REACTION OF HETEROAROMATIC COMPOUNDS WITH CARBENES (REVIEW)

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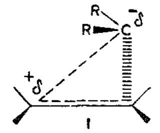
The literature data on the reactions of heteroaromatic compounds of various classes with halo-, alkyl-, alkoxy-, and ketocarbenes are examined. The mechanisms of these reactions and the effect of the methods used to generate the carbenes and the nature of the heterocycle on the direction of the reaction and the structures and yields of the final products are discussed. An estimate of the possibilities of the preparative utilization of the indicated reactions is given.

The intensive development of the chemistry of carbenes is associated with the involvement of diverse classes of organic compounds, including heterocyclic compounds, in carbene reactions. A number of reviews have been previously devoted to this problem [1-4]. However, new voluminous experimental data that require additional consideration for purposes of correlation and systematization have since been published.

The principal reactions of carbenes include cycloaddition to multiple bonds and insertion in single chemical bonds.

The addition of singlet carbenes to double bonds is a concerted one-step process and, according to calculated data [5], proceeds through unsymmetrical transition state I, which arises as a result of electrophilic attack of the vacant p orbital of the carbene on the π system of the olefin.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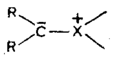
II

The effectiveness of stabilization of the partial positive charge that develops on the olefin carbon atom by the substituents attached to this atom and the ease of localization of the electron pair on the newly formed carbene–olefin C–C bond determine the activity of this olefin in reactions with carbenes. Thus substituents that are capable of stabilizing carbonium ions (Alk, Ar, Cl, OR) increase the activity of the olefin, while destabilizing substituents (COR, COOR, NO_2) decrease it. At the same time olefins in which the formation of a cyclopropane adduct requires considerable localization energy are inactive in reactions with carbenes as a consequence of disruption of the conjugated system of double bonds (polyene and aromatic compounds) (for example, see [6]). Aromatic compounds of the benzenoid series are inactive for the same reason and are often even completely inert in reactions with carbenes that do not have sufficient electrophilicity. Benzene, for example, reacts with methylene and monochlorocarbene but is inert with respect to dichloro- and difluorocarbenes [7].

The insertion of carbenes in single bonds occurs primarily if the substrate contains a labile hydrogen atom or a heteroatom that has an unshared pair of electrons. In the first case the reaction may proceed either via a synchronous three-center mechanism [8] or via a diradical detachment–recombination mechanism [9]. When a heteroatom that contains an unshared pair of electrons is present in the substrate, the reaction with singlet carbenes takes place primarily, according to [10], at the free electron pair of the heteroatom to give corresponding yields II, the stability of which is determined by the structure of the reagents, and their subsequent transformations may proceed via different pathways [10, 11].

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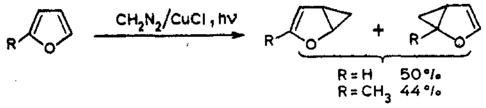
Reaction of Five-Membered Heterocycles with Carbenes Generated from Aliphatic Diazo Compounds

Aliphatic diazo compounds are highly reactive compounds that are quite easily deazotized to give carbenes:

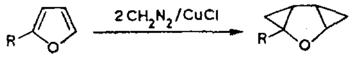
$$RR'CN_2 \xrightarrow[-N_2]{} RR'C:$$

As a consequence of the accessibility of these compounds and the relative ease of their carbene decomposition, which usually takes place under mild conditions, they are currently the principal sources of carbenes such as methylene, alkylcarbenes, ketocarbenes, alkoxycarbonylcarbenes, bis(alkoxycarbonyl)carbenes, aryl- and diarylcarbenes, etc. The carbenoid decomposition of diazo compounds can be realized photochemically, thermally, or catalytically. Whereas the formation of kinetically independent carbenes in the first two cases can be regarded as proved [12–14], in the catalytic reaction the true reacting particle is evidently a carbene–catalyst complex rather than a free carbene [15]. It has been noted [16] that the differences in the reactivities of free carbene and a carbene modified by the catalyst are absolutely distinct but not fundamental in character, and this makes it possible to examine their reactions simultaneously.

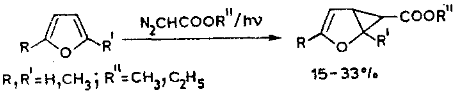
Furan and its derivatives in reactions with aliphatic diazo compounds form either products of addition of the carbene fragment to the double bond of the furan ring or acyclic substituted dienic ketones (or aldehydes). Thus diazomethane reacts with furan [17] and 2-methylfuran [18] to give, in both catalytic and photolytic reactions, substituted 2-oxabicyclo[3.1.0]hex-3-enes – products of addition of the methylene fragment to the double bond of the furan ring:



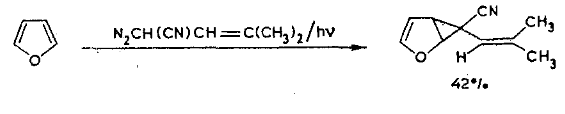
An adduct involving addition to the unsubstituted double bond (in a ratio of 1.5 : 1) is primarily formed in the reaction with 2-methylfuran; this is explained by the steric effect of the substituent [18]. The yields of adducts are higher in the catalytic reaction than in the photochemical reaction; this is probably due to the low stability of the bicyclic adduct with respect to UV irradiation. The use of excess diazomethane led to the formation, in addition to monoadducts, of 2-oxatricyclo[4.1.0^{3,5}.0^{1,6}]heptane in low yield:



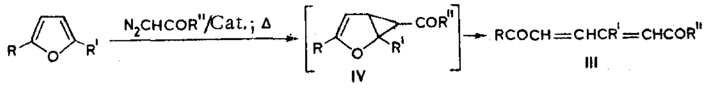
Under photolytic-decomposition conditions, methyl and ethyl diazoacetates react with furans in the same way as diazomethane to give esters of bicyclic carboxylic acids [19–22]:



Cyanovinylcarbene generated photolytically from isobutenyldiazoacetonitrile also reacts similarly with furan [23]:

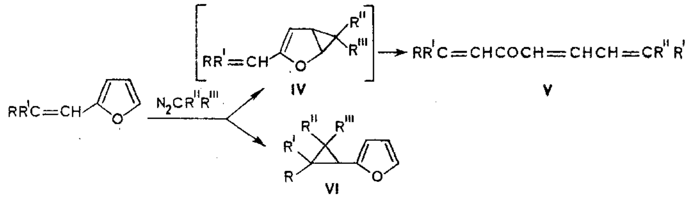


In contrast to photolysis, in thermal or thermocatalytic reactions methyl and ethyl diazoacetates, like diazoacetone, in most cases form products of opening of the furan ring – derivatives of doubly unsaturated ketones (or aldehydes) [22, 24–27]:



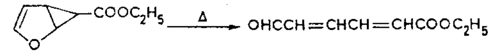
R=H, CH_3, $C(CH_3)_3$, $COOCH_3$, $(CH_2)_4COOC_2H_5$, R'=H; R=R'=CH_3 R''=CH_3 43–56%
R''=OCH_3 14–55%
R''=OC_2H_5 16–48%

The formation of similar acyclic products V is also observed in thermocatalytic reactions of aliphatic reactions of aliphatic diazo compounds with 2-alkenylfurans [28–33]; the reaction pathway that favors the formation of V or VI depends substantially on the presence of a substituent in the β position of the vinyl group of the starting 2-alkenylfuran [31-33] (see Table 1).

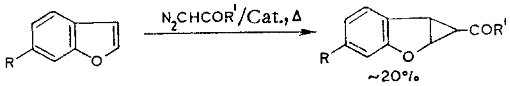


R, R'=H, CH_3
R''=H, R'''=$COCH_3$, $COOC_2H_5$
R''=R'''=$COOCH_3$

The bicyclic adduct initially formed in these reactions is probably unstable under the reaction conditions and undergoes rearrangement with ring opening. In fact, as shown in [21], ethyl 2-oxabicyclo[3.1.0]hex-3-ene-1-carboxylate undergoes rearrangement to ethyl 6-oxohexa-2,4-dienecarboxylate when it is heated to 160 °C. In the presence of $CuSO_4$ this rearrangement takes place at 80 °C [29]:

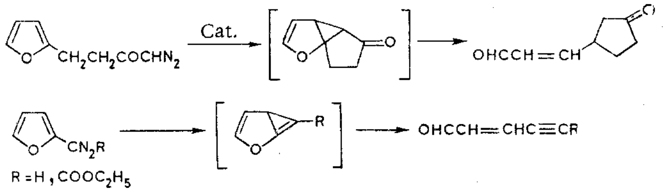


A similar mechanism of the formation of doubly unsaturated keto compounds in reactions of aliphatic diazo compounds with furan derivatives is also confirmed by the fact that coumarones in thermal or thermo-catalytic reactions with ethyl diazoacetate or diazoacetone form bicyclic adducts, which remain unchanged under the reaction conditions, since this sort of rearrangement is impossible for them [24, 34-36]:



R=H, Cl, Br, CF_3, CH_3, OCH_3; R'=CH_3, OC_2H_5

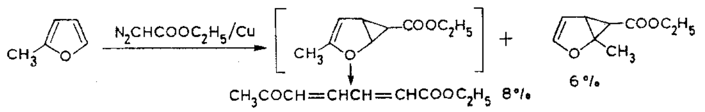
As in the case of diazomethane, substituted furans react with aliphatic diazo compounds to give primarily adducts involving the unsubstituted double bond of the furan ring [21, 22, 26, 27]. Only intramolecular reactions, in which addition to the unsubstituted double bond is hindered for steric reasons, constitute an exception [37-39]:



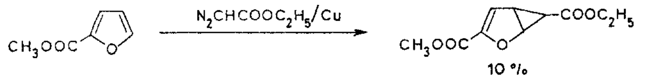
The reaction conditions have the primary effect on the stability of the adducts formed in the reactions of diazo compounds with furans; an increase in the temperature promotes the formation of an acyclic product [27]. In addition, the resistance to rearrangement of the resulting bicyclic adduct depends on the electronic effect of the substituent in the 3 position of the bicyclic system; electron-acceptor substituents increase the resistance, while electron-donor substituents decrease it. Thus, whereas furan in reactions with ethyl diazoacetate is capable of forming stable bicyclic adducts [27], 2-tert-butylfuran and 2,5-dimethylfuran [22] react only with opening of the bicyclic system. However, in the case of the reaction of ethyl diazoacetate with α-methylfuran, of the two resulting isomeric bicyclic adducts, only the adduct containing a methyl group in the 3 position undergoes rearrangement [22]:

TABLE 1. Yields of the Ketotriene (V) and Cyclopropane (VI) Products in the Reactions of 2-Alkenylfurans with Aliphatic Diazo Compounds

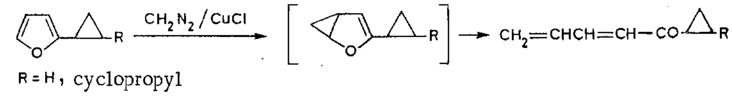
R	R'	$N_2CHCOCH_3/C_4SO_4$, 100°		$N_2C(COOCH_3)_2/CuSO_4$, 100—130°		$N_2CHCOOC_2H_5/CuSO_4$, 80—130°	
		V	VI	V	VI	V	VI
H	H	<1	44	<1	24	5,4	52
H	CH_3	11	32	13	6,2	46	26
CH_3	CH_3	12	34	11	6,7	47	29



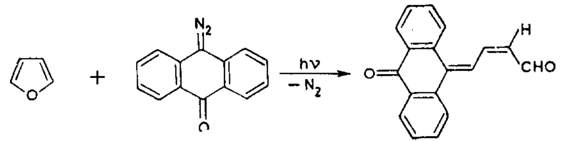
However, if an electron-acceptor group is found in the 3 position of the bicyclic system as a result of the reaction of a 2-substituted furan with carbene, this sort of rearrangement may not occur [22]:



In reactions with diazomethane both furan itself and 2-methyl- and 2,5-dimethylfurans, as we have already noted, form stable bicyclic adducts that undergo rearrangement only at temperatures that considerably exceed the reaction temperature. However, furans that contain a stronger σ donor such as the cyclopropyl group in the 2 position react to give doubly unsaturated ketones [33]:

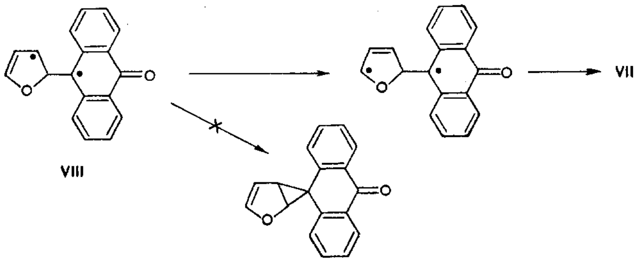


The mechanism of the thermal isomerization of bicyclic adducts to acyclic compounds was investigated in the case of 2-oxabicyclo[3.1.0]hex-3-enes [40], during which it was assumed that the rearrangement is a [2s + 2a + 2a]-concerted process involving opening of the bicyclic system. In conformity with the assumption of a concerted mechanism, this sort of rearrangement is not observed in the case of photolytic reactions by virtue of the rules of alternative prohibition [41]. The only exception is the reaction of furan with anthralidene generated photochemically from diazoanthrone, as a result of which aldehyde VII is formed [42]:

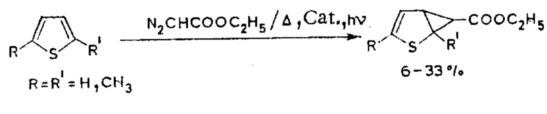


VII

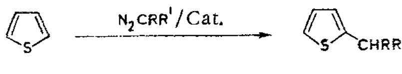
This rearrangement in all likelihood is due to the fact that anthralidene reacts in the triplet state, in which case the intermediately formed diradical VIII is stabilized to a considerable degree by delocalization of one of the unpaired electrons over the conjugated aromatic system, as a consequence of which opening of the furan ring occurs more rapidly than the formation of a three-membered ring:



As compared with furan, thiophene and its derivatives are considerably less active in reactions with aliphatic diazo compounds; this is in agreement with the more strongly expressed aromatic character of the thiophene ring. In contrast to furan, thiophene and its derivatives virtually do not form products of opening of the thiophene ring. Thus the thermal, thermocatalytic, and photolytic reactions of ethyl diazoacetate with thiophene and 2-methyl- and 2,5-dimethylthiophenes lead to the formation of stable cyclopropane adducts [19, 20, 22, 43, 44]:

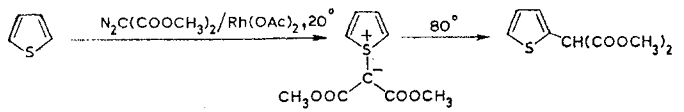


The same thing is also observed in the case of diazomethane [17]. However, diazoacetone and diazomalonate react with thiophene to give products of formal insertion in the α-C–H bonds of the thiophene ring [19, 20, 35, 45]:



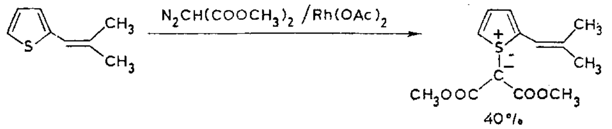
$R = H,\ R' = COCH_3$, 11%
$R = R' = COOCH_3$, 36%

When rhodium acetate was used as the catalyst in the reaction of thiophene with dimethyl diazomalonate, it was possible to lower the reaction temperature from 80 °C to 20 °C and to isolate stable sulfonium ylid IX, which upon heating underwent rearrangement to a product of formal insertion of bis(methoxycarbonyl)-carbene in the α-C—H bond of the thiophene ring [46]. On the basis of these results it has been assumed [46] that this mechanism is also common to other reactions of thiophenes with aliphatic diazo compounds.

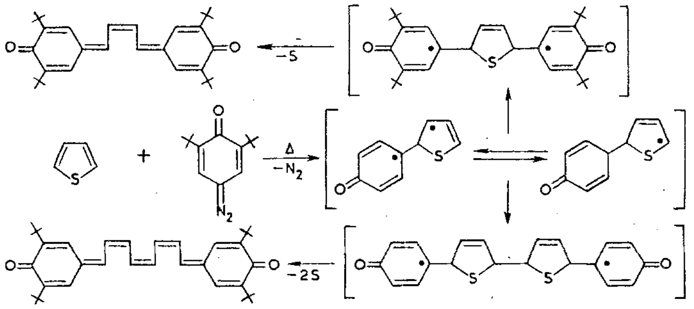


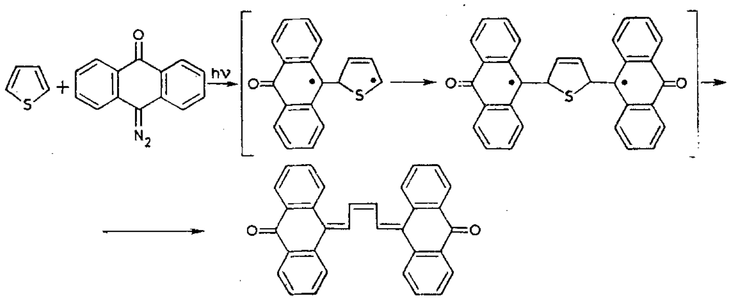
IX

We have recently observed the formation of stable ylids in the reaction of dimethyl diazomalonate with 2-alkenylthiophenes that have a shielded double bond such as 2-isobutenylthiophene [47]:



Opening of the thiophene ring is observed only in the reactions of thiophene with carbenes generated from quinone diazide and diazoanthrone [48, 49]:

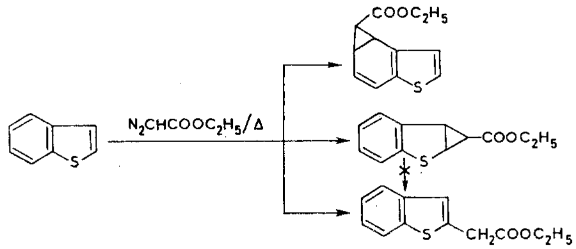




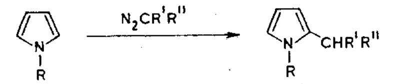
As in the case of furan, the anomaly in the occurrence of this reaction is evidently due to the triplet state of the reacting carbene and also to the effective resonance stabilization of the intermediately formed diradicals.

In contrast to esters of pyromucic acid, esters of thiophenecarboxylic acids do not react with ethyl diazoacetate under identical conditions [22]. In the case of thionaphthenes the lower activity of the thiophene ring is manifested in the fact that adducts involving the benzenoid ring are formed in up to 35% yields along with products of addition to the double bond of the thiophene ring in reactions with ethyl diazoacetate [50, 51]. It was recently found [52] that a product of formal insertion of ethoxycarbonylcarbene in the α-C—H bond of the starting thionaphthene is also formed in addition to adducts involving the double bonds of thionaphthene in this reaction; rearrangement of the cyclopropane adduct to give the insertion product does not occur under these conditions.

Both products are consequently obtained in parallel reactions. This conclusion has also been extended by Ernest and co-workers [52] to other reactions of thionaphthenes with diazo compounds.

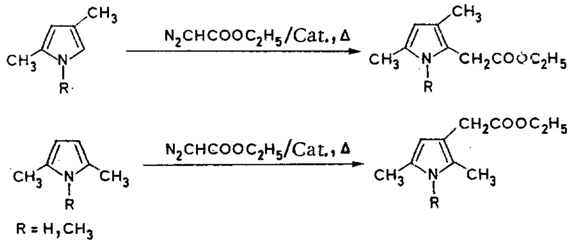


In contrast to furan and thiophenes, pyrroles do not form stable bicyclic adducts in reactions with aliphatic diazo compounds. The only products of these compounds are products of formal insertion of carbene in the C—H bond of the pyrrole ring [53-58]:

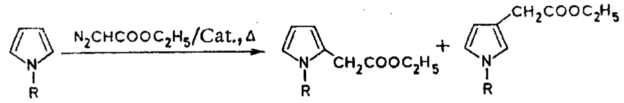


R=H, CH_3; R′=H, R″=$COCH_3$, $COOC_2H_5$; R′=R″=$COOCH_3$

Until recently it was assumed that substituted pyrroles in reactions with ethyl diazoacetate form only products of insertion in the C—H bonds in the unsubstituted α positions of the pyrrole ring, while insertion in the C—H bonds in the β positions occurs only when substituents are present in the 2 and 5 positions [55, 58]:

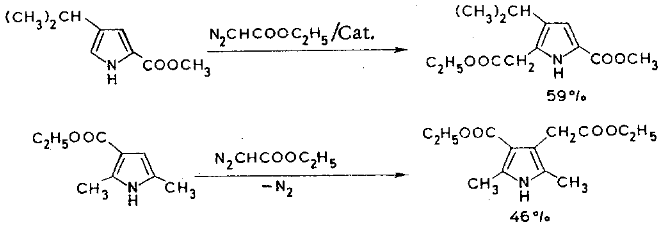


However, it was recently shown [57] that pyrrole and N-alkylpyrroles in thermal and thermocatalytic reactions with ethyl diazoacetate always form products of insertion of ethoxycarbonylcarbene in both the α and β positions:

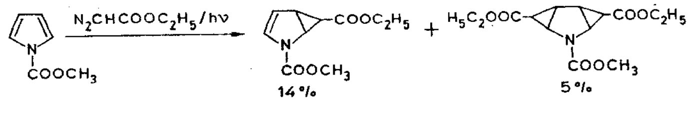


It was found that the regioselectivity of the thermocatalytic reaction in this case depends substantially on the nature of the catalyst; the ratio of the yields of products of insertion in the α and β positions of the pyrrole ring when various catalysts are used may range from 1.5 to 16.9, while their overall yield ranges from 20 to 50%.

Electron-acceptor C substituents of the pyrrole ring do not affect either the direction of the reaction or the yields of final products [53]:

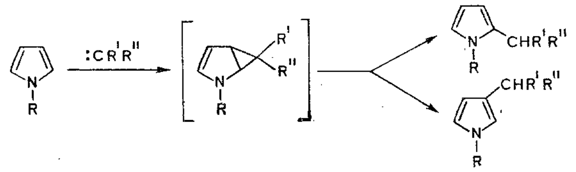


However, when there is an electron-acceptor substituent attached to the nitrogen atom, bicyclic and tricyclic adducts — products of addition, respectively, of one and two carbene fragments to the double bonds of the pyrrole ring — are formed in low yields [59]:

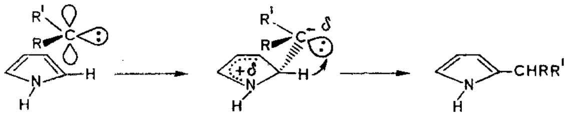


This anomaly in the course of the reaction is associated with the fact that the electron-acceptor substituent attached to the nitrogen atom dearomatizes the conjugated π system of the pyrrole ring, as a result of which this sort of pyrrole reacts like an ordinary diene.

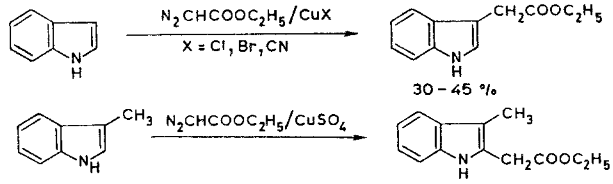
Up until now, the difference in the behavior of pyrroles in reactions with aliphatic diazo compounds from that of other five-membered heterocycles has been explained by the fact that the initial product in these reactions is a bicyclic adduct, which in the course of the reaction undergoes rearrangement via two nonequivalent pathways [4]:



However, in our opinion, the assumption of the intermediate formation of a bicyclic adduct in these reactions is not necessary. It is known that singlet carbenes have a free p orbital and display weak electrophilic properties in their reactions. In addition, pyrrole is one of the strongest aromatic nucleophiles, inasmuch as it reacts with the bromine cation $5 \cdot 10^6$ times faster than furan, $6 \cdot 10^8$ times faster than thiophene, and $3 \cdot 10^{18}$ times faster than benzene [60]. In addition, it is known that indole is capable of forming charge-transfer complexes (CTC) with electron-acceptor reagents such as iodine, trinitrobenzene, etc. [61]. All of this makes it possible to assume that the insertion of singlet carbenes in the C—H bond of pyrrole occurs through initial attack on the vacant p orbital of carbene by the π system of pyrrole. This attack is accompanied by localization of the electron pair on the resulting pyrrole—carbene C—C bond and the formation of a transition state (or, possibly, a metastable σ complex), as in the case of electrophilic aromatic substitution reactions with subsequent (and, possibly, synchronous) migration of a proton to the nonbonding σ pair of carbene:



Indoles react with aliphatic diazo compounds in the same way as pyrroles, except that insertion takes place primarily in the 3 position of the indole ring [62-66] rather than in the 2 position, as in the case of pyrroles. Insertion in the 2 position of indole occurs only when substituents are present in the 3 position [66]:

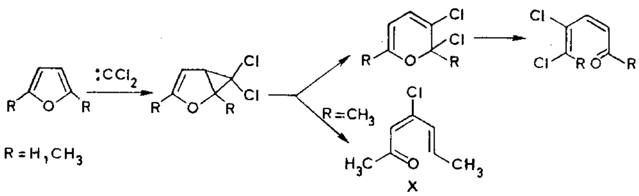


This change in the reaction pathway is in agreement with the mechanism proposed above, since it is known that electrophilic substitution reactions in indoles take place primarily in the 3 position of the indole ring [67]. Inasmuch as it is a weak electrophile, carbene displays greater selectivity than other electrophiles. This is expressed in the fact that in reactions with indoles insertion takes place in a single direction. Another piece of evidence in favor of the proposed mechanism is the fact that 2,3-dimethylindole proved to be inert under the same conditions for which indole reacted with ethyl diazoacetate to give an insertion product [62], although in the case of realization of a mechanism that assumed initial addition of carbene to the double bond of pyrrole one should have expected the formation of a stable bicyclic adduct.

Reaction of Five-Membered Heterocycles with Halocarbenes

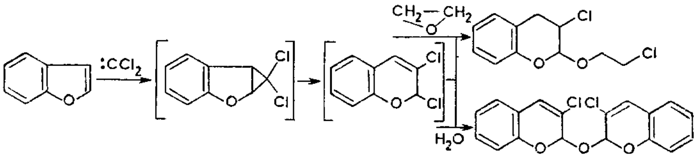
As compared with other carbenes, probably the greatest number of methods of preparation have been proposed for halocarbenes; the formation of free carbenes in most cases can be regarded as proved [68]. However, the method of generation often has a substantial effect on both the pathway and the structures and yields of the final products by virtue of the ambiguity of the reaction and the possibility of the occurrence of further transformations of the initially formed adducts, particularly in strongly basic media.

Furan and methylfurans react with dichlorocarbene to give products of addition to the double bond of the furan ring, which, however, were not isolated, since at the instant they were formed they underwent rearrangement to dichloro derivatives of 2H-pyran [69, 70]. The latter, like 3-chloro-2H-pyrans, upon heating undergo isomerization with ring opening to give doubly unsaturated chloro aldehydes (or ketones):



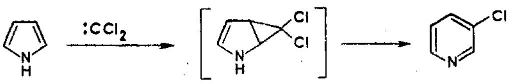
The mechanism of the formation of monochlorodienone X in this reaction is unclear.

Only ethers of 3-chlorochromene — products of hydrolysis of the initially formed 2,3-dichloro-2-chromene — were isolated in the reactions of dichlorocarbene with coumarone [71-73]:

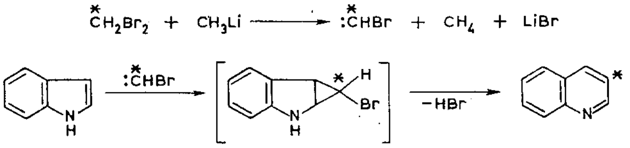


In contrast to the reactions of furan and its analogs, very little study has been devoted to the reaction of thiophene with dihalocarbenes. It is known only that the thiophene ring is more inert with respect to dihalocarbenes than the furan ring [73].

The reaction of pyrrole with halocarbenes proceeds with expansion of the pyrrole ring and the formation of pyridine derivatives. Thus in 1881 it was observed that pyrrole under alkaline conditions reacts with chloroform to give 3-chloropyridine in low yield [74]. Since it was later established that the alkaline hydrolysis of chloroform proceeds through the formation of dichlorocarbene [75], it was assumed [2] that the reaction proceeds through an intermediate unstable bicyclic adduct of dichlorocarbene with the double bond of the pyrrole ring, which under the reaction conditions undergoes rearrangement with splitting out of HCl to give 3-chloropyridine:

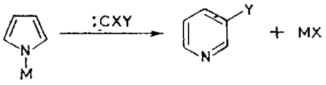


Quinoline with a labeled carbon atom in the 3 position of the quinoline system is formed in the reaction of indole with bromocarbene with a labeled carbon atom [76], and this serves as a confirmation of the proposed mechanism:

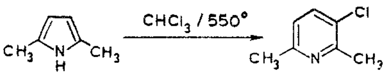


This reaction was subsequently extended to a number of other halocarbenes, and both pyrrole itself and various metal derivatives of pyrrole were used as the acceptor [77-81] (see Table 2). The effect of the method of generation of the halocarbenes on the yields of final products was also studied [82] (see Table 2). The yields of 3-substituted pyridines in the case of generation of the halocarbenes under alkaline conditions remained low ($\leq 32\%$). 2-Formylpyrroles were also formed in some cases in addition to 3-halopyridines in the case of generation of dihalocarbenes under the conditions of the Reimer—Tiemann reaction (by heating solutions of the pyrroles in chloroform with aqueous alkali at 65-70°C) [83, 84]. It is apparent from Table 2 that the highest yield of 2-chloropyridine was obtained in the gas-phase reaction of pyrrole with dichlorocarbene generated by pyrolysis of chloroform at 550°C; 2-chloropyridine was isolated in 2-5% yield in addition to 3-chloropyridine [79]. The yields of 3-chloropyridine and 2-chloropyridine were increased from 33% to 58% and from 5% to 28%, respectively, by prior heating of the chloroform introduced into the reaction to 250°C [80]. In the opinion of Burker and co-workers [80], the formation of 2-chloropyridine may be the result of initial attack of dichlorocarbene on the nitrogen atom or the α-carbon atom of the starting pyrrole. However, since 2,5-dimethylpyrrole forms only 2,6-dimethyl-3-chloropyridine (with the complete absence of 2-chloro-3,6-dimethylpyridine in the products) under these conditions, Burker and co-workers [80] excluded the possibility of initial attack on dichlorocarbene by the nitrogen atom of the pyrrole ring.

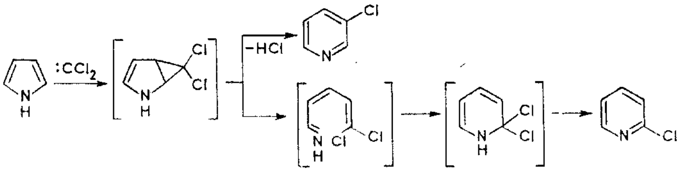
TABLE 2. Yields of 3-Substituted Pyridines in the Reaction



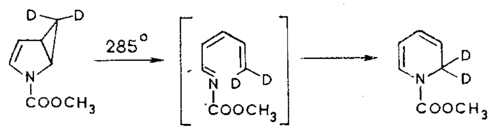
M	X	Y	Source of carbene: CXY		Yield,%	Literature
H	Cl	Cl	CCl_3COONa (80°)		7	82
H	Cl	Cl	$CHCl_3$ (550°)		33	81
Li	Cl	Cl	$CHCl_3$	The alkaline agent in all cases was the corresponding N-pyrrylmetal	12	78
Li	Br	Br	$CHBr_3$		8,6	78
Li	Cl	Ph	$CHPhCl_2$		1,3	78
Li	I	H	CH_2I_2		0	78
Li	Cl	H	CH_2Cl_2		32	79
Na	Cl	Cl	$CHCl_3$		1,6	78
Na	Br	Br	$CHBr_3$		0,5	78
Na	I	H	$CHBrCl_2$		0,5	78
K	Cl	Cl	$CHCl_3$		7,2	78
K	Br	Br	$CHBr_3$		10	78



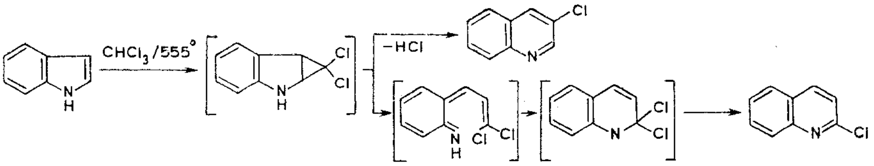
In our opinion, the formation of 2-chloropyridine from unsubstituted pyrrole, as in the formation of 3-chloropyridine, takes place via initial addition of dichlorocarbene to the double bond of the pyrrole ring to give bicyclic adduct XI, which undergoes further rearrangement not only with ring expansion but also with opening of the bicyclic system to give a doubly unsaturated imine; the latter then undergoes valence isomerization to give 1,2-dihydro-2,2-dichloropyridine, which splits out HCl to give 2-chloropyridine:



A similar rearrangement was similarly observed in the 2-azabicyclo[3.1.0]hexane series, and a mechanism was proposed for it on the basis of a study of the behavior of deuterium-labeled samples [61]:



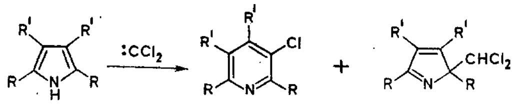
It was recently shown [85] that indole reacts with chloroform under similar conditions to give 2-chloroquinoline in less than 2% yield vis-a-vis 3-chloroquinoline in 38% yield. Such a low yield of 2-chloroquinoline is explained from the assumptions of the proposed mechanism by the fact that disruption of the aromatic system of the benzene ring is necessary in this case for its formation:



Neither 2- nor 3-methylindoles form 2-chloroquinoline derivatives at all in this reaction, whereas the corresponding 3-chloroquinolines were obtained in 40-55% yields [85].

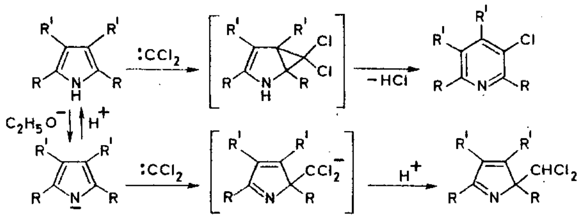
In contrast to pyrrole itself, methylpyrroles in liquid-phase reactions with dihalocarbenes form not only 3-halopyridines but also 2-dihalomethylpyrrolenine derivatives [82, 86]. It is apparent from Table 3 that the reaction to favor the formation of one or the other product in this case depends substantially on the conditions under which the dihalocarbene is generated [86].

TABLE 3. Compositions of the Reaction Products



R	R′	Source of the dichlorocarbene	Yield of 3-chloropyridine, %	Yield of 2-dichloromethyl-pyrrolenine, %
CH_3	H	$CHCl_3+C_2H_5ONa$	9	6
CH_3	H	CCl_3COONa (80°)	70	0
CH_3	CH_3	$CHCl_3+C_2H_5COONa$	5	12
CH_3	CH_3	CCl_3COONa (80°)	55	0
Ph	CH_3	$CHCl_3+C_2H_5ONa$	1	8
Ph	CH_3	CCl_3COONa (80°)	90	0

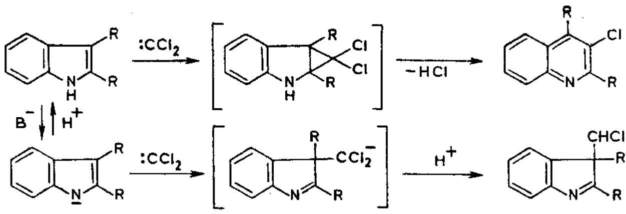
It is apparent from Table 3 that alkaline media substituted pyrroles give both pyrrolenines and 3-chloropyridines but in low yields, whereas in neutral media pyridines are formed in high yields, while pyrrolenines are not obtained at all. Although it is known that 2-halomethylpyrrolenines can undergo rearrangement to 3-halopyridines under alkaline conditions [87], it is extremely unlikely that this rearrangement takes place in neutral media [76, 86, 88]. The absence of pyrrolenines in neutral media is probably associated with the fact that pyridines are formed in these reactions as a result of the addition of dihalocarbene to the neutral pyrrole molecule, whereas pyrrolenines are the result of electrophilic attack of dichlorocarbene on the pyrryl anions, which in alkaline media are in equilibrium with the starting pyrrole:



The low yields of the products of these reactions when they are carried out in alkaline media are due to parallel solvolysis of the generated dichlorocarbene [86]:

$$:CCl_2 \xrightarrow[OH^-]{H_2O} CO + HCO_2^-$$

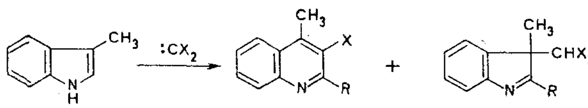
Alkylindoles react with dihalocarbenes in the same way as pyrroles, except that 3-dichloromethylindolenines are formed instead of the 2-dichloromethylpyrrolenines that are formed in the case of pyrroles [89-91]. Electrophilic attack of the carbene in the 3 position of the indole aromatic system is evidently preferable on passing from pyrrole to indole; according to the results of quantum-chemical calculations [92], this is due to the higher energy of localization of the electron pair on the newly formed bond in the 2 position of indole than in the 3 position, whereas the situation is the opposite in the case of pyrrole:



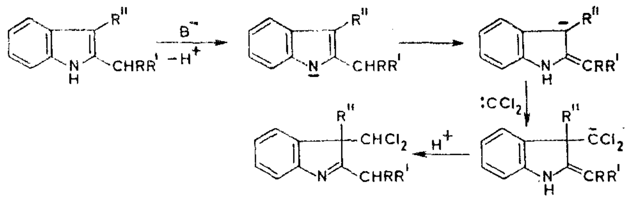
As in the case of alkylpyrroles, the reaction to favor the formation of derivatives of 3-haloquinolines or 3-halomethylindolenines depends substantially on the conditions under which the dihalocarbenes are generated (see Table 4) [90].

For the formation of 3-dihalomethylindolenines in the reaction of dihalocarbenes with indoles the presence of an alkyl substituent in the 2 position of the starting indole is necessary in addition to a strongly basic reaction medium. In fact, despite numerous attempts, dichloromethylindoleneines have not yet been identified in the reaction of indole and 3-methylindole with dichlorocarbene under alkaline conditions [90]; according to [91], this is explained by the following scheme for the formation of indolenines:

TABLE 4. Compositions of the Reaction Products

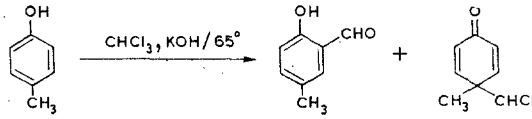


X	R	Source of dichlorocarbene	Yield of quinoline, %	Yield of indolenine, %
Cl	H	$CCl_3COOC_2H_5+CH_3ONa$	6,3	0
Cl	CH_3	$CCl_3COOC_2H_5+CH_3ONa$	9,6	4,6
Cl	CH_3	$CHCl_3+C_2H_5ONa$	11,3	13,1
Cl	CH_3	CCl_3COONa (80°)	24	9,2
Br	CH_3	$CHBr_3+C_2H_5ONa$	8,8	6,9
Br	CH_3	CBr_3COONa (80°)	20,8	3,2
F	CH_3	$CClF_2COONa$ (80°)	0	6,4

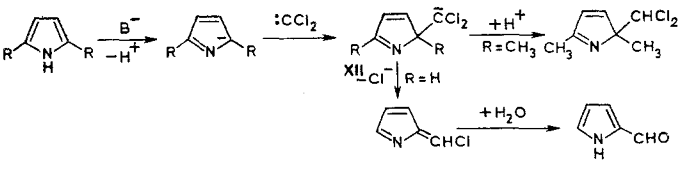


This principle is evidently also extendable to the pyrrole series. Thus in the case of pyrroles the presence of an alkyl substituent in the 2 position of the pyrrole ring is also necessary for the formation of dichloromethylpyrrolenines in the reaction with dihalocarbenes. In fact, in contrast to 2,5-dialkylpyrroles, pyrrole itself and 3,4-dimethylpyrrole do not form derivatives of dichloromethylpyrrolenines in the reaction with dichlorocarbene in alkaline media. However, in our opinion, the mechanism proposed in [91] to explain this principle has not been adequately substantiated. Thus, on the one hand, this mechanism assumes transfer of a proton from the α-alkyl group of indole to the nitrogen atom of the indolyl anion, which is unlikely considering the considerably more "acidic" character of the indole N−H bond as compared with the allyl C−H bond. On the other hand, it is known that under the conditions of the Reimer−Tiemann reaction (heating a mixture of chloroform and the substrate with aqueous alkali at 65-70°C) both pyrrole [84] and indole [82, 92] form 2-pyrryl- and 3-indolenylcarbaldehydes, respectively, in addition to 3-chloropyridine and 3-chloroquinoline.

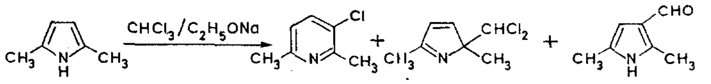
In addition, it is known that methyl-substituted phenols under the same conditions form dichloromethylphenols (the so-called anomalous Reimer−Tiemann reaction) in addition to aldehydes [93]:



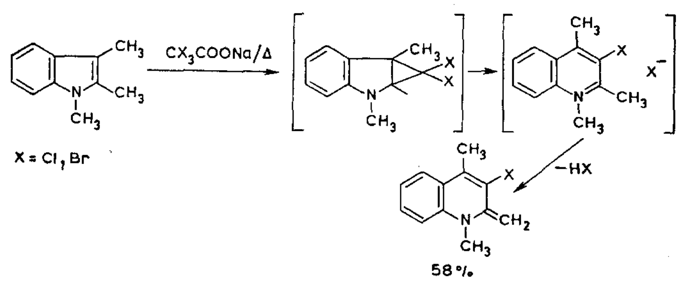
On the basis of these facts it is natural to assume that the reactions of methyl-substituted pyrroles and indoles and the reactions of methyl-substituted phenols have similar mechanisms and that the carbonyl and dichloromethyl derivatives in these reactions are formed through common intermediate XII:



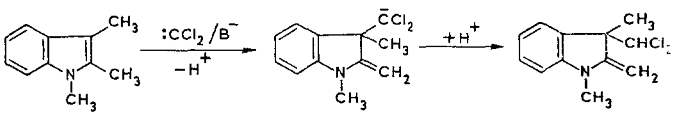
The formation of 2,5-dimethylpyrrole-3-carbaldehyde in the reaction of 2,5-dimethylpyrrole with dichlorocarbene generated by alkaline solvolysis of chloroform is an additional confirmation of this [82]:



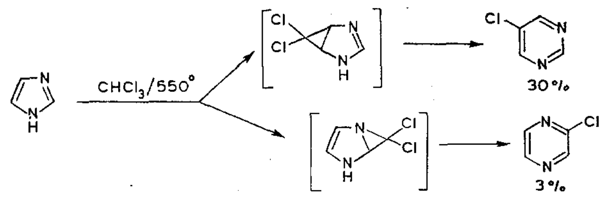
1,2,3-Trimethylindole reacts with dihalocarbenes in neutral media to give exclusively 3-halo-1,4-dimethyl-2-methylene-1,2-dihydroquinoline [90]:



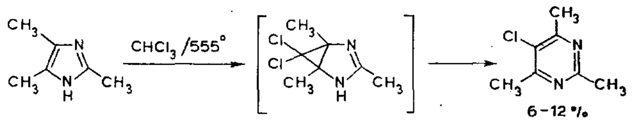
Only 1,3-dimethyl-2-methylene-3-dichloroindolenine is formed, on the other hand, under conditions of alkaline generation of carbene [90]. The role of the base in this case reduces to transfer of a proton from the α-methyl group to the negatively charged dichloromethyl group:



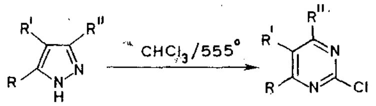
Imidazoles and pyrazoles react with dichlorocarbene under neutral conditions via the same pathways as pyrroles, and the presence of C = C and C = N bonds in these systems leads to halo derivatives of the corresponding heterocycles. Thus the reaction of imidazoles with dichlorocarbene obtained by pyrolysis of chloroform at 550°C gives a mixture of 5-chloropyrimidine and 2-chloropyrazine in a ratio of 10 : 1 [94], which indicates greater activity with respect to dichlorocarbene of the C = C bond as compared with the N = C bond:



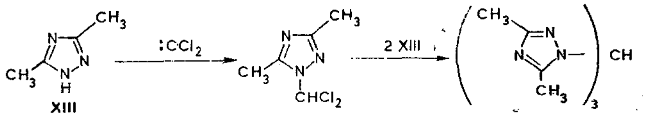
2,4,5-Trimethylimidazole reacts with dichlorocarbene under both alkaline and neutral conditions only at the C = C bond to give 2,4,6-trimethyl-5-chloropyrimidine [95]:



At the same time, pyrazole and C-methylpyrazoles react with dichlorocarbene in the gas phase exclusively at the N = C bond to give derivatives of 2-chloropyrimidines [96]:



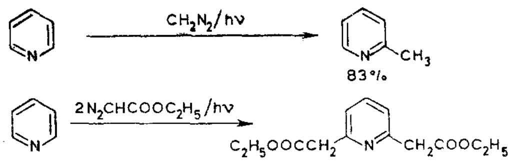
3,5-Dimethyl-1,2,4-triazole reacts with dichlorocarbene to give tris(3,5-dimethyl-1,2,4-triazol-1-yl)methane, which is formed through the N-dichloromethyltriazole — the product of insertion of dichlorocarbene in the N–H bond [95]:



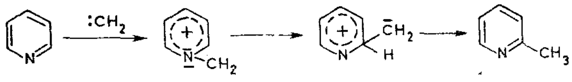
Thus the primary pathway of the reaction of halocarbenes with five-membered heterocycles is addition to the double bond of the heterocyclic ring, which leads to the formation of bicyclic adducts. Such adducts are usually unstable and undergo rearrangement with ring expansion during the reaction. In the case of furan derivatives the rearrangement gives compounds of the pyran series, which, in turn, in the case of gentle heating (often even under the reaction conditions) undergo valence isomerization with opening of the heterocyclic system to give unsaturated carbonyl compounds. Stable pyridine derivatives are formed as a result of this rearrangement in the case of nitrogen-containing heterocycles. It should be noted that the reactions of pyrrole derivatives with dihalocarbenes generated in alkaline media lead not only to ring-expansion products but may also take place with retention of the pyrrole ring and the formation of formyl and dichloromethyl derivatives of pyrrole due to the participation in the reaction of the pyrryl anion, which exists in equilibrium with the starting pyrrole in alkaline media.

Reaction of Six-Membered Heterocycles with Carbenes from Diazo Compounds

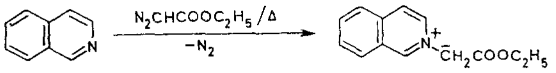
In contrast to five-membered aromatic heterocycles, as well as benzene derivatives, pyridine in reactions with carbenes does not form products of addition of the carbene fragment to the double bond of the aromatic ring. Thus it reacts with diazomethane and ethyl diazoacetate under conditions of photochemical decomposition of the latter to give exclusively products of insertion of the carbene fragment in the α-C—H bond [97, 98]:



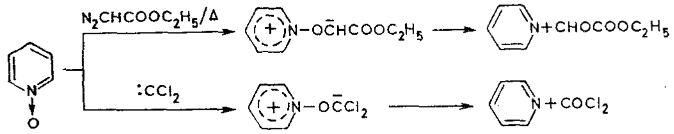
On the one hand, this may be associated with the more strongly expressed aromatic character of pyridines as compared with five-membered heterocycles. On the other hand, the absence in the reaction mixture of β- and γ-insertion products led to the conclusion [97] that this reaction proceeds through initial attack of the carbene on the nitrogen atom of pyridine to give an unstable ylid, which undergoes rearrangement under the reaction conditions to α-picoline:



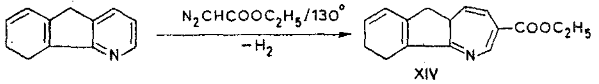
The reality of this mechanism is confirmed by the fact of the formation of a stable ylid in the reaction of isoquinoline with ethyl diazoacetate [99]:



Other reactions of pyridine derivatives with carbenes such as the reduction of N-oxides of pyridines [100, 101] and the formation of ethers in the reaction of 2-pyridone with ethyl diazoacetate [102, 103] also evidently have an ylid mechanism:

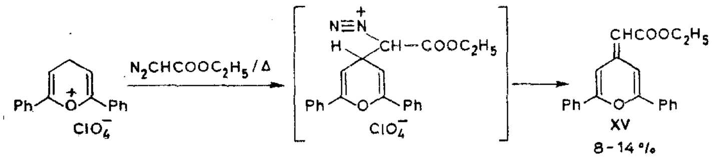


The thermal reaction of 4-azafluorene with ethyl diazoacetate leads to XIV, which is evidently formed as a result of initial addition of carbene to the double bond of the pyridine ring with subsequent ring expansion and dehydrogenation, the mechanism of which, however, is unclear [104]:

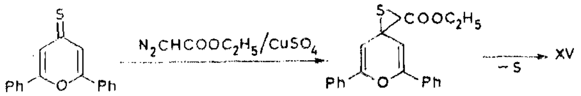


XIV

Pyrrylium cations react with ethyl diazoacetate to give derivatives of 4-methylene-4H-pyrans, which are probably formed via a noncarbene mechanism, viz., as a result of nucleophilic attack of the ethyl diazoacetate molecule in the 4 position of the starting cation with subsequent splitting out of nitrogen and the formation of a double bond [105]:



The same compounds, however, are formed in reactions of ethyl diazoacetate with pyran-4-thiones via a completely different mechanism (through direct attack of carbene on the C = S bond) [105]:



The examined data show that the reactions of heteroaromatic compounds with carbenes differ substantially from the reactions of their benzenoid analogs. Thus, in particular, as a consequence of the less strongly expressed aromatic character of the double bonds, heteroaromatic compounds, in contrast to benzenoid compounds, are capable of reacting with carbenes that have low electrophilicity. The adducts formed in these reactions are unstable and readily undergo rearrangement with ring expansion, which sometimes leads to a new aromatic heterocycle. In addition to this, rearrangements with opening of the bicyclic system and the formation of functionally substituted polyenes – rearrangements that virtually do not occur in the aromatic series – are characteristic for adducts of a number of heterocyclic compounds. Moreover, the heteroatom in the heteroring not only has an indirect effect on the reactivity of the double bond in this compound but itself may serve as the reaction center to which the attack of the carbene is directed, as a result of which ylids are formed. In addition, according to the existing ideas [10], this pathway should prevail if the heteroatom contains a free pair of electrons. Such ylids may be sufficiently stable for isolation in free form. However, if they are unstable, their intermediate formation nevertheless has a substantial effect on the reactivity of this heterocycle in reactions with carbenes and on the direction of these reactions, which also makes the reactions of carbenes with heterocyclic compounds fundamentally different from the reactions with their benzoid analogs. All of these chemical peculiarities open up great synthetic possibilities of the reactions of heterocyclic compounds with carbenes and make their further study promising from both a theoretical and synthetic point of view.

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KINETICS OF OPENING OF THE RING OF 5-ARYL-2,3-DIHYDROFURAN-2,3-DIONES UNDER THE INFLUENCE OF METHANOL*

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The kinetics of the opening of the ring of 5-aryl-2,3-dihydrofuran-2,3-diones under the influence of methanol, which leads to the formation of methyl esters of aroylpyruvic acids, were studied by PMR spectroscopy. A mechanism is proposed for the reaction.

It is known that the furan ring of 5-aryl-2,3-dihydrofuran-2,3-diones [1] is readily opened under the influence of nucleophilic reagents. Thus lower aliphatic alcohols react with I to give esters of aroylpyruvic acids when the reaction mixtures are heated at 60-70°C for 3 min [2]. The reaction of I with amines, hydrazines, and hydroxylamines is used as a method for the preparation of the corresponding derivatives of aroylpyruvic acids [3].

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