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SYNTHESIS OF HETEROCYCLES THROUGH NITRENES

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The reaction of triethyl phosphite with aromatic nitro compounds in which a nitrene intermediate was expected to intervene was investigated. Syntheses of certain indole derivatives, such as harman, pseudorutaecarpine, benz[a]-carbazole and β-carboline; and quinoline derivatives that are related to natural products are described in this review.

It is known that trivalent organophosphorous compounds, such as trialkyl phosphites and phosphines (X_3P) react with many oxygen containing compounds to give pentavalent phosphates.[1]

$$X_3P + [O] \longrightarrow X_3P = O$$

In 1962, Cadogan and co-workers applied this reaction to nitro and nitroso compounds. They found that carbazole derivatives (2) were obtained from 2-nitroso- and 2-nitrobiphenyls (1) by refluxing with triethyl phosphite.[2,3,4]

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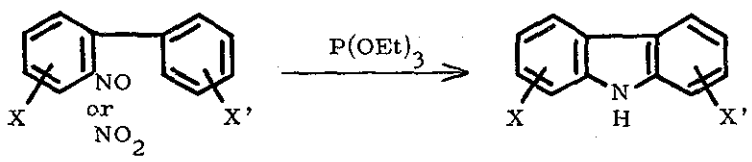
† On leave from Norwich Pharmacal Co., Div. of Morton-Norwich Products, Inc., U. S. A.



(1) (2)

X=X'=H, Cl, Br, Me or polymethyl

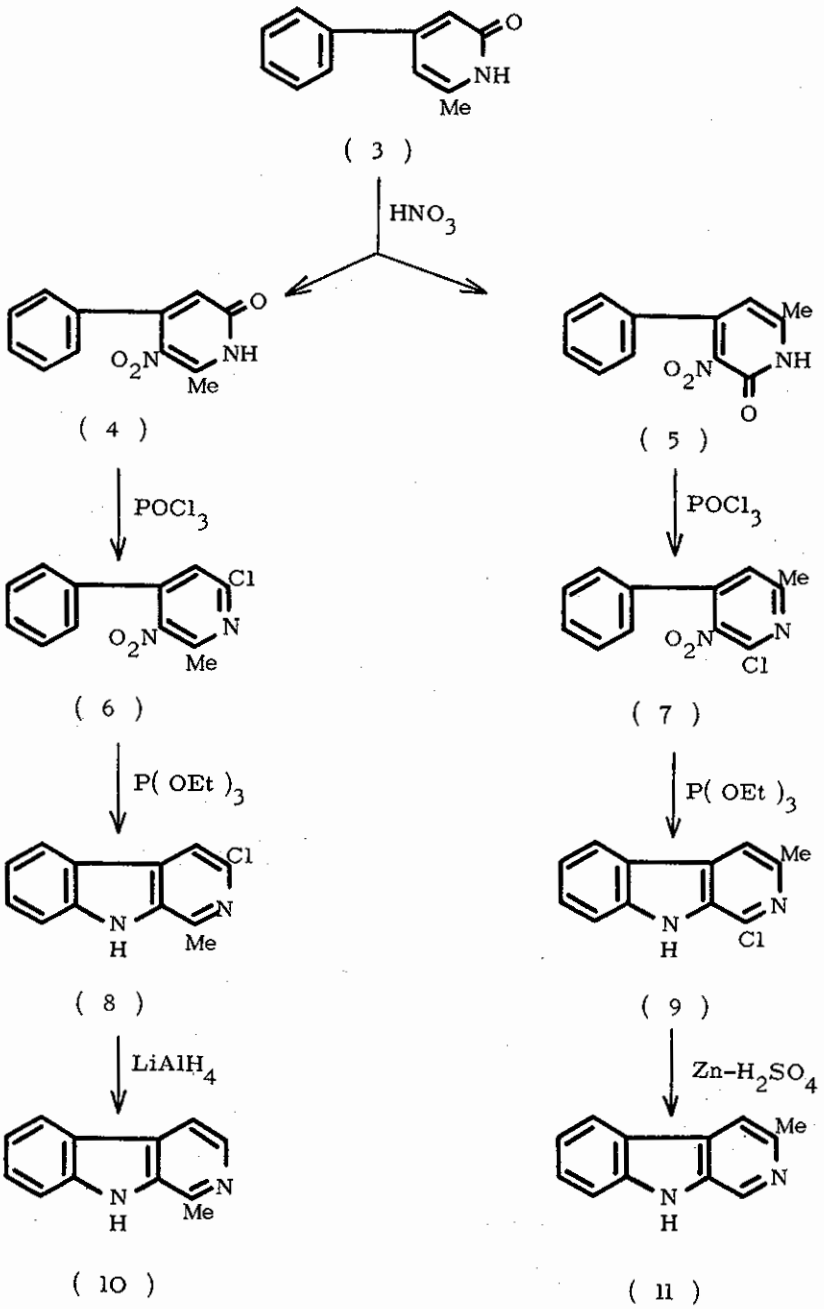
A characteristic of these reactions is the intermediacy of nitrene species.[5] The reactions of aromatic nitrenes by specific insertion, hydrogen-abstraction, ring expansion, addition to multiple bonds, bond formation with lone pair electrons and dimerization have led to a variety of nitrogen heterocycles.[5] However, Sundberg also proposed a non-nitrene mechanism involving an N-hydroxy intermediate for the triethyl phosphite reduction of some o-nitrostyrenes.[6]

This review covers our applications of the triethyl phosphite reduction to the synthesis of a number of naturally occurring nitrogen heterocycles, such as indoles, quinolines, carbolines, quinazolines and naphthyridines. The following results are classified into the types of aromatic nitro compounds reduced.

1. Pyridines

The application of the triethyl phosphite reduction to the synthesis of the simple alkaloid harman (10) from a nitropyridine derivative was described.[1] Nitration of 6-methyl-4-phenyl-2-pyridone (3),[8] gives a mixture of 5-nitro-(4) and 3-nitro-(5) pyridones. These compounds were difficult to separate; therefore, the mixture was treated with phosphorous oxychloride to give the chloro derivatives (6) and (7), respectively. Since these derivatives also were not easy to separate, a mixture was treated with triethyl phosphite to give only β-carboline (9), sterically

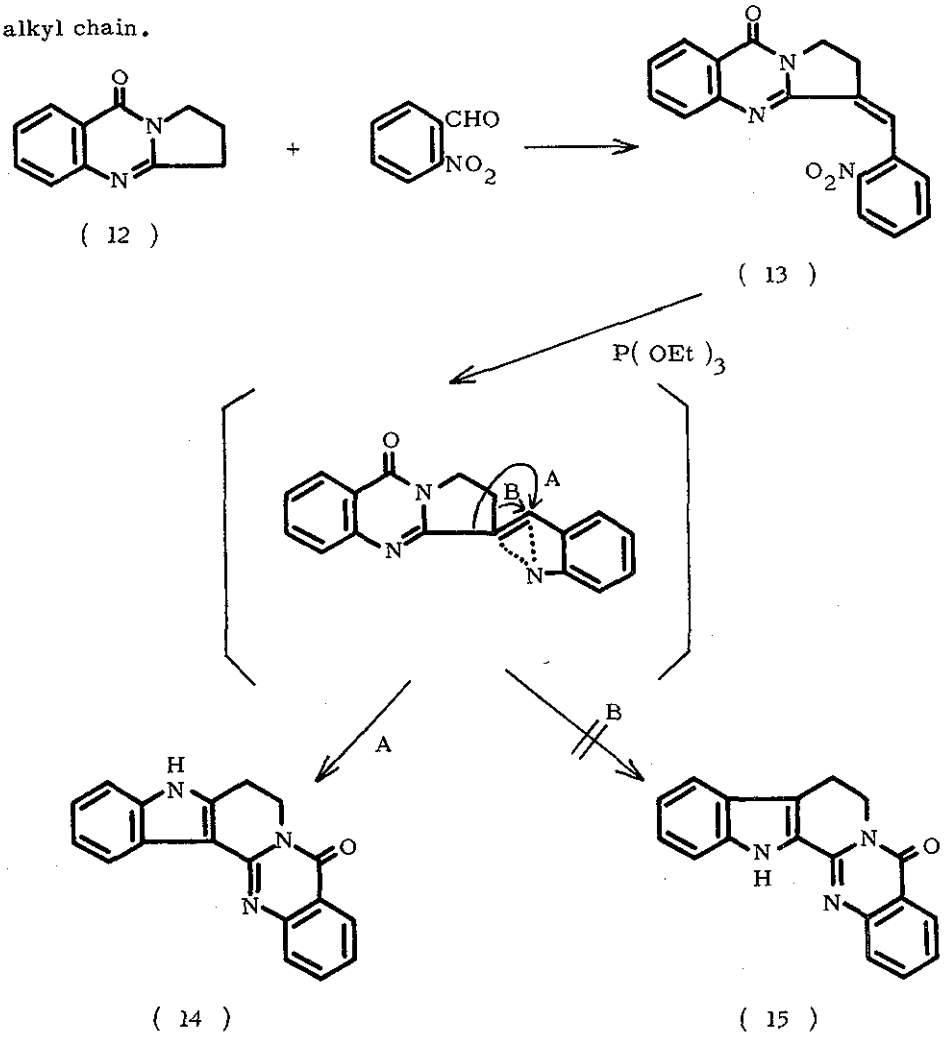
a more favored product because of the para situated methyl group. More drastic reaction conditions were necessary to give the expected 3-chloroharman (8).



Compounds (8) and (9) were then dehalogenated with lithium aluminum hydride and zinc and sulfuric acid[9] to give harman (10) and β-carboline derivative (11), respectively.

2. Styrenes

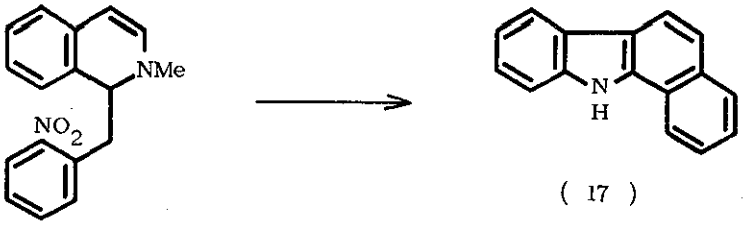
Synthesis of the natural product, rutaecarpine (15), from the o-nitrobenzal derivative (13) of desoxyvasicinone (12)[10] and triethyl phosphite was attempted.[11] However, only pseudorutaecarpine (14) is obtained through alkyl rearrangement (A), in preference to rearrangement (B) which involves a longer alkyl chain.



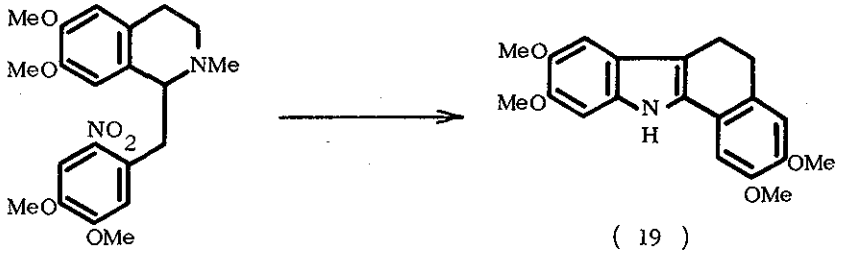
(12) (13) (14) (15)

3. Benzylisoquinolines

Reduction of 1-(2-nitrobenzyl)isoquinoline derivative (16) with triethyl phosphite produces benz[a]carbazole (17) by rearrangement and elimination.[12] It is interesting to note that this novel reaction involves the elimination of an N-methyl group and cyclization on an ortho-alkyl group. Although 6-nitrolaudanosine (18), which is a derivative of 1,2,3,4-tetrahydroisoquinoline, gives the corresponding 5,6-dihydrobenz[a]carbazole derivative (19), the quaternary salt (20) and the isoquinoline (22) afford only the amino (21) and azaberbinone (23) derivatives, respectively.[12] Structure (23) was proposed by Cava, Mitchell and Hill.[13] Though the mechanisms of these reactions are not explicable in detail,[14] the results indicate that: 1) the nitrogen atom at the 2-position should have an unshared pair of electrons, and 2) the reactant should be a 1,2-dihydro or a 1,2,3,4-tetrahydroisoquinoline derivative.



(16) (17)



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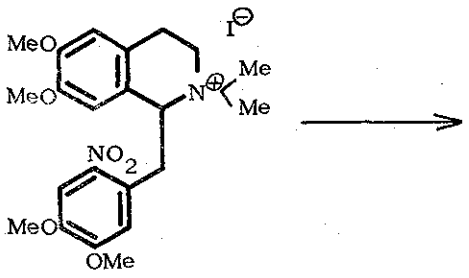

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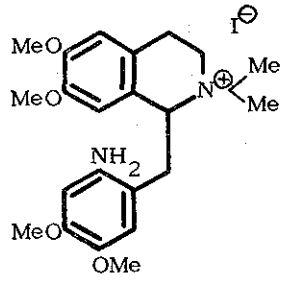

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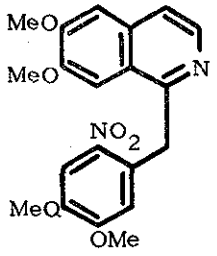

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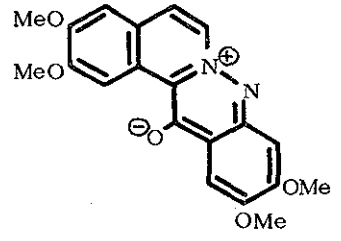
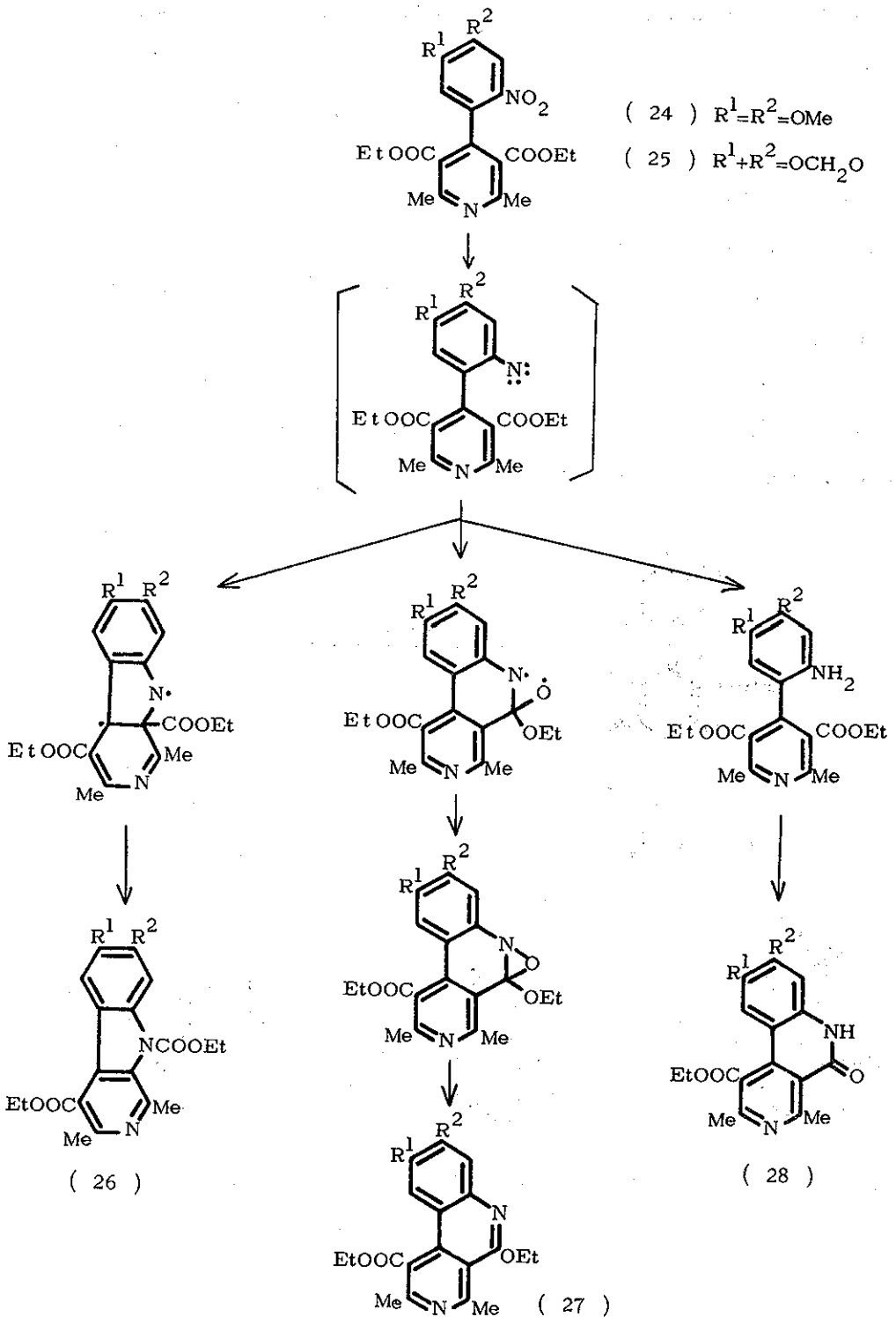


(23)

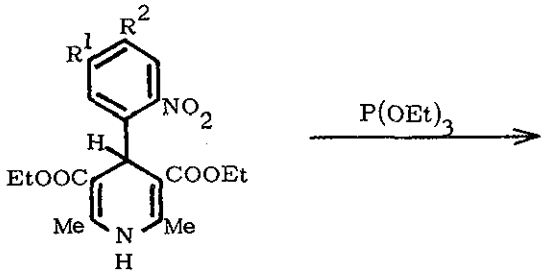
4. Phenylpyridinecarboxylates

Nitro-compounds which are substituted at the cyclizing position by carbonyl groups were also studied. Thus, reduction of 4-(o-nitrophenyl)poly-substituted pyridines (24) and (25) with triethyl phosphite affords β-carbolines (26) and benzo[c]naphthyridine derivatives (27) and (28).[15] These results indicate nitrene intermediates. Previously there had been no examples of nitrene insertion at an aromatic carbon-carbon bond α to a carbonyl group. Also the formation of (27) and (28) represents a novel method for synthesizing naphthyridine derivatives.


(24) R1=R2=OMe
(25) R1+R2=OCH2O
(26)
(27)
(28)

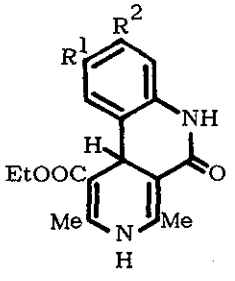
A similar reaction with the corresponding 1,4-dihydro-4-(o-nitrophenyl)poly-substituted pyridines (29) and (30) and triethyl phosphite was explored.[16] This reaction was not expected to proceed in the same manner, since pyridines (24) and (25) contain a nitro group in conjugation with and sterically adjacent to the position of cyclization; no such conjugation or steric relationship exists in the case of dihydropyridines (29) and (30).

Reduction of (29) and (30) gives a mixture of benzo[c][2,7]naphthyridines (31), β-carbolines (32) and indoles (33). As in the case of the pyridine derivatives, a mechanism involving a nitrene intermediate could account for the formation of the benzo[c][2,7]*naphthyridines* (31). *Non-nitrene reactions* probably lead to the formation of compounds (32) and (33).



(29) $R^1=R^2=OMe$

(30) $R^1+R^2=OCH_2O$



(31)

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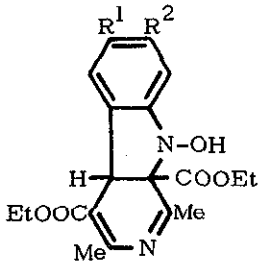

(32)

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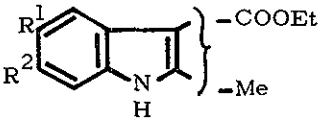
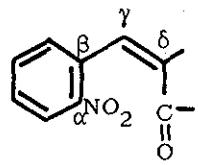


(33)

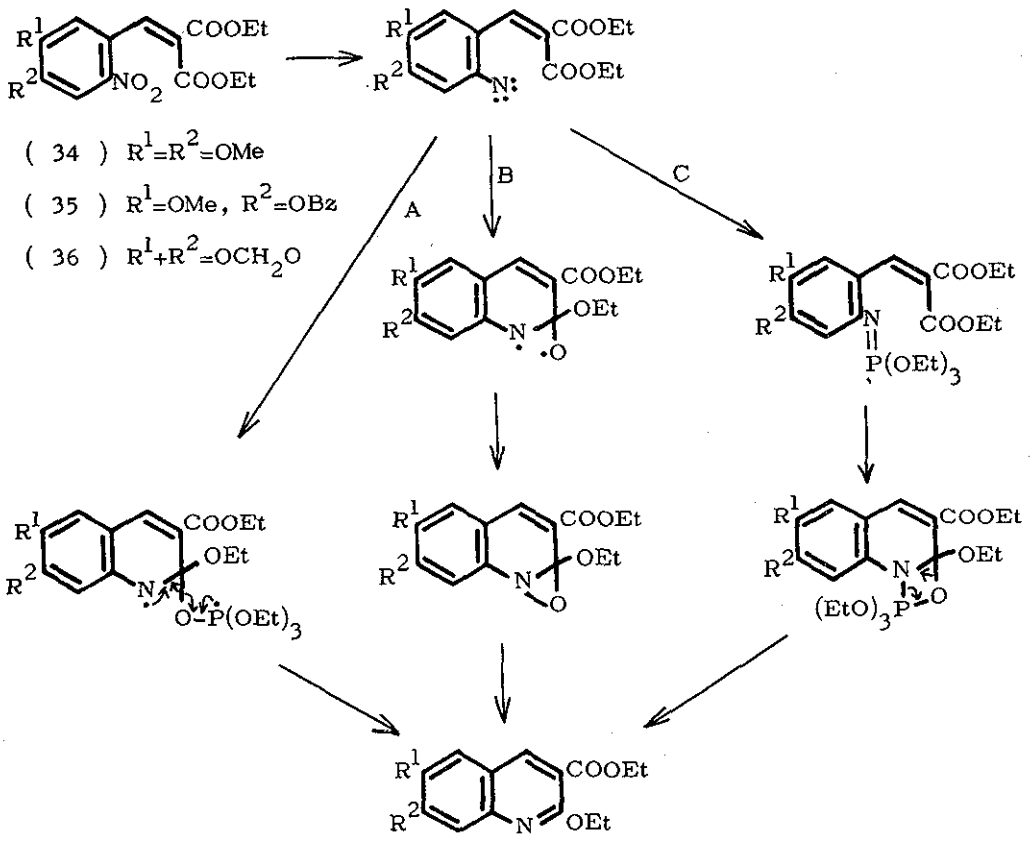
5. Benzylidene-carboxylates and Ketones

Sundberg and Yamazaki[17] reported that the reaction of β,β-disubstituted o-nitrostyrenes with triethyl phosphite produced rearranged indole derivatives, as was the case in our synthesis of pseudorutaecarpine (14). When one of the substituents is a carbonyl which is δ to a nitro group, as in the 4-(o-nitrophenyl) poly-substituted pyridines (24) and (25), the nitrene reacts with the carbonyl to form naphthyridines (27) and (28).



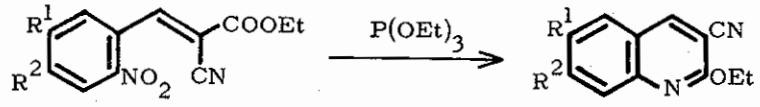
It was therefore of interest to examine other β,β-disubstituted o-nitrostyrenes containing at least one carbonyl substituent. When (o-nitrobenzylidene)malonates (34 - 36) are reduced with triethyl phosphite, quinolines (37) are obtained in good yields. These compounds may be produced through route (A), (B), or (C).[18]

Similarly, the reactions of triethyl phosphite and cyano(o-nitrobenzylidene)-acetates (38 - 40), so called Zabicky's ethyl cyanoacetates,[19] in which the o-nitrophenyl and carbonyl groups are in the trans-configuration, were examined. Unexpectedly, quinolines (41) are obtained in high yields.[20] In contrast, reduction of benzoylacetonitriles (42 - 44) with triethyl phosphite gives quinoline derivatives (45) in poor yields.[20]



(37)

In these reactions, compounds in which the nitro and carbonyl groups are trans presumably react with triethyl phosphite through "free rotation of the double bond" to give quinolines. Hindrance of free rotation because of the bulky benzoyl *group may* account for the low yields of (45).

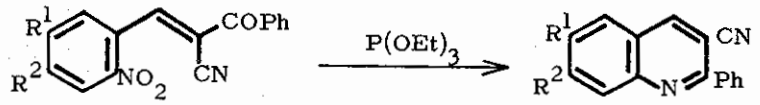


(38) $R^1=R^2=OMe$

(39) $R^1+R^2=OCH_2O$

(40) $R^1=OMe$, $R^2=OBz$

(41)

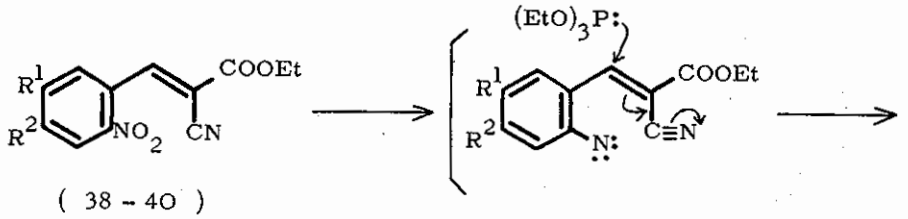


(42) $R^1=R^2=OMe$

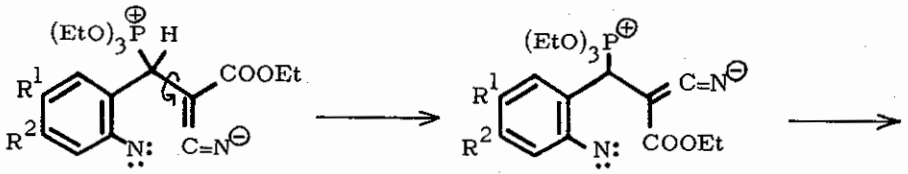
(43) $R^1+R^2=OCH_2O$

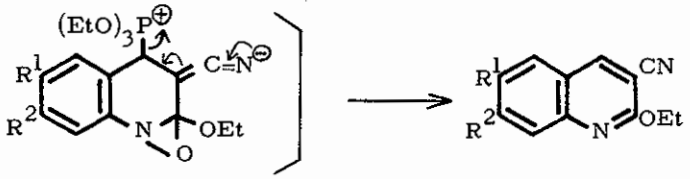
(44) $R^1=OMe$, $R^2=OBz$

(45)



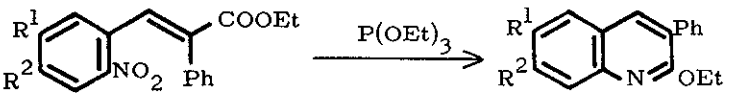
(38 - 40)





(41)

Reduction of ethyl trans-α-phenylcinnamates (46 - 49) (trans conformation of the nitro and carbonyl groups[21,22]) affords quinolines (50) and (52) and indoles (51).[23] In this case, the reaction may proceed not only through "free rotation of the double bond", but also by normal insertion of a nitrene into the π-bond, which is general for β,β-disubstituted o-nitrostyrenes.



(46) $R^1=R^2=OMe$

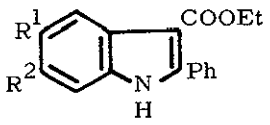
(47) $R^1+R^2=OCH_2O$

(48) $R^1=OMe$, $R^2=OBz$

(49) $R^1=R^2=H$

(50)

+



(51)

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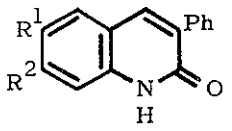
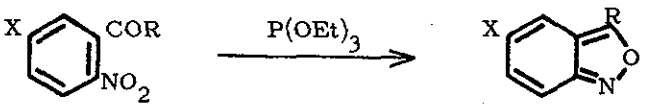


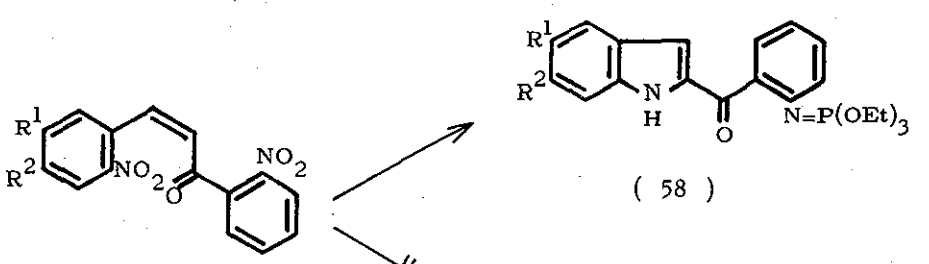
(52)

Cadogan and co-workers[24] obtained anthranils (2,1-benzisoxazoles) (54) from 2-nitrophenyl ketones (53):



(53) R=Ph, X=H; R=Me, X=Cl; R=PhCH=CH, X=H (54)

When this reaction was extended to 2,2'-dinitrochalcone derivatives (55 - 57), only 2-(2-triethylphosphorimidobenzoyl)indoles (58) are produced, instead of the expected quindolines (59) or indolylanthranils.[25]



(55) $R^1=R^2=H$

(56) $R^1=R^2=OMe$

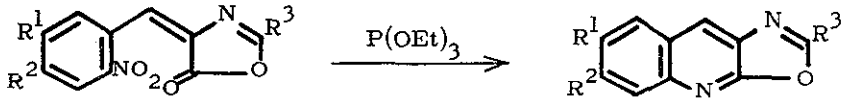
(57) $R^1+R^2=OCH_2O$

(58)

(59)

6. Benzylidene- and Benzoyllactones

When the carbonyl moiety is part of a cyclic grouping, reductive cyclization also takes place. Thus, the reaction of triethyl phosphite with benzylidene-oxazolone derivatives (60 - 63),[26,27] in which the phenyl and carbonyl group are cis, produces oxazoloquinolines (64) in good yields.[28]



(60) R^1=R^2=OMe, R^3=Ph

(61) R^1=R^2=OMe, R^3=Me

(62) R^1+R^2=OCH_2O, R^3=Ph

(63) R^1+R^2=OCH_2O, R^3=Me

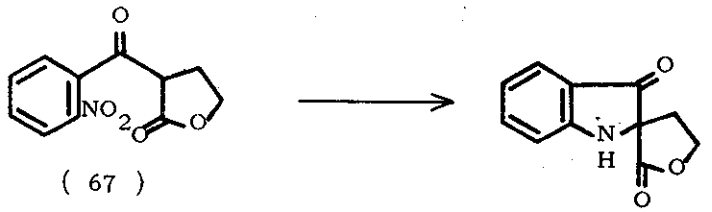
(64)

Reductive cyclization of α-(α-methoxy-o-nitrobenzylidene)butyrolactone (65) with triethyl phosphite, on the other hand, does not give the furoquinoline, dihydrodictamnine, but affords only the new heterocycle 3,4-dihydro-5-methoxy[1,3]-oxazino[3,4-a]indol-1-one (66).[29] This reaction probably proceeds through a nitrene intermediate with subsequent rearrangement.

(65)

(66)

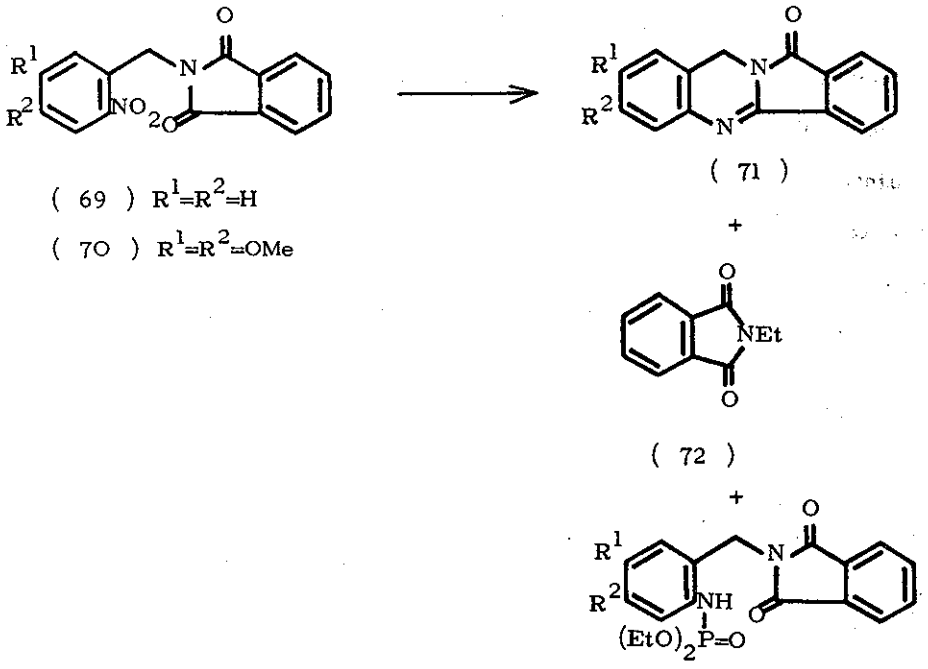
Rearrangement, coupled with O-ethylation, also occurs on reaction of triethylphosphite with α-(o-nitrobenzoyl)butyrolactone (67) to give the O-ethyl analogue of (66).[29] In addition, the major product is the spiro-indolinone (68), presumably formed by direct nitrene insertion at the α-position of the lactone.



(67) (68)

7. Benzylcarboxylic Acid Imides

The reaction of triethyl phosphite with N-(o-nitrobenzyl)phthalimides (69,70)[30] gives quinazolines (71) through reductive cyclization in addition to N-ethylphthalimide (72) and phosphoramidates (73).[31]



(69) $R^1=R^2=H$

(70) $R^1=R^2=OMe$

(71) + (72) + (73)

In analogy to (71) and (73), the corresponding quinazolines (76) and phosphoramidates (77)[32] are obtained in refluxing triethyl phosphite from N-(o-nitrobenzyl)-succimides (74,75).[30] In these reactions nitrene intermediates were suggested to participate by insertion into the imidocarbonyl group.

(74) $R^1=R^2=H$

(75) $R^1=R^2=OMe$

(76) + (77)

The results of these studies further illustrate the broad applicability of the triethyl phosphite reductive process, and the diverse nature of products that are obtainable. We have succeeded in utilizing this reaction for the synthesis of a variety of naturally occurring nitrogen heterocyclic systems, and we are continuing to explore other related synthetic applications.

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