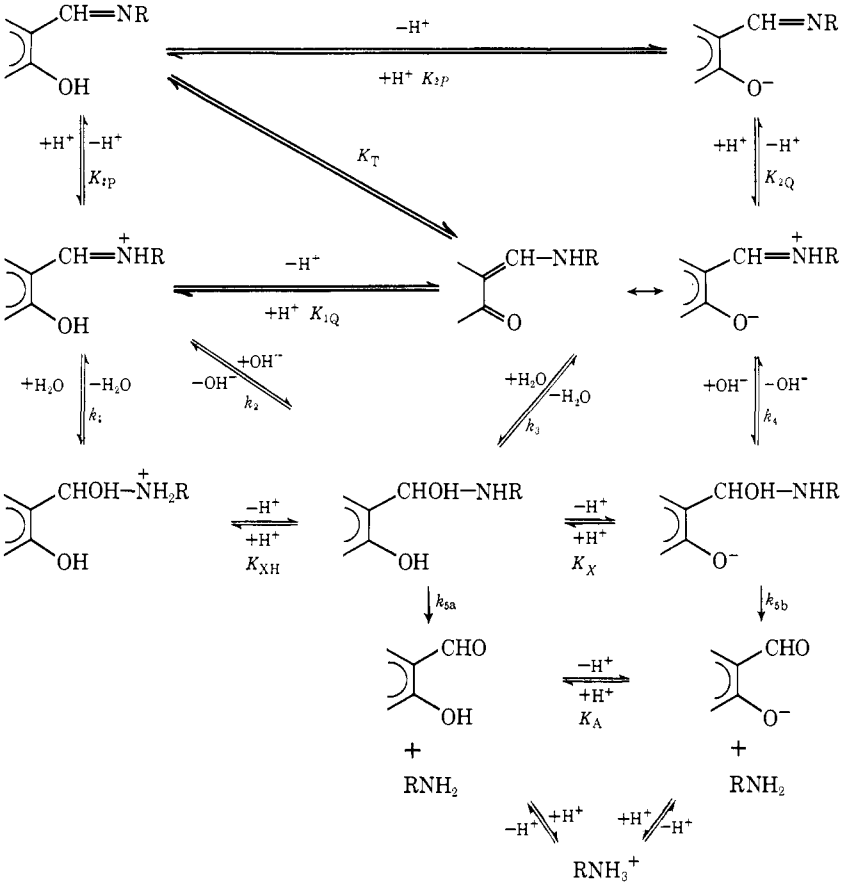
Scheme I. R = $CH(CH_3)_2$



ingly, the k_{obsd} at pH 14 are expected to be rather insensitive to substituent effects, while the other *a priori* conceivable mechanism, addition of water to the ion of the Schiff base, would cause a strong influence of substituents on $k_{(14)}$. As a matter of fact, the observed values of $k_{(14)}$ are about the same for all the substituted salicylidenes. If, however, reaction 4 is isolated, the calculated values of k_4 depend strongly on the σ's as may be seen in Figure 5 (ρ = 2.85).

All the kinetically important reactions, under the experimental conditions where hydrolysis was studied, are depicted in Scheme I.

Rates and Products of Addition of 4-Chlorobenzenesulfenyl Chloride to the *tert*-Butylethylenes[1]

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Abstract: The rates of addition of 4-chlorobenzenesulfenyl chloride to ethylene (**1**), *tert*-butylethylene (**2**), 1,1-di-*tert*-butylethylene (**3**), *cis*- (**4**) and *trans*-1,2-di-*tert*-butylethylene (**5**) and 1,1,2-tri-*tert*-butylethylene (**6**) have been measured in 1,1,2,2-tetrachloroethane at 25°. The relative rates of **1:2:3:4:5:6** are $1:1.5:4.9 \times 10^{-4}:13:8.2 \times 10^{-5}:1.3 \times 10^{-4}$. The rate difference of 1.6×10^5 between *cis*- and *trans*-1,2-di-*tert*-butylethylene is the largest yet reported for addition to a cis-trans pair of isomeric alkenes. All products are formed by stereospecific anti addition. The experimental results are interpreted in terms of rate-determining formation of episulfonium ion intermediates which are converted to products by displacement by chloride ion. The rate differences are primarily due to steric hindrance to the approach of the electrophile in the rate-determining transition state.

Alkenes substituted with bulky hydrocarbon groups are of considerable utility in both experimental and theoretical studies of the effects of structure on chemical properties. The large substituents distort the ground-state geometries of the molecules, and thereby affect their reactivities relative to unstrained analogs. In addition the transition-state energies for reactions of alkenes are affected in two opposing ways by bulky substituents. On the one hand, significant repulsions

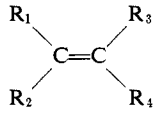
(1) Reactions of Sulfenyl Chloride and Their Derivatives. XI. For Part X, see G. H. Schmid and D. G. Garratt, *Can. J. Chem.*, **52**, 1807 (1974).

between large groups and adjacent cis substituents enhance processes that can reduce the repulsion by allowing the groups to move further apart. On the other hand, the bulky groups block access of reagents to the double bond and thereby inhibit reactivity. The manifestations of these properties of bulky groups have resulted in especially intense examination of the spectral properties[2] and reactivities[3] of alkenes substituted with *tert*-butyl groups, and various theoretical approaches have been presented to account for their structure and properties.[4]

The investigations of reactivity have concentrated particularly on the comparison of *cis*- and *trans*-1,2-di-*tert*-butylethylene, and have provided valuable mechanistic insights. However, these investigations have suffered from the absence of a systematic examination of the reactivity of the entire family of known *tert*-butylethylenes with any single reaction system. There has also been a particular dearth of quantitative measurements of the reactivity of alkenes with geminal di-*tert*-butyl groupings. Accordingly we have examined the rates and products of addition of 4-chlorobenzenesulfenyl chloride to all the known alkenes substituted only with *tert*-butyl groups.

Results

Rates of addition of 4-chlorobenzenesulfenyl chloride to ethylene (**1**), *tert*-butylethylene (**2**), 1,1-di-*tert*-butylethylene (**3**), *cis*- (**4**) and *trans*-1,2-di-*tert*-butylethylene (**5**), and 1,1,2-*tert*-butylethylene (**6**) in 1,1,2,2-tetrachloroethylene at 25° were measured by following the disappearance of the 4-chlorobenzenesulfenyl chloride absorption at 392.5 nm. The stopped-flow technique using a Durrum–Gibson spectrophotometer was used for **1**–**4** while the reactions of **3**, **5**, and **6** were monitored by conventional techniques using a Cary 16 spectrophotometer. The addition was found to exhibit normal second-order kinetics, first order in both alkene and sulfenyl halide, to 80% completion of the reaction. The rate data are presented in Table I.

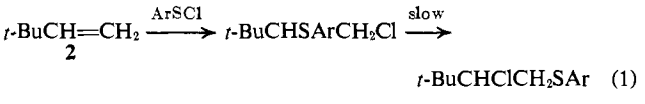


	R_1	R_2	R_3	R_4
1	H	H	H	H
2	*t*-Bu	H	H	H
3	*t*-Bu	*t*-Bu	H	H
4	*t*-Bu	H	*t*-Bu	H
5	*t*-Bu	H	H	*t*-Bu
6	*t*-Bu	*t*-Bu	*t*-Bu	H

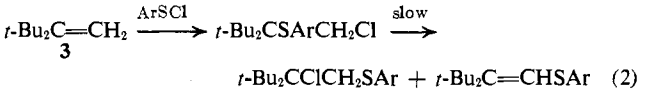
Table I. Specific Rate Constants for the Addition of 4-Chlorobenzenesulfenyl Chloride to a Series of *tert*-Butyl-Substituted Ethylenes at 25° in 1,1,2,2-Tetrachloroethane

Alkene	k_2, M^{-1} sec^{-1}	k_{rel}	No. of runs
CH_2=CH_2 (**1**)	65 ± 3	1	8
t-BuCH=CH_2 (**2**)	95 ± 3	1.5	5
t-Bu_2C=CH_2 (**3**)	0.0317 ± 0.005	4.9×10^{-4}	5
cis-*t*-BuCH=CH-*t*-Bu (**4**)	846 ± 11	13	6
trans-*t*-BuCH=CH-*t*-Bu (**5**)	0.00536	8.2×10^{-5}	5
t-Bu_2C=CH-*t*-Bu (**6**)	0.00816	1.3×10^{-4}	3

The addition of 4-chlorobenzenesulfenyl chloride to *tert*-butylethylene (**2**) and 1,1-di-*tert*-butylethylene (**3**) forms the adduct with anti-Markovnikov[5] orientation as the sole product in each case (eq 1 and 2). The



t-BuCHClCH$_2$SAr (1)

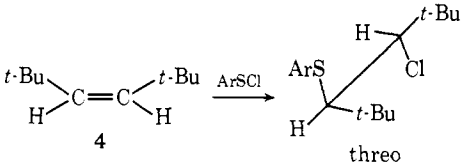


t-Bu_2CClCH$_2$SAr + *t*-Bu_2C=CHSAr (2)

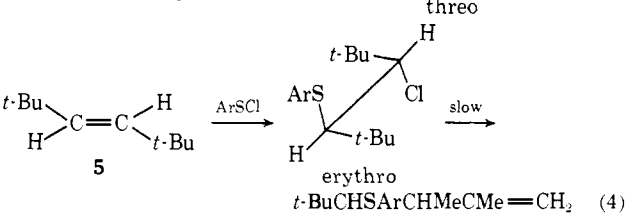
tert-butylethylene adduct slowly isomerizes (k_{iso} = 1.4×10^{-7} sec^{-1}; $t_{1/2}$ = 56 days) at 25° to the adduct with Markovnikov orientation (eq 1) while the adduct of **3** is slowly converted ($t_{1/2}$ = 2 months) to a mixture of 59% anti-Markovnikov and 26% Markovnikov adducts, with 15% elimination products (eq 2).

The regiospecificity of the adducts was established from the chemical shifts of the protons α to chlorine and sulfur in the pmr spectra. This assignment is based on the observation that protons adjacent to chlorine are deshielded relative to those α to sulfur.[6]

The addition is stereospecifically anti to *cis*- and *trans*-1,2-di-*tert*-butylethylene forming as the sole products the threo and erythro adducts, respectively (eq 3 and 4). The stereochemistry of these adducts is con-



(3)



t-BuCHSArCHMeCMe=CH$_2$ (4)

(2) (a) Nmr D. G. Garratt and T. T. Tidwell, *Org. Magn. Resonance*, **6**, 87 (1974); (b) uv G. J. Abruscato, R. G. Binder, and T. T. Tidwell, *J. Org. Chem.*, **37**, 1787 (1972); (c) vibrational spectra G. J. Abruscato and T. T. Tidwell, *J. Amer. Chem. Soc.*, **92**, 4125 (1970); (d) photoelectron spectra M. B. Robin, G. N. Taylor, N. A. Kuebler, and R. D. Bach, *J. Org. Chem.*, **38**, 1049 (1973).

(3) (a) Chlorination R. C. Fahey, *J. Amer. Chem. Soc.*, **88**, 4681 (1966); bromination (b) K. Yates and R. S. McDonald, *J. Org. Chem.*, **38**, 2465 (1973); (c) J.-E. Dubois and M. Lóizos, *C. R. Acad. Sci., Ser. C*, 274, 1130 (1972); (d) oxymercuration R. D. Bach and R. F. Richter, *J. Org. Chem.*, **38**, 3442 (1973); (e) hydroboration G. J. Abruscato and T. T. Tidwell, *ibid.*, **37**, 4151 (1972); (f) T. J. Logan and T. J. Flautt, *J. Amer. Chem. Soc.*, **82**, 3446 (1960); hydrogenation (g) R. L. Burwell, Jr., D. Barry, and H. H. Kung, *ibid.*, **95**, 4466 (1973); (h) R. B. Turner, A. D. Jarrett, P. Goebel, and B. J. Mallon, *ibid.*, **95**, 790 (1973); (i) R. B. Turner, D. E. Nettleton, Jr., and M. Perelman, *ibid.*, **80**, 1430 (1958); ozonolysis (j) P. S. Bailey, T. P. Carter, Jr., C. M. Fischer, and J. A. Thompson, *Can. J. Chem.*, **51**, 1278 (1973), also 3e; addition of radicals (k) G. D. Mendenhall, D. Griller, D. Lindsay, T. T. Tidwell, and K. U. Ingold, *J. Amer. Chem. Soc.*, **96**, 2441 (1974).

(4) (a) N. L. Allinger and J. T. Sprague, *J. Amer. Chem. Soc.*, **94**, 5734 (1972); (b) L. Radom, J. A. Pople, and W. L. Mock, *Tetrahedron Lett.*, 479 (1972); (c) O. Ermer and S. Lifson, *J. Amer. Chem. Soc.*, **95**, 4121 (1973).

(5) The isomer with Markovnikov orientation is defined as the one with a chlorine atom bonded to the more highly substituted carbon atom.

(6) (a) J. R. Caranaugh and B. P. Dailey, *J. Chem. Phys.*, **34**, 1093 (1961); (b) B. P. Dailey and J. N. Shoolery, *J. Amer. Chem. Soc.*, **77**, 3977 (1955).

Table II. Observed Proton and Carbon-13 Magnetic Resonance Parameters of the Adducts

Adduct	H_a	H_b	H_c	H_d
	^{1}H chemical shifts (δ, TMS)			
a b $ClCH_2CH_2SAr$	3.62 (m)	3.18 (m, AA'BB'; system)		
a b c *t*-BuCHSArCH_2Cl	1.06 (s, 9 H)	2.96 (dd, 1 H)	3.84 (dd, 1 H) 3.49 (dd, 1 H)	(ABC system)
a b c *t*-BuCHClCH_2SAr	1.13 (s, 9 H)	3.77 (dd, 1 H)	3.30 (dd, 1 H) 3.06 (dd, 1 H)	(ABC system)
a c *t*-$Bu_2CSArCH_2Cl$	1.28 (s, 18 H)		3.53 (s, 2 H)	
a c *t*-Bu_2CCCH_2SAr	1.23 (s, 9 H) 1.20 (s, 9 H)		2.82 (q, 2 H)	(AB system)
a b c d *t*-BuCHSArCHCl-*t*-Bu				
threo	1.05 (s, 9 H)	3.48 (d, 1 H)	4.16 (d, 1 H)	1.11 (s, 9 H)
erythro	1.11 (s, 9 H)	3.51 (d, 1 H)	4.05 (d, 1 H)	1.18 (s, 9 H)
a c d *t*-$Bu_2CSArCHCl$-*t*-Bu	1.14 (s, 9 H) 1.13 (s, 9 H)		3.96 (s, 1 H)	1.20 (s, 9 H)

^{13}C	C_a	C_b	C_c	C_d	C_e	C_f
a b c d e f $(CH_3)_3CCHClCHSArC(CH_3)_3$						
threo	28.33	38.48	71.26	58.90	37.49	27.78
erythro	28.53	38.47	73.74	68.98	38.30	28.33

firmed by the value of the vicinal coupling constants of the two isomers: J_{threo}^{H-H} = 0.5 Hz; $J_{erythro}^{H-H}$ = 3.2 Hz. This stereochemical assignment is substantiated by the results of an examination of the cmr spectra of a series of erythro–threo isomers.[7] As a general rule the chemical shifts of the tertiary carbons containing four different substituents of the erythro isomer are deshielded relative to those of the corresponding threo isomer.

While *threo*-4-chloro-2,2,5,5-tetramethylhex-3-yl 4′-chlorophenyl sulfide is stable to rearrangement and elimination for at least 6 months, the erythro isomer rearranges and eliminates HCl to form 4-(4′-chlorophenylthio)-2,3,5,5-tetramethyl-1-hexene as the major product within 24 hr at 25° in TCE.

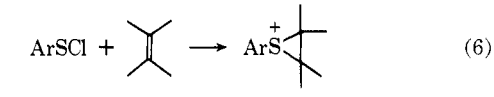
The addition to 1,1,2-tri-*tert*-butylethylene (**6**) gives the adduct with anti-Markovnikov orientation. The adduct rapidly undergoes rearrangement and elimination to give a number of products. On the basis of the pmr spectrum, the structure of the major product (approximately 60%) is believed to be 4-(4′-chlorophenylthio)-2,3,5,5-tetramethyl-4-*tert*-butyl-1-hexene (eq 5)

$$t\text{-}Bu_2C{=}CH\text{-}t\text{-}Bu \xrightarrow{ArSCl} t\text{-}Bu_2CSArCHCl\text{-}t\text{-}Bu \xrightarrow{slow} t\text{-}Bu_2CSArCHMeCMe{=}CH_2 \quad (5)$$

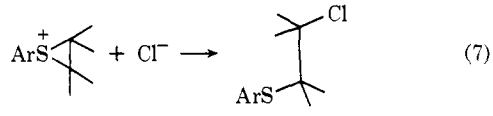
The pmr and cmr parameters for all the adducts are given in Table II.

Discussion

The mechanism proposed for the addition of arenesulfenyl chloride to alkenes involves a rate-determining formation (eq 6) of an episulfonium ion which is then attacked by chloride ion in the product-determining step (eq 7).[8]



(6)



(7)

Replacement of one hydrogen on ethylene by a *tert*-butyl group results in a small rate enhancement as expected for an electron donating alkyl group. However, the magnitude of the rate increase, namely a factor of 1.5, is less than that of 3.14 for replacing hydrogen on ethylene by a methyl,[9] suggesting a steric retardation by the bulky group. The steric effect of the *tert*-butyl group is far more pronounced in the product-determining step where the kinetically controlled product is only the one with anti-Markovnikov orientation. Such a result is consistent with the difference in steric hindrance between attack at a neopentyl-like carbon, which leads to the product with Markovnikov orientation, and at an ethyl-like carbon, which leads to the product with anti-Markovnikov orientation.

The most remarkable feature of these results is the enormous rate difference of 1.6×10^5 between *cis*-1,2-di-*tert*-butylethylene and the trans isomer. This is by far the greatest acceleration which has been observed for an addition to a cis–trans pair of isomeric olefins. This value can be compared with the k_{cis}/k_{trans} ratio of

(7) D. G. Garratt, unpublished observations.

(8) (a) W. L. Orr and N. Kharasch, *J. Amer. Chem. Soc.*, 78, 1201 (1956); (b) G. M. Beverly and D. R. Hogg, *Chem. Commun.*, 138 (1966); (c) W. H. Mueller and P. E. Butler, *J. Amer. Chem. Soc.*, 90, 2075 (1968); (d) G. H. Schmid, V. M. Csizmadia, V. J. Nowlan, and D. G. Garratt, *Can. J. Chem.*, 50, 245 (1972); (e) H. C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1972, pp 171–175, and references cited therein; H. C. Brown, J. H. Kawakami, and K.-T. Liu, *J. Amer. Chem. Soc.*, **95**, 2209 (1973).

(9) G. H. Schmid and D. G. Garratt, *Can. J. Chem.*, **51**, 2463 (1973).

0.37 for chlorination,[3a] and 46.4 for bromination[3b] of these same isomeric alkenes. However, the 1,1-di-*tert*-butyl and 1,1,2-tri-*tert*-butyl compounds show only very modest rate enhancements relative to the *trans*-1,2,di-*tert*-butyl compound. It is essential to account for these facts in an explanation of the reactivities of these compounds.

The observation that the electrophilic addition to cis alkenes is generally (but not always) faster than to the isomeric trans alkene has been explained by invoking a relief of ground-state steric strain in the rate-determining transition state of the addition to the cis isomer.[10]

However, this explanation cannot account for the results obtained herein, and accordingly appears not to be generally valid. The formation of kinetic products exclusively by anti addition from the *cis*- and *trans*-1,2-di-*tert*-butylethylenes supports bridged episulfonium intermediates as the only reasonable intermediates in the addition. If an open ion were formed from the cis isomer, it appears inconceivable that bond rotation would not occur, resulting in formation of the erythro adduct. The formation of the episulfonium intermediates results in at best very little relief of strain, and perhaps even an increase as the *tert*-butyl groups are forced closer together in this intermediate.[3a,b] Yet the cis isomer shows greatly enhanced reactivity, which must therefore be due to some other cause.

The effect of the *tert*-butyl groups on the relative rates of addition to **3**, **4**, and **5** can be explained by steric hindrance to the approach of the electrophile in the rate-determining transition state. Our results support a suggestion made previously[11,12] that the two trans *tert*-butyl groups seriously hinder the approach of an electrophile. The arenesulfenyl chloride cannot avoid the bulky *tert*-butyl groups in approach to the trans isomer **5**, but this steric repulsion can be avoided in addition to the cis isomer **4** if the arenesulfenyl chloride attacks the double bond off the perpendicular and approaches from the side opposite the *tert*-butyl groups. In the case of the 1,1-di-*tert*-butyl isomer all sides of the double bond are again blocked.

A comparison of the rates of addition to 1,1,2-*tert*-butylethylene (**6**) and *cis*-1,2-di-*tert*-butylethylene (**4**) provides further support for this argument. Placing a third *tert*-butyl group on the ethylene lowers the rate to a value similar to that for addition to **3** and **5**. The effect of this third *tert*-butyl group, placed on the opposite side of the other two in **4**, is to hinder the approach of the electrophile. The similarity of the rates **6**, **3**, and **5** suggests that the maximum hindrance is achieved when the *tert*-butyl groups are in the 1,1 or trans 1,2 positions. Addition of a further *tert*-butyl group has little effect on the rate.

The possibility that the rate-determining step may change as the steric bulk of the substituents on the alkene increase must be considered. Thus in the addition to the trans isomer **5** chloride attack upon the episulfonium ion intermediate might become rate determining. The fact that the relative rates of addition to 1,1- and *trans*-1,2-di-*tert*-butylethylenes are within a factor of 6 of each other makes this explanation unlikely. It has been observed for a wide variety of alkyl-substituted alkenes that the rates of addition of 4-chlorobenzenesulfenyl chloride to identically substituted 1,1- and trans 1,2-disubstituted alkenes are almost identical.[9,13] Such results have been interpreted in terms of the usual mechanism involving a bridged rate-determining transition state. The similarity in the rates of addition to **3** and **5** are consistent with this mechanism. Such a similarity in rates would not be expected if chloride ion attack were rate determining because the steric hindrance to chloride ion at the terminal carbon of **3** is considerably less than attack at the neopentyl-like carbons of **5**. Consequently the rate of addition to **3** would be expected to be much faster than to the isomer **5**.

These results may be compared to a recent study of the oxymercuration of *cis*- and *trans*-1,2-di-*tert*-butylethylene in which the threo product is reportedly formed in each case.[3d] These results suggest that there is a significant difference in the nature of the intermediates involved in the addition of sulfenyl halides and mercuric salts to olefins. The formation of the episulfonium ion intermediate is well established in sulfenyl halide additions.[8] A similar three-membered cyclic mercurinium ion, which has been proposed in the case of the oxymercuration reaction,[3d] appears incompatible with the results of the additions to *cis*- and *trans*-1,2-di-*tert*-butylethylenes.

In summary the additions of 4-chlorobenzenesulfenyl chloride to 1,1-di-*tert*-butylethylene, *trans*-1,2-di-*tert*-butylethylene, and 1,1,2-tri-*tert*-butylethylene are abnormally slow. This depression in rate can be explained by steric repulsion between the *tert*-butyl groups and the electrophile in the rate-determining transition state.

Table III. Analytical Data for Adducts of 4-Chlorobenzenesulfenyl Chloride and *tert*-Butyl-Substituted Ethylenes

Alkene	%C Calcd	%C Found	%H Calcd	%H Found	%S Calcd	%S Found	Mp, °C
1	46.39	46.32	3.89	4.04	19.48	15.50	27–28
2	54.76	54.65	6.12	6.06	12.18	12.28	*b*
3	60.18	60.22	7.58	7.65	10.04	10.06	65–70
4	60.18	60.28	7.58	7.68	10.04	10.18	29–32
5	60.18	60.18	7.58	7.55	10.04	10.00	*b*
6	*a*						*b*

[a] Sample too unstable for isolation in analytically pure form. [b] Samples colorless to yellow oils, decompose on attempted distillation.

Experimental Section

All melting and boiling points are uncorrected. Microanalyses were carried out by A. B. Gygli Microanalysis Laboratory, Toronto, Ontario, Canada.

4-Chlorobenzenesulfenyl chloride was prepared as previously described.[8d] **1,1,2,2-Tetrachloroethane** was purified as previously described.[8d] **Ethylene (1)**, ***tert*-butylethylene (2)**, and ***trans*-1,2-di-*tert*-butylethylene (5)** were obtained commercially and used without further purification. **1,1-Di-*tert*-butylethylene (3)** was prepared by the method of Newman.[14] ***cis*-1,2-Di-*tert*-butylethylene (4)** was prepared by the method of Hennion and Banigan.[15] **1,1,2-Tri-*tert*-butylethylene (6)** was prepared by the method of Tidwell.[2b]

Kinetic and product analyses were carried out or prepared as previously described.[8d] The elemental analysis of the adducts are

(10) G. Mouvier and J. Dubois, *Bull. Soc. Chim. Fr.*, 1441 (1968).
(11) Reference 25 in ref 3b.
(12) R. C. Fahey, private communication.
(13) C. L. Dean and G. H. Schmid, unpublished observations.
(14) M. S. Newman, A. Arkell, and T. Funkunaga, *J. Amer. Chem. Soc.*, **82**, 2498 (1960).
(15) G. F. Hennion and T. F. Banigan, *J. Amer. Chem. Soc.*, **68**, 1202 (1946).

reported in Table III. Carbon-13 nmr data were collected using a Varian Associates XL-100-15 spectrometer operating in the Fourier transformer mode at 25.160 MHz.

Acknowledgment. Continued financial support by the National Research Council of Canada is gratefully acknowledged. The technical assistance of Mr. Nick Plavac is greatly appreciated as is a University of Toronto Special Open Fellowship to D. G. G.

A New Purine Ring Closure and the Synthesis of 2-Substituted Derivatives of Adenosine Cyclic 3′,5′-Phosphate[1]

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Contribution from the ICN Pharmaceuticals, Inc., Nucleic Acid Research Institute, Irvine, California 92664. *Received November 29, 1973*

Abstract: A new and useful procedure for closure of the purine ring under relatively mild conditions is reported. Treatment of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamidine cyclic 3′,5′-phosphate (**2**) with aldehydes under mild oxidative conditions has provided a series of unusual 2-alkyl- and aryladenosine cyclic 3′,5′-phosphates. Trifluoroacetamide and **2** gave 2-CF_3-cAMP. Triethyl orthoacetate and orthopropionate and **2** gave 2-methyl- and 2-ethyl-cAMP, respectively. Ring closure of **2** with 1,1′-carbonyldiimidazole gave 2-hydroxy-cAMP, and **2** and 1,1′-thiocarbonyldiimidazole gave 2-thio-cAMP. Methylation of the latter compound gave 2-MeS-cAMP. Treatment of **2** with nitrous acid gave 2-aza-cAMP. The new cAMP derivatives are activators of a cAMP-dependent protein kinase and inhibit the hydrolysis of cAMP by phosphodiesterase.

We wish to report a new procedure for ring closure of an imidazole precursor to provide 2-substituted adenines under conditions which may have implications in the possible biochemical synthesis of such naturally occurring modified nucleic acid constituents as 2-methyladenine.[2]

The desire for derivatives of adenosine cyclic 3′,5′-phosphate (**1**, cAMP) with substituents in the 2 position of the adenine ring prompted a search for new synthetic procedures which would allow the introduction of such a substituent at the final step in the synthetic scheme. Classically, 2-substituted adenine derivatives have been synthesized from the appropriate 2-substituted 4,5,6-triaminopyrimidine or related derivatives by introduction of the C_8 carbon fragment.[3-5] This method is not generally useful in the direct synthesis of adenines with a substituent at the 9 position, a group comprising almost all adenine nucleosides and nucleotides of biological interest. Routes to 2-substituted adenines from 5(4)-aminoimidazole-4(5)-carbonitriles were available[6] but were of limited scope and required, for our purposes, difficultly obtainable intermediates.

We now wish to report methods which provide a wide variety of 2-substituted derivatives of adenine with a preintroduced substituent on the 9 position. In particular, the key intermediate 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamidine cyclic 3′,5′-phosphate[7] (**2**) has been treated with various reagents under mild conditions to furnish directly the desired 2-substituted cAMP derivatives. Of particular interest is the reaction of **2** with aldehydes under oxidative conditions. This new procedure, which should be generally applicable to 1-substituted 5-aminoimidazole-4-carboxamidines, readily provides a multitude of 2-alkyl and 2-aryl-9-substituted adenines.

The imidazole nucleotide **2** was also converted to 2-thio- and 2-hydroxy-cAMP and to 2-aza-cAMP by modifications of known procedures.

The attractive feature of these methods, for the purpose of this study, is the introduction of the 2 substituent in the final step of the scheme. This provides a direct route to the required cAMP derivative and avoids the more lengthy route of purine → nucleoside → 5′-nucleotide → cyclic 3′,5′-nucleotide[8] for each compound.

The rapid proliferation, in recent years, of literature regarding the biochemical and physiological functions of cAMP has encouraged studies in these laboratories of the effects of modification of the cAMP molecule on these various functions. Indeed, such compounds should provide useful tools for understanding of the biological mechanisms through which cAMP operates. We have previously studied substituents in the 1,[7] 6,[7,9,10] and 8[11,12] positions of the purine ring of cAMP,

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