra. The same compound **5a** could be obtained directly from the non-acetylated acid **3a**, but with lower yields (44%) of a less pure product.

The NMR spectrum of **5a** exhibits a long-range coupling between protons 1 and 4 (J = 2 c/s), certified by double resonance experiments of spin decoupling. The same phenomenon could be observed with other members of this series. The synthesis of the 4-methylated derivative **5b** revealed the distinction between the chemical shifts of protons 1 and 4. This was done by the cyclisation under similar conditions of the N-propionylphenylglycine-*o*-carboxylic acid (**3c**). The product **5b**, like **5a**, displayed a similar behaviour towards various solvents. The 4-position being blocked by the Me substituent, the remaining 1-proton absorbs in the aromatic region as a singlet at $\delta = 7.07$. Therefore the chemical shift of proton 4 in compound **5a** appears at the higher field ($\delta = 5.72$) and indicates a strong nucleophilic reactivity, which is actually the case.

An unambiguous assignment of the IR CO stretching absorption of the mesoionic oxazolone ring in **5a–b** was not possible since it overlaps that of the acetoxy group. The synthesis of tosylate **7** and of benzoate **8** made this possible. The former was prepared by elimination of the acetyl group of **5a** with boron trifluoride etherate and treatment with tosyl chloride of the resulting lactone **6a**. The benzoate **8** could be obtained in two ways: from **5a** in refluxing chloroform by adding benzoyl chloride or by the cyclisation of **3b** in benzoic anhydride at 140°.

The IR spectrum of tosylate **7** shows a CO absorption at 1765 cm^{-1} which compared with saturated oxazolinones-5 (ν_{CO} = 1820 cm^{-1}) or with azlactones of the type **9** (ν_{CO} = 1825 cm^{-1}) indicates an appreciable reduction of the double bond character. The benzoate **8** exhibits two distinct CO bands at 1755 and 1735 cm^{-1}, the latter being assigned to the ester group.

A remarkable feature of the new mesoionic oxazolones is the free, non-acylated position at C-1. The

†Dedicated to the 70th anniversary of Prof. E. Nenitzescu's birthday.

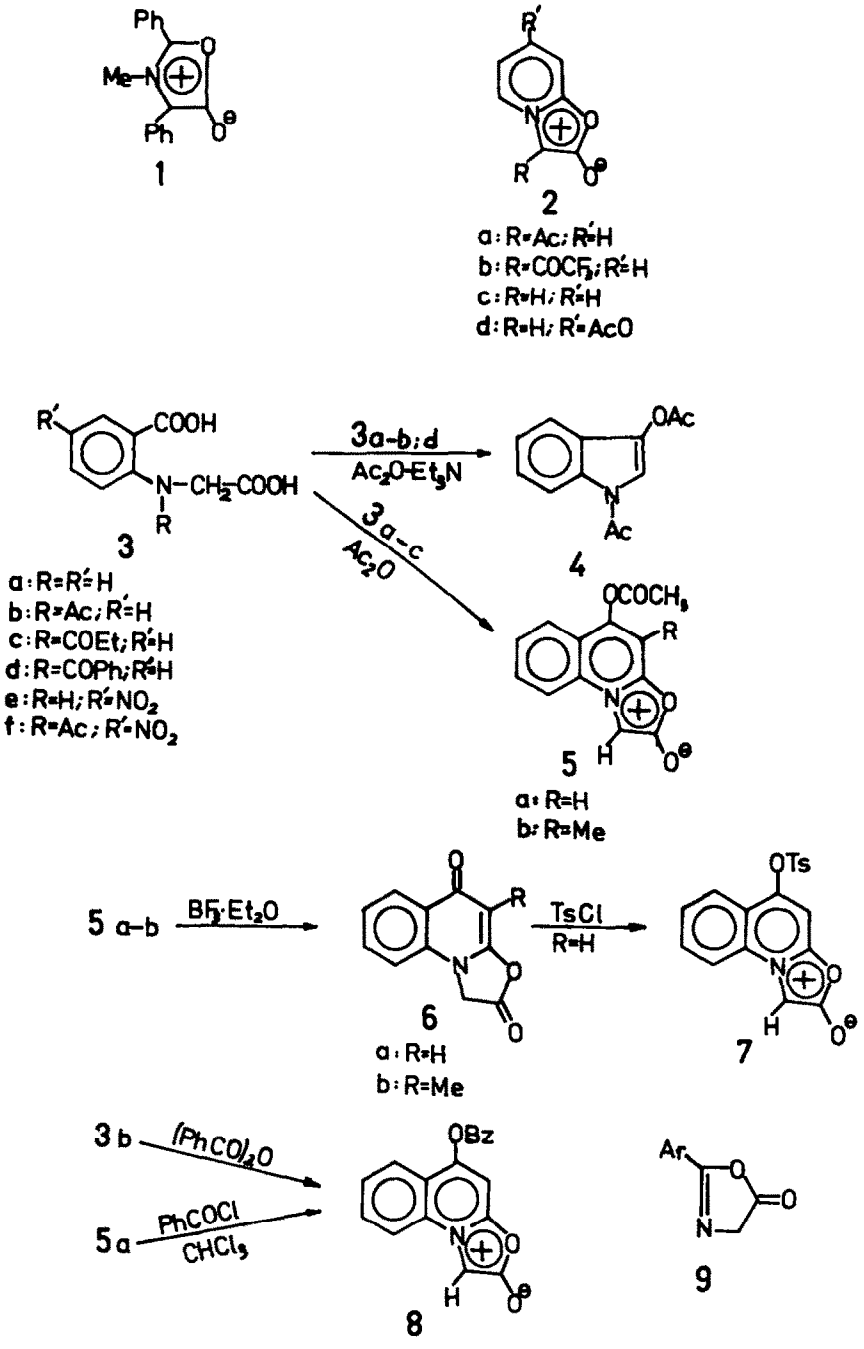


Chart I.

corresponding C–H stretching vibrations show the characteristic values of 3178 and 3194 cm^{-1} for the compounds **5a** and **b** respectively, which are very close to those of the sydnones.[12] It is known that the ν_{CH} vibrations in the aromatic and olefinic series seldom exceed the limit of 3100 cm^{-1}. It should be mentioned that spectra measured in KBr pellets are much more adequate for the study of the C–H stretching vibrations in the case of the 5-membered heterocycles.[13] In our case these bands could not be observed in solution.

A mesoionic hydroxyquinolinooxazolone. The spectral data of the hydroxyoxazolone **17** furnished new interesting data. Its synthesis starts from 2-chloro-4-nitrotoluene (**10**) which is oxidised[14] to 2-chloro-4-nitrobenzoic acid (**11**) and further reduced to the corresponding amino acid **12**. The latter by diazotisation and hydrolysis gives the 2-chloro-4-hydroxybenzoic acid (**13**) whose benzyl ether **14** on condensation with glycine affords the 5-benzyloxyphenylglycine-2-carboxylic acid (**15**). The last three stages followed the procedure reported[15] for the synthesis of the 4-benzyloxy isomer. Cyclisation in acetic anhydride furnished the mesoionic oxazolone **16** which by scission of the benzyl group on hydrogenolysis with Pd/C led to the final product **17**. When the cyclising agent was Ac_2O–Et_3N the corresponding indoxyl **18** resulted.

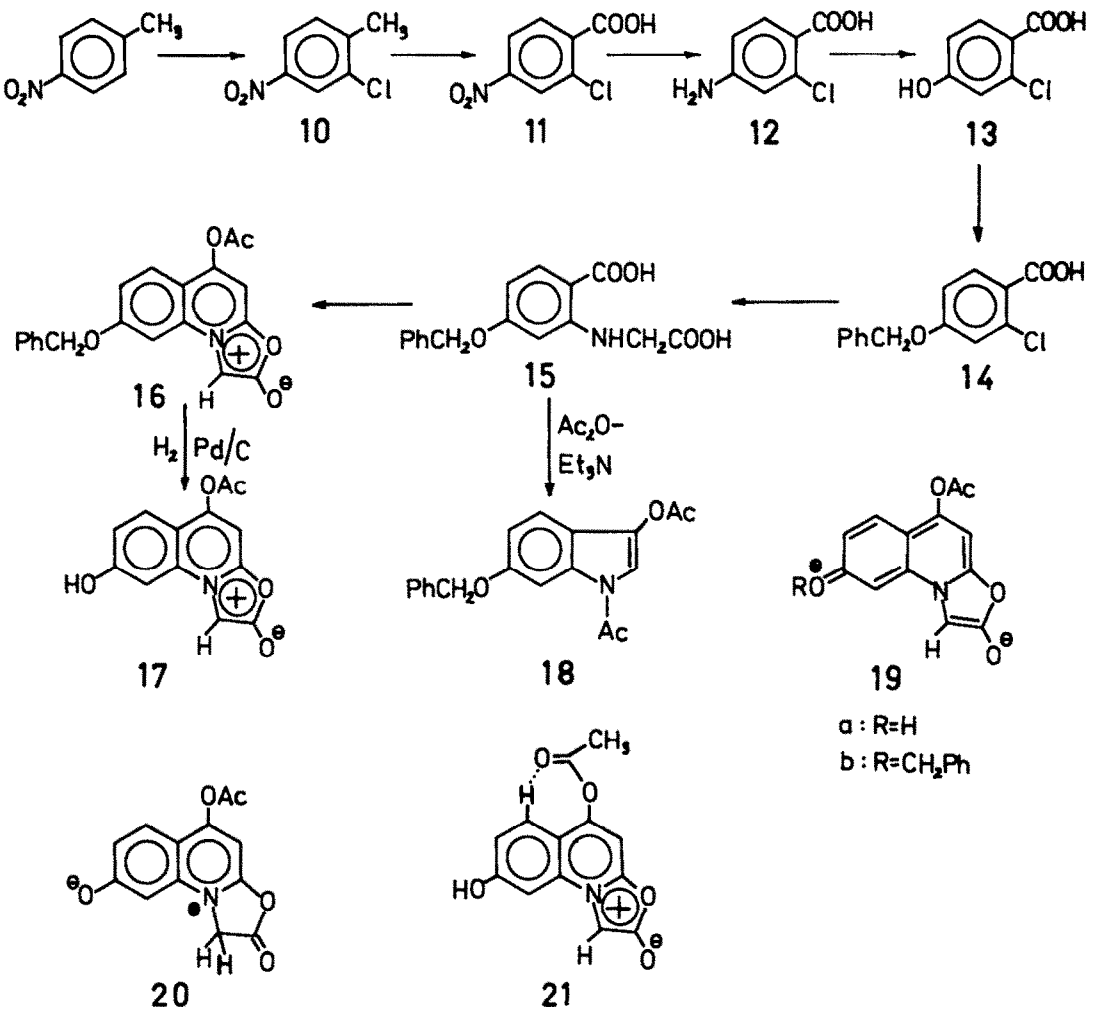
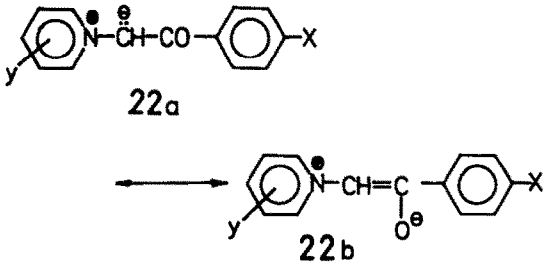


Chart II.

The CO stretching absorptions of mesoionic oxazolones **17** and **16** display unexpectedly low values of the wave number: 1710 and 1727 cm^{-1} respectively. It is known that sydnones absorb in the region 1730–1770 cm^{-1}, while the unstable isolated münchnones show CO absorptions at 1690–1700 cm^{-1}.[4a] The explanation of this phenomenon is given by the appearance of a new canonical structure **19**, which has an appreciable contribution to the resonance of the molecule allowing a supplementary polarisation of the CO. The presence of the possible betainic tautomer **20** has not been detected in the IR or in the NMR spectra. Compound **17** provides the identification of every aromatic proton. The most deshielded proton is located in the 6 position ($\delta = 8.12$). Its *peri*-substituent, the acetoxy group, makes the conformation **21** possible. Proton 9 is also deshielded by the adjacent positive nitrogen, whose effect is partially counterbalanced by the 8-OH group ($\delta = 7.47$) which also exerts a shielding effect on the remaining proton H-7 ($\delta = 6.95$).

The nitro acid **3e** could not be cyclised to the corresponding mesoionic compound. Instead the N-acetylated derivative **3f** was isolated.

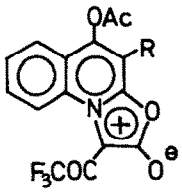
The low-field chemical shift of the oxazole ring proton as well as the capability of the π system to transmit a long-range coupling suggest an aromatic character of the mesoionic oxazolone. In this connection it should be mentioned that sydnones unsubstituted at the 4-position have a chemical shift of the corresponding proton to an appreciably higher field ($\delta = 6.45$–6.96).[16] The same can be said of the pyridinium ylides of type **22**, appreciably stable owing to the enol-betainic character (**22b**). The



corresponding chemical shifts appear in the range $\delta =$ 6.6–6.8.[17] The aromatic character also accounts for the very low basicity of these compounds and the resistance towards alkalies of the lactonic cycle. Compounds **5a–b** and **8** resisted hydrolysis in boiling 10% Na_2CO_3. They also remained unchanged in cold 10% HCl, while **5b** was soluble in trifluoroacetic acid without decomposition.

On the other hand, similar to the sydnones, the relatively high-frequency CO absorption band suggests a reduced contribution of the structures with a negative exocyclic oxygen, but it may be misleading to conclude that the aromatic character of both sydnones and mesoionic oxazolones is negligible.

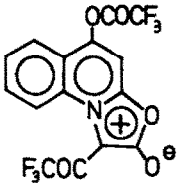
Acylation and deuteration. Attempts to acylate **5a–b** were unsuccessful except with trifluoroacetic anhydride (TFAA). At first sight, this finding seemed peculiar taking into account the behaviour of münchnones[4a] and of the oxazolopyridiniumoxide **2c**,[7,8] which could not be isolated in a non-acylated state but under special conditions, namely treatment of the corresponding perchlorates with triethylamine.[8,18] The stable acyl derivatives lose much of their mesoionic character owing to the delocalisation of the negative charge by the exocyclic CO. This is suggestively reflected in the very low values of the stretching frequency of the *exo*-CO and conversely in the high values for the *endo*-CO.[4a,8,18] In our case the trifluoroacetylated oxazoloquinolinium oxides could be obtained in two ways: by the action of TFAA on compounds **5a–b** and by the cyclisation of **3b** with the same anhydride. The former method afforded the compounds **23a** and **23b**, the acylation occurring in the position 1, while the latter led to the *bis*-trifluoracetylated derivative **24**. The IR CO-bands for **23a–b** appear at 1786 and 1665–1670 cm^{-1}, in accordance with the above observations, while for **24** they are registered at 1775 and 1698 cm^{-1}, as compared to 1715 for *m*-trifluoroacetyltoluene[19] and 1693 cm^{-1} for acetophenone. Still lower values were attributed to **2b**.[8]



23

a: R=H

b: R=Me



24

By recrystallisation from protic solvents, or by melting at 187° and resolidification or simply by leaving for several days, the *O*–$COCF_3$ group was readily eliminated[20] from **24** and a corresponding lactonic quinolone formed (ν_{CO} = 1787, 1718, 1669 cm^{-1}). However **24** can be kept unchanged for longer periods of time in a dry atmosphere and also it can be recrystallised from anhydrous aprotic solvents.

All the attempts to acylate **5a** failed with acetic anhydride, acetyl chloride, benzoyl chloride, oxalyl chloride, each either alone or in the presence of pyridine or $BF_3 \cdot Et_2O$.

The oxazoloquinolinium oxides **5a–b** could be readily deuterated in the 1-position in the presence of traces of CF_3COOD. The exchange occurs probably through the intermediate of structures of type **25**. The NMR spectra of **5a** in $CDCl_3$ in these conditions show the disappearance of 1-H while proton 4, long-range coupled to it, becomes a singlet. Also the lactones **6a–b** could be deuterated, the former both in the 4 position and the 1-CH_2.

Hydrolyses. Hydrolysis of **5b** in alkaline or acidic media (HCl, CF_3COOH) brings about the cleavage of the lactonic ring as well as the removal of the O-acetyl group. The resulting product is the quinoloneacetic acid **27a**. The intermediate stages of the hydrolysis can be observed by dilution with water of a trifluoroacetic solution of **5b**, when lactone **6b** separates as a precipitate. The NMR spectrum of the trifluoroacetic solution before dilution exhibits a completely deuterable methylene corresponding to the oxazoloquinolinium salt **25**. It is known that enolic esters are especially good for exchange with acids to give mixed anhydrides, the equilibrium being shifted by the excess of trifluoroacetic acid towards the formation of lactone **6b**:

$$\mathbf{5b} + CF_3COOH \rightleftharpoons \mathbf{6b} + CF_3COOAc.$$

When mesoionic compound **5a** is subjected to hydrolysis, the reaction is complicated by the presence of the unsubstituted and strong nucleophilic 4 position (NMR spectrum). In this case the hydrolysis was accompanied by self-acylation with formation of the "dimeric" acid **28a**, which was better characterised as its trimethylated derivative **28b**. The NMR and IR spectra are in accordance with this structure: two methylene, two methoxy and one carbomethoxy groups as well as a single β-quinolinic hydrogen and the ketonic *exo*-CO. The free acid **28a** appears in two crystalline forms. They probably correspond to a betainic structure (dec over 300°C) and to the undissociated acid, m.p. 218° (dec). The two forms are interconvertible by reprecipitation with acetic acid from dilute alkaline solutions and by boiling in distilled water. The "monomeric" ester **27b** could be obtained through the intermediate of the 1-carboxymethyl-2,4-dihydroxyquinolinium chloride (**26**) on treatment with diazomethane. Attempts to neutralise the salt led to the self-acylated product **28a** what indicates a great reactivity of the presumed free acid **27c**. Alkaline hydrolysis of ester **27b** furnished no well-defined products except small amounts of indigo resulted from a basic ring cleavage and recyclisation to indoxyl. In the NMR spectrum of **27b**, the chemical shift of the 1-H, $\delta = 5.20$ is characteristic which means a very high field even compared to that of the corresponding proton in **5a** ($\delta = 5.72$). Self-acylation was previously observed in the case of both münchnones[21] and oxazolopyridinium oxides.[8] However in these cases the substitution takes place at position 4 of the oxazole ring.

The ester **27b** does not regenerate **5a** on refluxing in acetic anhydride while this is true for the lactones **6** and the acid **27a**, which yield the corresponding mesoionic compounds **5a–b**.

Reactivity and resonance. One of the main feature of the 4-unsubstituted münchones and of the oxazolo[3,2-a]pyridinium oxide **2c** is that they are only isolable as acylated derivatives. The fact that **5a** and its congeners can not be "overacylated" except with TFAA may be rationalised if we consider the ambident nucleophile **29** as an intermediate whose phenoxide moiety is preferentially acylated. By examination of the various resonance structures (A–F; Chart IV), many experimental facts can be explained. For example the enol-betainic structure A corresponds to a vinylogous quinoline oxide, while structure B is a pyridinium ylide. Both canonical forms contain functional groups possessing a push–pull character which is expressed by a back-coordination[22] of electrons from the N-oxide or N-ylide group to the pyridine ring. This is visualised in resonance structures like C. The stabilising influence of the back-coordination

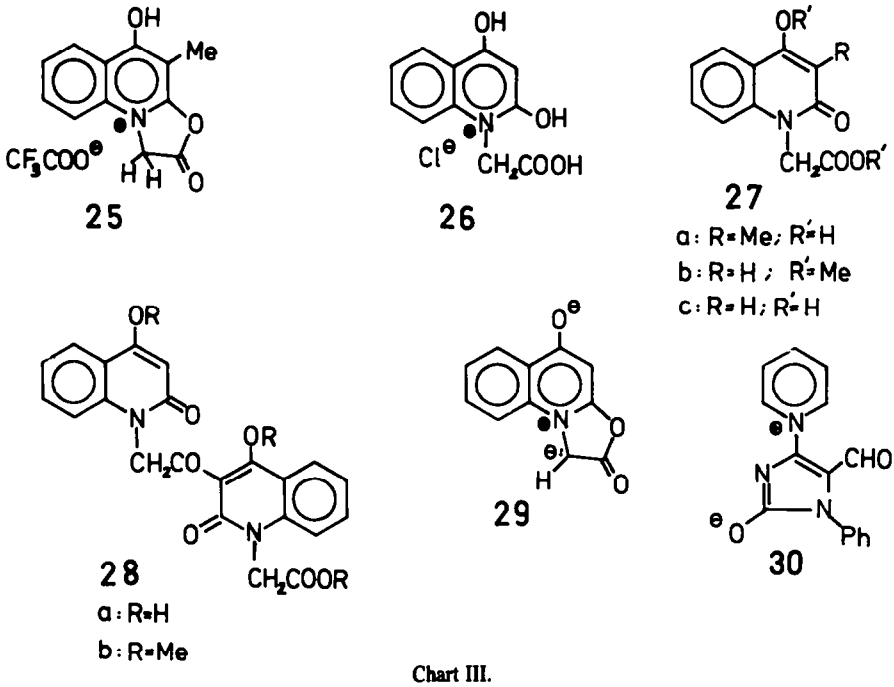


Chart III.

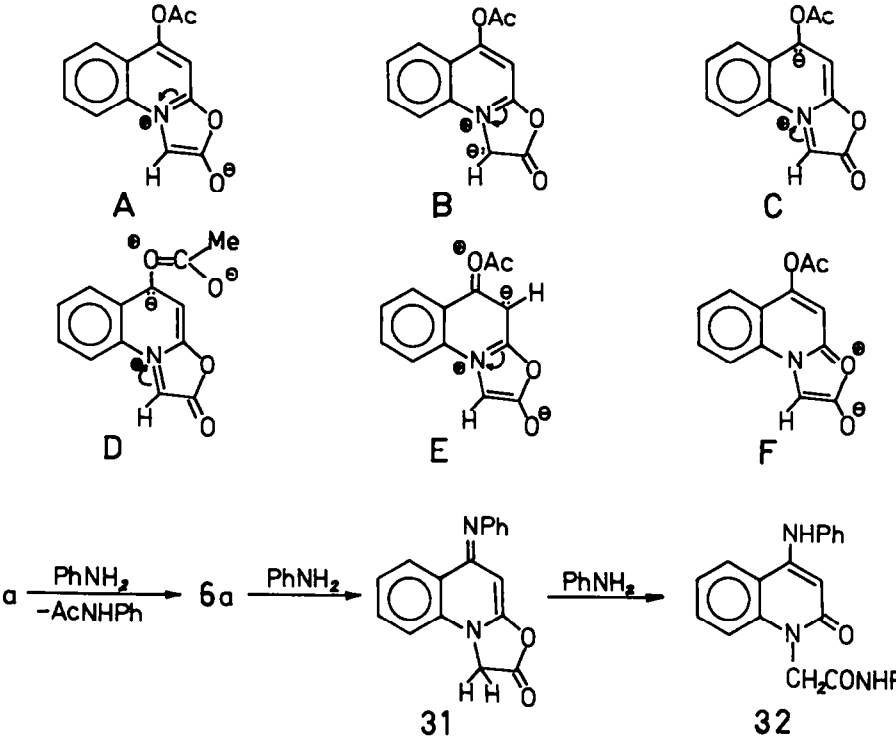


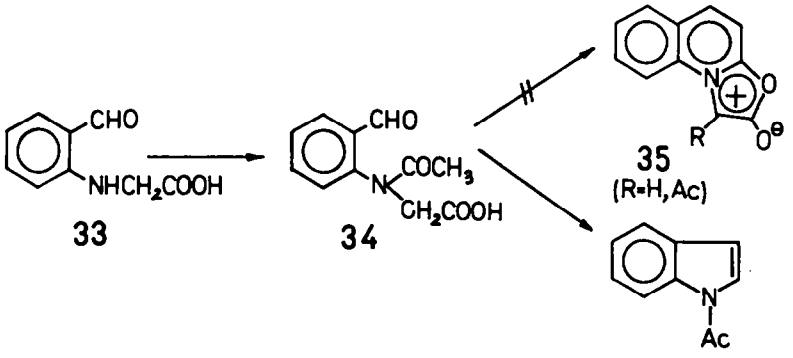
Chart IV.

effect is enhanced by the 5-acyloxy substituent, which can attract electrons by an inductive effect. Thus the contributions of the tetrapolar canonical structures **D** and **E** are increased, the latter being mostly responsible for the high-field absorption of proton 4. The appreciable delocalisation of electrical charges as deduced from resonance structures is reflected in both physical and chemical properties: insolubility and lack of reactivity in 10% HCl and hot 10% Na_2CO_3 as mentioned before, as well as low m.ps by comparison with pyridinium betaines like **30**, with m.p. 272°.[23] With nucleophilic reagents such as pyrrolidine and benzylamine no reaction occurs in refluxing dioxane. Therefore there is an increased stability as compared to ordinary lactones. However quite unexpectedly a quantitative reaction takes place with aniline, the product being the anilide of the 4-anilino-2-quinolone-N-acetic acid (**32**). The reaction probably occurs through several intermediates, namely the lactone **6a** and the corresponding anil **31**. Curiously, in refluxing acetone no reaction occurred between **5a** and aniline.

Another conclusion which can be drawn from the examination of the resonance structures is that an oxazoloquinolinium oxide of type **35** should be similar in behaviour to **2c** while **2d**, the pyridinium analogue of **5a**, should show the same stabilising effect of the acetoxy group.

Cyclization of N-*acetyl*-o-*aldehydophenylglycine.* It was thought that the double cyclisation of N-acetyl-*o*-aldehydophenylglycine would afford the desired compound **35**. Under the action of CaO[24] or a mixture Ac_2O–AcONa[25] the aldehyde **33** cyclised to indole, but in the absence of a base, or with acetic anhydride alone, another reaction path could be expected: acylation of **33** to **34** and the double cyclisation to **35**. Actually N-acetylindole resulted from the reaction which means that only the first step (acylation of **33** to **34**) took place according to the Scheme. This is proved by the fact that indole itself can not be acylated in refluxing Ac_2O.

Cyclization of phenylalanine-o-carboxylic acid. When the homologue of **3a**, the phenylalanine-*o*-carboxylic acid (**36a**) or its N-acetylated derivative (**36b**) was refluxed in acetic anhydride, the cyclisation followed the route of the Dakin–West reaction.[4b,26] Instead of the expected mesoionic oxazolone **37** the product proved to be an extremely stable oxazolo[3,2-a]quinoline, **38**, without any mesoionic character. Its only IR absorption in the CO region is the characteristic stretching vibration of a γ-quinolone[27] (1635 cm^{-1}) while the NMR spectrum exhibits a screened enamino ketonic proton ($\delta = 6.07$) and a cisoid homoallylic coupling between the two Me groups, verified by a double resonance experiment. The structure of oxazole **38** corresponds to a vinylogous ester, so that it can be easily hydrolysed in 20% NaOH, aqueous ethanol solution, to afford the keto-quinolone **39a**, which gave a dinitrophenylhydrazone and the methyl ether **39b**. In refluxing Ac_2O, the keto-quinolone



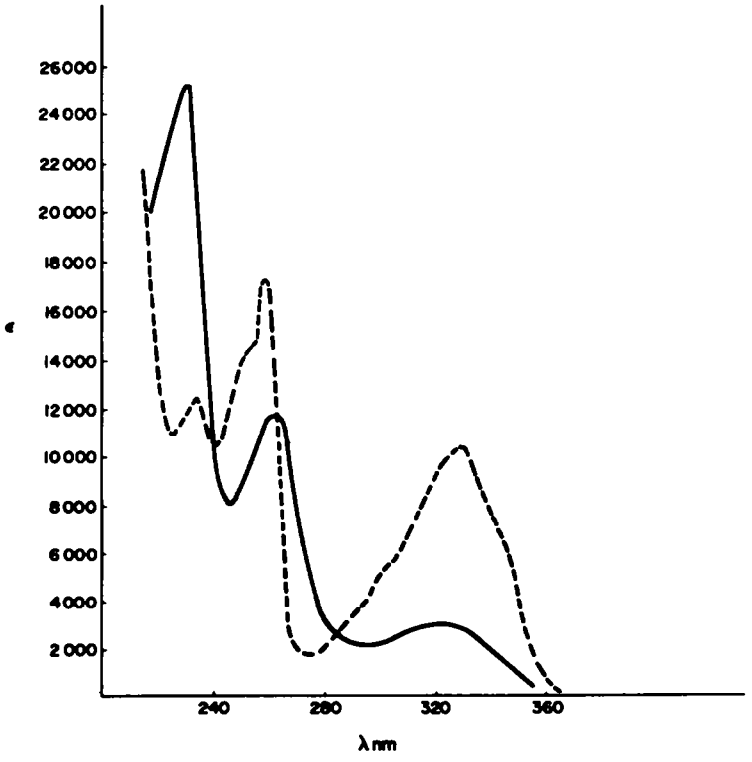


Fig. 1. UV spectra of **5a** (——) and of **38** (– – – –).

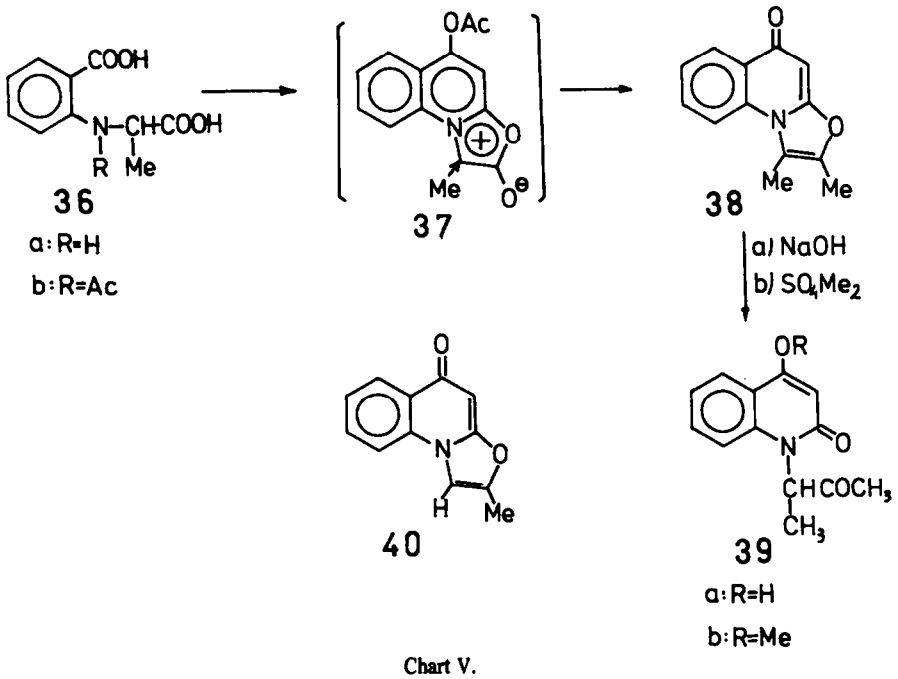


Chart V.

39a did not regenerate the oxazole nucleus of **38**. One lower homologue of **38**, compound **40**, has been described in literature[28] as being the cyclisation product of the N-acetonylanthranilic acid in Ac_2O. The UV spectra of compounds **38** and **40** are almost identical and quite different from those of **5a–b** (Fig. 1).

Discussion on the mechanism. Concerning the double cyclisation, the problem arising in the first place is which of the two new cycles is formed first (paths **A** and **B**). The N-methylanthranilic acid and its N-acetylated derivative can be cyclised in acetic anhydride to N-methyl-4-hydroxycarbostyril.[29,30] Within quite a large set of conditions, temperature from 60° to reflux, time from 10 min to 12 hr and various ratios of Ac_2O, the product was the same and no formation of the O-acetyl derivative was observed.[30] On the other hand, in our case would the free acid **27c** intervene as an intermediate, self-acylation should occur with formation of **28a**. As regards the route **B** it is known that cyclisation of secondary N-acylamino acids with Ac_2O to münchnones takes place at 55° while at 90° the Dakin–West reaction is completed by acylation of the same münchnones and CO_2 elimination.[4b] If we consider the structure of the intermediate mesoionic oxazolone **42** two features are obvious: the presence of an extremely reactive 2-Me group owing to the positive charge of the nucleus which in the mean time deactivates the 4-position towards electrophiles. The anhydridised carboxyl as an *o*- substituent exerts also a supplementary electron-withdrawing activity. On the other hand, the hypothetical quinoloneacetic acid **41** does not appear to be formed under the described conditions while the corresponding non-acetylated derivative **27c** should react with itself to give **28a**. From the above facts and considerations the conclusion can be drawn that there is more evidence in favour of the path **B**.

The mechanism of the cyclisation **3b**→**42** is described for related structures in the literature.[31] It consists of a nucleophilic attack of the amidic oxygen at the neighbouring anhydride CO, accompanied by the elimination of the acetate ion and subsequently of a proton (**43**).

The second ring closure occurs by an intramolecular Perkin type condensation between the anhydride CO and the activated Me substituent of the münchnone ring (**44**). The leaving group is an acetate ion and the intermediate, the ambident nucleophile **29**, follows the path described leading to **5a**.

The cyclisation of **3a–b** in refluxing Ac_2O–Et_3N[32] takes the different course of the well-known Heumann cyclisation to N,O-diacetylindoxyl (**4a**). Its mechanism has been described.[34] In the absence of Et_3N no proton transfer occurs from the methylene of the mixed anhydride of **2b** (**45**) and the cyclisation to the intermediate oxazolone **42** is preferred, which possesses a very active Me group. The double ring closure of **3b** is thus completed to **5a**. If Et_3N ($pK_a = 11.4$) is replaced by a weaker base such as pyridine ($pK_a = 5.2$) a mixture of approximately equal parts of the two products **4a** and **5a** is obtained. When the reflux temperature is lowered to 54° and maintained as such for 7 hr, the product formed is exclusively **4a**.

The mechanism of the formation of oxazoloquinolone **38** is a very pertinent example of how the sole inductive effect of a Me group can change the course of a reaction. In a first stage, the phenylalanine-*o*-carboxylic acid (**36a**) under the action of Ac_2O goes into the corresponding mesoionic oxazolone **37**, whose ylidic resonance structure has an important contribution to the real state of the molecule. It can be easily observed that the electron donating effect of the Me group enhances the reactivity at position 1, destabilising the molecule and making acylation possible. This means that the Dakin–West route will be followed. Usually this reaction takes place with N-acylated α-amino acids under the action of the Ac_2O–Py and the overall result is the replacing of COOH by an acetyl group. The formation of intermediate mesoionic oxazolones has provided the key to the understanding of the reaction mechanism.[4b,26] When the reaction is carried out with N-phenylamino acids the presence of pyridine is not necessary.[35] Besides, the occurrence of the fused-ring oxazolone **46** leads to a second key intermediate, the zwitterion **47** of the type

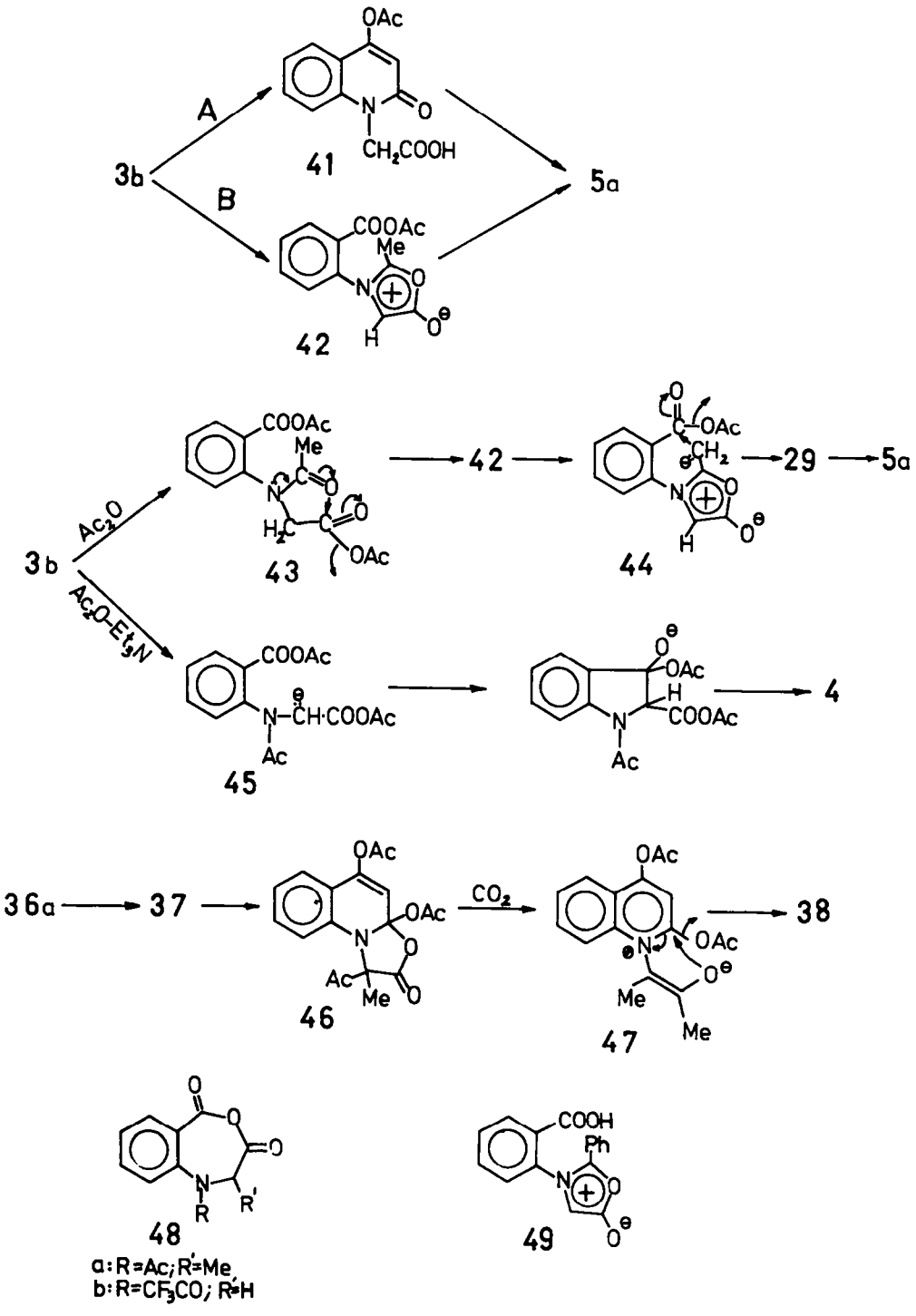


Chart VI.

described by Huisgen *et al.*[4b] The nucleophilic intramolecular attack of the enolate oxygen at the α-position of the quinoline nucleus leads directly to the final oxazole **38**. The exclusion of **39a** as a possible intermediate relies upon the fact that the Robinson–Gabriel synthesis of oxazoles from α-acylamino carbonilic compounds can not be accomplished with acetic anhydride but only with strong cyclodehydrating agents like polyphosphoric acid, HF or TFAA.[36]

Magnetic non-equivalence of methylene protons. All the N-acylated phenylglycine-*o*-carboxylic acids (**3b–d, 3f**) exhibit in their NMR spectra a magnetically non-equivalent methylene which appears as an AB quartet. This is a positive indication of molecular chirality. Since the molecule possesses neither a chiral center nor intrinsic asymmetry, the phenomenon is due to the existence of a preferred conformation whose lifetime is long enough on the NMR time-scale. Because of the crowded ortho substituents the coplanarity of the molecule is disturbed so that enantiomeric conformations are formed

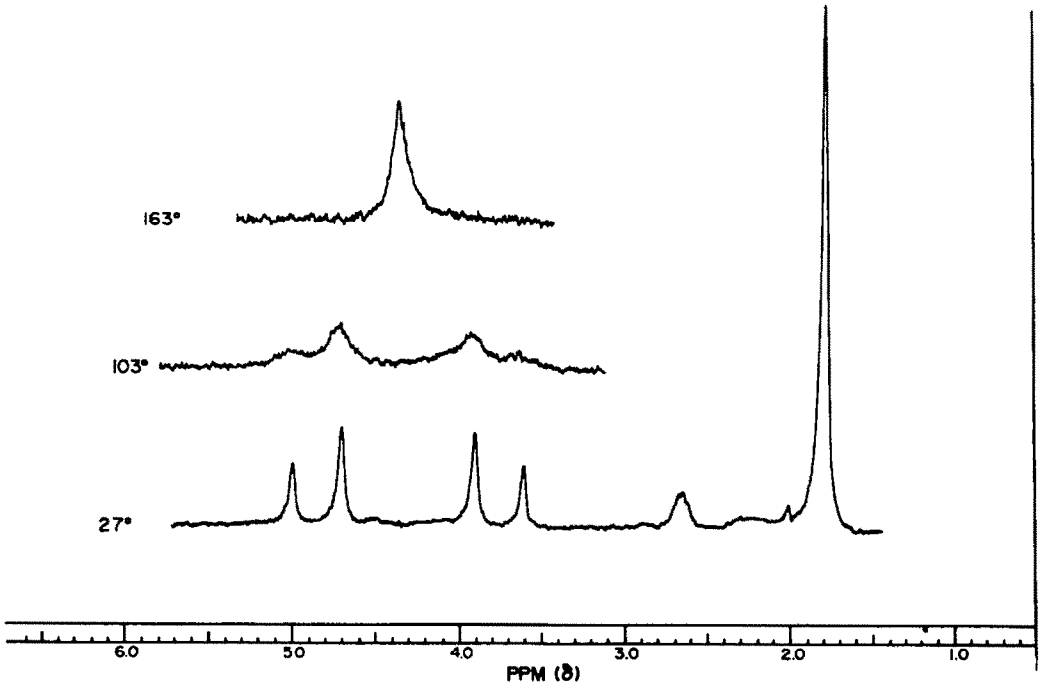


Fig. 2. PMR spectra of **3b** in DMSO-d_6 at different temperatures.

which at elevated temperatures interconvert rapidly, the methylene protons becoming magnetically equivalent. For **3b**, the AB-quartet coalescence takes place at about 160° (Fig. 2). N-Acetyl-N-phenacyl-*o*-substituted aromatic amines,[37] as well as the N-benzoyl-N-acetyl-*o*-toluidine,[38] also exhibit temperature dependent magnetic non-equivalence of the methylene protons.

If we take into account the N-acetylated phenylalanine-*o*-carboxylic acid (**36b**), a chiral center is now incorporated into the molecule. We shall have four species present: two diastereoisomers each present in its racemic modification. Two sets of peaks can actually be observed in the NMR spectrum, especially the Me doublets and the CH-quartets. Their unequal intensities were to be expected as the sterically less hindered conformer predominates. The same phenomenon can be observed to a much smaller degree in the acid **28a** and its ester **28b**.

7-Membered cyclic anhydrides. Anhydride **48a** (Chart VI) was obtained as the result of an attempt to isolate the intermediate mesoionic oxazolone **37** by heating **36a** in Ac_2O at 70° for several hours. The isolated anhydride could not be transformed into oxazole **38** on further refluxing in Ac_2O. The same observation has been proved for the sydnones.[39] Anhydride **48b** resulted on treatment of **3a** with TFAA. Both **48a** and **b** exhibited molecular chirality in the PMR spectra taken at 27°. In the molecule of **48b** we have the same magnetic non-equivalence of the methylene as in **3b–d** and **f** although the chemical shifts lie closer together. In this case the slowing down of the ring-flipping causes the chirality of the molecule, the nitrogen inversion being excluded by the amidic structure, like in the preceding cases. In the molecule of **48a** we have a chiral center similar to **36b** and actually two racemic diastereoisomers can be observed, one of these in predominance.

The formation of a cyclic anhydride was observed by NMR also in the case of an acid **3d** but it could not be isolated. The presence of the Ph group in **3d** makes a second ring closure of the hypothetical intermediate oxazolone **49** impossible. In refluxing Ac_2O neither **49** nor Dakin–West reaction products were formed but instead an exchange of the N-acyl group took place with formation of indoxyl **4** even in the absence of a base.

EXPERIMENTAL

All m.ps are uncorrected and were taken with a micro m.p. apparatus (Boetius). NMR spectra were recorded on a Varian A 60-A spectrometer with TMS as internal standard. UV spectra were measured with a Specord Carl Zeiss-Jena instrument and IR spectra with a UR-20 Carl Zeiss-Jena spectrometer.

Anhydro - 5 - acetoxy - 2 - hydroxyoxazolo[3,2-a]*quinolinium hydroxide* (**5a**)

(A) *From* **3b**. A suspension of 40 g of **3b**[32] in 600 ml Ac_2O was warmed gently unit dissolution occurred and subsequently was refluxed for 30 min. The Ac_2O was removed *in vacuo* and the residue well shaken with 700 ml water until crystallisation began. After standing over night the crystalline granules were filtered off and dried. By trituration of the raw crystalline material with 150 ml of alcohol and washing of the filtered ppt with another portion of 50 ml of alcohol, 25.5 g of **5a**, m.p. 130°, were obtained (yield 62%). Further purification for analysis was achieved by recrystallisation from 60% EtOH in small portions (1 g of **5a** in 30 ml of solvent) in the presence of active charcoal when very long straw-white acicular crystals with a silky fibrillar aspect were obtained, m.p. 130.5°. Sometimes however the presence of the active charcoal caused the alteration of the product. (Found: C, 64.39; H, 3.71; N, 5.48. Calc. for $C_{13}H_9NO_4$: C, 64.19; H, 3.73; N, 5.76%). Mol. wt. (Rast): 256. UV: λ_{max}^{EtOH} (log ϵ) = 322 (3.44), 263 (4.08), 231 (4.41); $\lambda_{max}^{CH_3CN}$ (log ϵ) = 325 (3.54), 262 nm (4.03). IR (KBr): 1758 (broadened; oxazolone and acetoxy carbonyls), 3178 (1-CH), 3147 cm^{-1} (4-CH). NMR ($CDCl_3$): δ = 2.30 (s, 3, CH_3), 5.72 (d, 1, 4-H), 7.12 (d, 1, 1-H), 7.35 (m, 2, 7- and 8-H), 7.68 (dd, 1, 9-H, J = 8 and 2 c/s), 8.15 (dd, 1, 6-H, J = 8 and 2 c/s); $J_{1,4}$ = 2 c/s.

(B) *From* **3a**. To 30 ml Ac_2O were added 2 g of **3a** and gentle heating was applied until dissolution occurred. After refluxing of the homogeneous mixture for 30 min the Ac_2O was removed *in vacuo* while the residue, strongly shaken with 60 ml water, separated as an oil sticking to the walls of the vessel. Overnight most of it crystallised and, by trituration with 6 ml and washing

with 3 ml alcohol, 1.1 g of **5a** were obtained, m.p. 128° (yield 44%).

N-*Propionylphenylglycine-o-carboxylic acid* (**3c**)

The method[32] used for the preparation of **3b** was slightly modified. In a soln of 1.25 g Na_2CO_3 in 125 ml water, 15 g of **3a** were dissolved and subsequently 14 g of propionic anhydride were added dropwise with stirring which was continued for 0.5 hr. After acidifying to pH = 3 with conc HCl, the soln was extracted three times, methylene chloride being used as a solvent. After drying and removing of the solvent, the solid residue was triturated with ether and used without further purification. The yield was 10.5 g (54.5%) of **3c** which after recrystallisation from nitromethane had m.p. 164–165°. (Found: C, 57.36; H, 5.21; N, 5.57. Calc. for $C_{12}H_{13}NO_5$: C, 57.31; H, 5.41; N, 5.46%). NMR ($CDCl_3$ + DMSO-d_6): δ = 0.98 (t, 3, OCH_2CH_3), 2.02 (q, 2, OCH_2CH_3), 3.61 and 4.86 (system AB, 2, N-CH_AH_B; J = 18 cps), 7.33–8.23 (m, 4, aromatic protons), 9.93 (s, 2, COOH).

N-*Benzoylphenylglycine-o-carboxylic acid* (**3d**)

To 98 g of **3a** dissolved in 500 ml 2N NaOH, 58 ml benzoyl chloride was added dropwise concomitantly with another portion of 250 ml 2N NaOH. Stirring was maintained throughout the addition of the reactants and afterwards for another 0.5 hr. The suspensions were filtered off and the pH brought to 3 by addition of conc HCl, when an oil separated which crystallised after 0.5 hr (stirring). After filtration and washing with water the dried ppt of **3d** weighed 137 g (91.3%) which after recrystallisation from aqueous EtOH (3:1) had m.p. 218–220°. (Found: C, 64.36; H, 4.56; N, 4.70. Calc. for $C_{16}H_{13}NO_5$: C, 64.21, H, 4.38; N, 4.68%). NMR (DMSO-d_6): δ = 3.92 and 4.83 (system AB, 2, N-CH_AH_B, J = 17 cps), 7.12–8.03 (m, 4, aromatic protons), 10.73 (s, 2, COOH).

N-*Acetyl-4-nitrophenylglycine-2-carboxylic acid* (**3e**)

4-Nitrophenylglycine-2-carboxylic acid[40] (2 g) was refluxed for 1 hr in 20 ml Ac_2O. After removal of Ac_2O under reduced pressure, the residue was triturated with nitromethane to give 1.8 g of **3e** (yield 63%). After recrystallisation from nitromethane, m.p. 201–3° (dec). (Found: C, 46.60; H, 3.95; N, 9.65. Calc. for $C_{11}H_{10}N_2O_7$: C, 46.81; H, 3.57; N, 9.92%). IR (KBr): 1724 cm^{-1}. NMR (CD_3COCD_3): δ = 3.88 and 4.88 (system AB, 2, N-CH_AH_B, J = 17.5 c/s), 6.50 (s, 2, COOH), 8.00 (d, 1, 6-H), 8.53 (dd, 1, 5-H), 8.85 (d, 1, 3-H); $J_{3,5}$ = 2.5, $J_{5,6}$ = 8.5 c/s.

Anhydro - 5 - acetoxy - 2 - hydroxy - 4 - methyloxazolo[3,2-*a*]*quinolinium hydroxide* (**5b**)

Compound **3c** (4 g) was added to 60 ml Ac_2O and refluxed for 30 min. After removal of Ac_2O *in vacuo*, the tarry and viscous residue was triturated with aqueous acetone to obtain 2.50 g (yield 62%) of **5b**, which on recrystallisation from MeOH gave white, silky crystals with m.p. 163°. (Found: C, 65.34; H, 4.53; N, 5.50. Calc. for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.44%). UV: λ_{max}^{EtOH} (ϵ) = 329 (2852), 268.5 (12357), 234 nm (21414). IR (KBr): 1760 (CO region), 3194 cm^{-1} (1-CH). NMR ($CDCl_3$): δ = 1.95 (s, 3, 4-CH_3), 2.28 (s, 3, $OCOCH_3$), 7.07 (s, 1, 1-H), 7.25–7.85 (m, 3, 7-, 8- and 9-H), 8.15 (dd, 1, 6-H; J = 8 and 1.5 c/s).

5H-*Oxazolo*[3,2a]*quinolin*-2,5(1H)-*dione*(**6a**)

To a soln of 1.5 g **5a** in 25 ml $CHCl_3$, 1.5 ml $BF_3 \cdot Et_2O$ was added. After a few moments with manual shaking, an oil separated which in about 0.5 hr began to crystallise. The next day the product was filtrated off and washed several times with $CHCl_3$. After recrystallisation from pyridine the yield of **6a** was 1 g (80%). Further recrystallisation from EtOH gave light-yellow fluffy crystals, m.p. 234–235° (dec). (Found: C, 65.70; H, 3.64; N, 7.16. Calc. for $C_{11}H_7NO_3$: C, 65.67; H, 3.51; N, 6.96%). UV: λ_{max}^{EtOH} (log ϵ) = 215 (4.50), 284 nm (4.30). IR (KBr): 1665 (quinolone) and 1785 cm^{-1} (oxazolone). NMR (DMSO-d_6): δ = 4.32 (s, 2, CH_2), 5.00 (s, 1, 4-H), 7.15 and 7.80 (multiplets, 2 + 2, aromatic protons).

4-*Methyl*-5H-*oxazolo*[3,2-a]*quinolin*-2,5(1H)-*dione* (**6b**)

(A) *With* $BF_3 \cdot Et_2O$. The same procedure was followed as for **6a**. Starting from 1 g of **5b**, 0.45 g of **6b** were obtained (54%) which on recrystallisation from dioxane–ethanol, m.p. 219–220° (dec). (Found: C, 66.71; H, 4.51; N, 6.78. Calc. for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51%). IR (KBr): 1785 (oxazolone) and 1667 cm^{-1} (quinolone). NMR (DMSO-d_6): δ = 1.70 (s, 3, 4-Me), 4.35 (s, 2, CH_2), 7.20 and 7.70 (multiplets, 2 + 2, aromatic protons).

(B) *With* CF_3COOH. See under **27a**, path *B*.

Anhydro - 2 - hydroxy - 5 - tosyloxyoxazolo[3,2-a]*quinolinium hydroxide* (**7**)

To a soln of 0.5 g of *p*-toluene sulfochloride in 5 ml dry pyridine, magnetically stirred, 0.5 g of **6a** were added. The temp of the mixture was maintained at −5° throughout the reaction. Stirring was continued for 1 hr at 0° and the mixture kept in the refrigerator over night. On dilution with water a crystalline ppt of **7** separated which was filtered off and further washed with water. The dry compound weighed 0.57 g (62%) and on recrystallisation from EtOH, m.p. 157–158°. (Found: C, 60.85; H, 3.84; N, 4.19; S, 8.80. Calc. for $C_{18}H_{13}NO_5S$: C, 60.85; H, 3.69; N, 3.94; s, 9.01%). IR (KBr): 1768 (CO), 3178 (1-CH), 3158 cm^{-1} (4-CH). NMR ($CDCl_3$): δ = 2.48 (s, 3, Me), 5.47 (d, 1, 4-H), 6.88 (d, 1, 1-H), 7.13–7.98 (m, 3, aromatic protons), 8.17 (dd, 1, 6-H); $J_{1,4}$ = 2 c/s.

Anhydro - 5 - benzoyloxy - 2 - hydroxyoxazolo[3,2-a]*quinolinium hydroxide* (**8**)

(A) *By cyclisation of* **3b** *in benzoic anhydride.* A mixture of 7 g of **3b** and 50 g benzoic anhydride was heated at 130–150° for 30 min with occasional shaking. The hot mixture which solidifies at about 90–100°, was poured into 300 ml of 10% Na_2CO_3 and the whole refluxed for 1.5 hr. Initially there was a strong evolution of CO_2. As the benzoic anhydride was being hydrolysed a surfactant oil arose which finally solidified. After filtration the dried product weighed 6.5 g (72.3%) and was recrystallised from acetonitrile, m.p. 180–181°. (Found: C, 70.79; H, 3.81; N, 4.55. Calc. for $C_{18}H_{11}NO_4$: C, 70.81; H, 3.63; N, 4.58%). UV: λ_{max}^{EtOH} (ϵ) = 232 (28915), 265 (14874), 302–306 nm (sh). IR (KBr): 1755 (oxazolone), 1734 (ester), 3193 (1-CH), 3147 cm^{-1} (4-CH)). NMR ($CDCl_3$): δ = 5.87 (d, 1, 4-H), 7.33 (d, 1, 1-H), 7.60 (m, 6, aromatic protons), 8.12 (m, 3, aromatic protons); $J_{1,4}$ = 2 c/s.

(B) *From* **5a** *with benzoyl chloride.* To a soln of 0.5 g of **5a** in 3.5 ml $CHCl_3$, 0.25 ml of benzoyl chloride was added and the whole refluxed for 45 min. On cooling white crystals appeared which were separated by filtration: 0.17 g of **8**, m.p. 165–173°. By evaporation of the filtrate *in vacuo*, trituration with acetonitrile and subsequent recrystallisation of the same solvent, 0.14 g were obtained, m.p. 180–181° (total yield 50%).

5-*Benzyloxyphenylglycine-2-carboxylic acid* (**15**)

Compound **11** was reduced to the corresponding amino acid **12** with Zn and AcOH using a procedure described.[41] This was further diazotised and then hydrolysed[15] to **13** obtained before by an indirect method.[42] To a soln of 5 g (0.029 moles) of **13** in 44 ml alcohol, 1.2 g NaOH (0.0295 moles) dissolved in 14.7 ml distilled water were added followed by 10.3 ml (11.3 g; 0.095 moles) benzyl chloride. The mixture was refluxed for 2 hr after which time a second portion of NaOH aq (6 g in 29 ml of water) was added dropwise during 2 hr, the reflux being maintained and continued for another hr. The resulted homogeneous soln was concentrated to a small volume and after addition of 100 ml water, extracted twice with benzene. The fluorescent aqueous layer was treated with active charcoal and acidulated with conc HCl. A white ppt separated which after recrystallisation from aqueous EtOH (1:1) afforded 5.6 g of **14**, m.p. 137° (yield 74%).

To a soln of 11 g KOH and 11 g K_2CO_3 in 176 ml distilled water, 22 g of **14** and 11 g glycine were added and gradually heated with manual shaking until complete dissolution occurred. A trace of copper bronze was introduced into the soln and the whole refluxed for 5 hr. After filtration of the catalyst the mixture was diluted with 1.5 l water and acidified with conc HCl. After washing and drying the ppt 25 g of the crude **15** were obtained which on recrystallisation from alcohol, m.p. 210° (dec). (Found: C, 64.29; H, 5.42; N, 4.65. Calc. for $C_{16}H_{15}NO_5$: C, 64.42; H, 4.73; N, 4.53%).

Anhydro - 5 - acetoxy - 8 - benzyloxy - 2 - hydroxyoxazolo[3,2-a]*quinolinium hydroxide* (16)

Acid **15** (5 g) in 75 ml Ac_2O was refluxed for 30 min. On cooling mesoionic **16** crystallised. After filtration and vacuum drying with NaOH, 3 g of crude product (yield 52%) were obtained which after recrystallisation from EtOH gave yellow crystals, m.p. 170–171°. (Found: C, 68.78; H, 4.53; N, 3.92. Calc. for $C_{20}H_{15}NO_5$: C, 68.76; H, 4.33; N, 4.04%). IR (KBr): 1733 (mesoionic oxazolone), 1768 (ester CO), 3124 (4-CH), 3159 cm^{-1} (1-CH). NMR ($CDCl_3$): $\delta = 2.27$ (s, 3, Me), 5.18 (s, 2, CH_2), 5.68 (d, 1, 4-H), 6.88 (m, 2, 7- and 9-H), 7.05 (d, 1, 1-H), 7.42 (s, 5, Ph), 8.07 (d, 1, 6-H); $J_{1,4} = 2$ c/s.

5-Acetoxy-8-hydroxyoxazolo[3,2-a]*quinolinium-2-oxide* (17)†

A soln of 0.17 g of **16** in 30 ml acetone was hydrogenated at ordinary pressure in the presence of 5% Pd/C. The H_2 absorption ceased after 3 hr. The catalyst was filtered off and the solvent removed to give 0.11 g of crude **17** m.p. 185–190° (yield 91%). Recrystallisation from aqueous EtOH (1:1) afforded crystals, m.p. 197°. (Found: C, 60.49; H, 3.90; N, 5.04. Calc. for $C_{13}H_9NO_5$: C, 60.23; H, 3.50; N, 5.40%). UV: λ_{max}^{EtOH} (log ϵ) = 213 (4.09), 251 (4.53), 316 nm (3.94). IR (KBr): 1710 (mesoionic oxazolone), 1762 (ester carbonyl), 3143 (4-CH), 3189 (1-CH), 3235 cm^{-1} (OH). NMR (DMSO-d_6): $\delta = 2.37$ (s, 3, Me), 5.93 (d, 1, 4-H), 6.95 (dd, 1, 7-H), 7.20 (d, 1, 1-H), 7.47 (d, 1, 9-H), 8.06 (d, 1, 6-H); $J_{1,4} = 2$; $J_{6,7} = 8$ and $J_{7,9} = 2$ c/s.

N,O-*Diacetyl-6-benzyloxyindoxyl* (18)

In a mixture of 5 ml Ac_2O and 1 ml Et_3N, 1 g of **15** was refluxed for 20 min. After removal of the excess anhydride under reduced pressure the residue was well shaken with water and left to crystallise. After recrystallisation from EtOH 0.4 g of **18** were obtained (37%) which after a second recrystallisation had m.p. 124°. On shaking with hot NaOH aq the corresponding indigo was formed. (Found: C, 70.38; H, 5.66; N, 4.36. Calc. for $C_{19}H_{17}NO_4$: C, 70.57; H, 5.30; N, 4.33%).

Anhydro - 5 - acetoxy - 1 - trifluoroacetyl - 2 - hydroxyoxazolo[3,2-a]*quinolinium hydroxide* (23a)

A mixture of 1 g of **3b** and 5 ml TFAA was manually shaken. An almost instantaneous vigorous reaction ensued when the mixture became dark and a white ppt separated which was filtered off next day to give 1.3 g of crude product (yield 96.2%), which on trituration with hot MeOH and recrystallisation from nitromethane, m.p. 207–209°. (Found: C, 53.46; H, 2.69. Calc. for $C_{15}H_8F_3NO_5$: C, 53.11; H, 2.38%). UV: λ_{max}^{EtOH} (log ϵ) = 278 (3.76), 362 nm (4.30). IR (KBr): 1786 (oxazolone CO), 1665 ($COCF_3$), 3168 cm^{-1} (4-CH). NMR spectrum could not be registered because of the lack of solubility.

Anhydro - 5 - acetoxy - 1 - trifluoroacetyl - 2 - hydroxy - 4 - methyloxazolo[3,2-a]*quinolinium hydroxide* (23b)

The same procedure was used as for **23a**: a white crystalline product was obtained (yield 71%) which after recrystallisation from CCl_4 had a m.p. 134–135°. (Found: C, 54.16; H, 2.98. Calc. for $C_{16}H_{10}F_3NO_5$: C, 54.40; H, 2.85%). UV: λ_{max}^{EtOH} (log ϵ) = 280 (4.00), 362 nm (4.58). IR (CCl_4 and KBr): 1785 (oxazolone CO), 1670 cm^{-1} ($COCF_3$). NMR ($CDCl_3$): $\delta = 1.95$ (s, 3, 4-Me), 2.38 (s, 3, $OCOCH_3$), 7.58 (m, 3, aromatic protons), 8.18 (d, 1, 6-H).

Anhydro - 5 - trifluoroacetoxy - 1 - trifluoroacetyl - 2 - hydroxyoxazolo[3,2-a]*quinolinium hydroxide* (24)

A suspension of 0.68 g of **3b** in 3.4 ml TFAA was magnetically stirred in the cold for 2 hr and then refluxed for another hr. The mixture was left in the refrigerator for two additional hr. The solid product was filtered off and thoroughly washed with ether to give 0.3 g (27%) of **24** which after several recrystallisations from nitromethane had m.p. 187°. (Found: C, 46.06; H, 1.59. Calc. for $C_{15}H_{15}H_{15}F_6NO_5$: C, 45.81; H, 1.28%). IR (KBr): 1694 ($COCF_3$), 1772 (oxazolone), 1810 (CF_3COO), 3176 cm^{-1} (4-CH). NMR (acetone-d_6): only aromatic protons.

4-Hydroxy-3-methyl-2-oxo-1(2H)*-quinolineacetic acid* (27a)

(A) *In alkaline medium.* Compound **5b** (3 g) was refluxed for 0.5 hr in a mixture of 30 ml EtOH and 53 ml 20% NaOH aq. Subsequently the alkaline soln was concentrated *in vacuo* and acidified to pH = 3 with HCl. The finely divided ppt was filtered off, thoroughly washed and after drying weighed 2.7 g (quantitative yield). After recrystallisation from MeOH, m.p. 245–247°. (Found: C, 61.97; H, 4.90; N, 5.74. Calc. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.00%). UV: λ_{max}^{EtOH} (log ϵ) = 217 (4.18), 257 nm (3.84). IR (KBr): 1688 (broad band with shoulders), 2400–3300 cm^{-1} (OH). NMR (DMSO-d_6): $\delta = 1.73$ (s, 3, 3-Me), 4.33 (s, 2, CH_2), 7.53 (m, 4, aromatic protons), 11.00 (very broadened, 2, OH).

(B) *In acid medium.* The mesoionic **5b** dissolved instantaneously in trifluoroacetic acid. When the soln was diluted with water and the separated ppt immediately filtered off, thoroughly washed and dried, the lactone **6b** was obtained. If the diluted mixture was left over night and filtered off only next day the acid **27a** resulted in nearly quantitative yield.

1-*Carboxymethyl-2,4-dihydroxyquinolinium chloride* (26)

To 180 ml of 10% HCl, 3 g of **5a** were added with stirring and progressive heating was applied until at 70–80° a clear soln resulted to which some active charcoal was added. After filtering and vacuum evaporation to dryness in a bath heated to no more than 80°, an amorphous solid with a vitreous foamy appearance was obtained which could not be induced to crystallise. A small sample obtained from very pure **5a** was submitted to elementary analysis, m.p. 143° (dec). (Found: C, 51.35; H, 4.10; N, 5.73; Cl, 14.12. Calc. for $C_{11}H_{10}NO_4Cl$: C, 51.70; H, 3.95; N, 5.48; Cl, 13.87%). IR (KBr): 1740, 1653 cm^{-1}. NMR (D_2O): $\delta = 4.08$ (s, 2, CH_2), 7.02–7.80 (m, 4, aromatic protons). H_2O signal taken as internal reference.

Methyl 4-methoxy-2-oxo-1(2H)*-quinolineacetate* (27b)

Without any purification the chlorohydrate **26** was treated with 200 ml of ethereal soln of diazomethane (about 0.2 moles, obtained from 22 g of moist N-nitroso-N-methylurea). After 2 hr the ppt was filtered off, 2 g of **27b** being obtained (yield 66%). The crude ester was dissolved in $CHCl_3$, treated with active charcoal and, after filtration, the crystallisation occurred by addition of CCl_4. After recrystallisation from $CHCl_3$–CCl_4 (1:2), m.p. 154–155°. (Found: C, 63.41; H, 5.52; N, 5.94. Calc. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66%). UV: λ_{max}^{EtOH} (log ϵ) = 259 (3.73; sh), 289 nm (3.46; sh). IR (CH_2Cl_2): 1721, 1689, 1630 cm^{-1}. NMR ($CDCl_3$): $\delta = 3.83$ and 3.85 (singlets, 6, OCH_3), 4.30 (s, 2, CH_2), 5.20 (s, 1, 3-H), 7.30 (m, 3, aromatic protons), 7.92 (q, 1, 5-H).

3 - (1,2 - *Dihydro - 4 - hydroxy - 2 - oxo - 1 - quinolinylacetyl*) - 4 - *hydroxy - 2 - oxo - 1*(2H) - *quinolineacetic acid* (28a)

(A) *Basic hydrolysis.* A suspension of 0.5 g of **5a** in 10 ml 5% NaOH aq was magnetically stirred over night when complete dissolution occurred. After acidification with HCl a ppt of **28a** separated which after filtration, washing and drying weighed 0.4 g (yield 89%) with m.p. 213° (dec). Lower yields were obtained with aqueous EtOH (1:4). When AcOH was used for neutralisation another crystalline form separated which decomposed without melting above 300° and could be recrystallised from distilled water (1:30) under 60°. When the aqueous soln was refluxed, a conversion to the former crystalline modification occurred and crystals began to separate with m.p. 218°. On cooling the separation was complete. (Found: C, 59.85; H, 4.27; N, 6.23. Calc. for $C_{22}H_{16}N_2O_7 \cdot H_2O$: C, 60.20; H, 4.14; N, 6.38%). UV: $\lambda_{max}^{H_2O}$ (log ϵ) = 282 (4.08), 333 nm (4.28). IR (KBr): ν (meltable form) = 1720, 1670, 1655; ν (unmeltable form) = 1690, 1650, 1610 cm^{-1}. NMR (DMSO-d_6): $\delta = 4.48$ and 4.85 (singlets, 2 + 2, CH_2), 6.45 (s, 1, β-H), 7.62 (m, 11, aromatic and acidic protons). On deuteration the β-H disappeared together with 3 protons of the aromatic region.

(B) *Acid hydrolysis.* The chlorohydrate **26** obtained from 2 g of **5a** was dissolved in 20 ml distilled water when a clear light-yellow

†Katritzky's nomenclature[43] for mesoionic compounds cannot be applied in this instance unambiguously, since there are formally two OH groups in the molecule, which both could be deprotonated.

soln was obtained. By addition of aqueous alkali the soln was brought to pH = 10 when no separation of a ppt was observed. On reacidification with conc HCl a voluminous ppt separated which after washing and drying gave 2 g of **28a** with m.p. 207° (yield 90%). When the alkalisation was done carefully, at pH = 4.5 an abundant ppt separated which after filtration, good washing and drying *in vacuo*, weighed 2.2 g and showed no m.p. up to 300° when it darkened.

Methyl 3(1,2 - *dihydro* - 4 - *methoxy* - 2 - *oxo* - 1 - *quinolinyl-acetyl*) - *methoxy* - 2 - *oxo* - 1(2H) - *quinolineacetate* (**28b**)

To 50 ml of ethereal soln of diazomethane obtained as before, 0.75 g of **28a** were added (any of the two forms) and the suspension was stirred for 2 hr when a deposit of white powder was obtained with a supernatant orange ether layer. The yield was 0.75 g of **28b** (91%). On repeated recrystallisation from MeOH, m.p. 230–232°. (Found: C, 64.70; H, 5.02; N, 6.04. Calc. for $C_{25}H_{22}N_2O_7$: C, 64.93; H, 4.80; N, 6.06%). UV: λ_{max}^{EtOH} (log ϵ) = 214 (4.48), 260 (4.14), 291 nm (4.10). IR (CH_2Cl_2): 1726, 1694, 1651 cm^{-1}. NMR ($CDCl_3$): δ = 3.82 and 3.85 (singlets, 6, OCH_3), 4.02 (s, 3, $COOCH_3$), 4.57 (s, 2, CH_2), 4.85 (d, 2, CH_2), 6.77 (t, 1, β-H), 7.35 (m, 6, aromatic protons), 7.92 (m, 2, aromatic protons; homoallylic coupling across an amidic bond: $J_{CH_2,\beta\text{-}H}$ = 2 c/s.

4-*Anilino*-2-*oxo*-1(2H)-*quinolineacetic anilide* (**32**)

To a soln of 1.2 g (5 mmole) of **5a** in 10 ml dioxane, 1.4 g (15 mmole) aniline were added and the whole refluxed for 2 hr. After removal of the solvent under reduced pressure the sticky residue was triturated with nitromethane when 1.8 g of anilide (quantitative yield) resulted. After recrystallisations from dioxane and nitromethane clean white crystals were obtained, m.p. 230°. (Found: C, 74.79; H, 5.26; N, 11.37. Calc. for $C_{23}H_{19}N_3O_2$: C, 74.78; H, 5.18; N, 11.37%). UV: λ_{max}^{EtOH} (log ϵ) = 306 nm (4.42). IR (KBr): 1660 (amide), 1650 (sh; 2-quinolone), 3285 and 3215 cm^{-1} (NH). NMR (DMSO-d_6): δ = 4.58 (s, 2, CH_2), 5.32 (s, 1, 3-H), 7.18 (m, 14, aromatic protons), 9.27 (s, 1, NH), 10.16 (s, 1, NH). Both NH-groups were deuterable.

Acylation and cyclization of o-*formylphenylglycine* (**33**)

The title compound was prepared from *o*-nitrobenzaldehyde through a sequence of five steps; formation of the oxime, the selective hydrogenation of the nitro group,[44] condensation of the resulting amine with chloroacetamide[24] and hydrolysis of the amide[24] and of the oxime[25] groups.

A soln of 0.65 g of **33** in 10 ml Ac_2O was refluxed for 30 min and the solvent removed under reduced pressure. The oily residue did not crystallise but could be distilled in vacuum to afford N-acetylindole whose IR and PMR spectra were identical to those of an authentic specimen.

Phenylalanine-o-*carboxylic acid* (**36a**)

To a soln of 21 g (150 mmole) K_2CO_3 in 80 ml distilled water were successively added and dissolved with gentle heating 12.5 g (80 mmole) chlorobenzoic acid and 9 g (100 mmole) alanine. A small amount of Cu powder (about 1 g) was introduced and the whole refluxed for 4 hr. After dilution with 150 ml distilled water and filtration the green soln was acidified with HCl to pH = 3. A white, bulky ppt separated which was filtered off and then purified by reprecipitation from a slightly warm ammoniacal solution or by recrystallisation from 400 ml 25% EtOH to give in the latter case, after vacuum drying, 8.5 g of **36a** (yield 51%) with m.p. 218° (dec). Litt.[45] m.p.: 216° (dec).

N-*Acetylphenylalanine*-o-*carboxylic acid* (**36b**)

The same procedure[32] was used as for **3b**. The product (**36b**) which separated by acidification was difficult to crystallise from ether m.p. 215–217° (dec). (Found: C, 56.99; H, 5.44; N, 5.80. Calc. for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.21; N, 5.58%). NMR (DMSO-d_6): δ = 1.67 (s, 3, $COCH_3$), 7.70 (m, 4, aromatic protons), 9.90 (broadened s, 2, COOH); J_{CHCH_3} = 7.5 c/s; diastereoisomers: δ_{CHCH_3} (d, 3) = 0.95 (84.5%) and 1.44 (15.5%), δ_{CHCH_3} (q, 1) = 4.80 (84.5%) and 4.09 (15.5%).

1,2-*Dimethyl*-5H-*oxazolo*[3,2-a]*quinolin*-5-*one* (**38**)

Procedure A. The acid **36a** (5 g) was refluxed in 72 ml Ac_2O for 1 hr. The excess anhydride was removed under reduced pressure and the residue shaken with water and left over night. The gelatinous ppt was triturated with 10 ml acetone when 1.7 g of white crystals of **38** were obtained (yield 33%). After recrystallisation from 50% EtOH, m.p. 210°, picrate m.p. 236° (yellow crystals) and chlorohydrate m.p. 250° with dec (obtained from hot alcoholic soln by addition of conc HCl). (Found: C, 73.03; H, 5.48; N, 6.79. Calc. for $C_{13}H_{11}NO_2$: C, 73.22, H, 5.20; N, 6.56%). UV: λ_{max}^{EtOH} (log ϵ) = 259 (4.18), 329 nm (4.05). IR (CH_2Cl_2): 1631 cm^{-1} (quinolone). NMR ($CDCl_3$; the sample was sublimed in vacuum in order to remove a trace of an undesirable impurity): δ = 2.25 and 2.55 (doublets, 3 + 3, CH_3), 6.07 (s, 1, 4-H), 7.15–8.03 (m, 3, aromatic protons), 8.5 (dd, 1, 6-H); $J_{Me\text{-}Me}$ = 1 c/s.

Procedure B. The residue from procedure A was eluted with acetone from a neutral alumina column, resulting in 1.6 g of **38**, m.p. 209° (yield 31%).

4-*Hydroxy*-1-(1-*methylacetonyl*)-2(1H)-*quinolone* (**39a**)

To a soln of 1.5 g of **38** in 15 ml EtOH, 25 ml 20% NaOH aq were added and the whole was refluxed for 2 hr. After concentration of the soln under reduced pressure to one third of its initial volume and acidification to pH = 3 with HCl a bulky ppt separated: 1.5 g (yield 89%) which after recrystallisation from acetonitrile and 50% aqueous MeOH, m.p. 266–267°. DNFH: dark yellow crystals with m.p. 276–278°. (Found: C, 67.88; H, 5.66; N, 6.12. Calc. for $C_{13}H_{13}NO_3$: C, 67.52, H, 5.67; N, 6.06%). IR (KBr); 1634 (quinolone), 1718 (acetonyl), 3413 cm^{-1} (OH). NMR ($CDCl_3$ + DMSO-d_6): δ = 1.53 (d, 3, $CHCH_3$), 2.00 (s, 3, $COCH_3$), 5.32 (q, 1, $CHCH_3$), 6.03 (s, 1, 3-H), 7.38 (m, 3, aromatic protons), 8.07 (dd, 1, 5-H), 11.2 (broadened s, 1, OH); $J_{CH\text{-}CH_3}$ = 7 c/s.

4-*Methoxy*-1-(1-*methylacetonyl*)-2(1H)-*quinolone* (**39b**)

A method[46] described for the esterification of hindered acids with Me_2SO_4 was utilised since no results were obtained with diazomethane. To the soln of 1 g of **39a** and 0.5 ml Me_2SO_4 in 10 ml dioxane, 0.8 g 25% NaOH aq was added. After refluxing for 30 min the Na_2SO_4 was filtered off and washed with dioxane. The residue obtained after evaporation *in vacuo* of the dioxane fractions was crystallised from acetonitrile to give 0.7 g of **39b**, which after recrystallisation from aqueous DMF had a m.p. of 175°. DNFH: orange needles with m.p. 233–4°. (Found: C, 68.54; H, 5.97; N, 5.88. Calc. for $C_{14}H_{15}NO_3$: C, 68.52; H, 6.16; N, 5.71%). IR (KBr): 1638 (quinolone), 1718 cm^{-1} (acetonyl). NMR ($CDCl_3$): δ = 1.60 (d, 3, $CHCH_3$), 2.03 (s, 3, $COCH_3$), 4.00 (s, 3, OCH_3), 5.65 (q, 1, CH–CH_3), 6.08 (s, 1, 3-H), 7.42 (m, 3, aromatic protons), 8.07 (dd, 1, 5-H); $J_{CH\text{-}CH_3}$ = 7 c/s.

Cyclization of **3b** *with* Ac_2O–Py

A soln of 20 g of **3b** in a mixture of 160 ml of Ac_2O and 40 ml of pyridine was kept for 24 hr at 55–60°. After removal of the excess anhydride under reduced pressure the viscous residue was vigorously shaken with 700 ml water and left over night. The ppt was filtered off and dried in vacuum yielding 16.5 g of **4** (90%). After elution with CH_2Cl_2 from a neutral alumina column m.p. 80°. No depression of the mixed m.p. with an authentic sample was observed while alkaline hydrolysis furnished indigo.

A reaction carried out at 55° for 7 hr gave a yield of 82%. When the mixture of the preceding experiments was refluxed for 20 min approximately equal amounts of **4** and **5a** were obtained as determined by NMR.

N-*Acetylphenylalanine*-o-*carboxylic anhydride* (**48a**)

A soln of 1.5 g of **36a** in 22 ml Ac_2O was kept for 5 hr at 70° in a thermostat. The excess anhydride was removed under reduced pressure by heating on a water-bath maintained under 75°. The yield was almost quantitative. After recrystallisation from ether with active carbon, m.p. 127°. (Found: C, 62.06; H, 4.91; N, 5.80. Calc. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.00%). IR (CH_2Cl_2): 1740 and 1819 cm^{-1}. NMR ($CDCl_3$): δ = 1.92 (s, 3, $COCH_3$), 7.32 (m, 3, aromatic protons), 8.17 (dd, 1, 3-H); diastereoisomers: δ_{CHCH_3} (d, 3) = 1.36 (15%) and 1.72 (85%), δ_{CHCH_3} (q, 1) = 3.96 (85%) and 4.51 (15%).

N-Trifluoroacetylphenylglycine-o-carboxylic anhydride (**48b**)

A suspension of 3 g phenylglycine-*o*-carboxylic acid in 4 ml TFAA was magnetically stirred in the cold. After a few minutes the mixture became homogeneous and a slight warming was observed. The stirring was continued for several hours after which time the clear soln was poured into 20 g ice-water. A powdery ppt separated which after filtration and drying gave 3.2 g of **48b** (yield 76%). After recrystallisation from $CHCl_3$ m.p. 100–102°. (Found: C, 48.12; H, 2.12. Calc. for $C_{11}H_6NO_4F_3$: C, 48.38; H, 2.21%). IR (KBr): 1761 and 1881 cm^{-1}. NMR (CD_3COCD_3): δ = 4.63 and 4.88 (system AB, 2, N-CH_AH_B, J = 16 c/s), 6.80 and 7.47 (multiplets, 2+2, aromatic protons).

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