# Reactions of Aromatic Trifluoromethyl Compounds with Nucleophilic Reagents

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Generally speaking, carbon–fluorine bonds are strong and fluorocarbons are stable compounds. Accordingly a trifluoromethyl group on an aromatic ring had been believed to be a very stable substituent, and little was known about its reactivity when we started our work in 1968. The book of Sheppard and Sharts[1b] describes only two reactions of benzotrifluoride: hydrolysis by concentrated sulfuric acid and conversion to a trichloromethyl compound by aluminum chloride.

On the other hand, trihalomethyl groups other than the trifluoromethyl group are very reactive and are easily converted to carboxylic acids or their derivatives in nucleophilic substitution reactions. Therefore, we thought that a trifluoromethyl group might be made to undergo such reactions by changing the electronic condition of the aromatic part.

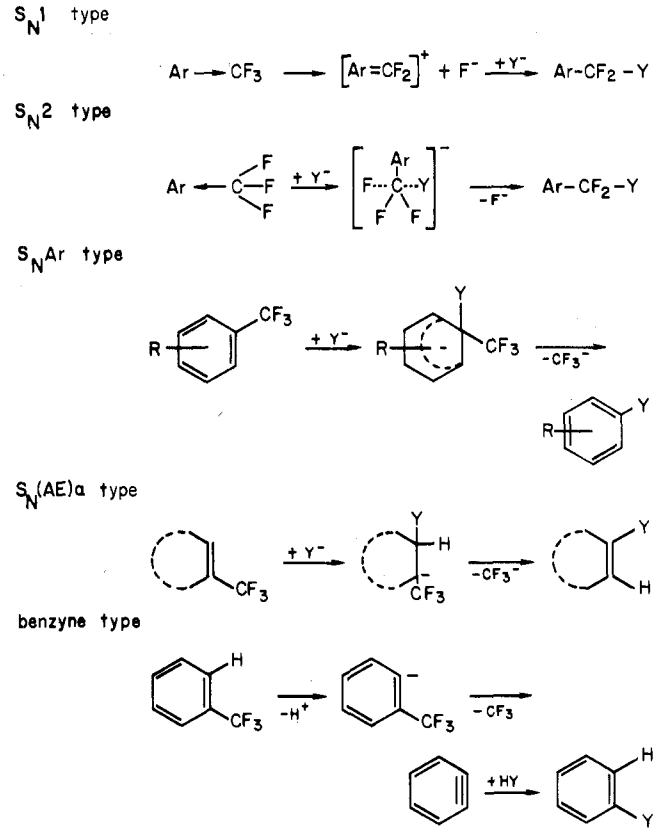
Furthermore, a trifluoromethyl group is often referred to as a pseudohalogen,[1a] but no reaction was known in which a trifluoromethyl group on an aromatic ring was replaced by a nucleophile as occurs with true halogen substituents. This kind of reaction seemed possible. Another consideration is that, since many of the trifluoromethylated compounds are now finding application, in medicine and elsewhere, it seemed important to elucidate the reactivity of the trifluoromethyl group toward understanding its biochemical behavior.

For these several reasons we examined reactions of a number of trifluoromethyl aromatics with nucleophilic reagents.

One can visualize several mechanisms for reactions of trifluoromethyl-substituted aromatic compounds with nucleophiles, as sketched in Chart I: first, the $S_N1$ mechanism, which is facilitated by electron-releasing substituents; second, the familiar $S_N2$ mechanism; both of these would bring about substitution at the carbon atom of the trifluoromethyl group; third, the common $S_NAr$ mechanism at the aromatic site to which the $CF_3$ is attached, causing loss of the $CF_3$ group; fourth, the rare $S_N(AE)a$ mechanism; finally, a benzyne type of mechanism.

To examine the electronic effect of the aromatic system on the reactivity of a trifluoromethyl group, we used heterocyclic compounds. Quinoline was chosen as a $\pi$-electron-deficient aromatic compound, and indole

Chart I




and benzofuran as $\pi$-electron-excessive aromatic compounds. As nucleophiles, sodium alkoxide or hydroxide in alcohol, sodium borohydride, lithium aluminum hydride, and sodium amide in liquid ammonia were used. Further, since we obtained many interesting results on these heterocyclic compounds, we examined the reactions of some substituted benzotrifluorides with sodium amide.

## Reactions of (Trifluoromethyl)quinolines

For the reactions with nucleophiles of quinolines substituted with a trifluoromethyl group on the pyridine ring,[2] two types of mechanisms were assumed a priori: (1) $S_N2$ reaction on the trifluoromethyl carbon atom, presumably assisted by the electron-withdrawing character of the quinoline ring;[3] this was expected to

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(1) W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry", W. A. Benjamin, New York, N.Y., 1969: (a) p 62; (b) p 410.

(2) Since the mass spectra of (trifluoromethyl)pyridines showed different patterns in fragmentation depending on the position of the trifluoromethyl group, these compounds were expected to show some interesting reactions. Cf. Y. Kobayashi, E. Nakano, and E. Chinin, *Chem. Pharm. Bull.*, 15, 190 (1967).

(3) In our case, as the attacking reagents are negatively charged, the reactions would be facilitated by electron withdrawal: E. S. Gould, "Mechanism and Structure in Organic Chemistry", Henry Holt and Co., Inc., New York, N.Y., 1960, p 283.

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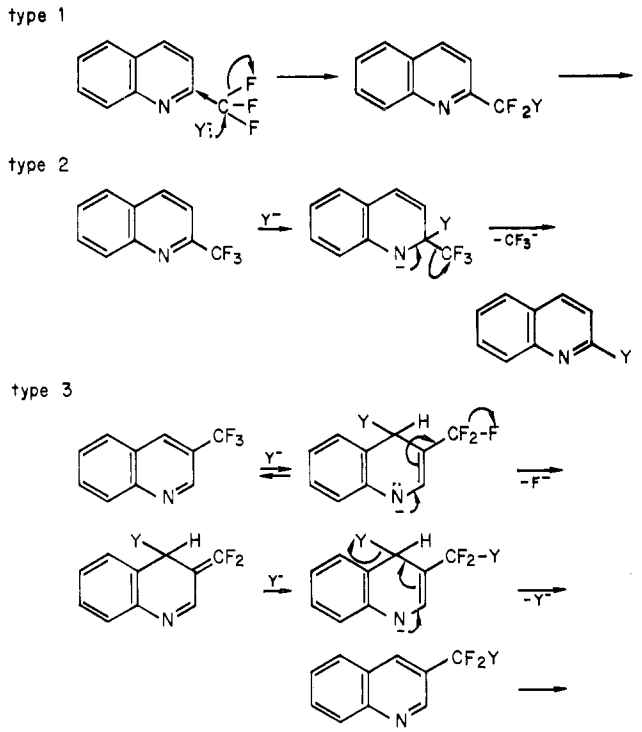
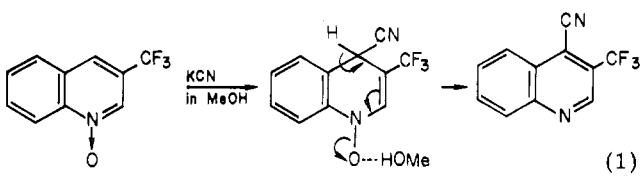
**Chart II**




occur in 2- and 4-(trifluoromethyl)quinolines (cf. type 1 in Chart II); (2) $S_NAr$ replacement of the trifluoromethyl group in the case of 2-(trifluoromethyl)-quinolines (cf. type 2 in Chart II). Further, in view of the known reaction of 3-(trifluoromethyl)quinoline 1-oxide with KCN to give 4-cyano-3-(trifluoromethyl)quinoline, in which the addition of cyanide ion to the 4-position occurs first (cf. eq 1),[4] the more




(1)

elaborate type 3 mechanism (Chart II) that starts with the reversible addition of a nucleophile to the 4-position of quinoline ring with ensuing unimolecular fission of the C–F bond was a conceivable possibility.

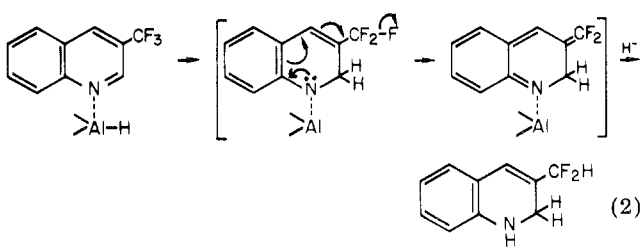
Ordinarily, nucleophilic attachment to the quinoline ring occurs at the 2- or the 4-position. Introduction of a trifluoromethyl group will not change this condition. Therefore, the attack of a nucleophile at the 3-position of 2-(trifluoromethyl)quinoline seems improbable.[4] Furthermore, even if addition occurred at the 3-position of the 4-trifluoromethyl compound, the $S_N(AE)a$ mechanism would seem more favorable. The type 3 was anticipated for 3-(trifluoromethyl)quinoline. Since addition reactions of a nucleophile of a small size to the quinoline ring seem to occur easily, reactions through an intermediate like benzyne appeared to be less probable.

The three isomers, 2-, 3-, and 4-(trifluoromethyl)-quinoline, were refluxed with sodium ethoxide in ethanol.[5] Only the 3-isomer underwent alcoholysis, while 2- and 4-isomers were recovered unchanged. This fact cannot be explained by the type 1 mechanism (in Chart II), because the three isomers ought to be more or less equivalently susceptible to it. The higher reactivity of the 3-isomer is ascribed to the type 3 mechanism. The first step is attack of ethoxide ion on the 4-position activated by the electronic effects of the hetero nitrogen and the trifluoromethyl group. In the resulting $\sigma$ complex, a C–F bond becomes labile by back-donation of an electron pair from the nitrogen anion. The second and third replacements of fluorine atoms by ethoxy groups may be favored by the lone-pair electrons of the oxygen atom of the first ethoxy group (cf. Chart III, C, course a). Conceivably the first attack of the nucleophile could be at the 2-position as shown in Chart IIICb. However, since nucleophilic attack of the cyanide ion on 3-(trifluoromethyl)quinoline 1-oxide occurs at the 4-position, as shown previously,[4] course a was provisionally adopted.

All of these (trifluoromethyl)quinolines were converted to the corresponding carboxylic acids when heated with NaOH in ethanol in a sealed tube at 120–130 °C.[5] However, benzotrifluoride was recovered from these drastic conditions. These results suggest that the electron-withdrawing effect of the quinoline ring favors $S_N2$ type reaction on the trifluoromethyl carbon atom in the first stage of hydrolysis (cf. Chart II, type 1).

Next, we studied the reactions of these (trifluoromethyl)quinolines with sodium borohydride in boiling ether.[6] Only 3-(trifluoromethyl)quinoline reacted, being reduced to 3-methylquinoline, while the 2- and 4-isomers were recovered quantitatively. These results were quite similar to those obtained in the reactions of the (trifluoromethyl)quinolines with sodium ethoxide in boiling ethanol. Apparently, the reduction of the 3-isomer proceeded via a similar 1,4-dihydro intermediate formed by attack of hydride ion at the 4-position (Chart II, type 3).

On the other hand, in the reactions of the (trifluoromethyl)quinolines with lithium aluminum hydride,[6] which is a much stronger reducing agent than sodium borohydride, the 2- and 4-trifluoromethyl compounds were reduced to 2- and 4-methylquinoline, respectively, while benzotrifluoride was recovered quantitatively. It appears that the electron-withdrawing effect of the quinoline ring also facilitated $S_N2$ displacement on the trifluoromethyl carbon atom (type 1 in Chart II) in this case. Interestingly, the 3-isomer was converted to 3-(difluoromethyl)-1,2-dihydroquinoline on reaction with $LiAlH_4$. This fact might be reasonably explained by the scheme shown in eq 2; the



(2)

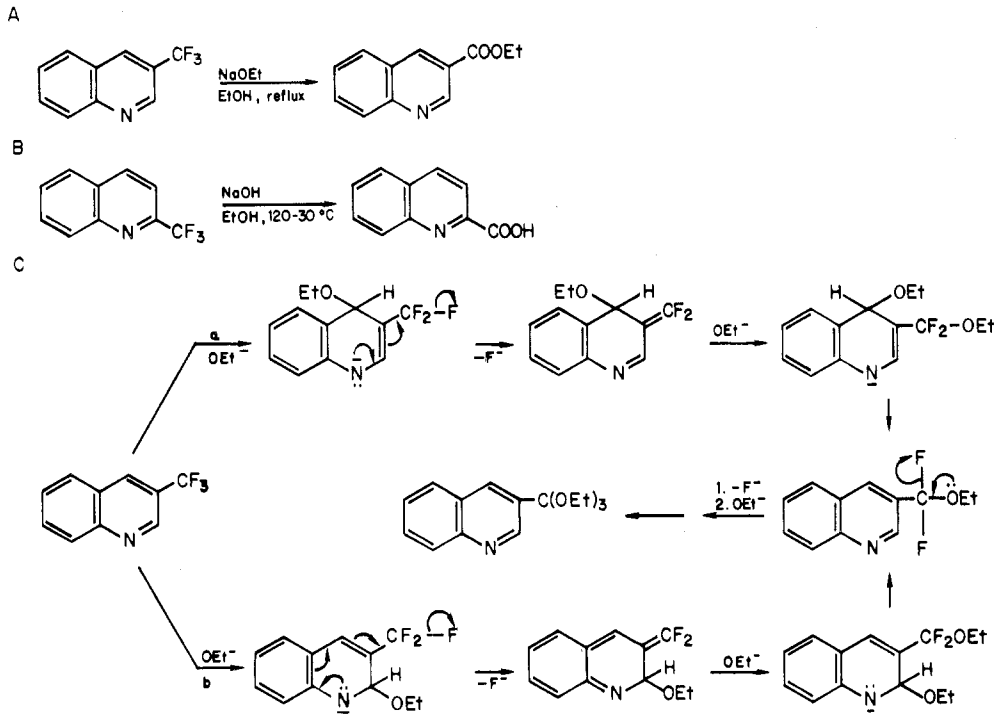
quinoline ring was first reduced to a 1,2-dihydro compound through coordination of aluminum to ni-

(4) Y. Kobayashi, I. Kumadaki, and S. Taguchi, *Chem. Pharm. Bull.*, 17, 2335 (1969).

(5) Y. Kobayashi, I. Kumadaki, and S. Taguchi, *Chem. Pharm. Bull.*, 19, 624 (1971).

(6) Y. Kobayashi, I. Kumadaki, and S. Taguchi, *Chem. Pharm. Bull.*, 20, 823 (1972).

**Chart III**

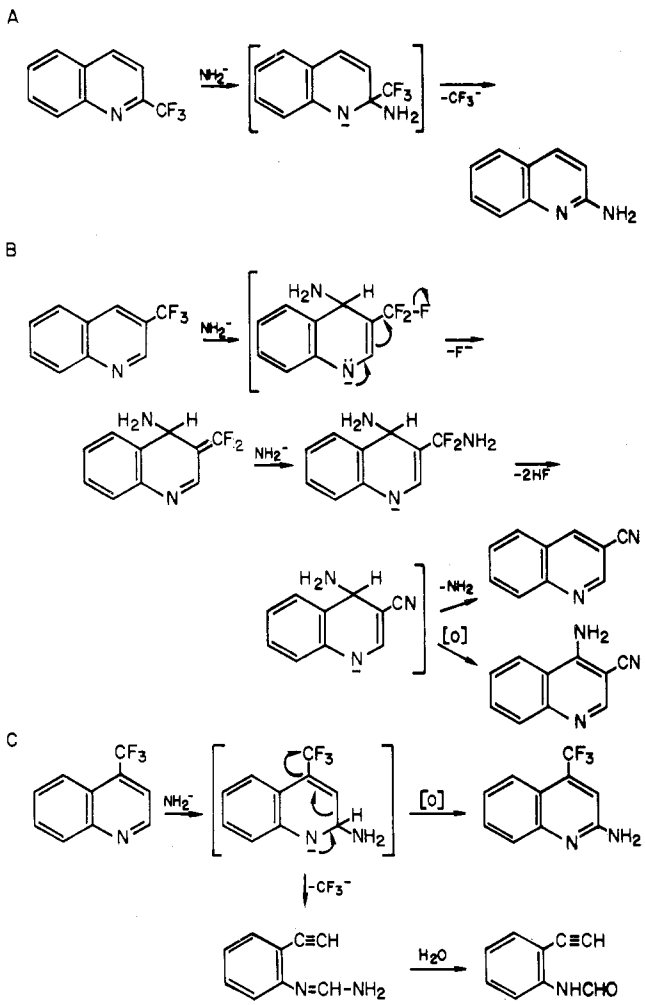



trogen, and then back-donation of an electron pair from the nitrogen atom occurred to effect unimolecular elimination of a fluoride ion, and finally there was addition of a hydride ion. This back-polarization was seemingly much weaker than that in the 1,4-dihydro form assumed in type 3 mechanism (in Chart II), since it was shielded by an aromatic double bond, and reduction stopped at the first stage. This difference of reactivity between $NaBH_4$ and $LiAlH_4$ supports the view that the intermediate of the type 3 mechanism is not the 1,2- but rather the 1,4-dihydro form.

In the reactions considered so far, evidence of type 1 and type 3 (in Chart II) behavior was encountered, but no product suggesting a type 2 mechanism, in which a trifluoromethyl group was replaced by a nucleophile, was observed. It seemed that such a product might be obtained with use of amide anion[7] as a nucleophile, for it is a stronger nucleophile than any examined so far and adds to the quinoline ring more easily than any. The well-known Chichibabin amination of quinoline involves such a step.[8] We therefore treated (trifluoromethyl)quinolines with sodium amide in liquid ammonia. The results are summarized in Chart IV together with the probable mechanisms.

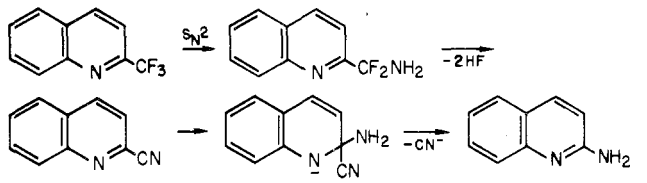
Reaction of 2-(trifluoromethyl)quinoline gave the 2-amino compound. Similarly, 2-(trifluoromethyl)-pyridine and 1-(trifluoromethyl)isoquinoline gave the corresponding amino compounds (Chart IVA). The mechanism for this reaction was determined to be of type 2 (in Chart II) as shown in Chart IV.[9] Another mechanism also seemed within the range of possibility; in that alternative, the trifluoromethyl groups were converted to a cyano group by $S_N2$ displacement of a fluoride ion by an amide ion, followed by dehydro-

**Chart IV**




fluorination, and then the cyano group was replaced by the amino group through the addition–elimination $S_NAr$ mechanism (eq 3). As the cyanide ion was actually

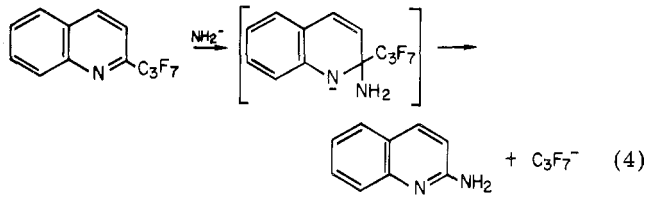
(7) Y. Kobayashi, I. Kumadaki, S. Taguchi, and Y. Hanzawa, *Tetrahedron Lett.*, 3901 (1970); *Chem. Pharm. Bull.*, **20**, 1047 (1972).
(8) M. T. Leffler, *Org. React.*, 1, 91 (1942).
(9) Y. Kobayashi, I. Kumadaki, Y. Hanzawa, and M. Mimura, *Chem. Pharm. Bull.*, **23**, 2044 (1975).



(3)

detected in the aqueous solution after workup of this reaction, the latter mechanism seemed preferable. However, the trifluoromethyl anion was a conceivable precursor of the cyanide ion. In fact, fluoroform was converted to cyanide ion under the same reaction condition. Therefore detection of cyanide ion cannot prove which mechanism operated in the reaction of 2-(trifluoromethyl)quinoline. 2-Cyanoquinoline, synthesized by another route, was treated with $NaNH_2$ in the same reaction condition as for 2-(trifluoromethyl)quinoline and it gave 2-aminoquinoline, but the yield was much lower than from the trifluoromethyl compound. This shows that the latter mechanism was not the main course for the reaction.

All of these results support the view that the type 2 mechanism was involved. To verify this conclusion, the reaction of 2-(heptafluoropropyl)quinoline with $NaNH_2$ was examined. In this case, 2-aminoquinoline was obtained in a better yield than from the 2-cyano compound. Thus, participation of the type 2 reaction was proved without ambiguity; a perfluoroalkyl group can be a leaving group in an $S_NAr$ reaction (cf. eq 4).



(4)

The reaction of 2-(trifluoromethyl)quinoline with $NaNH_2$ is the first example of a trifluoromethyl group being eliminated by a C–C bond fission from an aromatic ring as a leaving group.[10]

The observed formation of 3-cyanoquinoline from 3-(trifluoromethyl)quinoline might be explained by displacement of one fluorine atom by an amino group, followed by the elimination of 2 mol of hydrogen fluoride by the action of sodium amide. Benzotrifluoride did not react with $NaNH_2$ under these conditions. Therefore, the electronic effect of the quinoline ring would need to be invoked to rationalize the first step of the above process. However, the observed formation of 4-amino-3-cyanoquinoline as a by-product strongly indicates the type 3 mechanism for the formation of both products. Initially amide anion adds to the 4-position with activation by the hetero nitrogen atom and the trifluoromethyl group;[4] this step is followed by cleavage of the C–F bond by back-polarization of the electron pair on the nitrogen atom, addition of an amide anion, and two stages of dehydrofluorination. Elimination of the amide anion from the resulting intermediate gives the 3-cyano compound and its oxidation gives 3-cyano-4-aminoquinoline (Chart IVB).

(10) Chambers et al. reported that 4,5-bis(trifluoromethyl)-3,6-difluoropyridazine disproportionated on heating with fluoride ion to 4-(trifluoromethyl)-3,5,6-trifluoropyridazine and 3,5,6-tris(trifluoromethyl)-4-fluoropyridazine. This is the special case of interconversion of perfluoroalkyl groups: R. D. Chambers, Yu. A. Cheburkov, J. A. H. MacBride, and W. R. R. Musgrave, *J. Chem. Soc. C*, 532 (1971).

Chart V

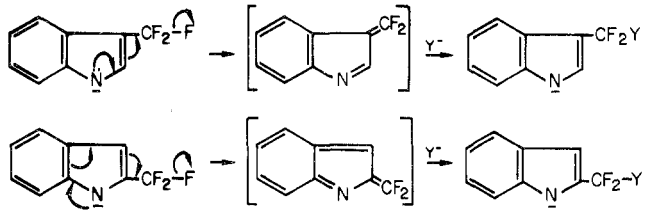
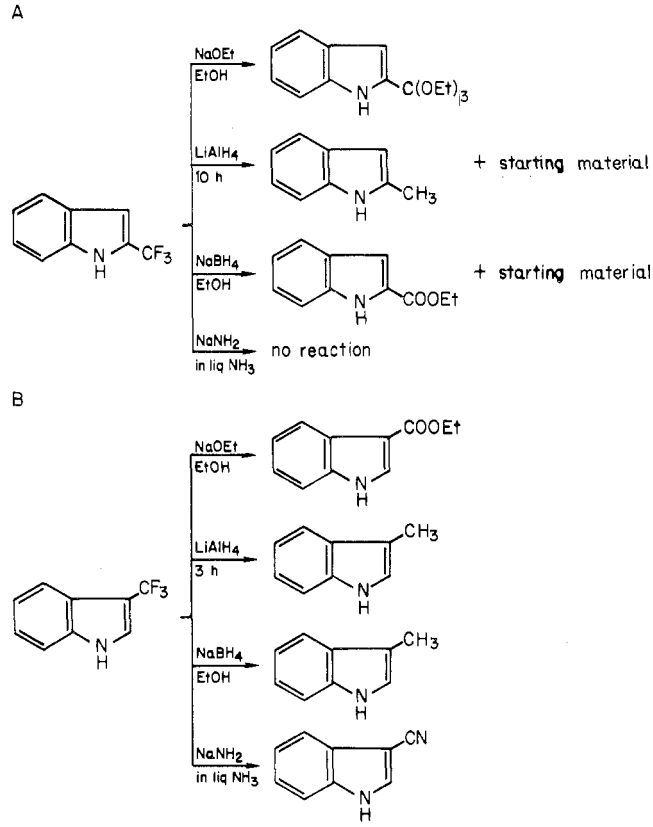


Chart VI



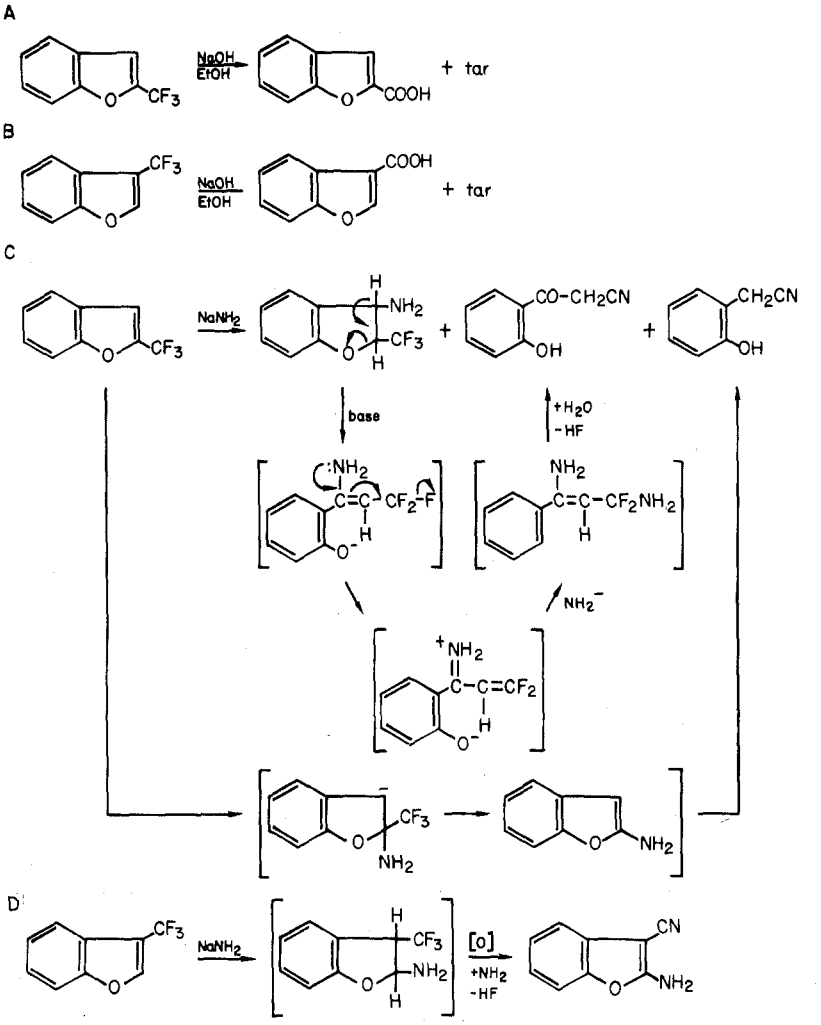
4-(Trifluoromethyl)quinoline was converted by reaction with $NaNH_2$ into 2-amino-4-(trifluoromethyl)-quinoline and 2-ethynyl-*N*-formanilide. The former is attributed to the Chichibabin reaction;[8] attack of amide ion occurred at the 2-position. In this case, the 4-trifluoromethyl group was unaffected, possibly because the electronic effect of the quinoline ring was compensated by the electron-donating effect of the amino group (Chart IVC). Much more interesting is the formation of the ring-opened compound with its acetylenic bond. In the probable mechanism, the trifluoromethyl group was eliminated as the $CF_3^-$ ion from the intermediate of the Chichibabin reaction with simultaneous ring-opening and finally partial hydrolysis of the resulting amidine.

In these reactions with $NaNH_2$, products attributable to all three of the postulated mechanisms, type 1 to type 3 in Chart II, were isolated together with a peculiar ring-opened product and a 1,2-dihydro compound. However, no products representing the $S_N(AE)a$ mechanism were isolated.

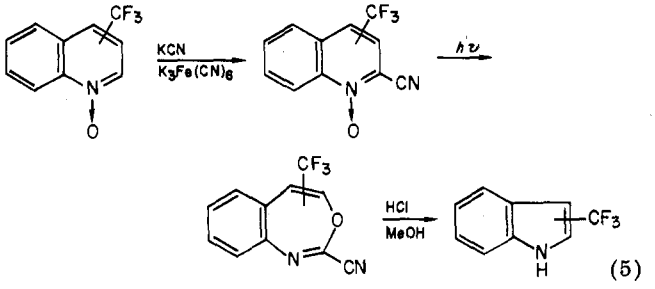
## Reactions of (Trifluoromethyl)indoles

Next to be taken up was the reactivity of a trifluoromethyl group on the $\pi$-electron-excessive indole

**Chart VII**



ring. We examined the reactions of 2- and 3-(trifluoromethyl)indole with nucleophiles. These compounds were synthesized from 2- and 3-(trifluoromethyl)quinolines as shown in eq 5.[11] 3- and 4-(Tri-



(5)

fluoromethyl)quinolines were converted to the corresponding *N*-oxides; the cyano group was introduced by oxidative cyanation by means of potassium cyanide and ferricyanide;[12] the cyano *N*-oxides were photolyzed to the oxazepine derivatives; and the latter were hydrolyzed and recyclized with hydrogen chloride in methanol to 2- and 3-(trifluoromethyl)indoles.

In these systems the electronic effect of the hetero nitrogen atom of indole was expected to promote reaction starting with $S_N1$-type cleavage of the C–F bond; the fluoride anion would be eliminated first from the trifluoromethyl group by electron donation from the indole ring, and then the nucleophile would attack the side-chain carbon atom, as sketched in Chart V. The propensity to expel fluoride ion would be greater in the conjugate base of the trifluoromethylindole than in the parent compound. This effect was expected to be more prominent for 3-(trifluoromethyl)indole than for the 2-isomer from consideration of the structures of the intermediates (cf. Chart V); the intermediate from the latter involves an ortho-quinonoid bond arrangement in the benzenoid ring, but the former has no such requirement. This is also expected from comparison of $\pi$-electron densities calculated by molecular orbital theory.[13] This expectation was confirmed by the reactions shown in Chart VI.

Both 2- and 3-(trifluoromethyl)indoles underwent alcoholysis when refluxed with sodium ethoxide in ethanol. With the 3-trifluoromethyl compound (Chart VIB) the ortho ester, which was observed by the NMR spectrum of the reaction mixture, was smoothly hydrolyzed to the ester on workup. This may have been due to the higher electron density at the 3-position than

(11) Y. Kobayashi, I. Kumadaki, Y. Hirose, and Y. Hanzawa, *J. Org. Chem.*, 39, 1836 (1974).

(12) Y. Kobayashi, I. Kumadaki and H. Sato, *Chem. Pharm. Bull.*, 18, 861 (1970); *J. Org. Chem.*, 37, 3588 (1972).

(13) For example, P. O. Lowdin and B. Pullman, "Molecular Orbitals in Chemistry, Physics and Biology", Academic Press, New York, N.Y., 1964, p 492.

that at the 2-position on the indole ring.

When refluxed with lithium aluminum hydride in anhydrous ether, 3-(trifluoromethyl)indole was easily reduced to skatole, while the 2-isomer required a much longer reaction time and a considerable amount of the starting material was recovered unchanged. The difference in reactivity between the 2- and 3-isomers was also apparent in their reactions with sodium borohydride. The 3-isomer was reduced to the methyl compound, skatole, smoothly, while most of the 2-isomer was recovered unchanged with formation of a small amount of ethyl indole-2-carboxylate. Formation of this ester is probably due to reaction with sodium ethoxide which slowly formed from reaction of ethanol with $NaBH_4$ during the long reaction times which were employed for the reaction of 2-(trifluoromethyl)indole.

The difference in reactivity between the 2- and 3-isomers was likewise observed in their reactions with sodium amide in liquid ammonia. Although the former was recovered unchanged, the latter gave 3-cyanoindole, formation of which is ascribed to the substitution of one fluorine atom by an amino group, followed by dehydrofluorination.

An interesting point is that the reactions of 3-(trifluoromethyl)indole resemble those of 3-(trifluoromethyl)quinoline. This may be due to the fact that the intermediates proposed for 3-(trifluoromethyl)indole and 3-(trifluoromethyl)quinoline (shown in Chart V and Chart II, respectively) are quite similar; both have the same enamine conjugation.

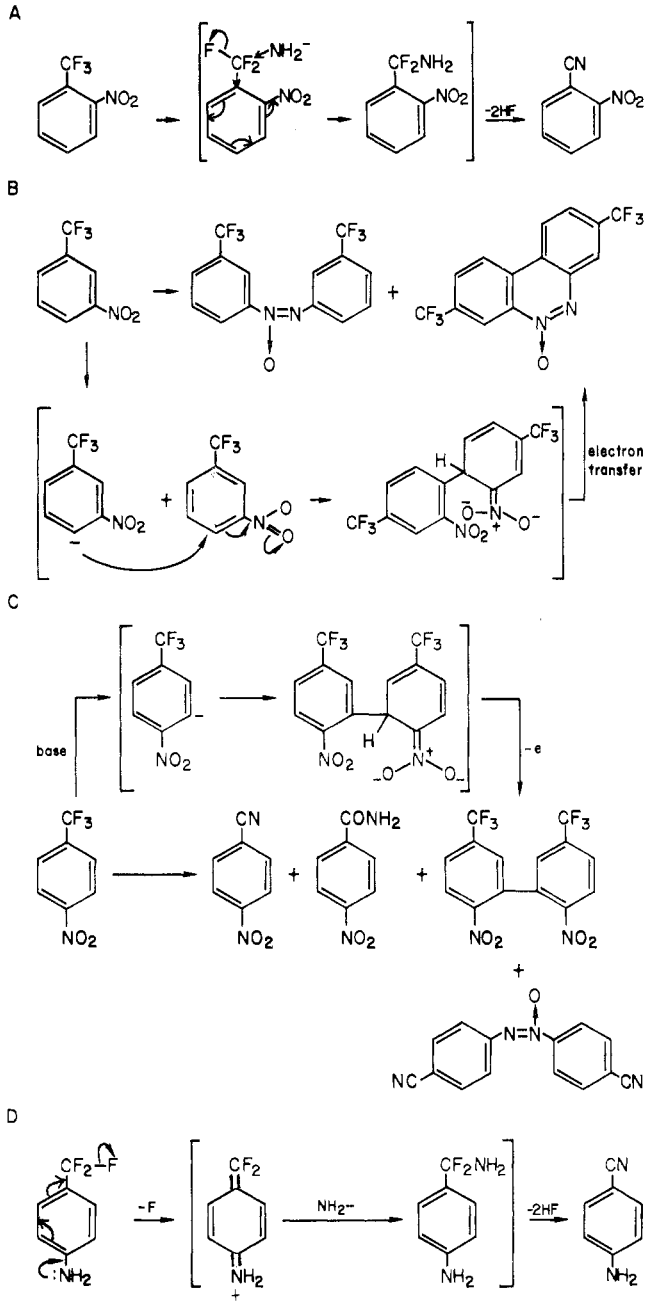
## Reactions of (Trifluoromethyl)benzofurans[14]

Next were examined the reactions of a trifluoromethyl group on a benzofuran ring in which the electron density at the $\alpha$ position was calculated to be a little higher than at the $\beta$ position.[13] Comparison of the reactivities of $\alpha$- and $\beta$-(trifluoromethyl)benzofurans seemed interesting. The (trifluoromethyl)benzofurans were synthesized from the corresponding bromobenzofurans with use of trifluoromethyl iodide and copper powder.[15]

When $\alpha$- and $\beta$-(trifluoromethyl)benzofurans were refluxed with alcoholic sodium ethoxide, both gave the corresponding carboxylic acids, but the yields were very low and much tar was formed. Therefore, comparison of the reactivities of the $\alpha$- and $\beta$-isomers was obscure, but activation by the benzofuran ring is judged to be responsible for this hydrolysis, in the same manner as in the indole series. Formation of tarry substances was probably due to attack of the nucleophile on the rather localized 2,3-double bond, followed by ring opening and polymerization. The addition of a nucleophile to the 2,3-double bond was demonstrated by the reactions of these (trifluoromethyl)benzofurans with sodium amide, as shown below.

Treatment of 2-(trifluoromethyl)benzofuran with sodium amide in liquid ammonia gave a mixture of 2-(trifluoromethyl)-3-amino-2,3-dihydrobenzofuran, *o*-hydroxybenzoylacetonitrile, and *o*-hydroxyphenylacetonitrile. The same reaction of 3-(trifluoromethyl)benzofuran gave a trace of 2-amino-3-cyano-

Chart VIII




benzofuran and a lot of tar. These results are summarized in Chart VIIC,D with the probable mechanisms.

Attack of an amide ion on the 3-position of 2-(trifluoromethyl)benzofuran and subsequent acquisition of a proton yield a 2,3-dihydro compound, which seems to be comparable to the intermediate postulated for the $S_N(AE)a$ mechanism.[16] In this case, however, the trifluoromethyl group was not eliminated but rather ring opening occurred, followed by unimolecular replacement of a fluorine atom of the trifluoromethyl group by an amino group, dehydrofluorination, and hydrolysis of the enamine group, thereby producing (2-hydroxybenzoyl)acetonitrile. This course was confirmed by experimental demonstration that treatment of the dihydro compound under these reaction conditions gave the latter product. When addition of the

(14) Y. Kobayashi, I. Kumadaki, and Y. Hanzawa, *Chem. Pharm. Bull.*, **25**, 3009 (1977).

(15) Y. Kobayashi and I. Kumadaki, *Tetrahedron Lett.*, 4095 (1969); Y. Kobayashi, I. Kumadaki, S. Sato, N. Hara, and E. Chikami, *Chem. Pharm. Bull.*, 18, 2334 (1970).

(16) T. Kauffmann, R. Nürnberg, and K. Udluft, *Angew. Chem.*, **80**, 614 (1968).

amide ion occurred at the 2-position, loss of the trifluoromethyl group preceded ring opening and the resulting 2-aminobenzofuran underwent prototropic ring opening and rearrangement to give 2-hydroxyphenylacetonitrile.

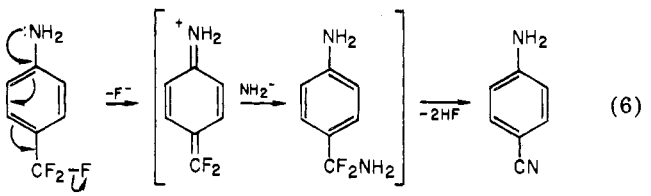
Similarly, amide ion attacked the 2-position of 3-(trifluoromethyl)benzofuran and subsequent oxidation formed 2-amino-3-cyanobenzofuran. The latter compound is rather unstable under the reaction conditions and the yield was poor.

Important features of these results were isolation of an adduct of the nucleophile to the aromatic C.2–C.3 double bond and the formation of ring-opening products. Isolation of the adduct shows that the C.2–C.3 double bond of the benzofuran is rather localized and activated for nucleophilic addition by the electronic effect of the trifluoromethyl group.

## Reactions of Substituted Benzotrifluorides

Although a trifluoromethyl group on an aromatic ring had been regarded as a very stable substituent, the experimental results described indicate that a trifluoromethyl group on a heterocyclic ring undergoes interesting reactions with nucleophiles owing to electronic interaction of the heterocyclic system with the trifluoromethyl group. Benzotrifluoride was recovered unchanged in the reactions mentioned above, but we expected interesting reactions to occur if an appropriate substituent were introduced into the benzene ring. Actually, *p*-amino- and *p*-hydroxybenzotrifluoride had been known to react with aqueous NaOH to give the corresponding carboxylic acids.[17] Therefore, we examined the reaction of substituted benzotrifluorides with sodium amide in liquid ammonia,[18] which seemed to give the most interesting reactions with heterocyclic trifluoromethyl derivatives.

First, *p*-aminobenzotrifluoride, which has an electron-donating amino group in the para position, was treated with $NaNH_2$ in ammonia to give *p*-aminobenzonitrile. This is reminiscent of the behavior of 3-(trifluoromethyl)indole. The reaction must have proceeded by an elimination–addition mechanism (cf. eq 6).

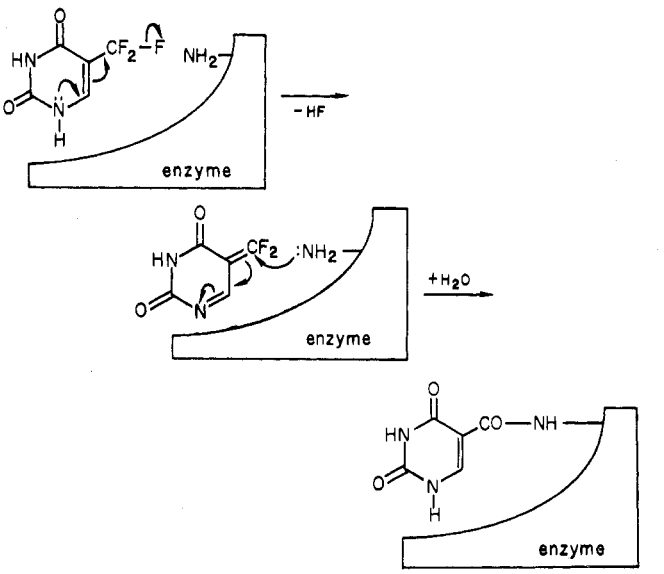



(6)

In contrast, if the substituent were an electron-withdrawing nitro group, it was conceivable that reaction might occur by the benzyne or $S_NAr$ mechanism with loss of the trifluoromethyl group. In fact, peculiar reactions were observed with nitrobenzotrifluorides, as shown in Chart VIII.

When *o*-nitrobenzotrifluoride was subjected to this reaction, a small amount of *o*-nitrobenzonitrile was formed, while most of the starting material was recovered. This can be rationalized in terms of an

**Chart IX**




$S_N2$-type displacement on the carbon atom of the trifluoromethyl group with subsequent dehydrofluorination (Chart VIIIA).

In the case of *m*-nitrobenzotrifluoride, 3,3′-bis(trifluoromethyl)azoxybenzene and 3,8-bis(trifluoromethyl)benzo[*c*]cinnoline 5-oxide were obtained. It should be noted here that a completely new type of reaction took place, an intermolecular dimerization that had not been observed in the reactions of heteroaromatic trifluoromethyl compounds. Speculation as to the mechanism of formation of these products is offered in Chart VIIIB. Formation of the benzo[*c*]cinnoline 5-oxide is explained as follows: the proton ortho to the nitro group, the acidity of which is increased by the electron-withdrawing effects of the nitro and trifluoromethyl groups, is abstracted by the amide anion; the anion produced in this way adds to another molecule of the starting material and then ring closure takes place by some process that necessarily involves some oxidation–reduction. Nitrobenzene was recovered quantitatively from these conditions;[19] therefore, the electronic effect of one nitro group is not sufficient to bring about these changes.

Under the same reaction conditions, *p*-nitrobenzotrifluoride yielded *p*-nitrobenzonitrile, *p*-nitrobenzamide, 2,2′-dinitro-5,5′-bis(trifluoromethyl)biphenyl, and 4,4′-dicyanoazoxybenzene. Formation of the former two products is presumably due to $S_N2$ type displacement on the trifluoromethyl carbon atom, followed by dehydrofluorination and partial hydrolysis. Formation of the biphenyl compound is thought to occur as follows: the proton ortho to the nitro group was abstracted by a base, as with meta isomer, and the anion thus formed reacted with another molecule of the starting material and was oxidized. The azoxy compound was presumably produced by the reduction of nitrobenzonitrile conjugated with the above oxidation. Since nitrobenzene was recovered in this reaction, as mentioned above, the trifluoromethyl group contributed in some way to these peculiar reactions.

(17) R. Belcher, M. Stacey, A. Sykes, and J. C. Tatlow, *J. Chem. Soc.*, 3846 (1954).

(18) Y. Kobayashi, I. Kumadaki, Y. Hanzawa, and M. Mimura, *Chem. Pharm. Bull.*, **23**, 636 (1975).

(19) W. Bradley and R. Robinson, *J. Chem. Soc.*, 1254 (1932), treated nitrobenzene with sodium amide in liquid ammonia in a sealed tube at room temperature for 10 days and obtained small amounts of products. However, our condition is much weaker than theirs.

### Concluding Remarks

We have been able to witness some interesting reactions of trifluoromethyl groups in heteroaromatic compounds with nucleophilic reagents. These results will assist understanding of other types of reactions of trifluoromethyl groups in organic chemistry and of the biochemical reactions of trifluoromethyl compounds, which now find some use in medicine. Concerning the latter point, Santi[20] recently proposed a mechanism for inhibition of thymidylylase by trifluorothymine, which is used as an antitumor agent, as shown in Chart IX. This mechanism is comparable to our type 3 mechanism of 3-(trifluoromethyl)quinoline (Chart II). Thus, the results of these experiments will help to understand the mechanisms of biological action, metabolism, and toxicity of some trifluoromethyl compounds.

(20) D. V. Santi and T. T. Sakai, *Biochemistry*, **10**, 3598 (1971).

# Metal-Induced Rearrangements and Insertions into Cyclopropyl Olefins

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The birth of small-ring chemistry was both difficult and painstaking. Because of numerous failures, the great masters of the time, Victor Meyer, Emil Fischer, and Baeyer, were firmly persuaded that carbocycles with fewer than six carbon atoms in a ring could not be capable of existence. The major breakthrough in this area was due to Perkin who in 1883 furnished a general approach for the synthesis of three-, four-, and five-membered ring compounds.

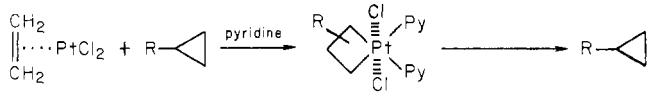
Earlier, Meyer advised young Perkin to abandon the idea of trying to prepare small rings and "work at something more promising and more likely to give positive results".[1b]

Perkin's findings stimulated von Baeyer to consider the ease of formation of small-ring compounds. He reasoned that because of angle strain ease of ring formation should follow the order $3 < 4 < 5$. This evolved in his "Spannungs Theorie",[1a] the now famous "strain theory".

Cyclopropane is a molecule of great interest, both experimentally and theoretically. A major advance in explaining bonding in this unusual molecule was made by Walsh[2] and by Coulson and Moffitt.[3]

The Walsh model of cyclopropane describes the higher occupied molecular orbitals (HOMO) as largely p orbital in character and suitable for overlap with adjacent $\pi$ electrons of a double bond, as in the case of vinylcyclopropane. In analogy with dienes, the interaction between the $\pi$ and $\sigma$ bonds could be detected by analysis of bond properties associated with either the central single bond (C2–C3) or the outer double bond (C1–C2) and the cyclopropane bond.[4,5]

The cyclopropane bonds are known to be weaker than normal $\sigma$ bonds and are consequently susceptible to attack by reagents which attack double bonds. An extra dimension was added to the similarity between cyclopropane and olefins when Tipper[6] reported that cyclopropane yields a dichloroplatinum complex (1)

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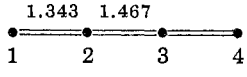
(1) (a) A. von Baeyer, *Ber.*, **18**, 2278 (1885); (b) W. H. Perkin, *J. Chem. Soc.*, 1347 (1929).

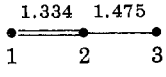
(2) A. D. Walsh, *Trans. Faraday Soc.*, **45**, 179 (1949).

(3) C. A. Coulson and W. E. Moffitt, *Phil. Mag.*, **40**, 1 (1949).

(4) Electron-diffraction measurements [A. de Meijere and W. Luttke, *Tetrahedron*, **25**, 2047 (1949)] indicate that the C2–C3 bonds both in butadiene




and in vinylcyclopropane




are significantly shorter than the normal $\sigma$ bond (1.522 Å), possessing 15 and 13% double-bond character, respectively.

(5) (a) MO calculations [P v. R. Schleyer and V. Buss, *J. Am. Chem. Soc.*, **91**, 5880 (1969)] indicate extremes of stabilization of 9–26 kcal/mol between bisected (i) and perpendicular (ii) conformations. See also: J.

i ii

Wolf, P. G. Harch, R. W. Taft, and W. J. Hehre, *J. Am. Chem. Soc.*, **97**, 2903 (1975); H. C. Brown and M. Ravindranathan, *ibid.*, **97**, 2895 (1975), and references cited therein. (b) The $\pi,\sigma$ interaction detected in the vinylcyclopropanes is further manifested by their ability to enter into cycloaddition reactions with electron-deficient olefins and dienophiles [see (a) R. Askani and J. P. Chesick, *Chem. Ber.*, **106**, 8 (1973); (b) S. Sarel, A. Felzenstein, and J. Yovell, *J. Chem. Soc., Chem. Commun.*, 753 (1974); 918 (1975); and references therein; *Tetrahedron Lett.*, 451 (1976); (c) S. R. Tanny and F. W. Fowler, *J. Org. Chem.*, **39**, 2715 (1974); (d) A. Padwa and Carlsen, *J. Am. Chem. Soc.*, **97**, 3862 (1975).

(6) G. F. H. Tipper, *J. Chem. Soc.*, 2045 (1955).

Shalom Sarel was born and educated in Jerusalem. He received the M.Sc. degree from the Hebrew University, and returned there as a member of the faculty in 1946 after earning the Ph.D. at the Daniel Sieff Institute in Rehovot with F. Bergmann. Following 2 years of postdoctoral work at Ohio State University with M. S. Newman, Professor Sarel was assigned, in 1956, to form a new Department of Pharmaceutical Chemistry at Hebrew University, which he now heads. His research interests center around strained small rings, organometallics, stereochemistry, and reaction mechanisms.

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