Journal of Organometallic Chemistry, 47 (1973) 281–309

THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS VIA TRANSITION METAL INTERMEDIATES

C. W. BIRD

Queen Elizabeth College, Campden Hill, London W8 7AH (Great Britain)

(Received April 26th, 1972)

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I. INTRODUCTION

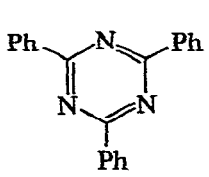
A remarkable variety of heterocyclic ring systems have been obtained by the application of reactions proceeding through transition metal intermediates to suitable acyclic substrates. Although several publications[1-3] provide extensive reviews of the transition metal catalysed reactions of organic substrates, covering the literature up to circa 1966, no previous attempt has been made to explicitly consider the synthesis of heterocyclic compounds by these methods. Of the several possible ways of presenting the material in this review the most profitable appeared to be in terms of the type of reaction leading to ring formation. Where possible, references quoted refer to definitive rather than preliminary publications.

II. CYCLOOLIGOMERISATION AND RELATED REACTIONS

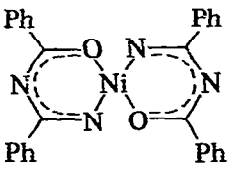
The first example of the formation of a heterocyclic compound by this type of reaction concerned the cyclotrimerisation of benzonitrile to 2,4,6-triphenyltriazine (1) on refluxing with iron pentacarbonyl[4]. Subsequently it was found that refluxing benzonitrile with Raney nickel provided a complex with the approximate composition $C_{21}H_{15}N_3Ni$ which yielded the triazine on crystallisation from acetic acid[5]. A subsequent publication[6] reported the formation of the complex (2) when the reaction was conducted in the presence of water and air. Further heating of this complex in benzonitrile yielded the triazine (1).

The cocyclisation of phenyl isocyanate and isoprene in benzene at 100° is catalysed by bis(triphenylphosphine)(maleic anhydride)palladium[7]. The products in 82% yield are the piperidones (3) and (4) in 1/1 proportion. Substitution of 1,3-butadiene for isoprene gave a similar yield of the two piperidinones (5) and (6) in which one of the exocyclic double

bonds has migrated into conjugation with the carbonyl group. The reaction of benzaldehyde with 1,3-butadiene under similar conditions provides the alcohol (7) and a mixture of the four isomeric pyrans (8)[8]. The catalyst system in this case was generated from triphenylphosphine, π-allylpalladium chloride and sodium phenoxide. The pyrans are the major products when the triphenylphosphine to palladium ratio exceeds two. The mechanistic sequence illustrated in Scheme 1 has been proposed for this reaction, based on the mechanism elucidated for the dimerisation of 1,3-butadiene[9]. The analogous reaction of formaldehyde with 1,3-butadiene provides a 2 to 1 mixture of the pyrans (9) and (10)[10]. It is not at present apparent why in this case the 1,3-butadiene units should couple together in the unprecedented manner necessary to yield the skeleton of (10).



(1)



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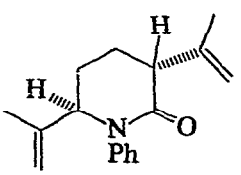

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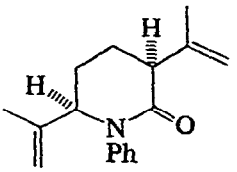
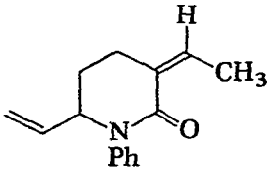


(4)



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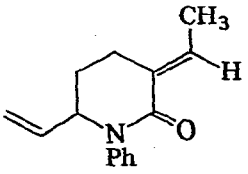

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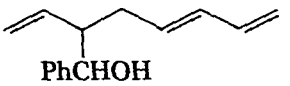

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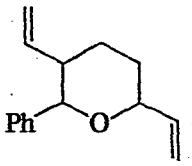

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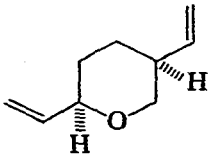

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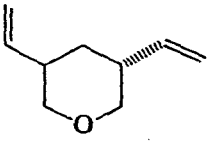
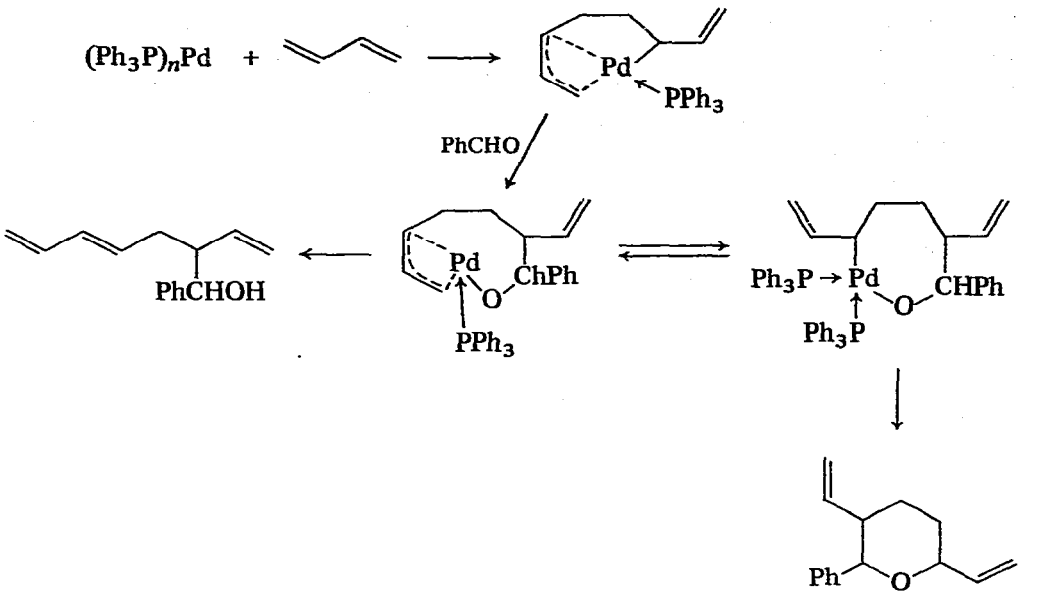


(10)

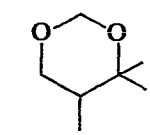
Monoolefins as their palladium chloride complexes react at 50° with formalin with the formation of 1,3-dioxanes[11]. In this manner 3-methyl-1-butene gave a 60–70% yield of (11) and (12), with the former compound predominating. The isobutene complex provided (38%) the dioxane (13) and the complexes of 1-butene and *cis*- and *trans*-2-



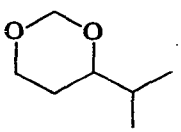
SCHEME 1

butene the dioxane (**14**). The same 1,3-dioxanes can be obtained directly from the olefins using catalytic amounts of palladium chloride in conjunction with cupric chloride, the best yields being obtained from branched chain olefins.

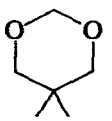
The cycloaddition of ethyl vinyl ether to benzylideneaniline is catalysed by dicobalt octacarbonyl in tetrahydrofuran at room temperature. The products, if air is not excluded, are 2-phenylquinoline (**15**) (39%) and *N*-benzylaniline. When the reaction is conducted in a nitrogen atmosphere the tetrahydroquinoline (**16**) is obtained as an additional product.



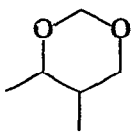
(**11**)



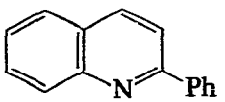
(**12**)



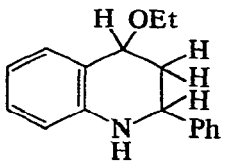
(**13**)



(**14**)



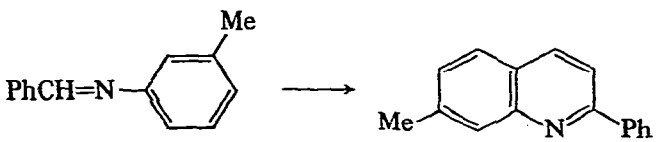
(**15**)



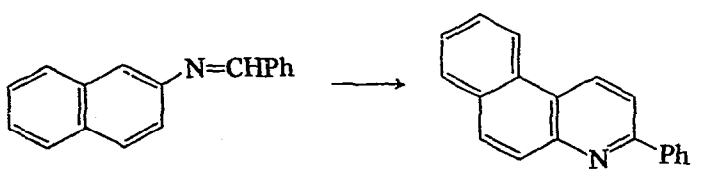
(**16**)

As expected, this compound yields 2-phenylquinoline on treatment with dicobalt octacarbonyl in tetrahydrofuran with oxygen present[12, 13]. Spectroscopic examination of these reaction mixtures revealed the presence of tetracarbonylcobalt hydride, which was shown to catalyse these reactions[14]. The structural requirements of this reaction have

been investigated. If either of the aryl groups of the Schiff's base bears an electron withdrawing group such as chloro or carbomethoxy no reaction occurs. However, an electron releasing group, such as methoxy, facilitates the reaction especially when present in the *N*-aryl ring. The cycloaddition reaction is precluded by an *o*-methyl group in the *N*-phenyl ring, and if the methyl group is in the *meta* position the only product (**17**) results from reaction at the ring position *para* to the methyl group. These features are presumably due to steric effects but it seems surprising that whereas the *N*-benzylidene derivative of 1-naphthylamine does not react, the corresponding derivative of 2-naphthylamine yields the benzo[*f*] quinoline (**18**). The Schiff's bases from aniline and acetophenone or propion-

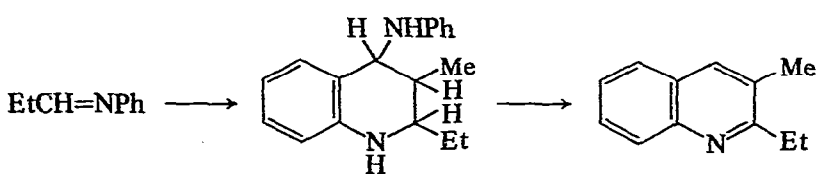


(**17**)



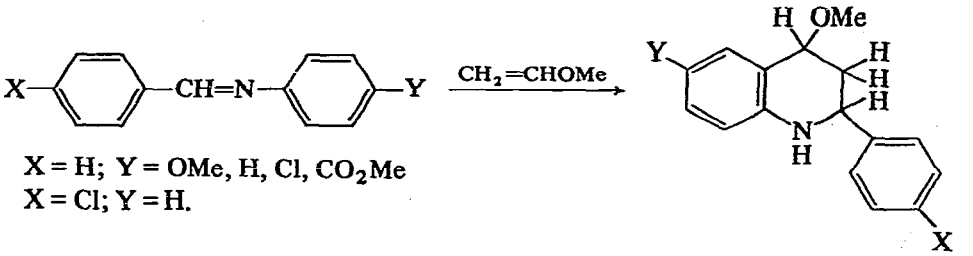
(**18**)

aldehyde do not react with ethyl vinyl ether, but the propionaldehyde derivative undergoes dimerisation via (**19**) leading to 2-ethyl-3-methylquinoline (**20**).



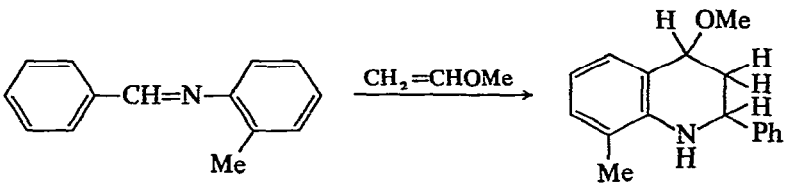
(**19**) (**20**)

The cycloaddition of methyl vinyl ether to Schiff's bases is also catalysed by nickel tetracarbonyl under the same conditions[13], but in this case the reaction does not proceed beyond the tetrahydroquinoline (**21**) stage. In contrast to the dicobalt octacarbonyl catalysed reaction, this cycloaddition is much less susceptible to electronic effects as illustrated by the potential range of groups Y in (**21**), or steric effects as typified by the conversion of *N*-benzylidene-*o*-toluidine to (**22**). As before *N*-propylideneaniline undergoes dimerisation to (**19**).



X = H; Y = OMe, H, Cl, CO_2Me
X = Cl; Y = H.

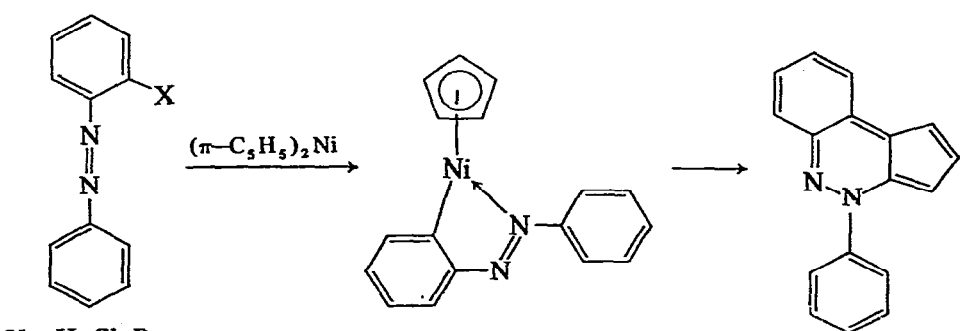
(21)



(22)

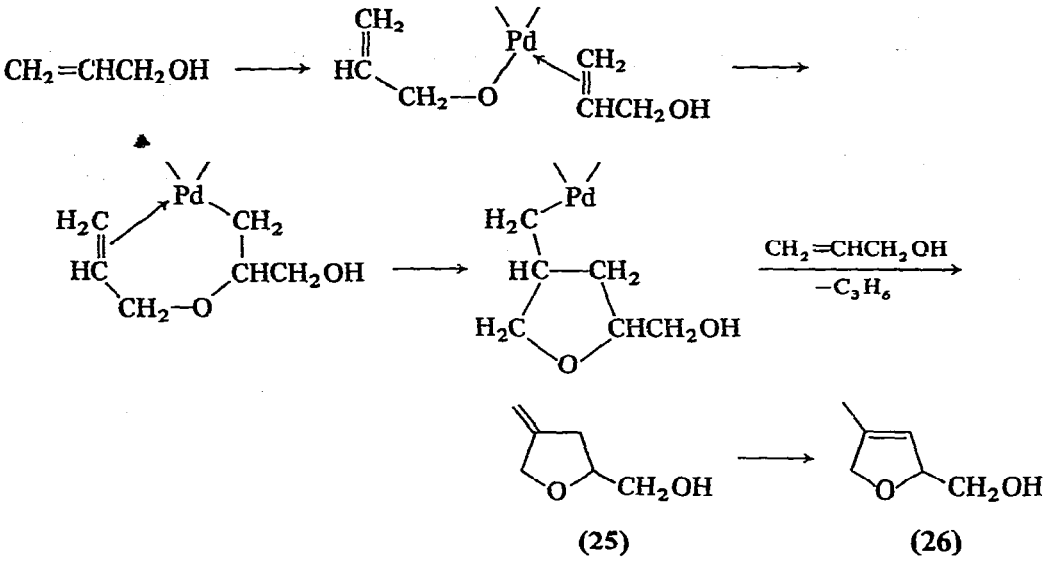
A far more exotic heterocyclic system has been obtained from nickelocene and azobenzenes[15]. These two reactants on brief heating together in xylene yield the complex (23), whose formation is facilitated by the presence of an *o*-chlorine or -bromine substituent in the azo compound. Longer heating of the complex in the presence of the azo compound, which presumably acts as a hydrogen acceptor, produces 4-phenylcyclopenta[*c*]quinoline (24). The same compound has also been obtained[16] in low yield by perbenzoic acid oxidation of the complex (23).

In contrast to most other olefins which are oxidized to carbonyl compounds by palladium salts, allyl alcohol undergoes an oxidative cyclodimerisation to 4-methylene-tetrahydrofurfuryl alcohol (25) and 4-methyl-2,5-dihydrofurfuryl alcohol (26)[17]. The other main product of the reaction is propene which apparently results from concomitant reductive hydrogenolysis of the allyl alcohol. The sequence illustrated has been suggested for the formation of these products.



X = H, Cl, Br

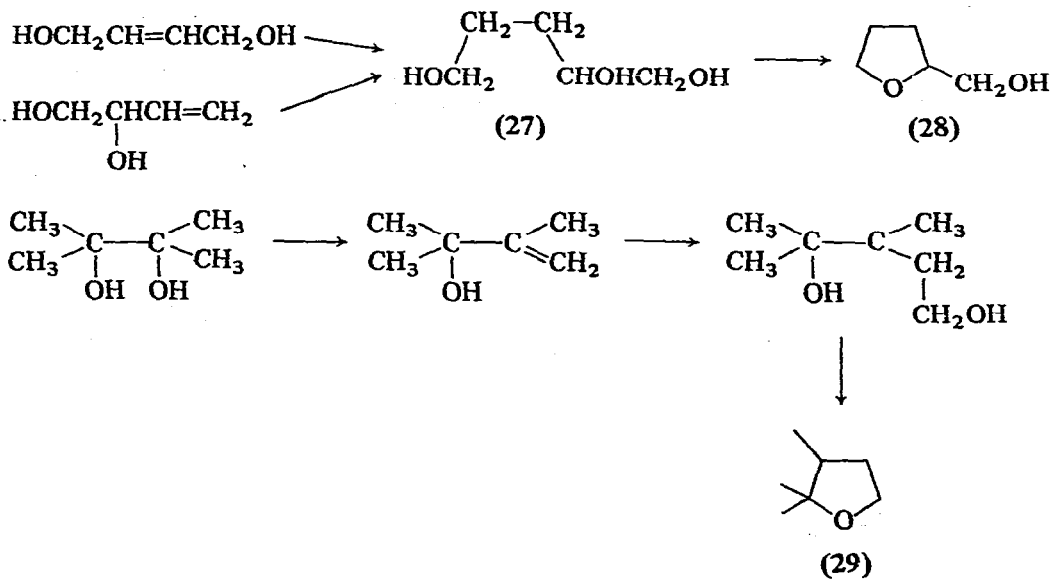
(23) (24)



(25) (26)

III. HYDROFORMYLATION REACTIONS

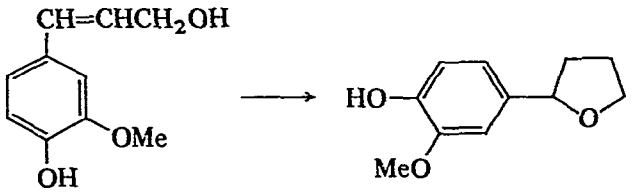
There are several examples in the literature of the formation of tetrahydrofuran derivatives during the hydroformylation of unsaturated alcohols. The earliest example is provided by the formation of tetrahydrofurfuryl alcohol (28) from either 1-butene-3,4-diol or 2-butene-1,4-diol[18]. The putative intermediate, 1,2,5-trihydroxypentane (27) was subsequently shown[19] to undergo conversion to (28) under the conditions of the hydroformylation reaction, presumably catalysed by the acidic tetracarbonylcobalt hydride. 2,2,3-Trimethyltetrahydrofuran (29) has been obtained[19] as a minor product of the



(27) (28) (29)

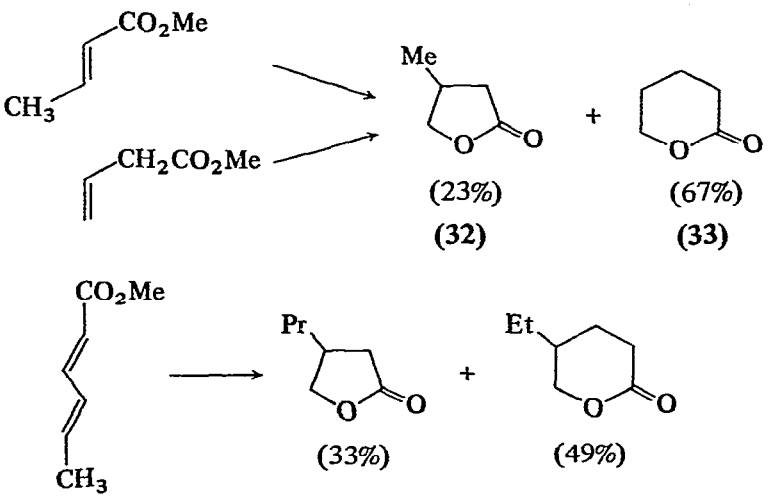
hydroformylation of pinacol, apparently being formed by the indicated route. A recent example is the formation of (31) from coniferyl alcohol (30)[20].

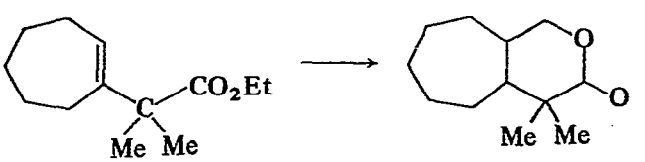
Good yields of tetrahydro-2-furanones and tetrahydro-2-pyranones can be obtained by hydroformylation of α,β-unsaturated esters[21]. The tetrahydro-2-pyranone being the major



(30) (31)

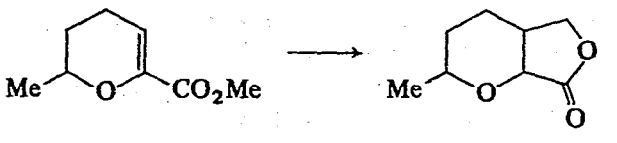
product when the double bond is able to undergo prior migration from α,β to β,γ, as illustrated by the formation of (32) and (33). Esters of the double unsaturated sorbic acid undergo partial reduction before hydroformylation. Competing hydrogenation of cinnamic esters can be averted by using an equimolar amount of dicobalt octacarbonyl. Typical conditions for these reactions utilise dicobalt octacarbonyl as catalyst in benzene solution with a carbon monoxide/hydrogen pressure of 300 atm at 250°. The application of this reaction to the production of fused ring compounds is exemplified by the synthesis of (34)[21] and (35)[22]. An unexpected cyclisation of (36) to (37) occurred when the hydroformylation of (36) was attempted[22].





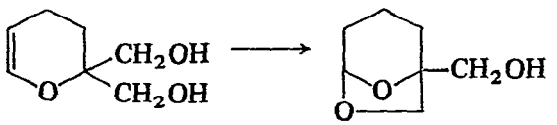
(94%)

(34)



(38%)

(35)



(78%)

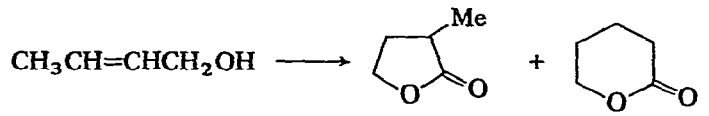
(36) (37)

The conversion of β-butyrolactone to tetrahydro-2-furanone has been reported[23] but as yet no further examples of hydroformylation ring expansion reactions have appeared.

IV. HYDROCARBOXYLATION AND RELATED REACTIONS

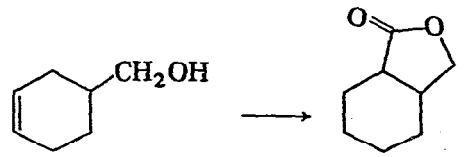
A variety of syntheses of heterocyclic ring systems can be envisaged in which hydrocarboxylation of a suitable ethylenic or acetylenic substrate provides a carboxylic acid, which in turn can undergo intramolecular ring closure with a suitably disposed substituent group. A good illustration is provided by the dicobalt octacarbonyl or rhodium chloride catalysed hydrocarboxylation of allyl alcohol to tetrahydro-2-furanone[24]. The yields in this case are low (1–2%) due to the concomitant isomerisation of allyl alcohol to propionaldehyde. However, a later study[25] has shown that yields as high as 60% can be obtained if acetonitrile, rather than benzene is used as a solvent, and a little pyridine also added.

Double-bond migration occurs under the reaction conditions as evidenced by the formation of (38) and (39) from crotyl alcohol, and (40) from 1,2,3,6-tetrahydrobenzyl



(2%) (0.5%)

(38) (39)

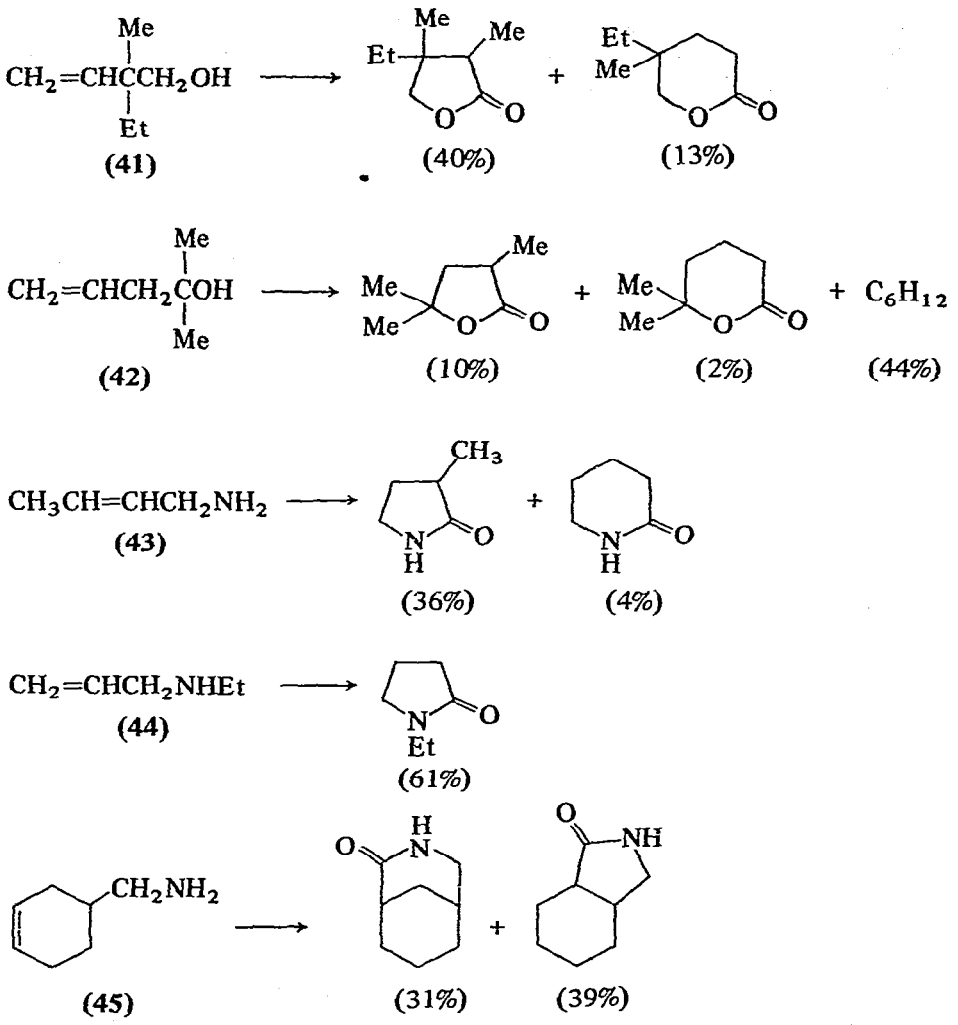


(16%)

(40)

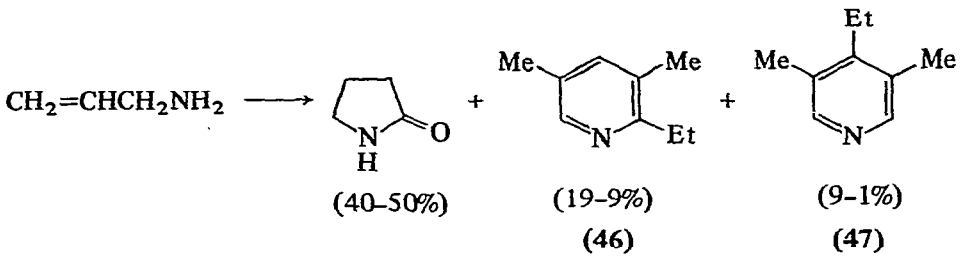
alcohol[24]. When migration of the double bond is precluded, as in the case of (41), both five- and six-membered ring products are formed resulting from attachment of the carboxyl group to either carbon atom of the double bond. Another side-reaction is observed when the hydroxyl group is attached to a tertiary carbon atom [*e.g.* (42)] when extensive hydrogenolysis occurs.

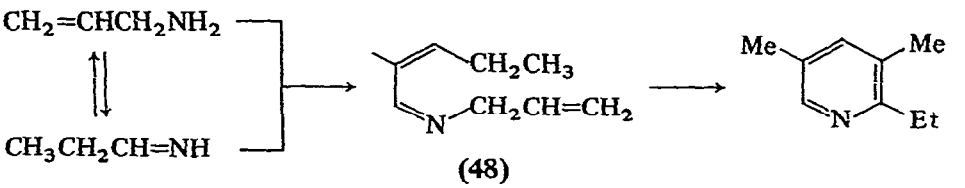
Analogous ring closure reactions have been effected with amino-olefins, as exemplified by the reactions of (43), (44) and (45). It will be noted that double-bond migration occurs

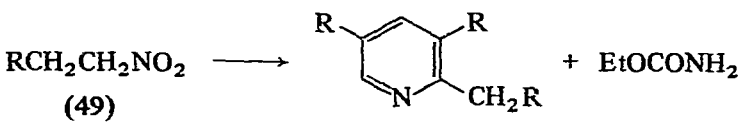


here also, but not so extensively as noted with olefinic alcohols. Allylamine itself produces not only pyrrolidone but also smaller quantities of the pyridines (46) and (47). The former pyridine is almost the sole reaction product if the dicobalt octacarbonyl catalyst is replaced by iron pentacarbonyl[27]. Under these conditions it is possible to isolate the compound (48) which is converted by treatment with iron pentacarbonyl to (46). The

apparent intermediate (48) is readily envisioned as being formed by condensation of propionaldehyde imine and allylamine. Other reactions capable of producing these intermediates also provide pyridines. Thus ethylene reacts with carbon monoxide, hydrogen and ammonia in the presence of iron pentacarbonyl yielding (46) and (47), in addition to *N*-n-propylpropionamide[28]. Treatment of benzene solutions of the oximes of propionaldehyde and butyraldehyde with carbon monoxide and hydrogen at 140° and 250 atm in the presence of dicobalt octacarbonyl generates 3,5-dimethyl-2-ethyl- (8%) and 3,5-diethyl-2-propylpyridine (24%) respectively[29]. The accompanying products (40%) are propionamide and butyramide. Acetoxime yields 2,4,6-trimethylpyridine (28%). Oximes are probably intermediates in the conversion of 1-nitroalkanes (49) into pyridines[30]. The reaction is effected by treating the nitroalkane in ethanol solution with carbon monoxide at 125–200° and 140–350 atm pressure with either palladium or rhodium on charcoal in conjunction with ferric chloride.







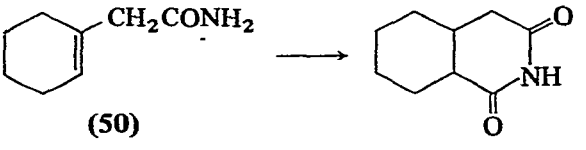
R = Et	(24%)	(39%)
Me	(52%)	(30%)
H	(0)	(18%)

Another substrate which gives rise to pyrrolidones is cyclopropylamine[31]. It is not clear whether the reaction proceeds via prior rearrangement to allylamine, but it is necessary to invoke such a reaction to account for at least one of the products which are pyrrolidone and its *N*-cyclopropyl, *N*-propyl and *N*-allyl derivatives. The amounts of individual components depend on the reaction temperature.

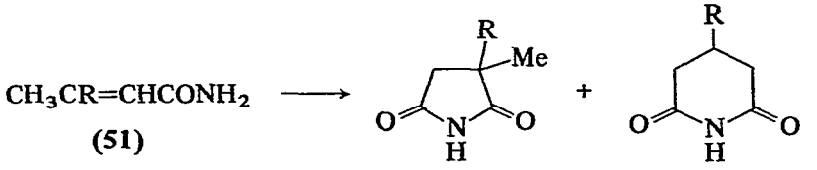
The dicobalt-octacarbonyl-catalysed hydrocarboxylation of unsaturated amides [*e.g.* **(50)**] provides a source of cyclic imides[32]. As in similar systems both five- and six-

membered rings may be formed due to prior double-bond migration. The proportions of products obtained from (**51**) reveal a pronounced sensitivity to the degree of alkylation of the acrylamide double-bond. *N*-Alkyl or *N*-aryl substituted acrylamides yield the corresponding *N*-substituted imides. The selective formation of *N*-allylsuccinimide from *N*-allylacrylamide, and none of the alternative *N*-acryloylpyrrolidone provides an interesting commentary on the relative reactivities of the two double-bonds[26].

The formation of the furanones (**52**), (**53**) and (**54**) from ethylene and carbon monoxide is the subject of several patents[33-36]. The reaction is effected at 180° and 500–1000 atm using a palladium compound as a catalyst and a solvent such as dioxane, ethyl acetate or acetonitrile. Both (**53**) and (**54**) are direct products of cyclisation of the putative intermediate, 4-oxohexanoic acid. Similar mixtures of lactones are formed by propene, butenes and 1,3-butadienes but their detailed structures have not been reported[35,36]. A closely related process is the formation of angelica lactone from 2-chlorobutadiene using practically identical reaction conditions[37]. The formation of *inter alia* (**55**) (20%) from the reaction of iodobenzene and styrene with nickel carbonyl in tetrahydrofuran or benzene at 50–60° probably follows an analogous pathway[38]. Replacement of styrene by acrylonitrile results in the obtention of (**56**). No reaction was

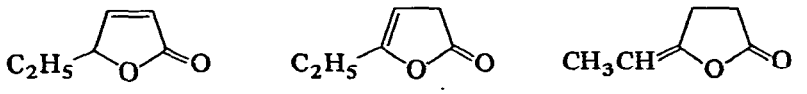


(**50**) (41%)

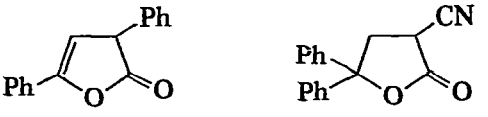


(**51**)

R = H	(68%)	(19%)
Me	(0)	(67%)



(**52**) (**53**) (**54**)

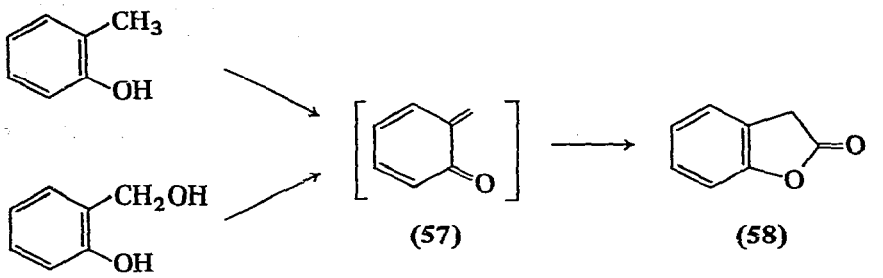


(**55**) (**56**)

observed with either cyclohexene or butadiene as substrates but lactonic products were detected from 1-octene.

A very attractive route to benzo-2-furanones (**58**) entails the dicobalt octacarbonyl catalysed reaction of *o*-methylphenols with carbon monoxide at 300° and 1000 atm[39]. The reaction is believed to proceed through the *o*-quinonemethide (**57**), as this species is also capable of generation from *o*-hydroxybenzyl alcohol, which is converted to (**58**) at 200°.

The formation of heterocycles by hydrocarboxylation of suitably substituted acetylenes has received limited attention, partly no doubt because the necessary nucleophilic substituents will often undergo facile addition to the triple bond. However, the acetylenic alcohols 4-pentynol and 5-pentynol are converted (20–30%) into (**59**) and (**60**) respectively by treatment with aqueous acidic nickel tetracarbonyl[40]. An unexpected example was encountered during the attempted hydrocarboxylation of *o*-nitrodiphenylacetylene which provided 3-benzylideneoxindole (**61**) as the sole characterisable product[41]. The *o*-nitro



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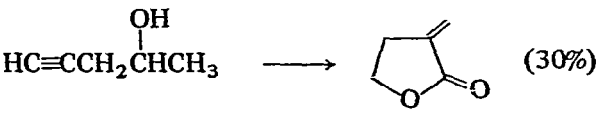
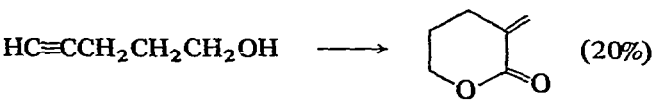


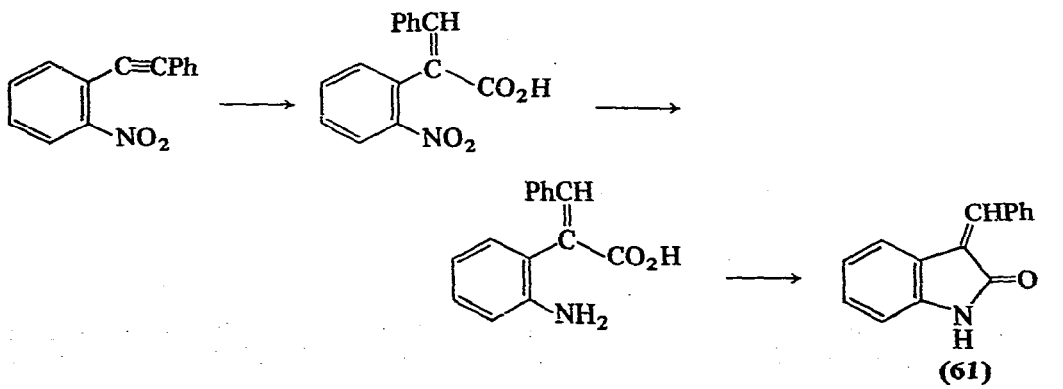
(30%)

(59)



(20%)

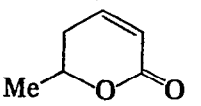
(60)



(61)

group markedly lowers the rate of the reaction and presumably the prolonged reaction time leads to the necessary reduction.

The carboxylation of acetylenes in the presence of allyl halides provides routes to several heterocyclic systems. The reaction of acetylene with an allyl halide and nickel carbonyl in an aqueous medium provides *cis*-2,5-dienoic acids[42]. Although a variety of other reagents converts these acids to phenols, treatment with 80% sulphuric acid gives 5,6-dihydropyrones [*e.g.* (62) and (63)] [43]. If the carboxylation reaction is conducted in a solvent such as acetone containing a small amount of water the furanone (64) is formed. Complete exclusion of water results in incorporation of the acetone leading to (65) and (66). The observation that *cis*-2,5-hexadienoyl chloride reacts with acetylene and nickel tetracarbonyl in acetone, forming (64) and (67), lead to the discovery that acid chlorides will react with acetylene and nickel tetracarbonyl with formation of furanones (68)[44]. Increasing the flow rate of acetylene into the reaction medium promotes the formation of 3H-oxepin-2-ones (69).

$CH_2{=}CHCH_2Cl \longrightarrow CH_2{=}CHCH_2CH{=}CHCO_2H \longrightarrow$ 

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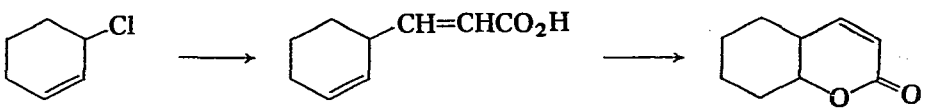

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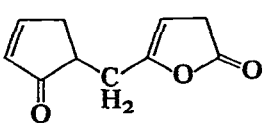

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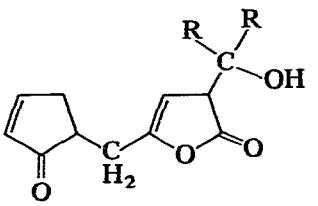

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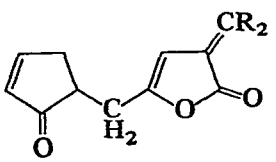
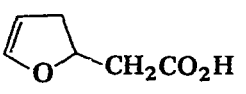


(66)



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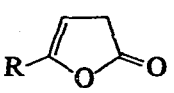

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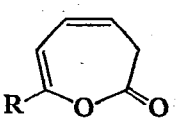
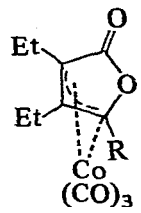


(69)

The foregoing reactions are clearly mechanistically related to the reaction of acylcobalt tetracarbonyls with 3-hexyne in ether solution at room temperature, in the presence of carbon monoxide, which provide complexes of structure (70)[45]. These complexes are hydrogenated to tetrahydro-2-furanones (71), or oxidised by iodine to the dimer (72). When the R group in (70) is capable of activating the adjacent hydrogen atom, treatment with a strong base such as dicyclohexylethylamine generates the 2,4-pentadiene-4-lactones (73).

The use of compounds containing functional groups other than double or triple bonds capable of permitting the introduction of carboxyl groups has received limited study. The conversion of *cis*-1-chloro-2-buten-4-ol (74) into 3,6-dihydro-2-pyrone (75) has been



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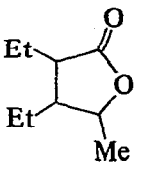

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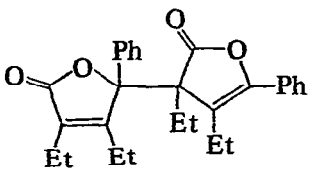

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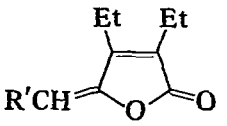
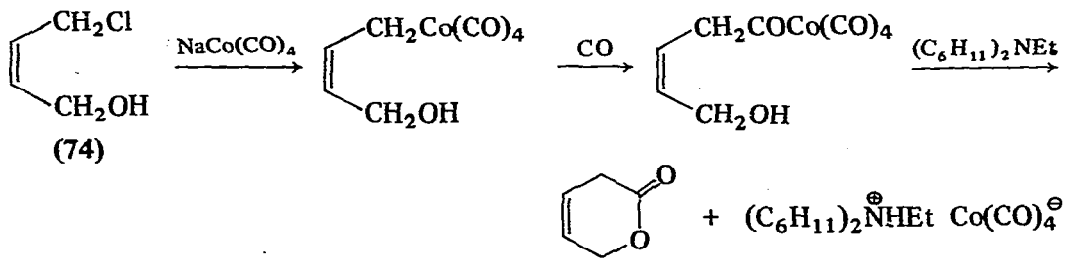


(73)

R′ = CN, CO_2Et, *p*—$NO_2C_6H_4$, $CH{=}CHCO_2Et$



(74)

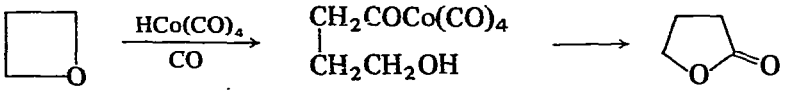
(75)

demonstrated[46], by treatment with sodium tetracarbonylcobaltate and carbon monoxide in tetrahydrofuran at room temperature, followed by addition of dicyclohexylethylamine.

Oxetane (76) reacts with cobalt hydrocarbonyl at room temperature in ether solution with the absorption of a mole of carbon monoxide[46]. The resulting 4-hydroxybutyryl-cobalt tetracarbonyl undergoes cyclisation to (77) on heating or by treatment with di-cyclohexylethylamine. Ring expansions of oxetane and its 3,3-dimethyl derivative have

also been effected at 160° and 250 atm using dicobalt octacarbonyl with carbon monoxide[47]. The analogous transformation of tetrahydrofuran to tetrahydro-2-pyrone can also be carried out[48].

A novel synthesis of the imidazole ring system from olefins has been observed under hydrocarboxylation conditions. The reaction of ethylene with carbon monoxide and concentrated aqueous ammonia in the presence of a rhodium catalyst at 150° and 250 atm produces only 15% of the anticipated propionamide and a 52% yield of 2,4,5-triethylimidazole (79)[49]. Comparable yields of 2,4,5-tripropyl- and -tributylimidazoles were obtained from propene and 1-butene respectively. An indication as to the reaction pathway was provided when the reaction was repeated using a dilute ammonia solution. The product (40%) was the acylamino ketone (78), which is readily envisaged as undergoing cyclisation with ammonia. The earlier stages in the reaction appear to entail the



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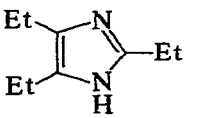
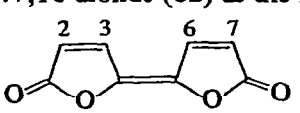


(78) (79)

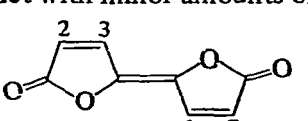
conversion of ethylene to 3,4-hexanedione, which then undergoes reductive condensation with propionamide producing (78). Experimental support for this stage was obtained by demonstrating that 2,3-pentanedione and propionamide produce 2,4-diethyl-5-methyl-imidazole under the reaction conditions.

V. CARBONYLATION REACTIONS

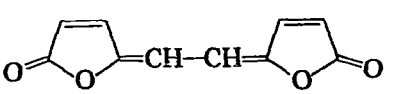
The reaction of carbon monoxide with acetylene at 90–120° and 100–1000 atm is catalysed by dicobalt octacarbonyl and forms the *trans*-bifurandione (80) together with small amounts of the *cis*-isomer (81)[50,51]. The *trans*-bifurandione is converted into the more stable *cis*-isomer by acid or base treatment. The preferred reaction solvents for bifurandione formation are acetonitrile, ethyl acetate and acetone. The same reaction in benzene at lower pressures provides the *cis* and *trans* isomers of 2,4,6,8-decatetraene-1,4:7,10-diolide (82) as the major product with minor amounts of bifurandione[53]. A



(80)



(81)



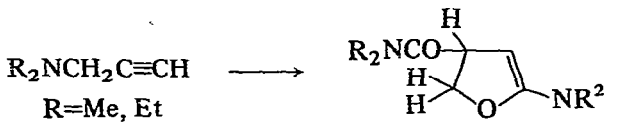
(82)

variety of acetylenes have been converted into bifurandiones. Unsymmetrically substituted acetylenes yield mixtures of positional isomers. Propyne gives both *cis* and *trans* isomers of 2,6- and 2,7-dimethylbifurandione[52]. The reaction follows a different course with 3-dialkylaminopropynes giving the furan derivatives (83) and (84)[54].

The mode of formation of the bifurandione system is not established. Although the structure of the lactonic complex (85) which is formed by carbonylation of acetylene-dicobalt hexacarbonyl suggests a possible origin, complexes of this type do not appear to be the normal precursors of bifurandiones[56]. An alternative route is suggested by the conversion of acetylene in methanol under similar reaction conditions to dimethyl succinate[57]. Successive additions of cobalt hydrocarbonyl to acetylene followed by carbonyl insertion would provide the complex (86). Subsequent elimination of two molecules of cobalt hydrocarbonyl leaves the bisketene which is in equilibrium with the carbene (87). Dimerisation of (87) then yields the bifurandione. Some support for this sequence is provided by the demonstration that dehydrochlorination of succinyl chlorides generates bifurandiones, presumably by way of the bisketen (86a)[58].

A very interesting reaction in this context is the nickel catalysed reaction of *tert*-butylisonitrile with acetylenes, which gives very good yields of pyrroles (88)[59]. Unsymmetrically substituted acetylenes yield a mixture of the two possible pyrroles. An attractive, though unsubstantiated mechanism may be suggested as proceeding via a bisketeneimine.

The carbonylation of compounds having the generalised structure (89) has proved a fruitful source of nitrogen heterocycles. In the case of Schiff bases [(89): X = CH and R = aryl or alkyl] reaction with carbon monoxide in benzene occurs at 200–230° and 100–200 atm using dicobalt octacarbonyl as catalyst[60–65]. Benzylideneaniline gives an



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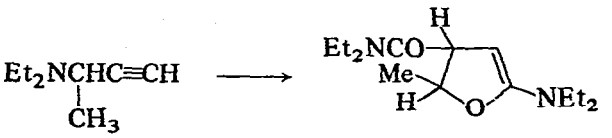

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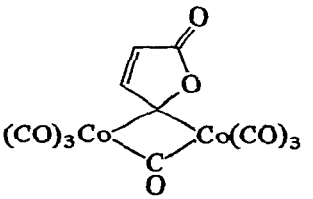
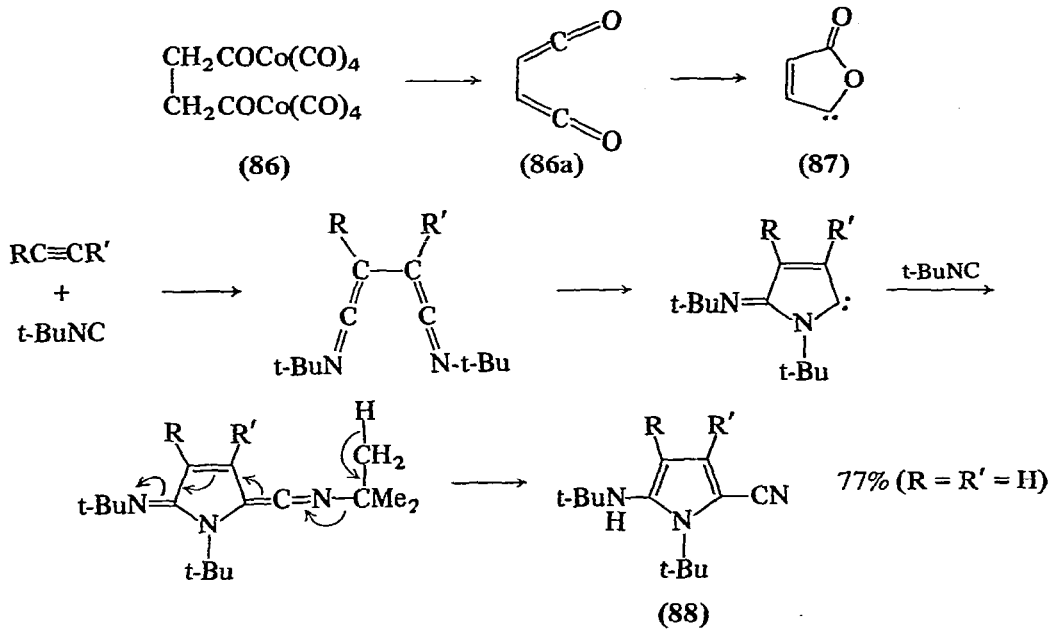


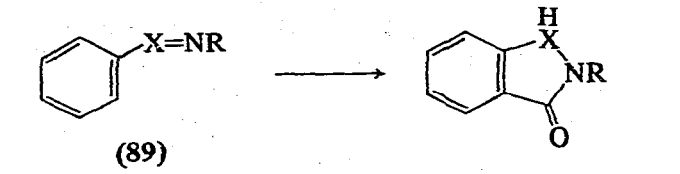
(85)



84% yield of 2-phenylpthalimidine under these conditions. Lower yields are obtained with iron or rhodium carbonyls as catalysts. The mechanism of the reaction is suggested by the formation of the complex (**90**) from the Schiff's base and diiron nonacarbonyl under mild conditions[66]. Oxidation of (**90**) by ferric chloride gives the phthalimidine. Introduction of substituents into the *N*-aryl group of Schiff bases has little effect on yields unless the substituents are in *ortho*-positions when yields are lowered. Replacement of X = CH by X = CR in (**89**) does not have a detrimental effect on the cyclisation. Information concerning the role of substituents in the C-aryl group is very limited. The most noteworthy feature is that the *m*-methoxyphenyl compound produces a low yield of 5-methoxy-2-phenylphthalimidine (**91**), whereas the *m*-hydroxy and *m*-(dimethylamino)phenyl compounds give excellent yields of the 7-substituted phthalimidine (**92**)[62]. Carbonylation of the anil of 1-naphthaldehyde gives the anticipated product (**93**), but the anil of 2-naphthaldehyde gives (**94**) as a result of an unexpected cyclisation at 3-C rather than 1-C.

A Schiff base intermediate is apparently involved in the conversion of benzonitrile into 2-benzylphthalimidine (**95**) at 230–240° and 270 atm of carbon monoxide containing a little hydrogen. Dicobalt octacarbonyl is used as the catalyst, and a 22% yield of (**95**) was obtained if a little pyridine was added. The yield is boosted to 41% if benzylamine is also added thereby lending support to the indicated route. Other products of the reaction are benzamide and dibenzylurea.

Carbonylation of ketoximes provides phthalimidines rather than the anticipated *N*-hydroxy compounds, which presumably undergo hydrogenolysis. Benzophenone oxime and its *O*-methyl ether give 80% yields of 3-phenylphthalimidine[68–70]. This compound was also obtained from the oxime of 2-benzoylbenzoic acid[68], but it seems likely that in this case the oxime was reduced to the primary amine followed by intramolecular amide formation. Alkyl aryl ketoximes give only low yields of phthalimidines accompanied by a



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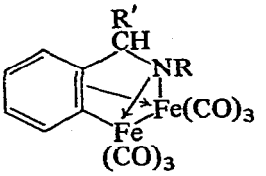

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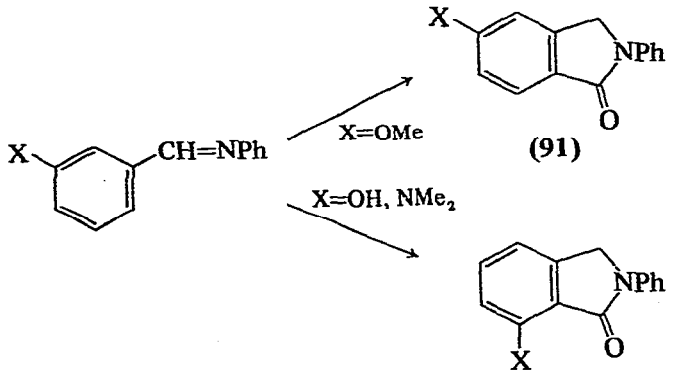
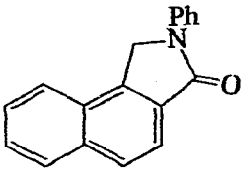


(92)

variety of side-products[68]. Thus the major product from the oxime of 2-acetylnaphthalene is the benzoquinoline (96) and only small amounts of the benzophthalimidine (97)[72]. Control experiments show that (96) is formed by thermal condensation[71]. Phenyl benzyl ketoxime cyclises in both directions giving 3-benzylphthalimidine (98) and lesser amounts of the isocarbostyryl (99)[68]. Attempts to ensure cyclisation with the formation of six-membered rings only have been unsuccessful. The oximes of dibenzyl ketone and phenyl-3-butanone undergo preferential reduction to the primary amines, which are subsequently converted to *N*-formyl derivatives and ureas[70]. Preferential reduction also occurs exclusively with aromatic aldoximes[73]. Attempted carbonylation of the *N,N'*-dimethyl derivative of α-benzil dioxime gave a small quantity of tetraphenylpyrazine[69]!

Appropriate semicarbazones [(89), X = CPh, R = $NHCONH_2$] can also serve as phthalimidine precursors. Benzophenone semicarbazone at lower temperatures gives the azine and reduction products but at 240° phthalimidine (100a,b) formation occurs[75]. The azine also yields phthalimidines. Benzaldehyde semicarbazone also appears to undergo carbonylation via the azine. The products in this case are a mixture of phthalimidines (101a,b,c) and a benzodiazepine derivative (102)[74].

Phthalimidines have also been obtained in good yields from phenylhydrazones. 2-Phenylphthalimidine (104) is produced in 50% yield from benzaldehyde phenylhydrazone



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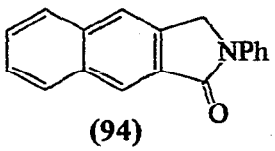
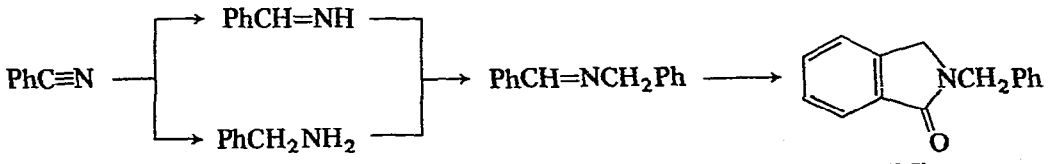


(94)



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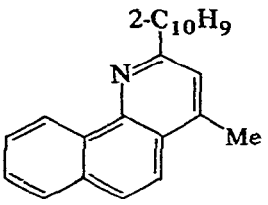

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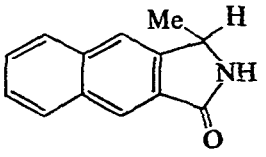
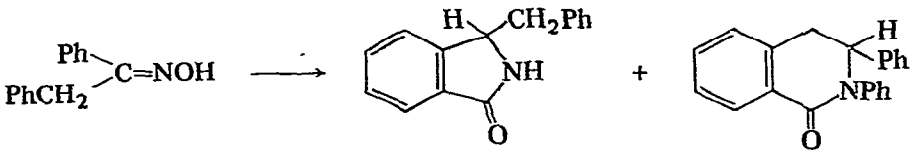
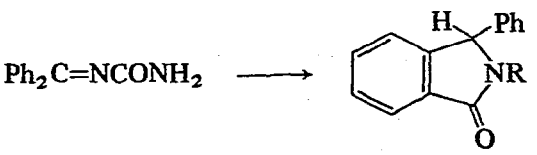


(97)

(103)[76]. Accompanying products are benzaldehyde, benzonitrile and diphenylurea. The origin of the ring nitrogen was indicated by appropriate labelling. The phenylhydrazone of 1-naphthaldehyde yields the phthalimidine (93). The phenylhydrazones of arylketones behave somewhat differently in that either nitrogen atom may be lost, as exemplified by

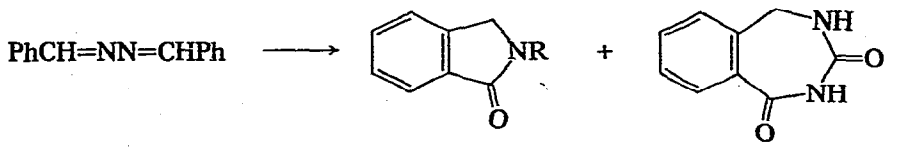


(98) (99)



(100)

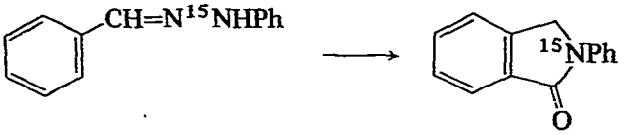
(a) R = H
(b) R = CONHCHPh$_2$



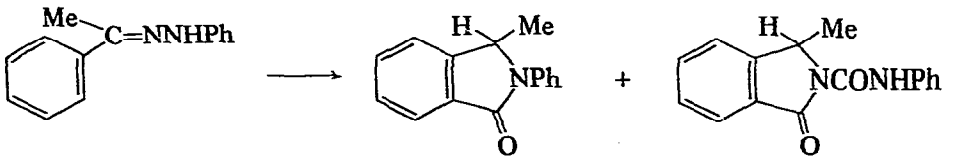
(101) (102)

(a) R = H (13%) (12%)
(b) R = CH_2Ph (16%)
(c) R = $CONHCH_2Ph$ (5%)

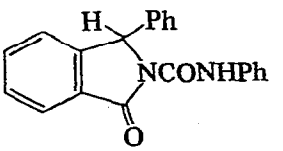
acetophenone phenylhydrazone which yields a mixture of (**105**) and (**106**). Benzophenone phenylhydrazone gives a 70% yield of (**107**), but at lower temperatures the predominant product is 3-phenylphthalimidine thereby indicating that the phenylcarbamoyl group is added subsequent to the cyclisation. The only information so far available concerning the



(103) (104)



(105) (106)

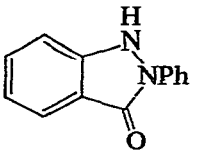


(107)

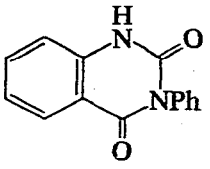
relative reactivities of aryl rings is provided by 4-methylbenzophenone phenylhydrazone which gave both phthalimidines in equal amounts[77]. The carbonylation of the phenylhydrazone of deoxybenzoin to 3-benzylphthalimidine derivatives is accompanied by thermal cyclisation to 2,3-diphenylindole, and exclusive indolisation occurs with the phenylhydrazone of dibenzyl ketone[78].

Another kind of substrate for carbonylation reactions of this general type is provided by azobenzenes [(**89**), X = N]. The original investigations employed dicobalt octacarbonyl as a catalyst at 170–190° and 150 atm pressure of carbon monoxide. The major product under these conditions is the 2-arylindazolone (**108**) with minor amounts of 3-arylquinazoline-2,4-dione (**109**), the lactam (**110**) originally formulated as (**111**) and diphenyl-

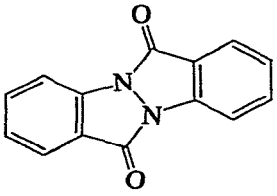
urea[62,79]. At higher temperatures, 220–230°, the quinazolinedione (**109**) is the predominant product, and its formation from the indazolone has been demonstrated. The best medium for these transformations is benzene as solvents such as ethanol, water and tetrahydrofuran inhibit the reaction, whilst potential hydrogen donors like hexane, cyclohexane and tetralin promote the formation of diphenylurea via its precursor hydrazobenzene. Lower yields were obtained using iron pentacarbonyl as the catalyst, while nickel tetracarbonyl yields mainly (**110**)[80]. Small amounts of quinazolinediones (**109**) have also



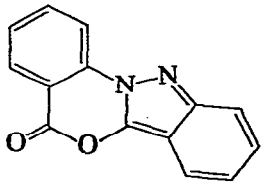
(**108**)



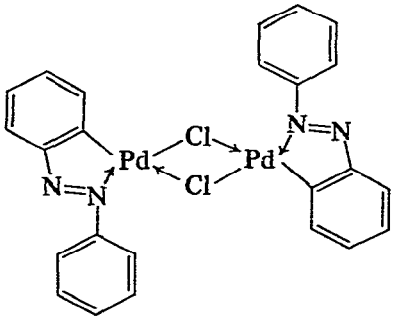
(**109**)



(**110**)



(**111**)



(**112**)

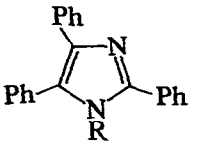
been obtained[81] as by-products of the iron pentacarbonyl catalysed reduction of nitrobenzenes to azobenzenes at 200°. Three mono-substituted azobenzenes carrying *p*-dimethylamino, *p*-methyl and *p*-chloro substituents have been converted to 5-substituted indazolones. No reactions occur with *p*-cyanoazobenzene or α- and β-azonaphthalenes. An alternative method of converting azobenzenes to indazolones entails initial reaction with palladium chloride to form the complex (**112**), followed by treatment with carbon monoxide in water or ethanol solution at 100° and 100–150 atm[82]. The quoted yields (80–97%) are appreciably higher than those obtained using dicobalt octacarbonyl catalysed carbonylation. The mixtures of indazolones obtained from 4-methoxy, 4-methyl and 4-

chloroazobenzene were further carbonylated [$Co_2(CO)_8$] to the quinazolinediones. Hydrolysis in each case gave a mixture of aniline and the 4-substituted aniline whose relative proportions were determined. The proportionate amount of cyclisation occurring onto the substituted ring was 4-methoxy 100%, 4-methyl 75% and 4-chloro 25%.

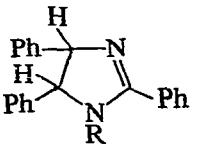
VI. REACTIONS WITH CARBON TETRACHLORIDE

The reaction of amines with carbon tetrachloride in the presence of a metal carbonyl has recently been found to provide heterocyclic compounds. Thus benzylamine reacts with carbon tetrachloride at 150° in the presence of dicobalt octacarbonyl yielding the triphenylimidazole (**113**) and the imidazoline (**114**) with benzaldehyde and dibenzylamine as accompanying products[83b]. At reaction temperatures below 120° no debenzylated products (**113a**, **114a**) are obtained. Shortening the reaction time leads to a preponderance of the imidazoline (**114**), while using a lower reaction temperature and shorter time results in $PhCH{=}NCH_2Ph$ becoming the major product. It is apparently immaterial to the course of the reaction whether it is conducted in an atmosphere of nitrogen or carbon monoxide. Replacement of dicobalt octacarbonyl by either molybdenum hexacarbonyl or bis(π-cyclopentadienylmolybdenum tricarbonyl) results in the formation of the imidazoline (**114**) and dibenzylamine. Clearly the main function of the carbon tetrachloride in these reactions is to act as an overall hydrogen acceptor by undergoing conversion to chloroform and hydrogen chloride. It appears that the initial product of reaction is the imidazolidine which then undergoes dehydrogenation. It is of particular interest in this context that *o*-chlorobenzylamine yields only the imidazolidine (**115**), presumably the *o*-chloro substituents hinder the approach of the hydrogen abstracting species to the ring hydrogen atoms.

While under similar conditions some anilines react with carbon tetrachloride in the presence of carbon monoxide and a metal carbonyl forming amidines [*e.g.* (**116**)], others

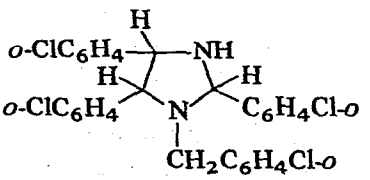


(**113**)

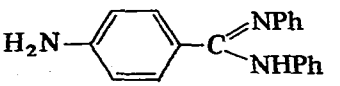


(**114**)

(a) R = H
(b) R = CH_2Ph

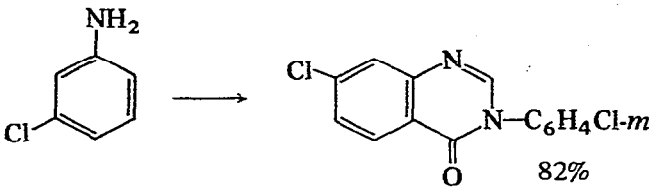


(**115**)

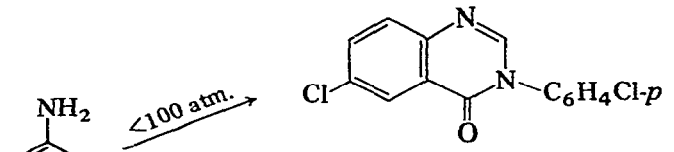


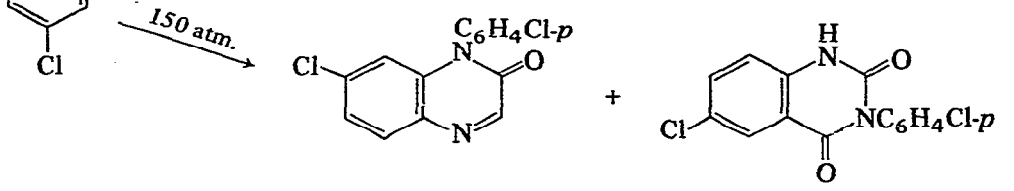
(**116**)

yield a variety of heterocyclic compounds[83a]. *m*-Chloroaniline at 150° and 100 atm provides (82%) of the quinazolinone (**117**) but at 120° only bis(*m*-chlorophenyl)urea is formed. The best catalysts are molybdenum hexacarbonyl, π-cyclopentadienylmolybdenum tricarbonyl dimer and chromium hexacarbonyl, with dicobalt hexacarbonyl being less

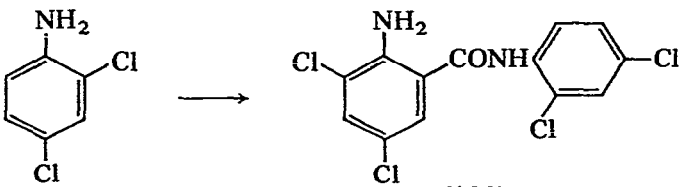


(**117**)





(**118**) (**119**)



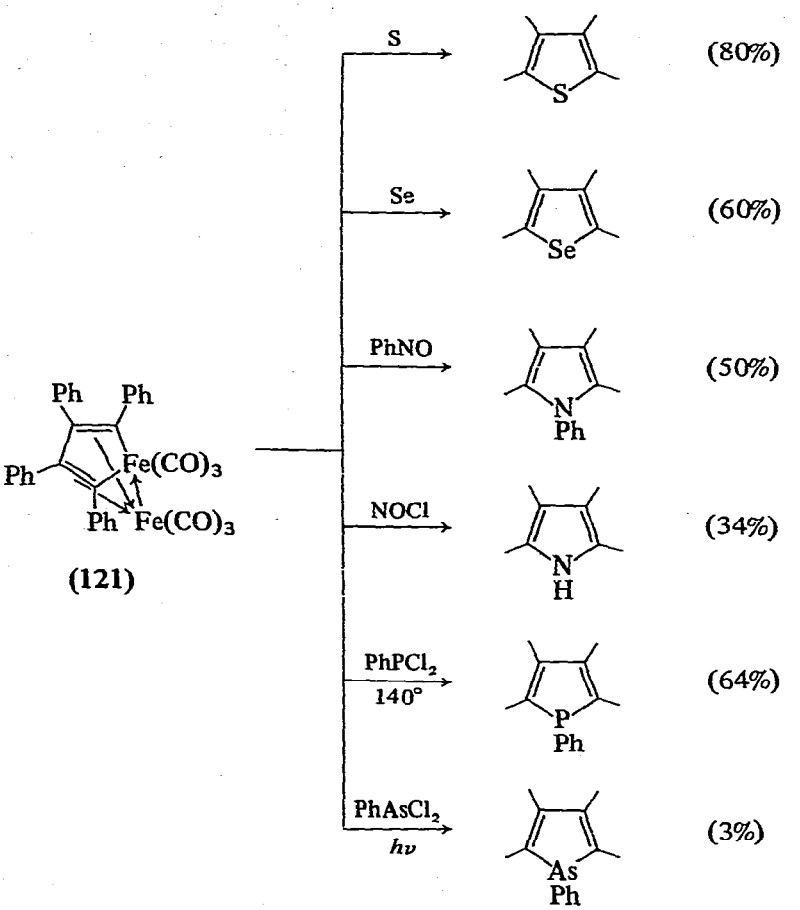
(**120**)

effective. *m*-Bromo and 3,4-dichloroaniline also yield quinazolinones but *p*-chloroaniline, while giving the quinazolinone at pressures below 100 atm, at 150 atm produces the quinoxaline (**118**) and the quinazolinedione (**119**). The latter type of compound is also obtained from *m*- and *p*-toluidine, and 3,4-dimethylaniline while 2,4-dichloroaniline gives the benzamide derivative (**120**). A mechanistic rationalisation of these reactions is difficult at this stage since it is not clear which carbon atoms are provided by the carbon tetrachloride and which by the carbon monoxide.

VII. REACTIONS WITH PREFORMED ORGANOMETALLICS

A variety of organometallic compounds are available from the reaction of acetylenes with transition metal derivatives, and some of these have proved useful precursors of heterocyclic systems.

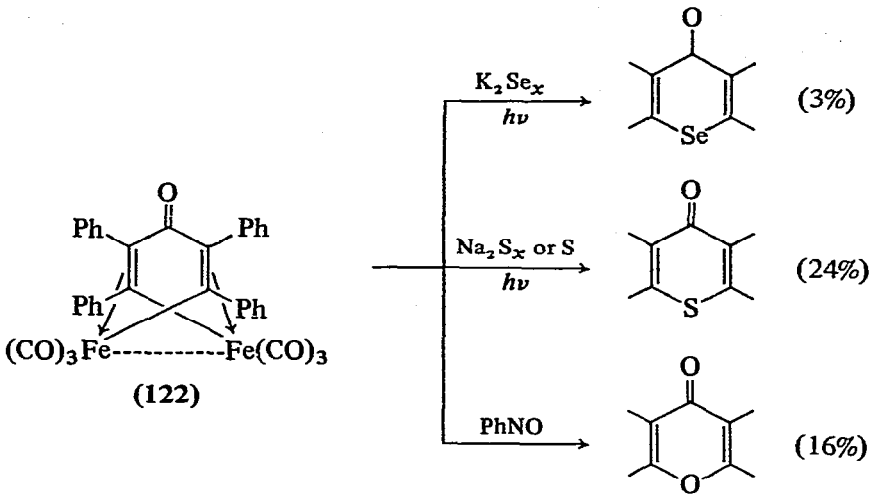
Two of the principal types of organometallic systems resulting from reactions of acetylenes with iron carbonyls are represented by (121) and (122), which have been converted to the heterocycles illustrated[84–87]. The use of complexes corresponding to



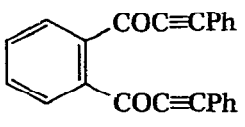
(121)

(121) for the synthesis of 2,3,4,5-tetrakis(methoxycarbonyl)-, 2,5-dimethyl-3,4-diphenyl-, 2,5-diphenyl- and 3,4-diphenylthiophenes has also been reported.

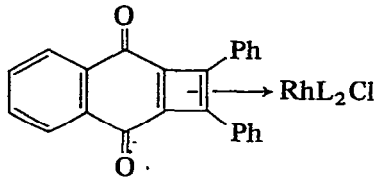
The treatment of diacetylenes such as (123), (125) and (127) with tris(triphenylphosphine)rhodium(I) chloride results in the generation of the complexes (124), (126) and (128) respectively[88,89]. In all cases reaction of these complexes with sulphur or selenium provides the corresponding thiophenes: (129), (130), (131), (X = S) and selenophenes (X = Se); the yields of thiophenes being generally much higher than those of the selenophenes. The reaction of complex (124) with oxygen gives a modest yield of furan [(129),



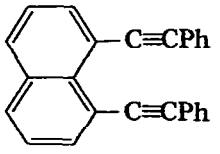
(122)



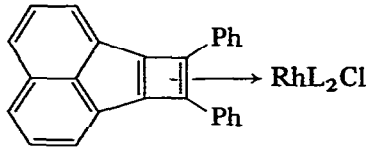
(123)



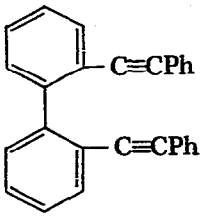
(124)



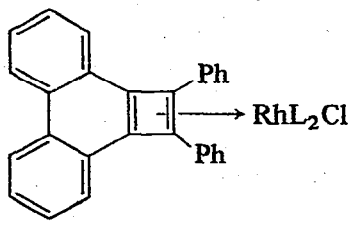
(125)



(126)

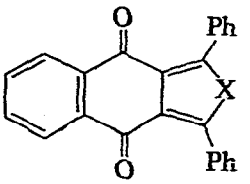


(127)

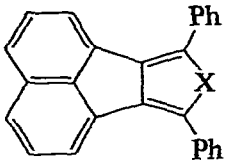


(128)

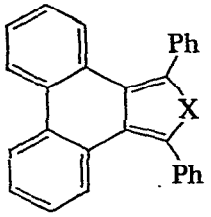
X = O], while complex (126) gives primarily the ketone (132) with only a small amount of the furan [(131), X = O].



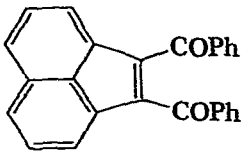
(129)



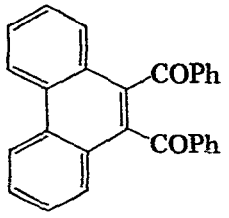
(130)



(131)



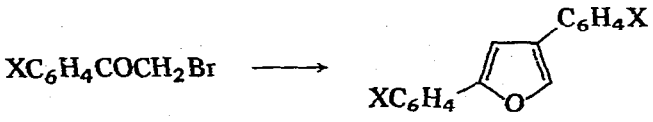
(132)



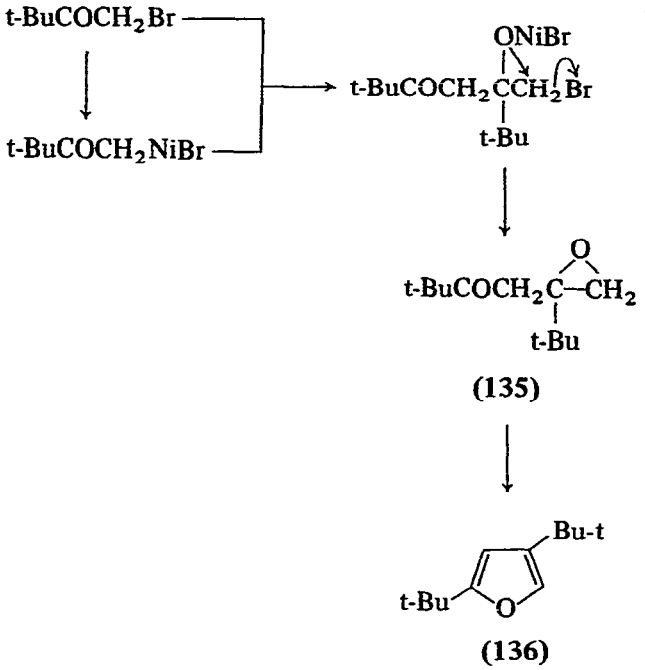
(133)

VIII. HALIDE COUPLING REACTIONS

The reaction of phenacyl bromides with nickel carbonyl in dimethylformamide produces 2,4-diarylfurans (134). The course of this reaction, which deviates from the normal behaviour of activated halides, is indicated by a subsequent report that α-bromo derivatives of dialkyl ketones provide epoxy ketones [*e.g.* (135)] under these conditions, possibly by the route indicated. The epoxy ketones undergo thermal rearrangement to furans (136).



(134)



(135)

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REFERENCES

1 C.W. Bird, *Transition Metal Intermediates in Organic Synthesis*, Logos Press, London,1967; Japanese edition, Hirokowa Publishing Co., Tokyo, 1970.
2 J. Falbe, *Synthesen mit Kohlenmonoxyd*, Springer-Verlag, Berlin-Heidelberg-New York, 1967.
3 I. Wender and P. Pino (Eds.), *Organic Syntheses via Metal Carbonyls*, Vol. I, Interscience, New York, 1968.
4 S.F.A. Kettle and L.E. Orgel, *Proc. Chem. Soc.*, (1959) 307.
5 W.Z. Heldt, *J. Organometal. Chem.*, 6 (1966) 292.
6 G. Oehme and H. Pracejus, *Z. Chem.*, 9 (1969) 140.
7 K. Ohno and J. Tsuji, *J. Chem. Soc. D*, (1971) 247.
8 K. Ohno, T. Mitsuyasu and J. Tsuji, *Tetrahedron Lett.*, (1971) 67.
9 G. Wilke, *Angew. Chem., Int. Ed. Engl.*, 2 (1963) 105.
10 P. Haynes, *Tetrahedron Lett.*, (1970) 3687.
11 S. Sakai, Y. Kawashima, Y. Takahashi and Y. Ishii, *Chem. Commun.*, (1967) 1073; *Kogyo Kagaku Zasshi*, 72 (1969) 1715; *Chem. Abstr.*, 72 (1970) 21646.
12 T. Joh and N. Hagihara, *Tetrahedron Lett.*, (1967), 4199.
13 T. Joh and N. Hagihara, *Kogyo Kagaku Zasshi*, 91 (1970) 378; *Chem. Abstr.*, 73 (1970) 45294.
14 T. Joh and N. Hagihara, *Kogyo Kagaku Zasshi*, 91 (1970) 383; *Chem. Abstr.*, 73 (1970) 45295.
15 Yu.A.Ustynyuk and I.V. Barinov, *J.Organometal. Chem.*, 23 (1970) 551.
16 Yu.A. Ustynyuk, I.V. Barinov and E.J. Sirotkina, *Dokl. Akad. Nauk SSSR*, 187 (1969) 112.
17 W. Hafner, H. Prigge and J. Smidt, *Justus Liebigs Ann. Chem.*, 693 (1966) 109.
18 L.E. Craig, R.M. Elofson and I.J. Ressa, *J. Amer. Chem. Soc.*, 72 (1950) 3277.
19 I. Wender, S. Metlin and M. Orchin, *J. Amer. Chem. Soc.*, 73 (1951) 5704.
20 L.S. Nahum, *J. Org. Chem.*, 33 (1968) 3601.
21 J. Falbe, N. Huppes and F. Korte, *Chem. Ber.*, 97 (1964) 863.
22 J. Falbe and F. Korte, *Chem. Ber.*, 97 (1964) 1104.
23 Y. Mori and J. Tsuji, *Bull. Chem. Soc. Jap.*, 42 (1969) 777.
24 J. Falbe, H.J. Schulze-Steinen and F. Korte, *Chem. Ber.*, 98 (1965) 886.

25 A. Matsuda, *Bull. Chem. Soc. Jap.*, 41 (1968) 1876.
26 J. Falbe and F. Korte, *Chem. Ber.*, 98 (1965) 1928.
27 J. Falbe, H. Weitkamp and F. Korte, *Tetrahedron Lett.*, (1965) 2677.
28 A. Striegler and J. Weber, *J. Prakt. Chem.*, 29 (1965) 281.
29 J. Falbe and F. Korte, *Brennstoffchemie*, 46 (1965) 276.
30 A.G. Mohan, *J. Org. Chem.*, 35 (1970) 3982.
31 A.F.M. Iqbal, *Tetrahedron Lett.*, (1971) 3381.
32 J. Falbe and F. Korte, *Chem. Ber.*, 95 (1962) 2680.
33 P. Hayden, *Brit. Pat.*, 1,148,043; *Chem. Abstr.*, 71 (1969) 60758.
34 I.C.I. Ltd., *Neth. Appln.*, 6,511,995; *Chem. Abstr.*, 65 (1966) 7064.
35 N. Von Kutepow, F. Meier and D. Neubauer, *Ger. Pat.*, 1,276,029; *Chem. Abstr.*, 70 (1969) 37229.
36 B.A.S.F., *Neth. Appln.*, 6,516,507; *Chem. Abstr.*, 65 (1966) 16870.
37 D.M. Fenton, *U.S. Pat.*, 3,564,020; *Chem. Abstr.*, (1971) 5289.
38 E. Yoshisato, M. Ryang and S. Tsutsumi, *J. Org. Chem.*, 34 (1969) 1500.
39 H.E. Holmquist, *J. Org. Chem.*, 34 (1969) 4164.
40 E.R.H. Jones, T.Y. Shen and M.C. Whiting, *J. Chem. Soc.*, (1950) 230.
41 C.W. Bird and E.M. Briggs, *J. Chem. Soc. C*, (1967) 1265.
42 G.P. Chiusoli, *Chim. Ind. (Milan)*, 41 (1959) 506.
43 G. Agnes and G.P. Chiusoli, *Chim. Ind. (Milan)*, 49 (1967) 465; 50 (1968) 194.
44 M. Foa, L. Cassar and M.T. Venturi, *Tetrahedron Lett.*, (1968) 1357.
45 R.F. Heck, *J. Amer. Chem. Soc.*, 86 (1964) 2819.
46 R.F. Heck, *J. Amer. Chem. Soc.*, 85 (1963) 1460.
47 H. Nienberg and G. Elschnig, *Ger. Pat.*, 1,066,572; *Chem. Abstr.*, 55 (1961) 10323.
48 W. Reppe, H. Kroper, H.J. Pistor and O. Weissbarth, *Justus Liebigs Am. Chem.*, 582 (1953) 87.
49 Y. Iwashita and M. Sakuraba, *J. Org. Chem.*, 35 (1970) 3927).
50 J.C. Sauer, R.D. Cramer, V.A. Engelhardt, T.A. Ford, H.E. Holmquist and B.W. Howk, *J. Amer. Chem. Soc.*, 81 (1959) 3677.
51 G. Albanesi and M. Tovaglieri, *Chim. Ind. (Milan)*, 41 (1959) 189.
52 G. Albanesi, *Chim. Ind. (Milan)*, 46 (1964) 1169.
53 G. Albanesi, R. Farina and A. Taccioli, *Chim. Ind. (Milan)*, 48 (1966) 1151.
54 J.C. Sauer, B.W. Howk and R.T. Stiehl, *J. Amer. Chem. Soc.*, 81 (1959) 693.
55 H.W. Sternberg, J.G. Shukys, C.D. Donne, R. Markby, R.A. Fridel and I. Wender, *J. Amer. Chem. Soc.*, 81 (1959) 2339.
56 P. Pauson, private communication.
57 P. Pino, A. Miglierina and E. Pietra, *Gazz. Chim. Ital.*, 84 (1954) 443; H.W. Sternberg, J.G. Shukys, C.D. Donne, R. Markby, R.A. Friedel and I. Wender, *J. Amer. Chem. Soc.*, 81 (1959) 2339.
58 C.W. Bird and D.Y. Wong, *Tetrahedron Lett.*, 1970, 4433.
59 M. Jautelat and K. Ley, *Synthesis*, (1970) 593.
60 S. Murahashi, S. Horiie and T. Jo, *Nippon Kagaku Zasshi*, 79 (1958) 72.
61 S. Murahashi, S. Horiie and T. Jo, *Nippon Kagaku Zasshi*, 79 (1958) 75.
62 S. Murahashi and S. Horiie, *Annu. Report Sci. Works, Fac. Sci., Osaka Univ.*, 7 (1959) 89.
63 S. Horiie, *Nippon Kagaku Zasshi*, 80 (1959) 1043.
64 S. Murahashi, S. Horiie and T. Jo, *Bull. Chem. Soc. Jap.*, 33 (1960) 81.
65 S. Horiie and S. Murahashi, *Bull. Chem. Soc. Jap.*, 33 (1960) 247.
66 M.M. Bagga, P.L. Pauson, F.J. Preston and R.I. Reed, *Chem. Commun.*, (1965) 543.
67 A. Rosenthal and J. Gervay, *Can. J. Chem.*, 42 (1964) 1490.
68 A. Rosenthal, R.F. Astbury and A. Hubscher, *J. Org. Chem.*, 25 (1960) 1037.
69 A. Rosenthal, *Can. J. Chem.*, 38 (1960) 2025.
70 A. Rosenthal and M. Yalpani, *Can. J. Chem.*, 43 (1965) 711.
71 A. Rosenthal, *J. Org. Chem.*, 26 (1961) 1638.
72 A. Rosenthal and A. Hubscher, *J. Org. Chem.*, 25 (1960) 1562.
73 A. Rosenthal and J.P. O'Donnell, *Can. J. Chem.*, 38 (1960) 457.
74 A. Rosenthal and S. Millward, *Can. J. Chem.*, 42 (1964) 956.
75 A. Rosenthal and S. Millward, *Can. J. Chem.*, 41 (1963) 2504.
76 A. Rosenthal and M.R.S. Weir, *J. Org. Chem.*, 28 (1963) 3025.
77 A. Rosenthal and M.R.S. Weir, *Can. J. Chem.*, 40 (1962) 610.
78 A. Rosenthal and M. Yalpani, *Can. J. Chem.*, 43 (1965) 3449.
79 S. Murahashi and S. Horiie, *Bull. Chem. Soc. Jap.*, 33 (1960) 88.
80 W.W. Pritchard, *U.S. Pat.*, 2,769,003; *Chem. Abstr.*, 51 (1957) 7412.
81 J.E. Kmiecik, *J. Org. Chem.*, 30 (1965) 2014.

82 H. Takahashi and J. Tsuji, *J. Organometal. Chem.*, 10 (1967) 511.
83 (a) Y. Mori and J. Tsuji, *Tetrahedron*, 27 (1971) 3811.
(b) Y. Mori and J. Tsuji, *Tetrahedron*, 27 (1971) 4039.
84 E.H. Braye, C. Hoogzand, W. Hubel, U. Kruerke, R. Merenyi and E. Weiss, *Advances in the Chemistry of Coordination Compounds*, Proc. 6th Int. Conf. Coordn. Chem., Detroit, (1961) 190.
85 E.H. Braye and W. Hubel, *Chem. Ind. (London)*, (1959) 1250.
86 W. Hubel, ref. 3, p. 330–334.
87 E.H. Braye and W. Hubel, *J. Organometal. Chem.*, 3 (1965) 25.
88 E. Muller and E. Langer, *Tetrahedron Lett.*, (1970) 735.
89 E. Muller, R. Thomas, M. Sauerbier, E. Langer and D. Streichfuss, *Tetrahedron Lett.*, (1971) 521.
90 E. Yoshisato and S. Tsutsumi, *Chem. Commun.*, (1968) 33.
91 E. Yoshisato and S. Tsutsumi, *J. Amer. Chem. Soc.*, 90 (1968) 4488.