"point" in stability between the square pyramid and trigonal bipyramid. Such a member would be expected to have a most rapid exchange rate, perhaps high enough to allow quantum mechanical tunneling to become a significant process. Observance of the resultant spectroscopic splittings would then provide the necessary evidence to distinguish critically among exchange pathways.[74]

*The National Science Foundation is thanked for support of work described in this review. I am very happy to acknowledge the valuable contributions of colleagues, past and present, in these studies.*

(74) B. J. Dalton, *J. Chem. Phys.*, **54**, 4745 (1971), has detailed the effect of a rapid Berry process on rotational levels.

# A New Series of Nitrene-Induced Aromatic Rearrangements

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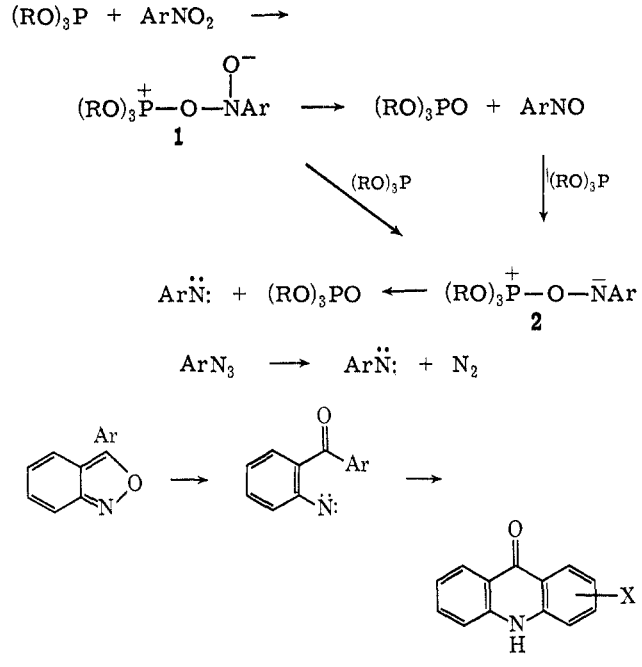
This Account describes a new series of rearrangements, induced by aryl nitrenes or their precursors, leading to a wide variety of nitrogen-containing heterocyclic compounds. Aryl nitrenes may be produced by the phosphite reduction of nitro compounds[1,2] (Scheme I) and by photolysis and thermolysis of aryl azides.[3]

**Scheme I**




More recently the long known, but less familiar, anthranil–acridone transformation[4] (Scheme I) has come to be regarded in terms of nitrene participation.[5,6]

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The first two routes, particularly, have been used to synthesize a wide variety of heterocyclic compounds,[2,3] the methods working best when a resulting five-membered nitrogen-containing ring was possible. An exception to this was the successful conversion of aryl 2-nitrenoaryl sulfides into the six-membered phenothiazines (Scheme II), and it was assumed that

**Scheme II**


X = $N_3$ at 180° or $NO_2$, $(C_2H_5O)_3P$ at 150°

this involved direct insertion at the ortho position in the receiving ring. During investigations of this reaction carried out simultaneously in the United Kingdom and France it became clear that the latter reaction, in fact, proceeded *via* rearrangement. Close on the heels of this it was found that the anthranil–acridone transformation (Scheme II) also proceeded with rearrangement.[6] Hence within the space of only 6 weeks in 1968, three independent reports of a new nitrene-induced rearrangement had appeared. Many further examples and extensions of the rearrangement have since been reported.

As will be seen below, it is possible to generalize the reaction as in Scheme III wherein the nitrene **3** or its precursor may react *via* a five-membered spirodienyl intermediate (**4**) which regains aromaticity, by various pathways depending on the nature of the bridging

(1) (a) J. I. G. Cadogan and M. Cameron-Wood, *Proc. Chem. Soc., London*, 361 (1962); (b) P. J. Bunyan and J. I. G. Cadogan, *ibid.*, 78 (1962).

(2) (a) J. I. G. Cadogan, *Quart. Rev., Chem. Soc.*, **22**, 222 (1968); (b) *Synthesis*, **1**, 11 (1969).

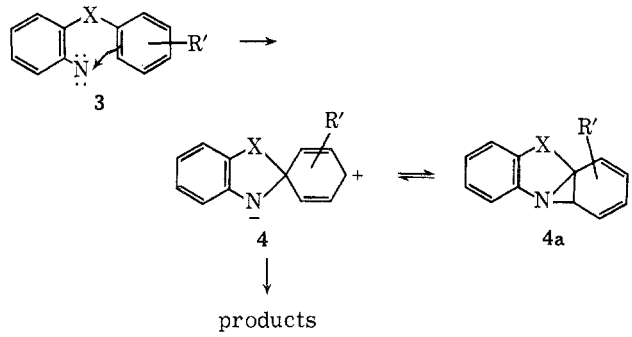
(3) P. A. S. Smith in "Nitrenes," W. Lwowski, Ed., Wiley, New York, N. Y., 1970, p 99.

(4) A. Kliegl, *Ber.*, **42**, 591 (1909).

(5) P. L. Coe, A. T. Jukes, and J. C. Tatlow, *J. Chem. Soc. C*, 2020 (1966).

(6) R. Kwok and P. Pranc, *J. Org. Chem.*, **33**, 2880 (1968).

**Scheme III**



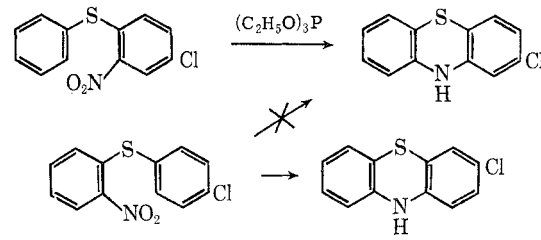

atom, X, to give products. It should be noted that the reactions can also be depicted in terms of the very much more strained azanorcaradiene **4a**, derived from **4**. We adhere to **4** for simplicity of discussion, although there is no direct evidence for either form. In general, also for simplicity, we refer to the intermediacy of discrete nitrenes, although sometimes it is not possible to exclude nitrene precursors, *e.g.*, **1** or **2** (Scheme I), in the phosphite reaction or to discount the possibility of loss of nitrogen concerted with cyclization in the decomposition of azides.

Since 1968, work has continued apace and systems **3** (Scheme III) where the bridging atom X is S, O, *N*-acyl, $CH_2$, $SO_2$, and CO have been shown to rearrange to give phenothiazines, thiazepines, phenoxazines, oxazepines, dihydrophenazines, indoloazepines, acridones, and related ring systems. Moreover, new routes to trigonally bipyramidal heterocyclic aminophosphoranes have arisen as a result of these investigations.

## Rearrangements in Sulfur-Bridged Compounds (3, X = S)

**The Phenothiazine Rearrangement.** The medicinally important phenothiazine nucleus can be obtained by the long-known decomposition of 2-azidoaryl aryl sulfides[7] or by triethyl phosphite deoxygenation of the more easily obtained 2-nitroaryl aryl sulfides (Scheme II).[8] Both reactions were presumed to proceed *via* a six-membered intermediate formed by direct attack at a position ortho to the sulfide link. Closer examination of substituent effects, however, revealed that this was not so, and the first example of the molecular rearrangement, now reviewed, came to light.[9] Thus, whereas 4-chloro-2-nitrophenyl phenyl sulfide gave the expected 2-chlorophenothiazine, the isomeric 2-nitrophenyl 4-chlorophenyl sulfide did not, giving instead 3-chlorophenothiazine (Scheme IV). Similar behavior was exhibited with other substituents ($CF_3$, $CH_3$, $t$-$C_4H_9$) and also in thermolysis of the corresponding 2-azidophenyl aryl sulfides.[9] A few weeks after the publication of these results,[9a] Messer and Farge reported[10] the same

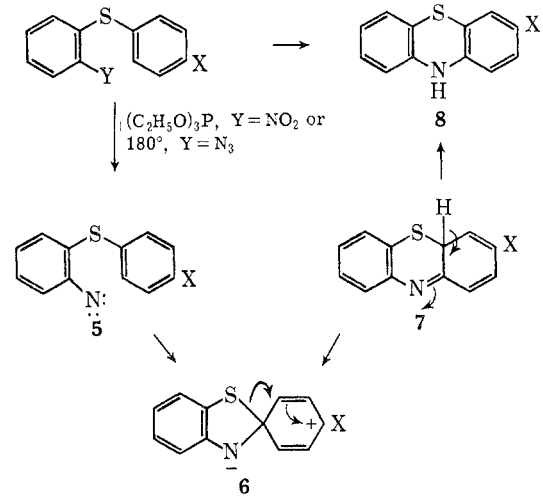
**Scheme IV**




rearrangement during a study of the synthesis of phenothiazines *via* decomposition of azides.

These results point to the mechanism outlined in Scheme V whereby a first-formed nitrene (**5**) attacks

**Scheme V**




X = $CF_3$, Cl, $CH_3O$, $CH_3$, $t$-$C_4H_9$, D

the 1′ position to give a spirodiene intermediate (**6**) which then undergoes sigmatropic followed by prototropic shifts to give the observed "rearranged" 3-substituted phenothiazine. Thus the initial cyclization conforms with the general pattern of cyclizations observed previously[2] in that a five-membered heterocyclic ring containing nitrogen is first formed, before rearrangement, in this case, to the six-membered ring. A similar rearrangement is also evident in the case of the corresponding 2-substituted derivatives.[10,11]

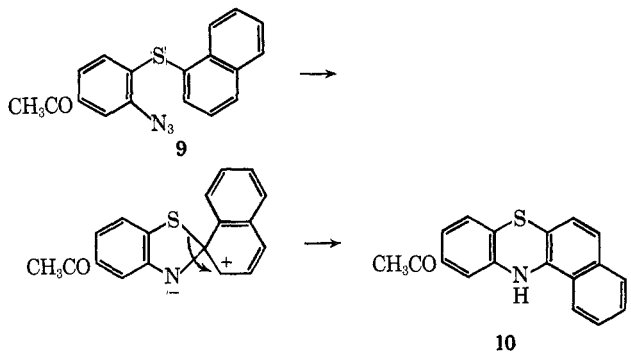
Clearly, the phenothiazine rearrangement is detectable only in those cases where the ring undergoing attack by the nitrene is substituted. A convincing demonstration that the rearrangement occurs in all cases was provided by the conversion of [4-$^2$H]phenyl 2-nitrophenyl sulfide by triethyl phosphite into the resulting *rearranged* deuteriophenothiazine (Scheme V; **8**, X = D). The question of the identity of the latter (3-$^2$H if rearrangement had occurred, 2-$^2$H if it had not) was resolved by the esr spectrum of the cation radical produced on dissolution in sulfuric acid.[9b,12] Thus Scheme V obtains even in the unsubstituted case.

The reaction is more complicated in cases involving cyclization onto the naphthalene nucleus, however.[13]

(7) B. B. Brown, R. K. Putney, R. F. Reinisch, and P. A. S. Smith, *J. Amer. Chem. Soc.*, **75**, 6335 (1953).
(8) J. I. G. Cadogan, R. K. Mackie, and M. J. Todd, *Chem. Commun.*, 491 (1966).
(9) (a) J. I. G. Cadogan, S. Kulik, and M. J. Todd, *ibid.*, 736 (1968); (b) J. I. G. Cadogan, S. Kulik, C. Thomson, and M. J. Todd, *J. Chem. Soc. C*, 2437 (1970).
(10) M. Messer and D. Farge, *Bull. Soc. Chim. Fr.*, 2832 (1968).
(11) J. I. G. Cadogan and S. Kulik, *J. Chem. Soc. C*, 2621 (1971).
(12) J. I. G. Cadogan, S. Kulik, and C. Thomson, *Chem. Commun.*, 436 (1970).
(13) M. Messer and D. Farge, *Bull. Soc. Chim. Fr.*, 4955 (1969).

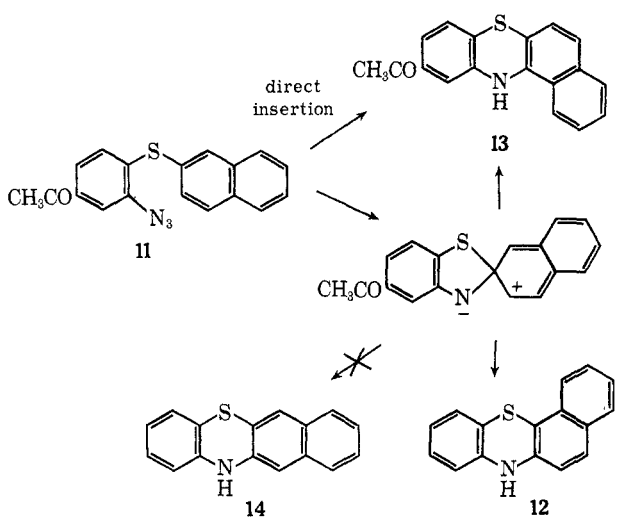
Thus, thermolysis of 2-azido-4-acetylphenyl 1-naphthyl sulfide (**9**) and deoxygenation of the 2-nitro analog proceed solely *via* rearrangement to give 2-acetylbenzo[*a*]phenothiazine (**10**; Scheme VI), but the isomeric

**Scheme VI**



2-azido-4-acetylphenyl 2-naphthyl sulfide (**11**) gives a mixture of the "rearranged" benzophenothiazine (**12**) and the unrearranged isomer (**13**): the other possible product (**14**) derived from the spirodiene was not detected (Scheme VII). Whether the unrearranged

**Scheme VII**

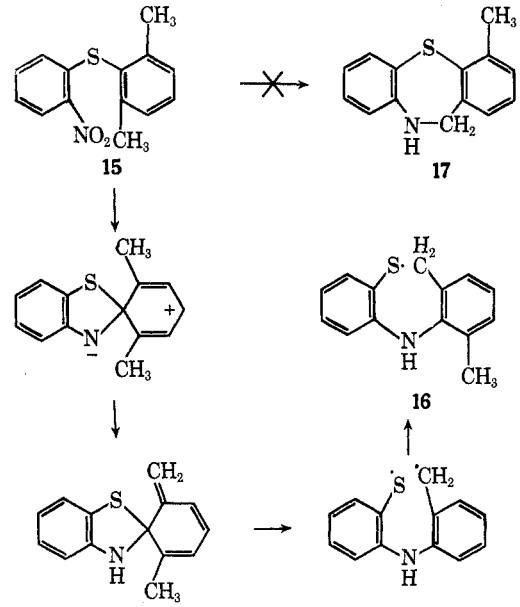


product (**13**) arises from direct insertion *via* a six-membered intermediate or *via* a competitive 1,2-nitrogen shift is open to question.

**The "Blocked-Ortho" Effect in the Phenothiazine Rearrangement.** The mechanism postulated (Scheme V) for rearrangement of simple 2- and 4-substituted aryl 2-nitrenoaryl sulfides requires the intermediacy of the hydroaromatic species **7**, which can easily tautomerize as a result of the bridgehead hydrogen atom originally ortho to the sulfur link. It was not surprising, therefore, that a series of intriguing new molecular rearrangements arose when both ortho positions in the starting sulfide were blocked.[11]

Thus, 2,6-dimethylphenyl 2-nitrophenyl sulfide (**15**; Scheme VIII) gave 5,11-dihydro-4-methyldibenzo[*b*,*e*][1,4]thiazepine (**16**) rather than the isomeric 10,11-dihydro-4-methyldibenzo[*b*,*f*][1,4]thiazepine (**17**) which might have been expected to be formed by nitrene insertion into one of the side-chain C–H bonds.[11] The

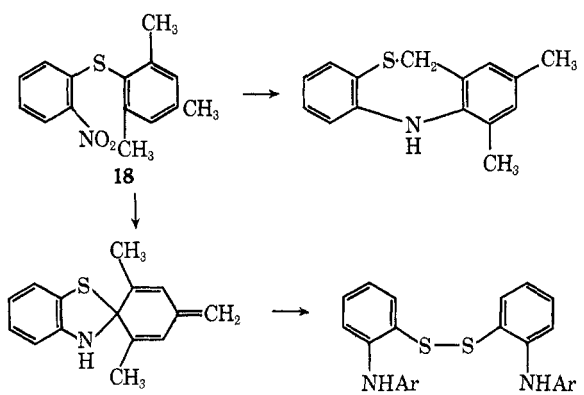
**Scheme VIII**



formation of this product is rationalized in terms of a spirodiene intermediate also, which reacts *via* a diradical recombination rather than by 1,3-suprafacial sigmatropic shift of sulfur, which is thermally forbidden unless participation of the d orbitals of sulfur is invoked.[14]

In accord with this, the related 2,4,6-trimethyl derivative **18** (Scheme IX), which can now present both

**Scheme IX**



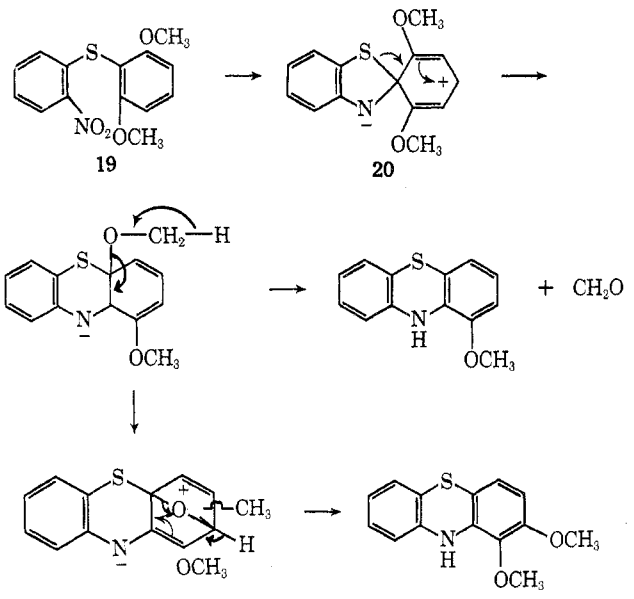
Ar = 2,4,6-$(CH_3)_3C_6H_2$

a *p*- as well as an *o*-benzyl-type radical, gave, in addition to the thiazepine, a disulfide derived by dimerization of a canonical form of the *p*-benzyl radical, which cannot ring-close to give a thiazepine.[11] Similar reactions occurred in the case of the corresponding azides.

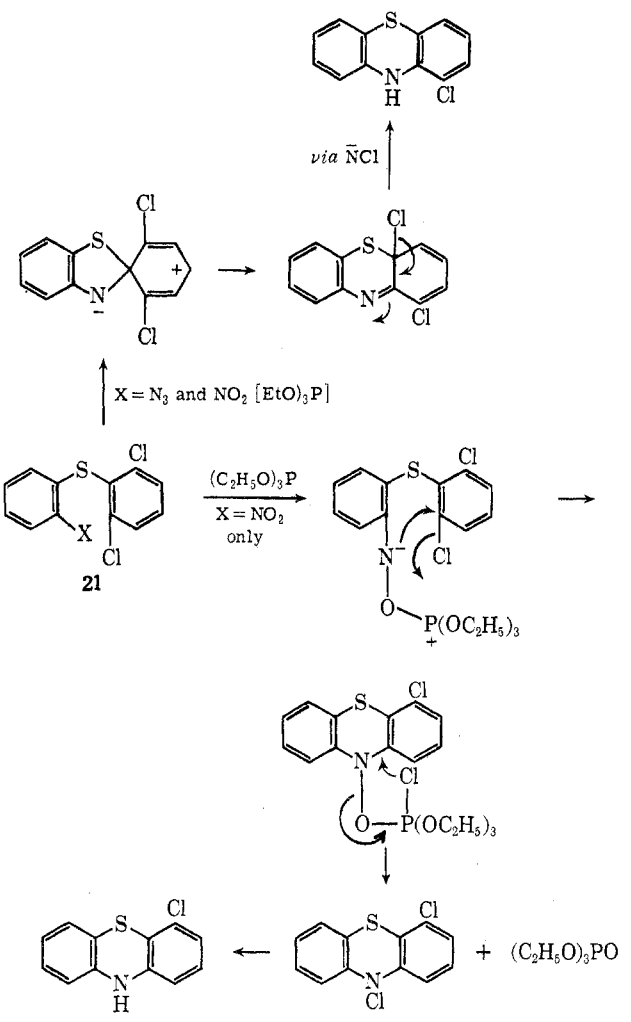
Deoxygenation of 2,6-dimethoxyphenyl 2-nitrophenyl sulfide (**19**) gave equally interesting results (Scheme X).[11] Thus 1-methoxyphenothiazine and 1,2-dimethoxyphenothiazine were obtained. Here again the results can be rationalized in terms of formation of the spirodiene intermediate **20**, which in this case undergoes a 1,2-sigmatropic shift to give a nonaromatic ring, which is stabilized by either demethoxylation to

(14) J. Kwart and W. Johnson, *J. Amer. Chem. Soc.*, 92, 6064 (1970).

**Scheme X**



**Scheme XI**



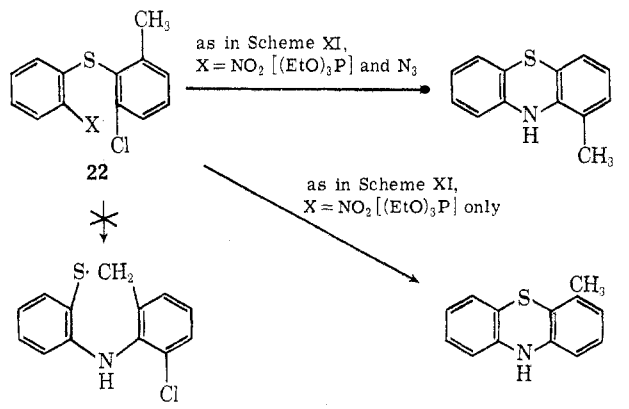
give 1-methoxyphenothiazine and formaldehyde (a corresponding amount of this was subsequently sought and found) or by the novel transmethoxylation shown in Scheme X. Similar reactions occur in the case of the corresponding azides.

2,6-Dichlorophenyl 2-nitrophenyl sulfide (**21**, X = $NO_2$) displays still different behavior,[11] and this is the only case so far discovered in this series which proceeds differently in the cases of the nitro compound and the corresponding azide. The azide **21** (X = $N_3$) gave mainly 1-chlorophenothiazine (40%), with a trace of 4-chlorophenothiazine (5%). The formation of the 1-chloro isomer can be rationalized in terms of the intermediacy of the spiorodiene followed by sigmatropic 1,2-sulfur shift followed by rearomatization involving loss of $Cl^+$. This would give the *N*-chloro-1-chlorophenothiazine which would lose the *N*-chlorine under the conditions of the experiment (Scheme XI). The small amount of 4-chloro derivative formed can arise either by direct insertion *via* a six-membered intermediate or *via* 1,2-sigmatropic shift of *nitrogen* rather than sulfur in the spirodiene; both of these alternatives might be favored by the relatively low electron density induced by the two nuclear chlorine atoms.

The case of the corresponding 2-nitrophenyl 2,6-dichlorophenyl sulfide is quite different (Scheme XI). Deoxygenation (at the same temperature as thermolysis of the corresponding azide) gave 4-chlorophenothiazine as the major product (52%), together with the 1-chloro isomer (37%). This clearly points to the participation of a different intermediate. In this case this could reasonably be the precursor of the nitrene $ArN^-OP^+R_3$, which, due to steric crowding and proximity to the activated nuclear chlorine atom (Scheme XI), could cyclize before loss of triethyl phosphate, as shown. This would lead to, predominantly, the 4 isomer, as observed, the 1 isomer arising *via* competitive formation and reaction of the nitrene.

In the case of 2-chloro-6-methylphenyl 2-nitro- and 2-azidophenyl sulfides (**22**, X = $NO_2$ or $N_3$), the route to the thiazepine is not favored, and in accord with the case of the 2,6-dichloro analogs the azide **22** (X = $N_3$) gave 1-methylphenothiazine (32%) while the nitro compound **22** (X = $NO_2$) gave 1-methyl- (20%) and 4-methyl- (30%) phenothiazine (Scheme XII).[11]

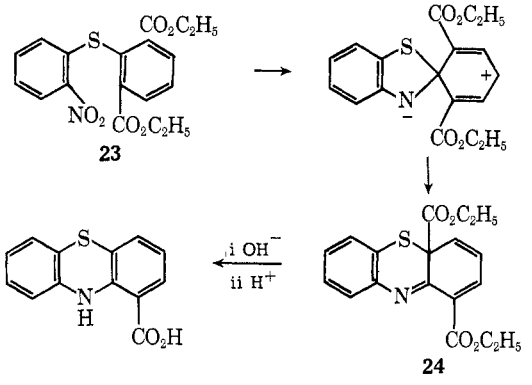
**Scheme XII**



2,6-Dicarbethoxyphenyl 2-nitrophenyl sulfide (**23**) gave perhaps the most interesting result of all.[11] Deoxygenation gave 1,4a-dicarbethoxy-4a*H*-phenothiazine (**24**) which corresponds to the nonaromatic intermediate postulated in many of the above rear-

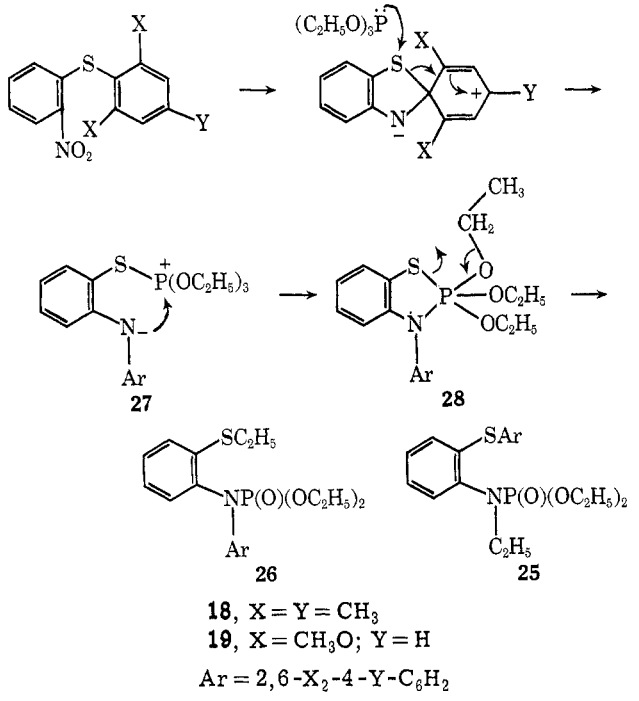
rangements. This product, which is dark violet in color as a result of its extended conjugated chromophore, was converted into 1-carbethoxyphenothiazine on treatment with hydrochloric acid. The proposed mechanism of its formation follows the general pattern and is given in Scheme XIII.

**Scheme XIII**



**Formation of Thioaminophosphorane-Derived Products.** Phosphoramidates are frequently formed as by-products in the phosphite–nitro group reaction,[2] and compounds originally formulated[11] as diethyl *N*-ethylphosphoramidates (**25**; Scheme XIV) were isolated in

**Scheme XIV**

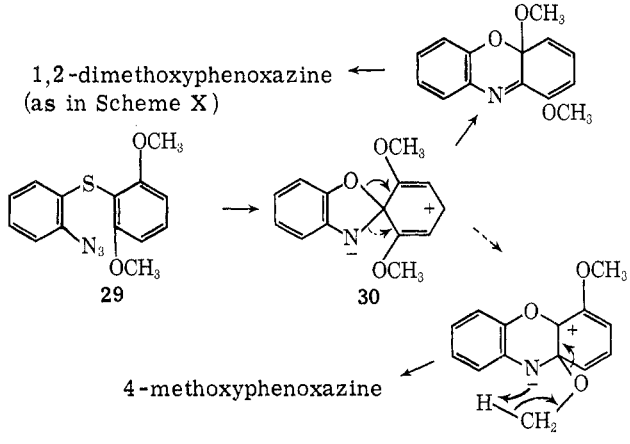


reactions involving triethyl phosphite and the nitro compounds **18** and **19**. The fact that these have been shown very recently[15] to be the isomeric *N*-arylphosphoramidates (**26**) has important mechanistic consequences, pointing again to the intermediacy of a spirodiene. In this case it can gain aromaticity by undergoing attack by phosphite to give **27** and hence the thioaminophosphorane **28** and then **26**. In Scheme XIV this is shown as intramolecular, but despite the, at first sight, attractive steric situation arising from trigonal-bipyramidal geometry it is more likely to be an intermolecular transalkylation, for which there is precedent,[16] due to the difficulty of linear alignment of the O–C–S centers. Support for this postulate, as we shall see below, arose in the investigation of the corresponding ethers, when the analogous aminotetroxyphosphorane, which has no tendency for rearrangement, was actually isolated as a crystalline product.

## Rearrangements in Oxygen-Bridged Compounds (3, X = O)

**Formation of Phenoxazines, Dibenzoxazepines, and Amidophosphoranes.** An early attempt to extend the phenothiazine synthesis to phenoxazines, by thermolysis of 2-azidophenyl phenyl ether, failed:[7] the product was a black tar, as was that from the attempted cyclizations of 2-phenoxy-3-nitropyridine[17] and 2-azidophenyl 4-methoxyphenyl ether.[15] Application of the blocked-ortho effect led to isolable products, however. Thus 2-azidophenyl 2,6-dimethoxyphenyl ether (**29**) gave 4-methoxyphenoxazine (35%) and 1,2-dimethoxyphenoxazine (15%).[18] It is noteworthy that, while the corresponding sulfide behaved similarly in giving 1,2-dimethoxyphenothiazine (Scheme X), it gave 1- rather than 4-methoxyphenothiazine. This is in accord with the expected higher migratory aptitude of sulfur over nitrogen in the intermediate **20** in Scheme X, whereas that of oxygen and nitrogen in **30** would be more nearly equal (Scheme XV).

**Scheme XV**



Thermolysis of 2-azidophenyl 2,4,6-trimethylphenyl ether (**31**, X = $N_3$) proceeded as expected, by analogy with the corresponding sulfide (**18**, Scheme IX), to give 5,11-dihydro-2,4-dimethyldibenzo[*b*,*e*][1,4]oxazepine (**32**; 15%),[17] but phosphite deoxygenation of 2-nitrophenyl 2,4,6-trimethylphenyl ether (**31**, X = $NO_2$) proved to be far more interesting, giving the penta-

(15) J. I. G. Cadogan, D. S. B. Grace, P. Lim, and B. S. Tait, unpublished observations; *Chem. Commun.*, 520 (1972).

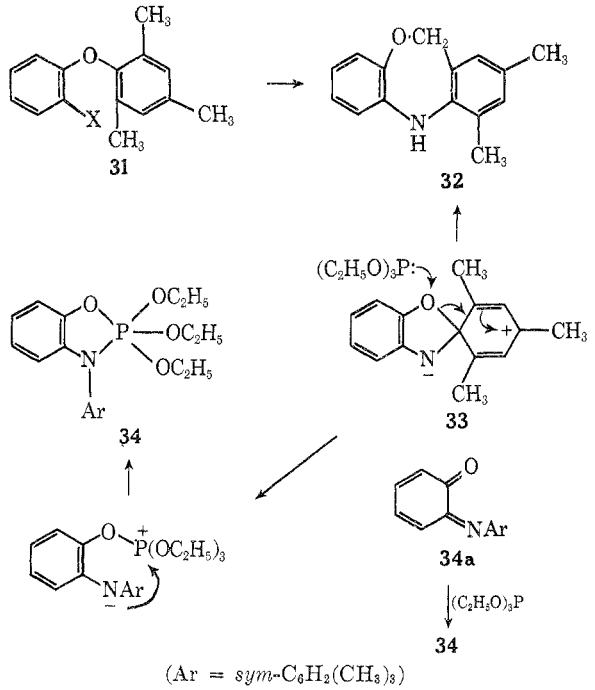
(16) A. J. Burn, J. I. G. Cadogan, and H. N. Moulden, *J. Chem. Soc.*, 5540 (1961).

(17) J. J. Eatough, L. S. Fuller, R. N. Good, and R. K. Smalley, *J. Chem. Soc. C*, 2437 (1970).

(18) J. I. G. Cadogan and P. Lim, *Chem. Commun.*, 1431 (1971).

covalent phosphorus containing heterocycle **34** in greater than 50% yield,[15] in addition to the oxazepine. Clearly, in the presence of triethyl phosphite, the intermediate spirodiene **33** is able to aromatize either *via* attack of phosphite on the bridgehead oxygen, leading eventually to the aminotetroxyphosphorane (**34**) (Scheme XVI), or by formation of the *o*-quinone imine

**Scheme XVI**




(Ar = *sym*-$C_6H_2(CH_3)_3$)

**34a** and hence, by reaction with phosphite, to **34**.

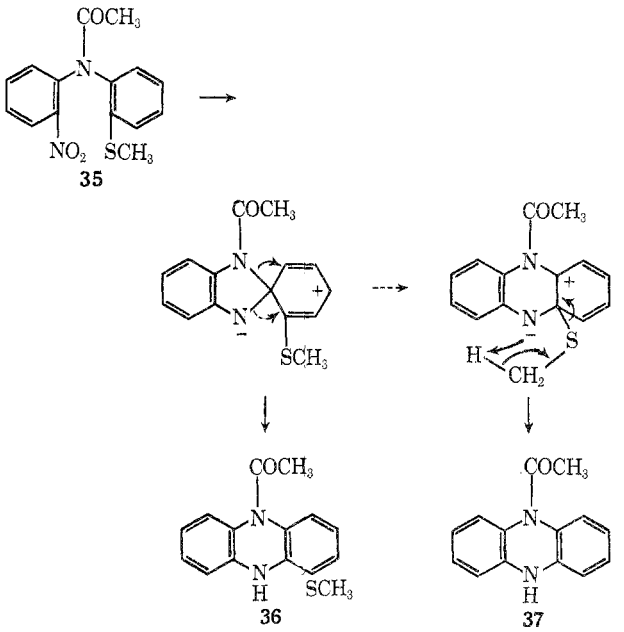
## Rearrangements in Nitrogen-Bridged Compounds (3, X = NR)

**Formation of Dihydrophenazines.** Recently[19] the phosphite–nitro group reaction has been extended to include the synthesis of dihydrophenazines. Thus *N*-acetyl-2-nitro-2′-methylthiodiphenylamine (**35**; Scheme XVII), in which the vulnerable bridgehead N–H is protected,[2] on reaction with triethyl phosphite gave 1-methylthio-5-acetyl-5,10-dihydrophenazine (**36**; 22%) and 5-acetyl-5,10-dihydrophenazine (**37**; 2%). The reaction therefore proceeds as would be expected on the basis of earlier work on related sulfur-bridged compounds (*e.g.*, **19**; Scheme X): rearrangement of the spirodienyl intermediate gave both possible hydroaromatic species, one of which undergoes demethylthiylation to give **37** while the other tautomerizes to give **36** (Scheme XVII).

## Rearrangements in Methylene-Bridged Compounds (3, X = $CH_2$)

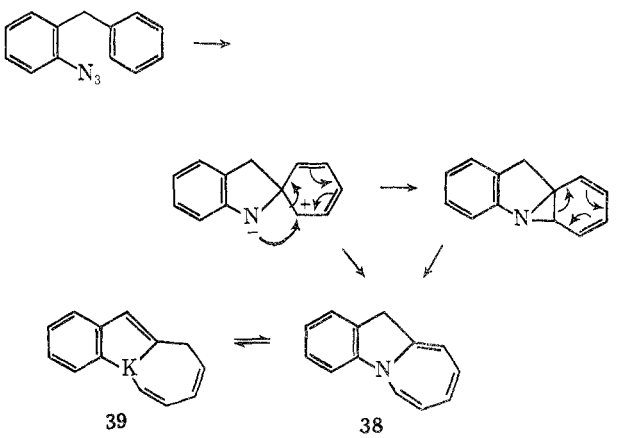
**Formation of Azepinoindoles.** Krbechek and Takimoto[20] formulated the product of thermolysis of 2-azido-

**Scheme XVII**




diphenylmethane as a 11*H*-azepinoindole (**38**), although this was later amended to the isomeric 10*H* derivative **39**[21] (Scheme XVIII). The reaction has been shown to

**Scheme XVIII**



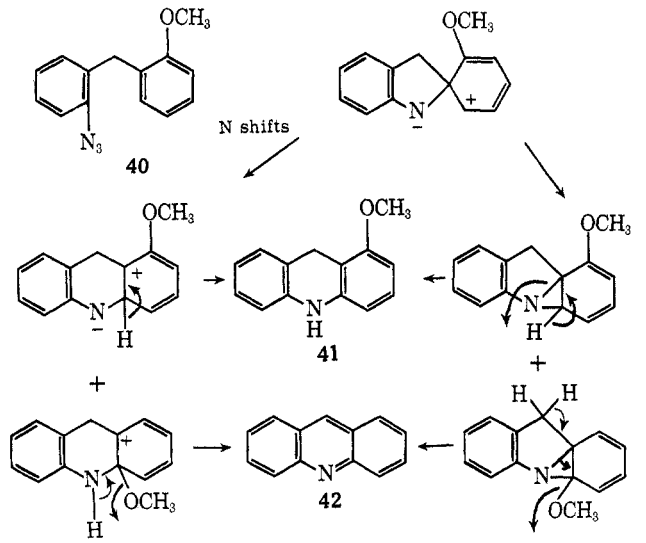

have some generality.[22]

The case of *o*-(2-methoxybenzyl)phenyl azide (**50**) is complicated in that eleven products are formed, the major ones being 1-methoxyacridan (**41**; 26%), acridan (10%), 1-methoxyacridine (**42**; 7%), and acridine (3%). Since formaldehyde was not detected, in contrast to the reaction of the corresponding sulfur-bridged cases (Scheme X), it was assumed by Cliff and Jones[22] that demethoxylation involved loss of methanol, although this was not detected either, thus bringing out another important difference between the methylene- and sulfur-bridged compounds. Cliff and Jones rationalize the formation of these products wholly in terms of an azanorcaradiene intermediate (Scheme XIX), but reaction *via* the precursory spirodiene is equally likely.

Whereas thermolysis of 1-(2-azidobenzyl)-2,4,6-tri-

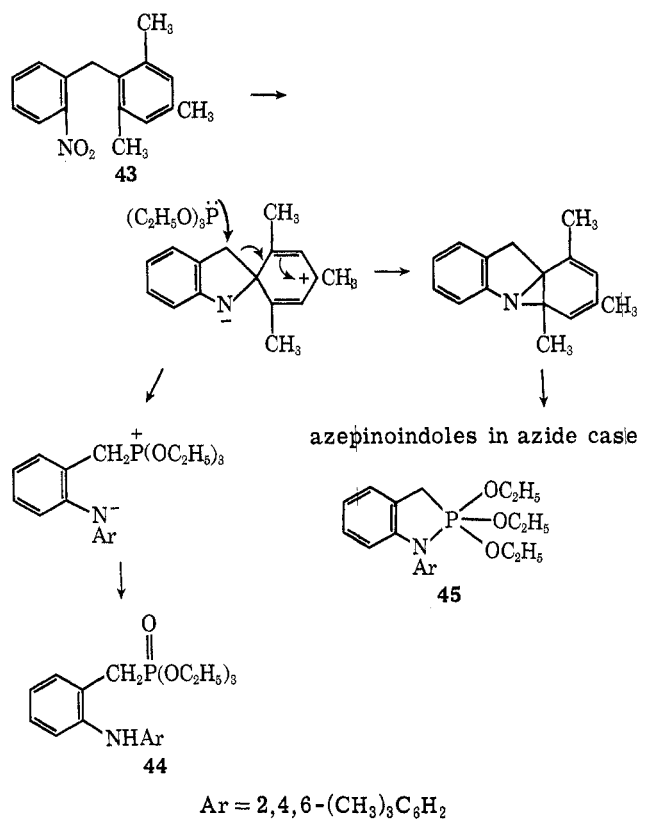
(19) Y. Maki, T. Hosokami, and M. Suzuki, *Tetrahedron Lett.*, 3509 (1971).
(20) L. Krbechek and N. Takimoto, *J. Org. Chem.*, **33**, 4286 (1968).
(21) G. R. Cliff, E. W. Collington, and G. Jones, *J. Chem. Soc. C*, 1490 (1970).
(22) G. R. Cliff and Gurnos Jones, *ibid.*, 3418 (1971).

Scheme XIX




methylbenzene gave a mixture of azepinoindoles[21] as major identified products, the phosphite deoxygenation of the corresponding 2-nitrobenzyl derivative **43** (Scheme XX) gave, in addition, the substituted diethyl

Scheme XX




Ar = 2,4,6-$(CH_3)_3C_6H_2$

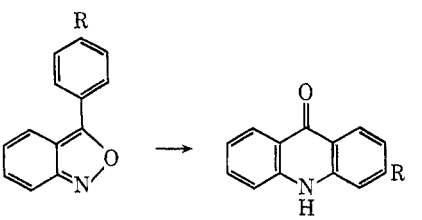
benzylphosphonate **44**,[22] which provides strong though circumstantial evidence for the intermediacy of a spirodienyl species.

The proposed mode of formation of **44** closely resembles that of the aminotetroxy phosphorane **34** described in Scheme XVI, and it is an intriguing possibility which is being investigated that **44** is also formed *via* the corresponding methylenetetroxyphosphorane **45** (Scheme XX).

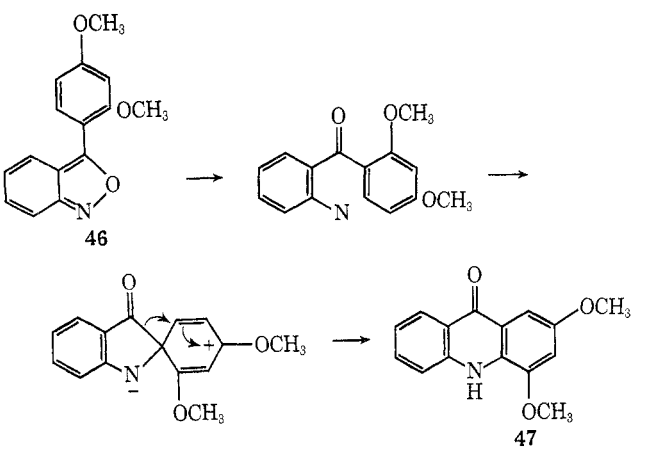
## Rearrangements in Carbonyl-Bridged and Sulfonyl-Bridged Compounds (3, X = CO or $SO_2$)

**Formation of Acridones and Phenothiazine 9,9-Dioxides.** Thermal[4] or nitrous acid induced[23] rearrangements of anthranils to acridones are well-known reactions (Scheme XXI), and in the latter case positional rearrangement of the aryl substituent has been reported not to occur. The thermolytic reaction was later postulated to involve a nitrene,[5] and recently evidence of rearrangement in this reaction was reported by Kwok and Pranc;[6] again, a spirodienyl intermediate was invoked (Scheme XXII). Thus, 3-(2,4-dimethoxy-

Scheme XXI




Scheme XXII




phenyl)anthranil (**46**) gave 2,4-dimethoxyacridone (**47**) rather than the "unrearranged" 1,3 isomer.

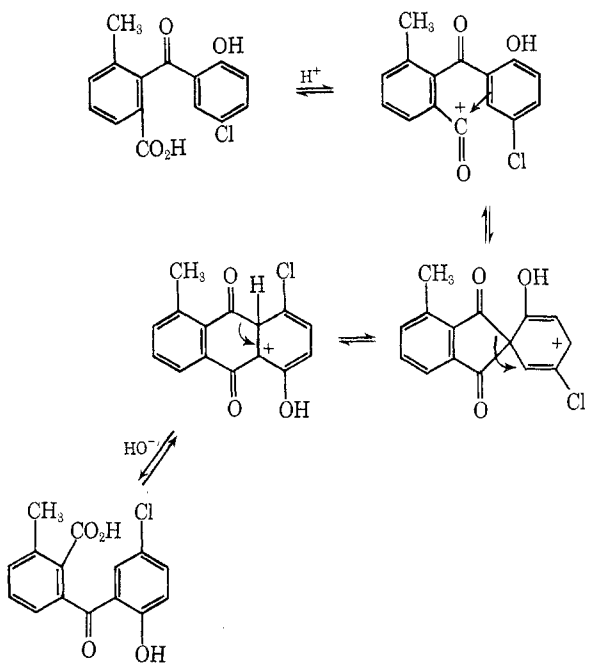
In the case of the monomethoxy analog both "rearranged" and "unrearranged" products were obtained, suggesting shifts of both the acyl and nitrogen functions.

A similar situation exists in the corresponding conversion of 2-nitrophenyl 4-chlorophenyl sulfoxide into a mixture of 2- and 3-chlorophenothiazine oxides.[24]

**Related Rearrangements.** There is no direct analog of the present series of rearrangements. By far the closest is the Hyashi rearrangement[25] of carboxybenzophenones in strong acid (Scheme XXIII), but this is similar only to the first step of the nitrene-induced rearrangement in that both reactions involve attack of an electron-deficient species at position 1′ of the

(23) I. Tanasescu, C. Anghel, and A. Popescu, *Stud. Univ. Babes-Bolyai, Ser. 1*, **8**, 141 (1963); *Chem. Abstr.*, 61, 13279*d* (1964).
(24) J. I. G. Cadogan and P. Lim, unpublished observations.
(25) M. Hayashi, *J. Chem. Soc.*, 2516 (1927); R. B. Sandin, R. Melby, R. Crawford, and D. McGreer, *J. Amer. Chem. Soc.*, **78**, 3817 (1956).

**Scheme XXIII**



molecule to give a spirodienyl intermediate followed by 1,2 shifts. In the Hyashi case this is followed by ring opening rather than retention of the ring.

## Conclusion

Rearrangements of the type outlined in Scheme III, induced by nitrenes or their precursors, *via* the phosphite–nitro group reaction or decomposition of azides, appear to be general and hence of potentially wide applicability in the synthesis of nitrogen-containing heterocycles.

In terms of mechanism, the present experimental results can be explained *via* a spirodienyl intermediate or on the basis of the isomeric azanorcaradiene, although the question of whether these are merely canonical forms of a nonclassical intermediate, or are discrete species, could be the subject of interminable debate.

The very recent detection of aminophosphoranes in this series of reactions also has mechanistic overtones and is likely to open up a new area of heterocyclic chemistry.