SOME REACTIONS OF PYRIDINES AND RELATED HETEROCYCLES WITH ACETYLENIC ESTERS

(REVIEW)

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The types of compounds obtainable from acetylenemono- and acetylenedicarboxylic esters with a variety of pyridines are reviewed. The structures previously proposed for a number of products formed from 2-methylquinolines and thiazoles have been revised on the basis of x-ray diffraction studies. Mechanisms accounting for the production of the various compounds are considered.

Diels and Alder were the first [1] to investigate reactions between heterocycles and acetylene derivatives. During 1929-1940 they examined the products obtained from acetylenedicarboxylic acid, and its dimethyl ester which often behaved differently, with a number of heterocycles. Complex mixtures were often produced, and as separation depended entirely on recrystallization, and structural elucidation on chemical degradation, it is remarkable what progress was made. The early experimental work is of high quality and is reproducible. Interest in this general area of study lapsed from 1940 until 1954, when interest began to revive [2]; the first review appeared in 1963 [3], and since then very many publications concerning additions of acetylenes to heterocycles have appeared. A comprehensive review is being prepared [4] and the present account concerns mainly work carried out in Oxford with relatively simple nitrogen-containing heterocyclic compounds.

By far the most popular electrophilic acetylene for these reactions is dimethyl acetylenedicarboxylate (DMAD). Dicyanoacetylene is much more reactive but is difficult to obtain [5]; diacetylacetylene (3-hexyn-2,5-dione) has been little investigated because no satisfactory preparation is available [6]; and dibenzoylacetylene appears to be relatively unreactive [7], possibly because of steric hindrance. Monosubstituted acetylenes such as methyl propiolate (XIV) [8] and acetylacetylene (3-pentyn-2-one) [9] are less reactive, as might be anticipated. The electron-attracting group also facilitates loss of the acetylenic proton to yield carbanions [e.g., (XV)] which can lead to new types of product.

The products obtained from an activated acetylene and a heterocycle can depend enormously on the precise conditions, purity of the reactants, and the solvent. The cleanest reactions often take place in highly polar solvents such as acetonitrile or dimethylformamide, possibly because the first-formed zwitterions [e.g., (I)] are strongly solvated, thereby increasing their changes of discrete reactions rather than self-condensations leading to red tars, which are almost inevitable "by-products." The unintentional presence of traces of water, or other proton donors, can complicate the situation by satisfying the negative center of the zwitterion (I), and at the same time providing an anion to react with the cationic system. Chromatographic separation of the reaction products is almost always essential, and usually eliminates the tar, for in only a few instances single compounds are mainly formed. Dimethyl fumarate, and the polymers and decomposition products of DMAD [10], may also be present.

1. Reactions with Pyridines Involving Attack at Nitrogen

Pyridine with DMAD in aprotic solvents must initially yield the zwitterion (I), formed by electrophilic attack at the nitrogen atom (Scheme 1). If the nitrogen atom is insufficiently nucleophilic, for example, if a 2-chlorine atom is present, reaction does not occur [11]. The zwitterion has been trapped in many ways, one of the simplest being with carbon dioxide [12] at −60°C. This leads to a separable mixture of unstable (E)-

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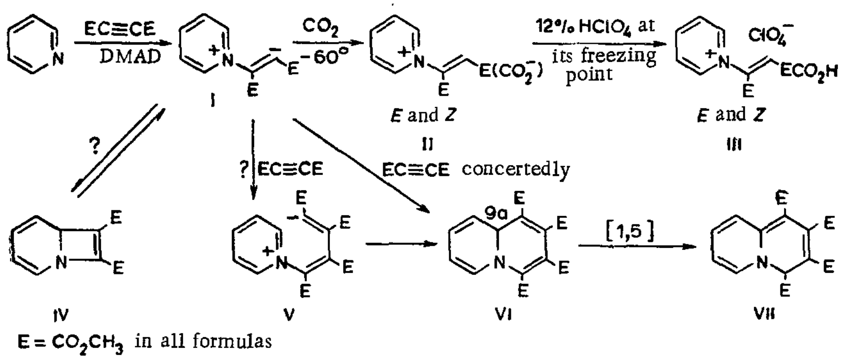
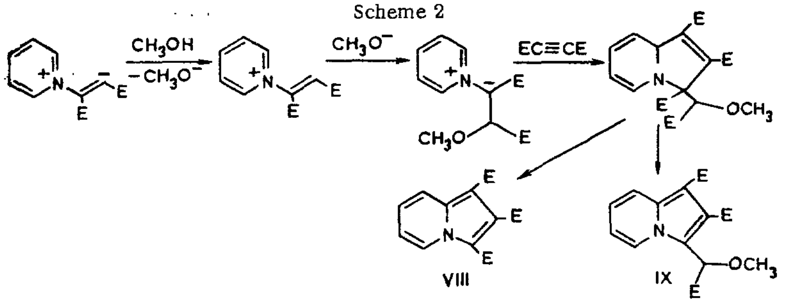
Scheme 1



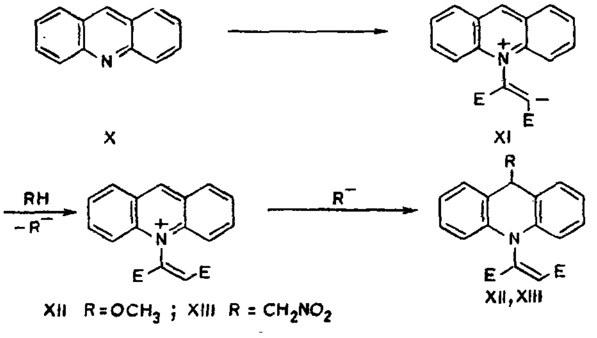
and (Z)-pyridiniumcarboxylates (II) which can be converted to the relatively stable perchlorates (III). No direct physical evidence is available to confirm the existence of the intermediate (I), which could possibly cyclize and be in equilibrium with the bicyclic structure (IV). The NMR spectrum of a solution of pyridine and DMAD in dichloromethane at −80°C shows [13] resonances due only to the constituent materials. On raising the temperature to −50° the resonances due to the 9aH proton of (VI) appeared and at −35° resonances were seen corresponding to exactly those expected for all the ring protons of the 9aH-quinolizine (VI), on the basis of those observed for other more stable alkyl-substituted 9aH-quinolizines [14]. Although the ring proton arrangements for structures (IV) and (VI) are the same, it is unlikely that their chemical shifts would be similar. The nitrogen atom of the quinolizine (VI), by analogy with similar thiazole derivatives [e.g., (XLVI)] [15], has an sp^2 configuration and bears substantial positive charge. This would not be expected of the azetine structure (IV). The main product isolable from pyridine with 2 moles of DMAD under aprotic conditions is the 4H-quinolizine-1,2,3,4-tetracarboxylate (VII). The stability of 9aH-quinolizine-1,2,3,4-tetracarboxylates [e.g., (VI)] relative to the 4H-isomers [e.g., (VII)] increases with substitution, and in the case of the 7,9-dimethyl derivative the rearrangement has been shown [16] to take place by a [1,5]-sigmatropic shift. The formation of the 9aH-quinolizine from the zwitterion (I) could take place by a concerted pathway, or by a stepwise mechanism involving another zwitterion (V). There is, as yet, no direct experimental evidence concerning this.

Scheme 2

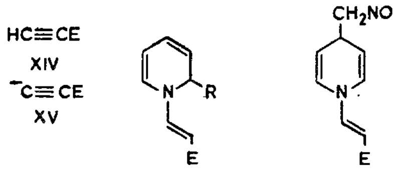


When pyridine is treated with DMAD in the presence of methanol the product is a mixture of the indolizines (VII) and (IX) which could be formed [3, 17] as shown in Scheme 2. In the case of acridine (X) the reaction course (Scheme 3) is simpler [2] because the methoxide anion formed merely adds to the heterocyclic ring to give (XII). Even nitromethane, when used as solvent [8], is acidic enough to satisfy the carbanion (XI), formed from acridine, and yields (Scheme 3) a comparable product (XIII). In contrast, pyridines under the same conditions form only 9aH-quinolizines [cf. (VI)], so the intermediate zwitterion (I) is more susceptible to electrophilic attack from another molecule of the acetylene than from a proton released from nitromethane.

Scheme 3



1,2-Dihydropyridines [e.g., (XVI)] are obtainable from methyl propiolate (XIV) and the corresponding pyridine, presumably by a route analogous to Scheme 3, involving addition of the anion (XV) of the acetylenic ester. If methanol is employed as solvent, then 2-methoxy compounds (XVII) are formed, while other anions, such as those derived from nitromethane, acetylacetone, and similar proton sources, add [8] at position 4

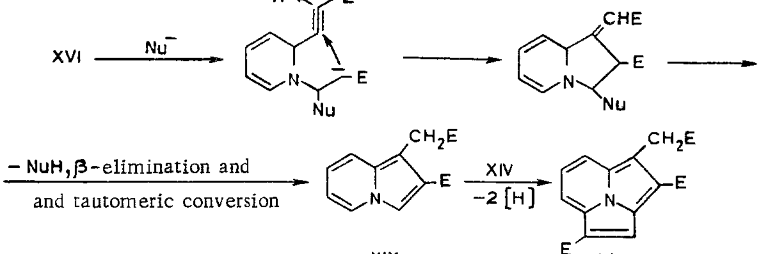


XVI,XVII XVIII

XVI R = C≡CE ; XVII R = OCH_3

yielding 1,4-dihydropyridines such as (XVIII). The conditions employed for the synthesis of the dihydropyridine (XVI) are critical, for cyclization to the indolizine (XIX) and subsequent addition of a further mole of the acetylene (Scheme 4) to give the cycl[3.2.2]azine (or pyrrolo[2,1,5-cd]indolizine) (XX) can take place [18].

Scheme 4

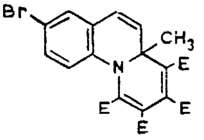


XIX XX

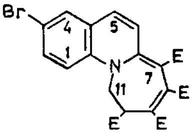
Nu = nucleophile

2. Reactions with Pyridines Involving Electrophilic Attack at Ring Substituents

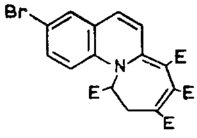
The methyl groups of 2-alkylpyridines are usually insufficiently activated to yield carbanions susceptible to attack by electrophilic acetylenes, but this is not the case for 2-methylquinolines and a number of other heterocycles possessing a similar activated system. The products from 2-methylquinoline, and various derivatives, with DMAD have been examined in considerable detail. Using acetonitrile as solvent the main products are the quinolizine possessing a bridgehead methyl group [e.g., (XXI)], and isomeric yellow adducts in which the original 2-methyl group has disappeared. Analysis of the NMR spectra of many similar compounds from various 2-methylquinolines, 1-methylisoquinolines, and 6-methylphenanthridines [19] showed that $-CH_2-CH\langle$ groups were present; that the hydrogen atom present originally at position 3, in the case of the quinolines, had moved strongly downfield; that substantial conjugation was present ($\lambda_{max} \sim 450$ nm); and that a fragment corresponding to methyl acrylate was lost in the mass spectrometer to give the base peak. Two isomers of this type were obtained from 6-bromo-2-methylquinoline, the most significant difference being that one possessed



XXI

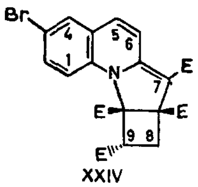


XXII

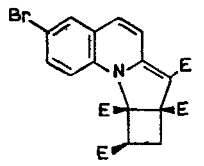


XXIII

a very-high-field aromatic proton and a high-field ester-methyl group in its NMR spectrum. Structures (XXII) and (XXIII) were put forward [19] for these compounds, the high-field aromatic proton being in the deshielding region of the 11-ester carbonyl group, and the ester methyl being in the shielding region of the carbocylic ring in the case of (XXIII). Tracer experiments [20] using ^{13}C-methyl-labelled quinoline showed that the ^{13}C atom was associated with two hydrogen atoms in both (XXII) and (XXIII), and although the formation of both of these compounds can be accommodated by a mechanistic scheme involving a spiro intermediate (cf. (XXVI), some steps suggested for the formation of (XXIII) were not convincing. An x-ray structure determination was therefore carried out [21] for this compound, which actually turned out to possess the remarkable structure (XXIV) which includes a four-membered ring. The isomeric compound (XXII) must be re-formulated as (XXV), on the basis of the near identity of its ^{13}C NMR spectrum with that of (XXII), and similar reassignments are necessary



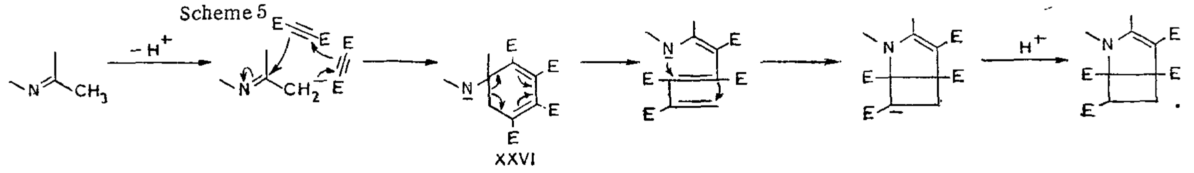
XXIV



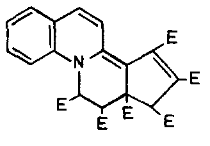
XXV

for many compounds in the literature previously described as azepines on the basis of analogy with (XXII). The hydrogen atom corresponding to that at position 8 of the original quinoline is in the shielding zone of the 9a-ester carbonyl group in (XXIV), but not in the geometrical isomer (XXV). The formation of these compounds, and the ^{13}C data, is accounted for by Scheme 5, which shows only partial structures. The initial proton loss may be caused by a carbanion [e.g., (I)] developed in a competing reaction, and the formation of a spiro intermediate (XXVI) is an essential part of the scheme. The cyclohexadiene system could open by a concerted or a nonconcerted process. The easy zipping up of this intermediate to form a 5 : 4 bicyclic ring system, which has a general structural relationship to the skeleton of penicillin, is remarkable.

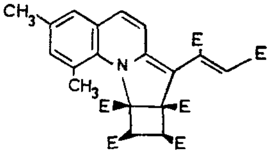
Scheme 5



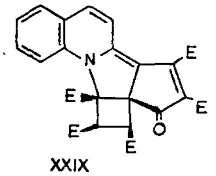
Deep red isomeric 1 : 3 molar adducts (two), along with purple (1 : 3 molar−MeOH) and deep blue (1 : 4 molar−MeOH) are also obtained from 2-methylquinolines in these reactions but are better prepared using methanol as reaction medium. The deep red adducts have been formulated [22] as geometrical isomers based



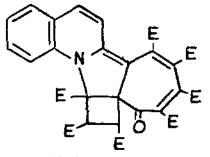
XXVII



XXVIII



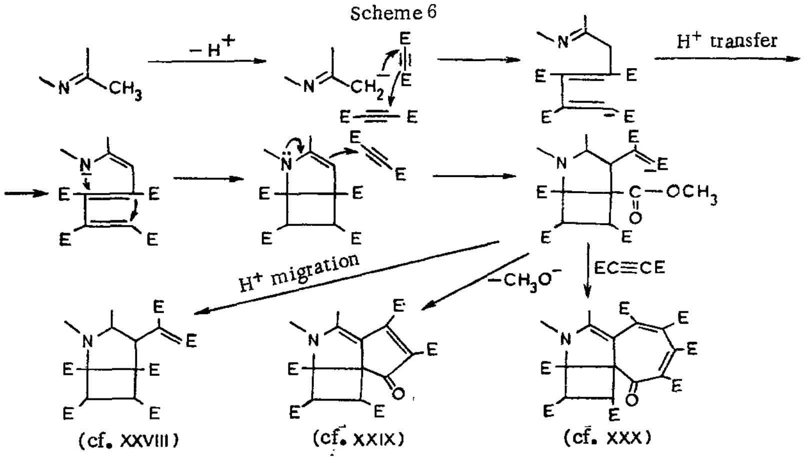
XXIX



XXX

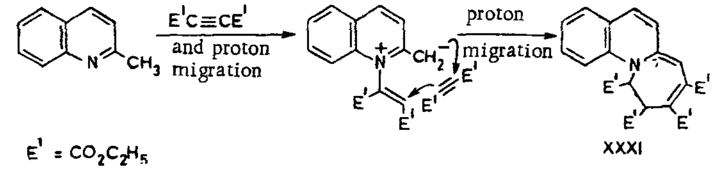
on formula (XXVII), but an x-ray investigation [23] of one compound of the group has shown that it possesses structure (XXVIII). A similar study [24] of the purple compound shows it must be written as (XXIX), while the deep blue 1 : 4 molar adduct−MeOH may well be represented by structure (XXX). These compounds are closely related structurally to the yellow adduct (XXV) and could be formed by a similar route (Scheme 6) not involving a spiro intermediate. Only one of the various possibilities is shown.

Scheme 6

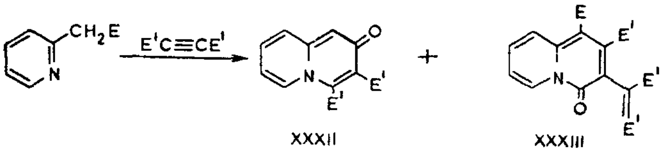


Another type of adduct, exemplified by (XXXI) which is obtained [19] as a minor product from 2-methylquinoline and diethyl acetylenedicarboxylate, could be built up as in Scheme 7.

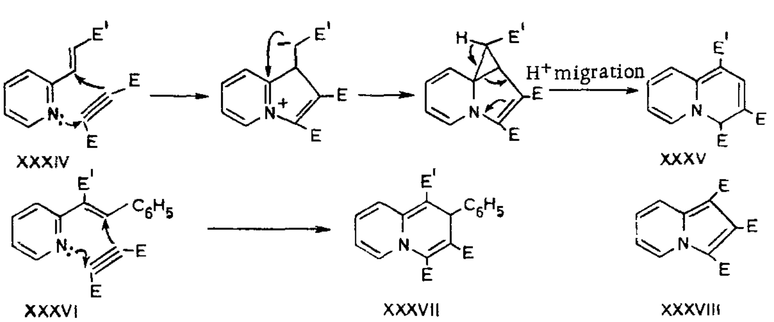
Scheme 7



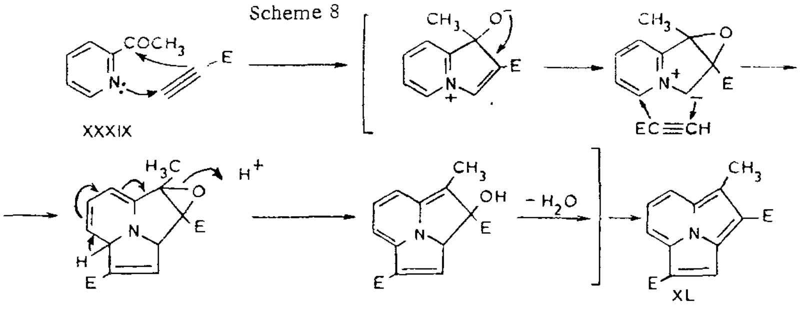
A small number of other pyridines with 2-substituents have been treated with acetylenic esters. Methyl pyridyl-2-acetate with diethyl acetylenedicarboxylate (methyl propiolate is similar) yields [11] a mixture of



the 2- (XXXII) and 4-quinolizines (XXXIII), suggesting that electrophilic attack by the acetylene can take place both at the nitrogen and sidechain carbon atoms, respectively. Ethyl 3-(2-pyridyl)-trans-acrylate (XXXIV) with DMAD gave [25] the quinolizine triester (XXXV), while another pyridylacrylate (XXXVI) gave [26] the 2H-quinolizine (XXXVII). Although 2-acetylpyridine (XXXIX) with hot DMAD gives [27] only trimethyl indolizine-1,2,3-tricarboxylate (XXXVIII), the cyclazine (XL) is obtained (Scheme 8) in 29% yield if hot methyl propiolate is employed [28].



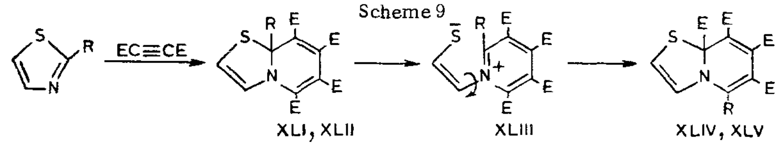
Scheme 8



3. Reactions with Azoles and Related Heterocycles

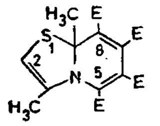
The products from thiazole, and a number of derivatives, with DMAD were examined in 1964 by two research groups, and their conclusions have been corrected recently [29, 30]. Initial reaction (Scheme 9) in dimethylformamide, takes place at the nitrogen atom and presumably 1 : 2 molar adducts such as (XLI) are

Scheme 9

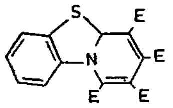


XLI R=H ; XLII R=CH_3 ; XLIV R=H ; XLV R=CH_3

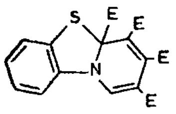
formed. Ring-opening (XLIII), followed by cyclization in the alternative mode, or a [1,5] sigma-tropic shift of the sulfur atom to give an equivalent result, now occurs to yield the product (XLIV). In the case of 2-methylthiazole the structure of the product (XLV) has been determined by x-ray methods [29]. Similar rearrangements take place in reactions involving 4- and 5-methyl-, and 2,5-dimethylthiazole, and benzothiazole which gives (XLVIII). However, x-ray studies [29] show that the product from 2,4-dimethylthiazole is formed without rearrangement, and has structure (XLVI). The relative stability of (XLVI), compared with its analogs which rearrange, can be associated with increased steric hindrance to the formation and rotation of the ring-opened intermediate [cf. (XLIII)], or to the [1,5] shift. In the case of thiazole, unsuccessful attempts were made [13] to detect (XLI) or other possible intermediates [cf. (I)] by carrying out the reaction using fully deuterated dimethylformamide as solvent in an NMR spectrometer. The temperature was raised slowly from −40° to +34°, the reaction started at about +5°, and only starting materials and the rearranged adduct (XLIV) could be observed. A minor product in the case of benzothiazole, (isolated more easily using methanol as reaction medium) is (XLIX), the structures being established by x-ray diffraction [30]. This compound is clearly formed from the same intermediate (XLVII) which leads to (XLVIII) but by a competing [1,5] hydrogen shift as in the quinolizine series where (XI) rearranges to (VII). In similar reactions 1-methylbenzimidazole gives a mixture of compounds analogous to (XLVIII) and (XLIX), while benzoxazole only yields the oxygen analog of (XLIX). Another compound (L) formed from benzothiazole and identified by x-ray crystallography has been associated with the presence of water in the reaction medium (Scheme 10) [30].



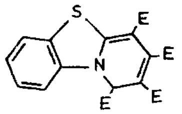
XLVI



XLVII

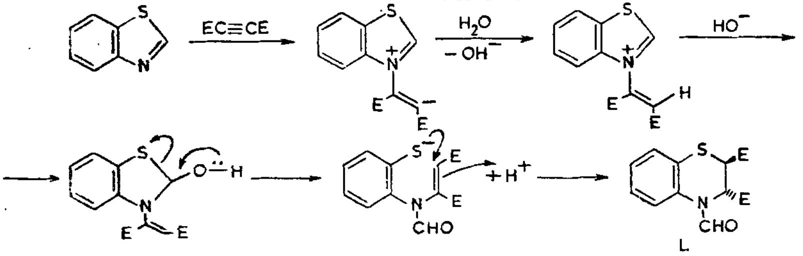


XLVIII



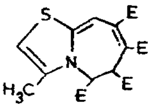
XLIX

Scheme 10

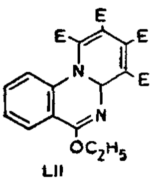


L

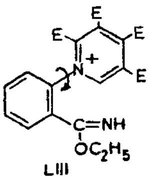
The effect of solvent on these types of reactions is particularly well illustrated by the case of 2,4-dimethylthiazole for in dimethylformamide (XLVI) is obtained, in acetonitrile or dimethyl sulfoxide a mixture of (XLVI) and (LI), and using tetrahydrofuran, dichloromethane, or nitromethane essentially only (LI) is obtained [13, 31]. This last compound (LI) could be formed in the same way (Scheme 7) as (XXXI), and analogs have been obtained from 2-ethylthiazole, suitably substituted benzothiazoles [31], benzimidazoles, and related heterocycles [32].



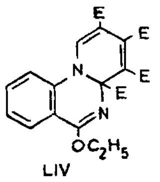
LI



LII

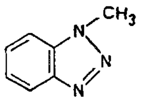


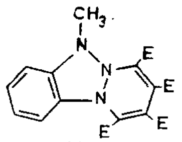
LIII

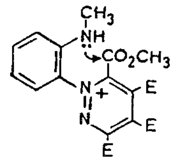


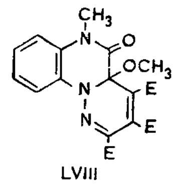
LIV

Rearrangements involving ring closure and recyclization similar to that of (XLI) to (XLIV) have been shown to occur in other reactions of DMAD with heterocycles. 4-Ethoxyquinazoline with the ester [33] gives first the 1 : 2 molar adduct (LII), which can be isolated provided that every trace of acid is removed from the acetonitrile employed as solvent. Traces of acid cause protonation to give (LIII), which cyclizes in the alternative mode to form (LIV). In a similar example [34] 1-methylbenzotriazole (LV) yields (LVI) which undergoes a similar acid-catalyzed rearrangement via (LVII) to give (LVIII).


LV


LVI

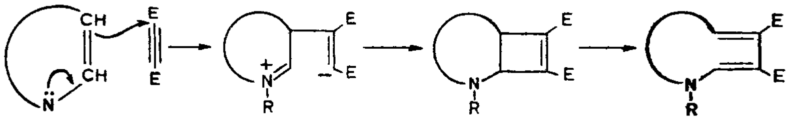

LVII


LVIII

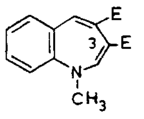
4. Reactions with Some Heterocyclic Enamines

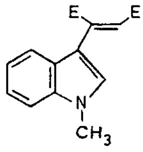
Enamines (LIX) readily combine with DMAD and methyl propiolate to yield cyclobutenes (LX) by a stepwise process (Scheme 11), and in suitable cases the four-membered ring can then open to give ring-expanded products

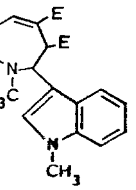
Scheme 11


LIX LX LXI LXII

(LXII). Although this type of reaction has not been effected with pyrroles, 1-methylindole in pure acetonitrile gives [35] the corresponding azepine (LXIII), along with small quantities of the maleate (LXIV) and corresponding fumarate which could be formed by a net tautomerism of the intermediate zwitterion [cf. (LX)]. If a trace of acid is present, protonation of the azepine at position 3 is followed by electrophilic attack from position 2

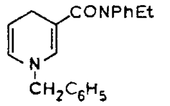

LXIII

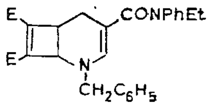

LXIV

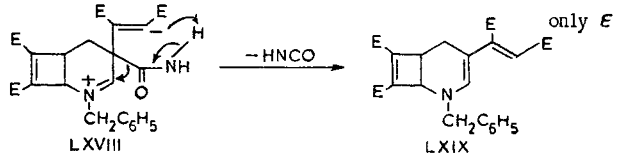

LXV

on another 1-methylindole molecule to yield (LXV). Indole reacts similarly with DMAD to form a zwitterion [cf. (LX)], but then this behaves in a complicated fashion leading to many products, 14 of which have been separated and identified [35].

1,4-Dihydropyridines, such as (LXVI), yield stable cyclobutenes [e.g., (LXVII)] with DMAD quite readily. If a 3-carbamoyl or carboxyl group is present, further attack of DMAD occurs, leading through a six-membered cyclic transition state (LXVIII) to elimination of the 3-substituent and formation of the dihydropyridine (LXIX).

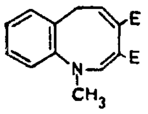

LXVI


LXVII

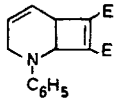


LXVIII LXIX

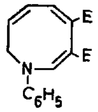
This elmination only occurs if suitable proton abstraction from the 3-substituent is possible [36]. Although all attempts to open the four-membered rings in these compounds have been unsuccessful, 1-methyl-1,4-dihydroquinoline with DMAD gives the expected cyclobutene which [37] decomposes rapidly at room temperature to the azocine (LXX). In a similar way, 1-phenyl-1,2-dihydropyridine gives the azocine (LXXII) with DMAD, the cyclobutene (LXXI) being detected as an intermediate by NMR spectroscopy [38]. Recently this reaction has been applied [39] to some dihydropyrazines (LXXIII) and cyclobutene formation (LXXIV) is followed by ring expansion (LXXV) and recyclization in an alternative mode to form (LXXVI).



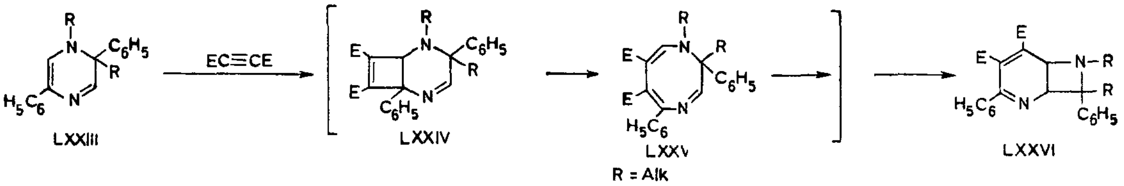
LXX



LXXI



LXXII



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FORMYLATION OF 2-PHENYL- AND 3-PHENYL-5-HYDROXYBENZOFURAN DERIVATIVES

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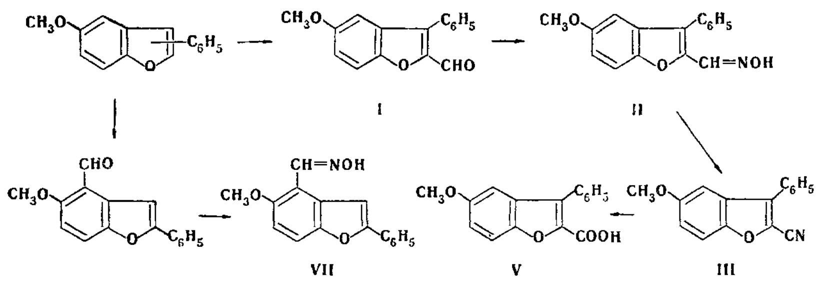
UDC 547.727.728:543.422.25

The Vilsmeier formylation of 2-phenyl- and 3-phenyl-5-hydroxybenzofuran derivatives was studied. It is shown that 2-phenyl-5-methoxybenzofuran is formylated in the 4 position, whereas 3-phenyl-5-methoxybenzofuran is formylated in the 2 position.

In a previous study of electrophilic substitution reactions it was noted that substituents enter primarily the benzene ring in the bromination and nitration of 2(3)-phenyl-5(6)-hydroxybenzofurans. The acetoxy derivatives of the same benzofurans are brominated and nitrated only in the free position of the furan ring [1]. Continuing our investigation of electrophilic substitution reactions in the benzofuran series, we studied the Vilsmeier formylation of 2-phenyl- and 3-phenyl-5-hydroxybenzofuran derivatives. It was found that in the reaction of phosphorus oxychloride and dimethylformamide (DMF) with 3-phenyl-5-methoxybenzofuran [2] the formyl group enters the 2 position of the molecule to give 2-formyl-3-phenyl-5-methoxybenzofuran (I) in 98% yield. Aldehyde I is converted to the corresponding oxime (II) on treatment with hydroxylamine hydrochloride. 2-Cayno-3-phenyl-5-methoxybenzofuran (III) was obtained by the action of acetic anhydride on II, and 2-formyl-3-phenyl-5-methoxybenzofuran O-acetyloxime (IV) was obtained as a side product. Alkaline hydrolysis of III gives 3-phenyl-5-methoxybenzofuran-2-carboxylic acid (V). The thiosemicarbazone (VI) was obtained for aldehyde I.



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