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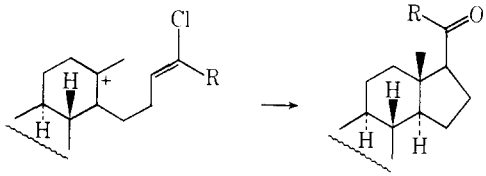
Model Studies for Steroid C/D Ring Synthesis. Stereoselective Hydrindan Formation by Means of Acetylene–Cation Cyclization

Peter T. Lansbury,* Timothy R. Demmin, Grant E. DuBois, and Virginia R. Haddon

Contribution from the Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14214. *Received July 15, 1974*

Abstract: Intramolecular attack upon a 1-methylcyclohexyl cation by the triple bond of an adjacent 3-hexynyl side chain provides a synthetic entry into the acylhydrindan system characteristic of many 20-ketosteroids. *trans*-Decalyl substrates bearing an equatorial alkynyl side chain at C_1 and a potential tertiary carbonium ion at C_2 cyclize stereoselectively to yield predominantly *trans*- or *cis*-hydrindan systems, depending on whether carbonium or episulfonium ions are involved.

During studies of chloroalkene-carbonium ion cyclization relating to annelation of cyclopentanes, cyclohexanes, and cycloheptanes,[1] we investigated such reactions for assembling the C/D trans-fused hydrindane portion of 20-keto steroids,[2] *e.g.*

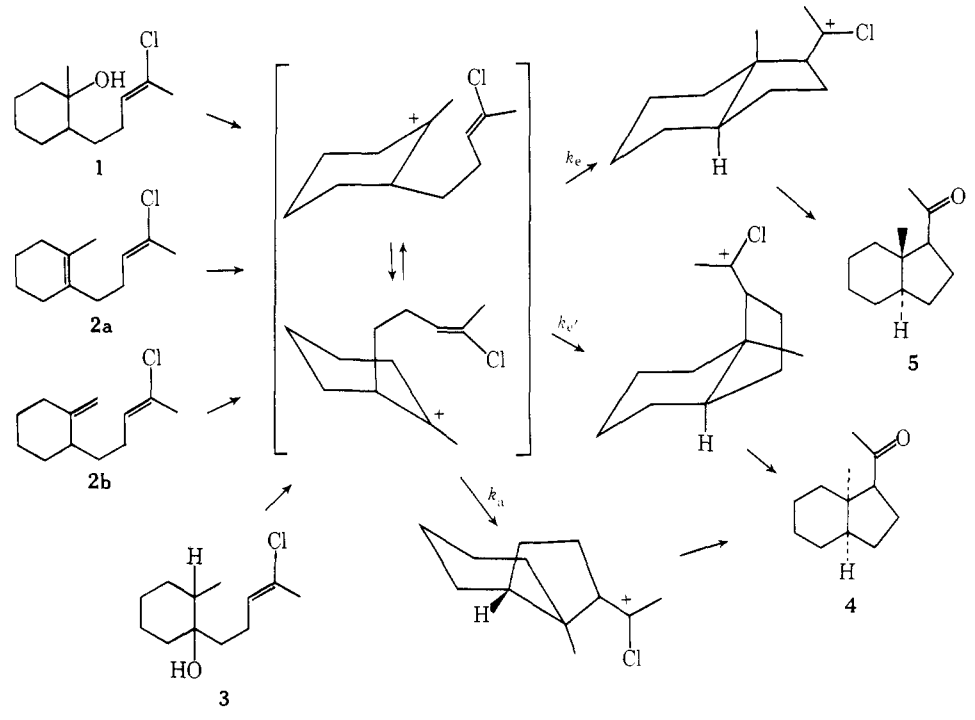


Initially it was observed that monocyclic model compounds such as **1–3** cyclized efficiently during formolysis but with predominating formation of cis-fused hydrindans (the ratio of **4:5** was usually *ca.* 75:25). The product ratios were essentially identical regardless of carbonium ion precursor,[3] thus leading to our assumption that, by means of deprotonation-reprotonation equilibria, the same classical carbonium ion was probably involved in each case. Reasoning that conformationally flexible carbonium ions derived from **1–3** might favor cis-fused product by cyclizing more rapidly from that conformer with an axial side chain ($k_a > k_e$ and/or $k_{e'}$), we subsequently investigated the appropriate *trans*-decalyl system in which a "k_a-like process" (Scheme I) would only come about *via* higher energy "twist-boat" conformers and thus be a less serious complication.[4a] Scheme II shows that during mild solvolysis in 97% formic acid,[5] wherein hydrolysis of the initially produced α-chlorocarbornium ion essentially eliminates retroyclization,[1] the expected change in stereoselectivity occurred: however, the twofold preference for trans-fused hydrindans could not be improved to the higher levels needed for incorporating this approach into steroid synthesis.

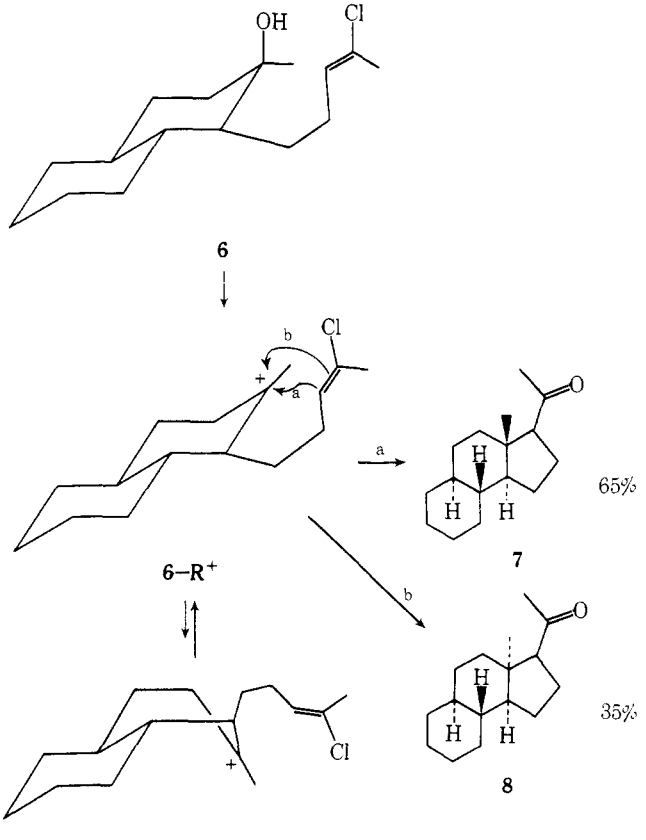
From considerations of molecular geometry it appeared likely that an acetylenic cyclization[6] could have a different stereochemical outcome from the corresponding chloroalkene one, since the predominantly linear side chain might have a grossly different steric requirement from the angular vinyl one for axial *vs.* equatorial approach to the cyclization terminus. At the same time, however, solvolysis of **9** could result in six-membered ring formation (→**10**) as well as five (→**4** and **5**) (Scheme III). This expectation was based originally on previously observed product compositions resulting from intramolecular alkynyl participation in solvolysis of secondary substrates[7] as well as rearrangements of cycloalkenyl triflates.[8] If acetylenic cyclization could be directed toward methylenecyclopentanes, an additional useful possibility would be regiospecific electrophilic funtionalization of the initial enol derivative.

The present investigation began about 5 years ago[3] with acid solvolysis of **9**, the acetylene analog of **1**, since information on *tert*-carbonium ion–alkyne combination was then not available. Carbinol **9** was readily prepared by alkylating the cyclohexylimine salt of cyclohexanone with 3-pentynyl tosylate and treating the resultant ketone with methyllithium. Formolyses and trifluoroacetolyses[9] of **9**, followed by saponification of the resultant enol esters, resulted in a ketone mixture containing all of the products expected (*vide supra*). These are shown in Scheme IV, which also summarizes how the decalones were independently prepared[10] and the hydrindans degraded.[2,3] Gas chromatography allowed separation of the acetylhydrindans **4** and **5** from the longer retention time decalones **13** and **14**; in addition, nmr spectral examination of the angular methyl group signals in **4**

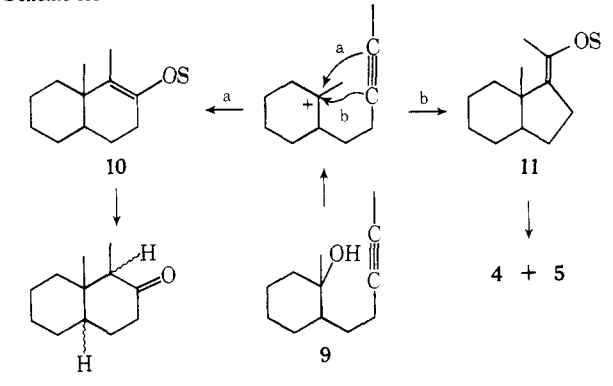
Scheme I



Scheme II



Scheme III

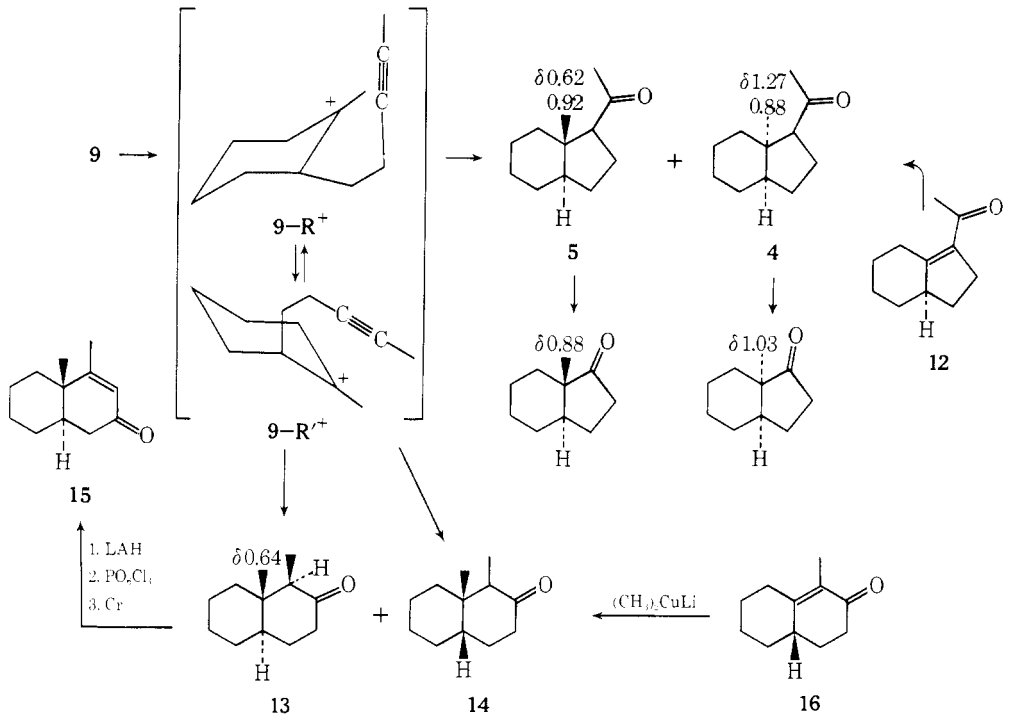


and **5** (Scheme IV) and their integration permitted estimation of the stereomer ratios.[11] Table I summarizes the results of a number of cyclizations.[12]

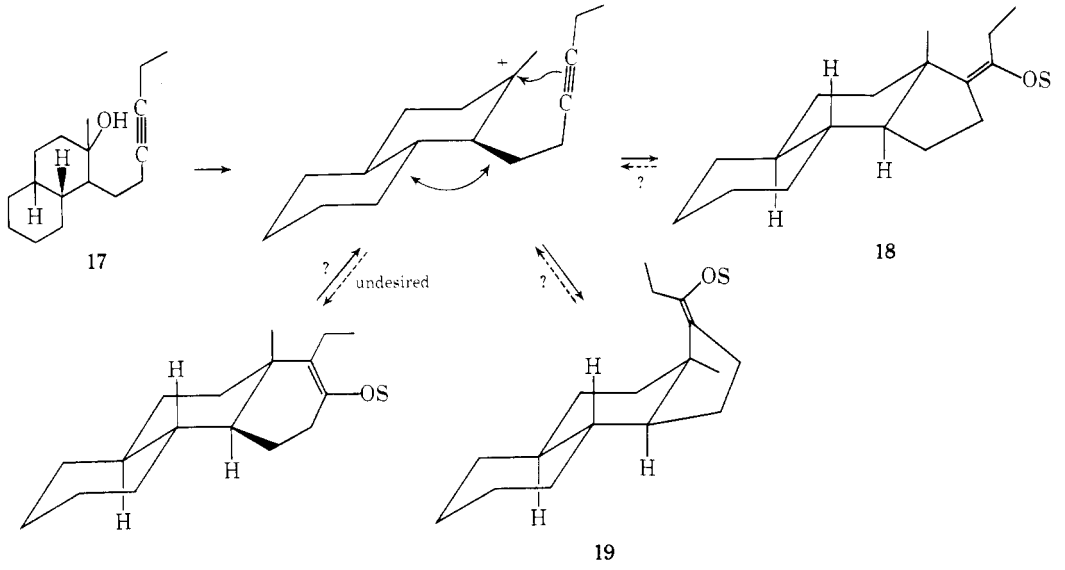
The mild formolyses are probably irreversible,[1] whereas anhydrous trifluoroacetolysis may occur reversibly (*vide infra*), especially under extended, vigorous conditions (*cf.* run 5). Besides the not unexpected predominance of cis-fused acetylhydrindans, there was a substantial proportion of trans-fused decalones in *all* runs, especially extended trifluoroacetolysis. It is conceivable that cation **9-R'**$^+$ is a major source of the *cis*-hydrindanones[4b] and **9-R**$^+$ the decalones. Neither trend was encouraging in that our eventual goal was the synthesis of 6/5 trans-fused vinyl esters from an ion of type **9-R**$^+$. However, a subsequent series of model experiments dovetailing those with **9** was not only designed to prevent closure *via* axially oriented side chains (*e.g.*, →**4** and **14**) but also to minimize formation of 6/6-fused compounds (*e.g.*, → **13** and **14**). Thus, it was anticipated that decalol **17** would provide a conformationally homogeneous carbonium ion in which nonbonded interactions between the remote ring (corresponding to the steroidal B ring) and the cyclizing side chain (arrows) would encourage the latter to kinetically favor cyclopentanoid cyclization. In the event of reversible behavior, the gauche effect would hopefully again be minimized in the desired product (**18**) rather than the cyclohexenoid one (Scheme V).

In choosing a synthetic approach to the bicyclic carbinol **17**, consideration was given to finding a route that would ultimately be applicable to the steroids themselves; that is, a trans,anti,trans tricyclic carbinol conforming to rings A, B, and C should also be accessible. Such a path is outlined in Scheme VI, in which the solvolysis products and their characterization also appear. The transformation **20** → **21** → **22** avoids the problematic reductive alkylation[13] of $\Delta^{1(9)}$-2-octalone with 1-iodo-3-hexyne; such reactions frequently result in loss of site- and stereoselectivity,[14] as well as permitting over-alkylation. It is noteworthy that lithium–ammonia

Scheme IV



Scheme V



reduction of enone **21** proceeded stereoselectively at −75° with no observable reduction of the alkyne group.[15] Methyllithium addition to **22** completed the preparation of **17**; the latter apparently was a single isomer whose stereochemistry was not rigorously established.[16] Fortunately configuration was apparently not of crucial importance since in the case of **9** either epimeric carbinol gives the same carbonium ion.[9,12] A large number of formolyses and trifluoroacetolyses were performed. In the former case, 97% formic acid and anhydrous formic acid (alone or with up to 20% added acetic anydride) were both used at temperatures of 10–100° and for reaction times of 1–80 hr. Trifluoroacetolyses typically involved *ca.* 3:1 mixtures of the acid and anhydride at temperatures of −15 to 60° for *ca.* 2 hr. After quenching the solvolysis mixtures in water, the initially formed enol esters (sometimes accompanied by ketones, in the case of long term formolysis) were saponified and the epimeric mixtures of **23** and **24** identified *inter alia* by their angular methyl group nmr signals (see Scheme VI), either before or after equilibration of the ketonic side chains was complete. To augment these results, degradation of the acyl groups in **23** and **24** was carried out as described previously,[2] and the resulting tricyclic ketones **25** and **26,** now two stereochemically homogeneous species, were analyzed and further characterized. Ketone **25,** expected from both acyl epimers of **23,** was also a synthetic goal and hence independent confirmation of its relative configuration seemed imperative. This was readily established by unambiguous transformations of **27,** provided by Dr. G. Nomine of Roussel-Uclaf, into authentic **25** and establishment of the identity of this material with that obtained from **23.** In general, formolyses afforded 90–95% yields of cyclized ketones, of which 60–70% was trans-fused isomer **23** and the remainder cis. Trifluoroacetolysis gave comparable combined yields of **23** and **24,** but a greater proportion of the former. At −15° after 2 hr, the ratio **23/24** was 83/17, which exceeded the typical 75% of **23** encountered at reflux,[17] but which could not be further improved.

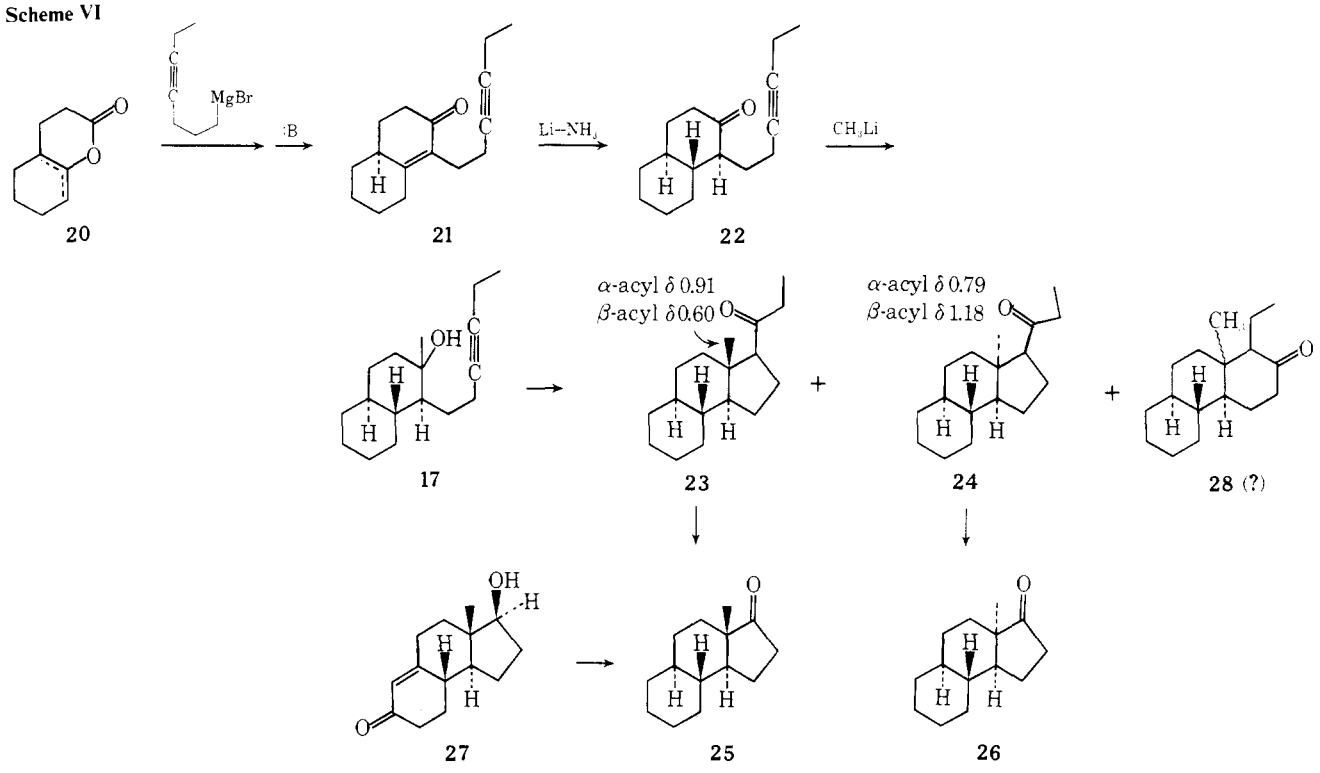
It is noteworthy that no detectable products of six-membered annelation (*i.e.*, structure **28**) resulted from **17,** in

Table I. Solvolytic Cyclization of Carbinol **9**

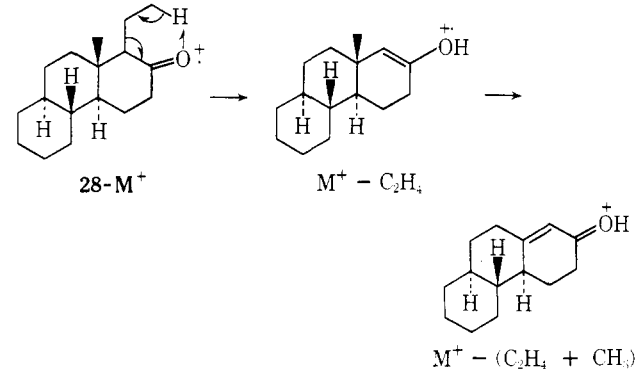
Run no.	Conditions	% **4** + **5**	Trans (**5**)/cis(**4**)	% **13** + **14**	Trans (**13**)/cis(**14**)
1	97% HCOOH; room temp, RT 15 hr	82	0.4	18	1.6
2	97% HCOOH; reflux, 45 min	79	0.5	21	2.7
3	CF_3COOH;[a] −15°, 4 hr	64	1.4	36	~100
4	CF_3COOH;[a] 0°, 9 hr	63	1.2	37	~50
5	CF_3COOH;[a] reflux, 8 hr	55	0.42	45	4.6

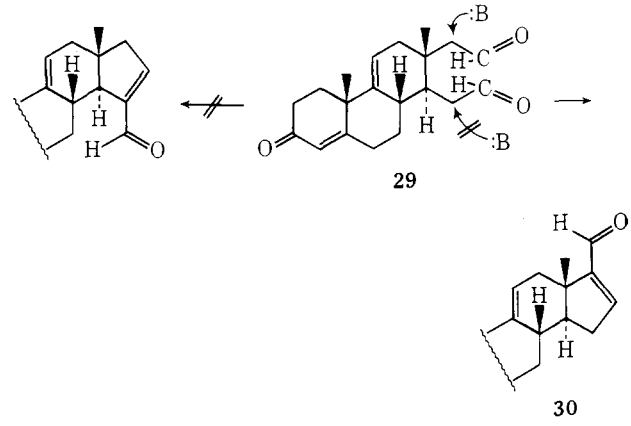
[a] 10% trifluoroacetic anhydride was added to maintain anhydrous conditions prior to hydrolytic work-up.

Scheme VI



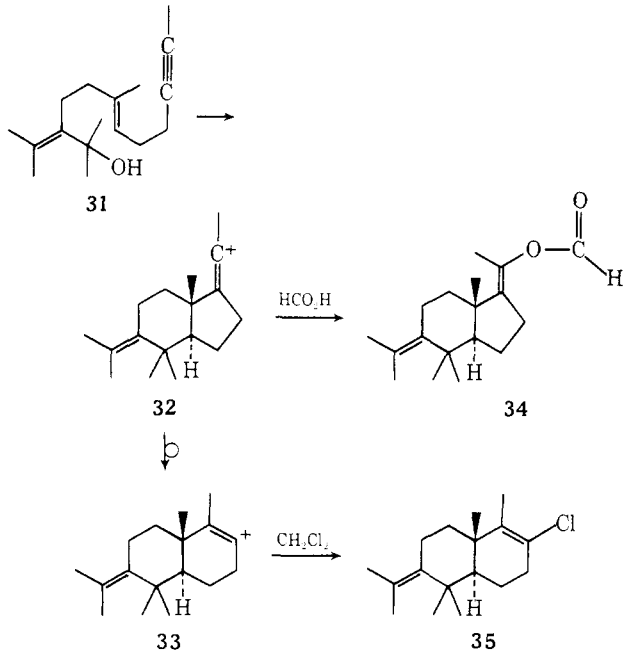
contrast with the behavior of **9.** It was expected that **28,** regardless of stereochemistry, should undergo characteristic mass spectral fragmentation as indicated.





Neither of the above fragment ions was noted upon mass spectroscopic analysis of the minor reaction products after vinyl ester hydrolysis.[18] Not only is this a gratifying result, in terms of potential for steroid synthesis, but also a surprising one in view of the substantial proportions of 6/6 transfused material derivable from **9.** It appears, then, that the aforementioned steric buttressing effect of "ring B" has a noticeable influence on the regioselectivity of this intramolecular reaction. Similar arguments were used by Woodward[19] to explain the direction of ring D formation *via* aldolization of tricyclic steroid intermediate **29** to **30.**

At the time we first reported our steroid ring D synthesis *via* acetylenic annelation,[17] Johnson and his group also presented the first[20a] of an ongoing series of communications[20] on polyenynyl cyclizations leading to 20-keto steroids with results in general accord with ours. However, Johnson stressed the need to trap the initially expected tetracyclic vinyl cation with good nucleophiles such as formic acid and vinylene carbonate, as well as intramolecular double bonds, in order to avoid possible rearrangement to six-membered D rings. In a model study, formolysis of **31** gave vinyl ester **34,** whereas in the supposedly nonnucleophilic solvent methylene chloride, **35** was the observed product,[21] allegedly by rearrangement of ion **32** or its halonium ion equivalent.[22] These findings would seem to be at variance with the ob-

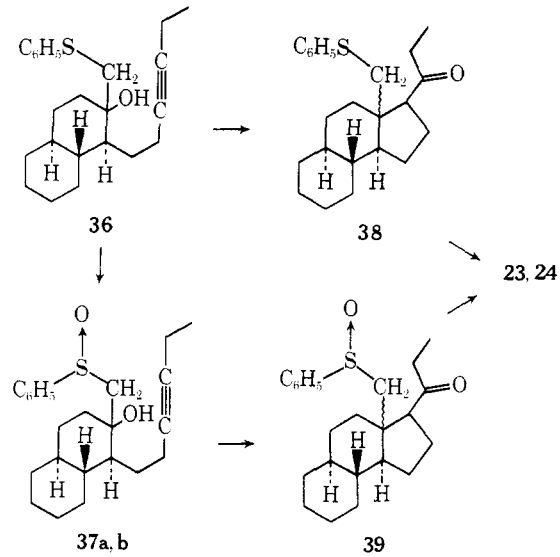


served reactions of **17** (*vide supra*) and related carbinols,[20] perhaps because the rearrangement **32** → **33** is particularly favored in this nonsteroid system and not necessarily a general occurrence.

Concerning possible rearrangement of initially formed vinyl cation derivatives from cyclization of **17,** we did make some preliminary observations which suggest that **18** and **19** may be equilibrating *via* reversible fragmentation[23] (Scheme V, dotted lines). Such an event could lead to stereomutation of the C/D ring fusion, without concomitant rearrangement to six-membered ring products as we have already noted to be the case. Thus, although **17** undergoes almost immediate quantitative cyclization in dry trifluoroacetic acid to **18** and **19,** the first-formed enol ester mixture (saponified and analyzed as **23** and **24**) undergoes a small but reproducible change in stereomer composition upon extended exposure to reaction conditions.[24] Specifically, work-up of one-third of such a reaction, after 1 hr at −15 to 0°, afforded over 95% cyclization product showing a stereomer distribution of 81% **23** and 19% **24.** After the remaining mixture was allowed to warm to 25° during 5.5 hr, work-up of a second third gave 78% of **23** and 22% of **24.** Finally, heating the last portion for an additional 16 hr at 60° again changed the isomer ratio to 76:24, still favoring trans. Similar product spreads were observed by DuBois[17] in separate short- and long-term trifluoroacetolysis experiments in which the products were degraded back to cyclopentanones **25** and **26.** Unfortunately, these results could also arise from slight preferential loss of **18** (or **23**) during the long-term reactions. Until pure samples of **18** and **19** (OS = trifluoroacetate) can be brought to equilibrium from each side, we must regard the fragmentation hypothesis as only tentative. For the present we note that acetylenic closures to produce fused acylcyclopentanes have a greater propensity for trans ring fusions than chloroalkene cyclizations. Rearrangement of initial intermediates to cyclohexenoid esters is apparently not a serious problem. Finally, initially generated vinyl ester intermediates provide additional functionalization opportunities which can be advantageous in generating 17-functionalized-20-keto steroids.[20c]

Attempts to include a "handle" for functionalizing the angular methyl group, if desired, while simultaneously improving the stereoselectivity of ring D acetylene annelation (*i.e.*, **17** → **23**) were undertaken. For example, replacement of methyl in **17** by an α-thioanisyl group (*i.e.*, **36** below) would allow subsequent desulfurization of the arylthio portion after cyclization and assessment of the resultant ratio of **23** to **24.** Secondarily, the sulfur substituent, or its derived sulfoxide **37,** provides a variety of opportunities for further alkylation and/or oxidation of the latent angular methyl group (Scheme VII). Carbinol **36** was obtained in

Scheme VII



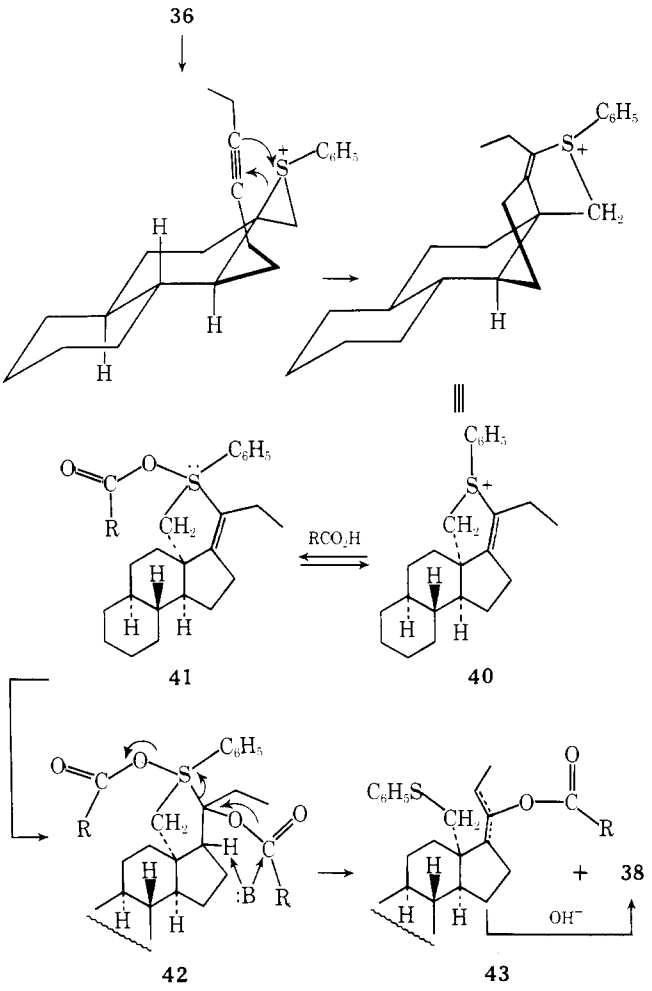
87% yield by addition of α-lithiothioanisole[25] to decalone **22;** sulfoxide carbinols **37a,b** in turn, were obtained by chemospecific *m*-chloroperbenzoic acid oxidation[26] of the sulfide function in **36.** On the basis of earlier results with **17,** a series of mild, nonequilibrating formolysis and trifluoroacetolysis experiments with **36** were conducted with the expectation that the proportion of trans-fused annelation products would be greatest. As before, any initially formed vinyl esters were saponified if still present; Raney nickel hydrogenolysis of **38** subsequently afforded the desulfurized ketones **23** and **24** in high yields. The latter were equilibrated to provide the previously established ratios of acyl epimers and analyzed by glpc. It was clear in all cases that a dramatic change to predominantly cis-fused products had occurred. For example, mild trifluoroacetolysis (0°, 1 hr) afforded over 80% yield of cyclized vinyl ester of which 96% was cis (*i.e.*, leading eventually to **24**); similarly, in 97% formic acid (45°, 1 hr) **36** provided 82% of cyclic ketones **38** (after saponification of enol formate) whose hydrogenolysis revealed a cis content (**24**) of 91% *vs.* 9% of trans. Several additional extended formolyses of **36** (up to 50 hr at reflux) gave rise to not less than 86% of **24!** The stereochemical outcome was not altered by switching from **36** to the individual epimeric sulfoxides, **37a** and **37b,** whose formolysis (70°, 3 hr) gave a more complex product mixture. Nevertheless, after ester hydrolysis and chromatography, tricyclic ketosulfoxides (**39**) were isolated in *ca.* 50% yield; the ratios **23**/**24** from hydrogenolysis of **39** were 8/92 and 3/97, essentially the same within experimental error regardless of sulfoxide configuration.

Methods had now been developed for controlling this steroid ring D annelation to give either stereochemical outcome in great preponderance. Clearly, an explanation for these findings was desirable and a plausible one, conducive to further testing, is herein offered.

To begin with, conformational rigidity in the *trans*-decalyl framework restricts the cyclizing side chain in both **17** and **36** to an equatorial position (at C_1). However, the conformations of the side chain itself, and hence product stereochemistry,[4] may differ from **17**-R^+ if the predominating

ion originating from ionization of **36** is actually a specific *thiiranium ion,*[27] rather than a carbocation. In the latter situation the polarizable acetylenic π-system might be attracted by the electrophilic sulfonium center, as had been reported for a variety of nucleophiles,[28] with resultant sulfurane species arising[28] and then collapsing[29] as pictured in Scheme VIII. Once sulfonium ion **40** is formed, further

Scheme VIII

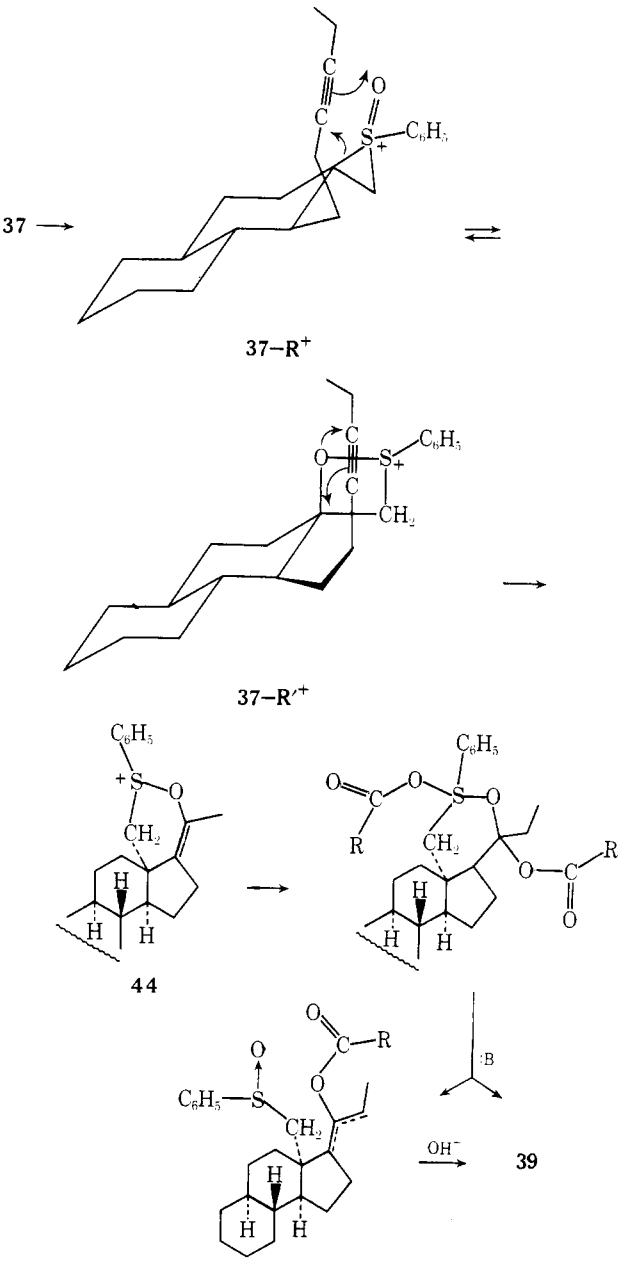


transformations involving direct C–S cleavage by nucleophilic attack are sterically (at the neopentyl carbon) and/or electronically (at vinyl and aryl carbon) unfavorable, as is E2 elimination. Hence, sulfurane **41** resulting from carboxylate attack on sulfur is a plausible intermediate[28] and one that could lead to **42.** In particular, the vinyl sulfide moeity in **41** affords the opportunity for electrophilic addition of formic acid to the π-bond and subsequent breakdown of the adduct to **43** and/or **38** as formulated above.

The stereochemical outcome of solvolytic cyclization using sulfoxide carbinol **37** can be rationalized in an analogous manner (Scheme IX), employing the possible intermediacy of sulfurane oxides.[30] The cyclohexyl cation derivable from **37** could alkylate either nucleophilic atom of the sulfoxide[30] (resulting in **37-R**$^+$ and/or **37-R′**$^+$); π-attack thereupon followed by bond reorganization would lead to **44** which, in turn, would ultimately add two formate residues prior to collapsing to **39.** The latter, accompanied by enol ester **45,** was saponified and hydrogenolyzed to provide nearly pure **24.**

We stress that the observed cis stereoselectivities given by **36** and **37** upon acidic cyclization do not *require*[4b] the intervention of sulfonium ions and sulfuranes; however, the known properties of such intermediates[28-30] are not in dis-

Scheme IX



agreement with our provisional interpretation, which hopefully can be buttressed by further experimentation. Furthermore, the idea of employing transient sulfonium ion $\rightleftarrows$ sulfurane intermediates as stereochemical control elements[31] may well become widely relevant in the design of stereorational syntheses.

Experimental Section[32]

General Considerations. Melting points, determined on a "Mel-Temp" capillary tube apparatus, and boiling points are uncorrected. Infrared spectra were recorded on a Beckmann IR-5A spectrometer and were calibrated using the 6.23 μ band of polystyrene. Ultraviolet spectra were recorded on a Perkin-Elmer Model 202 instrument. Nuclear magnetic resonance spectra were obtained with Varian A-60 and/or Joelco 100MHz spectrometers using TMS as internal standard in chloroform-*d* or carbon tetrachloride. Mass spectra were obtained on a Perkin-Elmer Hitachi RMU-6E mass spectrometer at 70 eV ionization potential. Vapor phase chromatography analyses and separations were performed on a F and M model 720 instrument, using triangulation and/or cutting and weighing of peaks to estimate composition of mixtures; columns used varied from case to case and are specified in individual

experiments. When referring to "standard work-up," a reaction mixture was partitioned between ether and aqueous layers; the former was washed with saturated sodium chloride solution, dilute acid, or base where necessary and finally dried over anhydrous magnesium sulfate. After solvent removal, product mixtures were subjected to glc, tlc, and column chromatography as noted. Bulb-to-bulb distillations were performed with a "Kugelrohr" apparatus, with recorded temperatures referring to the heating oven.

2-(3-Pentynyl)cyclohexanone. This compound was synthesized by the imine alkylation procedure of Stork and Dowd.[33] The imine salt prepared from *N*-cyclohexylidenecyclohexylamine[34] (7.16 g, 0.04 mol) and ethylmagnesium bromide (0.045 mol) in THF (100 ml) was treated with 3-pentynyl *p*-toluenesulfonate[35] (0.04 mol) and then heated to reflux for 10 hr. Hydrolysis using 5% HCl at room temperature for 1.5 hr, followed by normal work-up and chromatography over silica gel (120 g) using 3–6% ether in hexane as eluent, yielded 2-(3-pentynyl)cyclohexanone (3.0 g, 46%) as a colorless oil: nmr ($CDCl_3$) δ 0.92–2.68 (m), 1.70 (t, J = 2.5 Hz, CH_3); ir λ_{max} (film) 5.84 (C=O); mass spec *m/e* (rel intensity) 164 (M^+, 8), 98 (100). An analytical sample was prepared by Kugelrohr distillation: bp 95–102° (1.8 mm).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.31; H, 9.75.

After three recrystallizations from ethanol–water, the semicarbazone of 2-(3-pentynyl)cyclohexanone had mp 142.5–143°.

Anal. Calcd for $C_{12}H_{19}N_3O$: C, 65.13; H, 8.65. Found: C, 65.16; H, 8.70.

1-Methyl-2-(3-pentynyl)cyclohexanol (9). 2-(3-Pentynyl)cyclohexanone (0.50 g, 3.05 mmol) in ether (10 ml) was treated with 3 equiv of ethereal methylmagnesium iodide. After 9 hr at room temperature the reaction mixture was subjected to standard work-up, yielding 1-methyl-2-(3-pentynyl)cyclohexanol (0.51 g, 93%) as a colorless viscous oil, 99% pure by vpc analysis (12 ft SE-30, 170°). Two stereoisomers were detected in a 4:1 ratio with retention times of 27.7 and 28.9 min, respectively: nmr ($CDCl_3$) δ 0.8–2.5 (m), 1.05 (s, minor isomer C_1-CH_3), 1.17 (s, major isomer C_1-CH_3), 1.72 (t, J = 2 Hz, $CH_3C{\equiv}C$); ir λ_{max} (film) (major isomer) 2.82 (-OH), (minor isomer) 2.86 (-OH); mass spec *m/e* (rel intensity) (major isomer) 180 (M^+, 10%), 147 (55), 96 (56), 81 (100); (minor isomer) 180 (M^+, 6), 147 (71), 109 (68), 67 (100). The analytical sample was obtained by Kugelrohr distillation, oven temperature 88–92° (0.1 mm).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.86; H, 11.02.

Trifluoroacetolysis of 9. Product Isolation and Characterization. A large number of formolyses and trifluoracetolyses of **9** were carried out, with key experimental conditions and product information summarized in Table I (additional experiments with **17** and **36** are described below). In a typical run, scaled up to allow product isolation in quantities suitable for degradations in addition to spectral characterization, 3.9 g of **9** in 45 ml of trifluoroacetic acid and 5 ml of trifluoracetic anhydride was kept at room temperature, under nitrogen, for 8 hr. Hydrolysis and ether extraction, followed by standard work-up, afforded a mixture of vinyl trifluoroacetates **10** and **11**: ir λ_{max} (film) 5.58 μ (trifluoroacetate); nmr ($CDCl_3$) angular methyl singlets at δ 0.93, 1.00, 1.11, 1.25, vinyl methyl triplets ($J \simeq$ 1.5–2.0 Hz) at δ 1.51 and 1.98.

The stereomeric mixture of **10** and **11** was saponified (10% aqueous KOH, 50°, 1 hr), then worked up to give 2.86 g (73%, based on **9**) of ketones **4, 5, 13,** and **14** showing common ir absorption at 5.84 μ and loss of the 5.58 μ band. Glpc on a 12 ft SE-30 column at 200° allowed elution of hydrindans **4** and **5** prior to decalones **13** and **14.**

The mixture of **4** and **5** exhibited the expected four angular methyl singlets (see Scheme IV), in accordance with Djerassi's report,[36] and each compound showed M^+ at *m/e* 180. The assignment of the peaks at δ 0.88 and 1.27 to the acetyl epimers of **4** was further corroborated by synthesis *via* lithium dimethylcuprate conjugate addition to enone **12.**[37] A semicarbazone prepared from the mixture of **4** and **5** had mp 183.5–185.5 (from ethanol–water).

Anal. Calcd for $C_{13}H_{23}N_3O$: C, 65.78; H, 9.76. Found: C, 65.60; H, 9.94.

Three-step degradation[12] of **4** + **5** (peroxytrifluoroacetic acid, ester saponification with aqueous KOH, followed by Jones oxidation) gave *cis*- and *trans*-8-methyl-1-hydrindanones, separable by glpc on 6 ft Carbowax 20M (150°). These ketones were converted to the known[38] semicarbazones: cis, mp and mmp 219–220°; trans, mp and mmp 238–240°.

Decalones **13** and **14** were characterized by conversion of the former into the previously reported[10] trans-fused octalone **15** and by independently synthesizing **14** from **16** in unambiguous fashion. The semicarbazone of **13,** prepared from ketone isolated by preparative vpc, had mp 208.5–210.5° (from ethanol–water).

Anal. Calcd for $C_{13}H_{23}N_3O$: C, 65.78; H, 9.76. Found: C, 65.73; H, 9.75.

A 100-mg sample of **13** (containing *ca.* 20% cis-fused **14**) was reduced by excess lithium hydride in tetrahydrofuran and the crude alcohol was dehydrated with phosphorous oxychloride in pyridine (5°, 15 hr). Normal work-up yielded the desired product (85 mg, 93%): nmr ($CDCl_3$) δ 0.92 (angular CH_3, s), 1.58 (vinyl methyl, quartet, $J \simeq$ 2 Hz), 5.16 (vinyl H, broad multiplet). Allylic oxidation of the above alkene (81 mg) was carried out according to Dauben's procedure,[39] using 1.75 g of chromium trioxide–pyridine complex in methylene chloride. After 24 hr, standard work-up afforded 47 mg (52%) of enone **15** (containing *ca.* 20% of cis-fused isomer); this material was shown to have identical spectral and vpc properties when compared with an authentic specimen provided by Professor R. Coates.

In order to characterize decalone **14,** we initiated an independent synthesis based upon conjugate organocuprate addition to 1-methyl-$\Delta^{1(9)}$-2-octalone (**16**), a process well known to yield *cis*-decalones in such a situation.[40] Accordingly, ethylmagnesium bromide (0.125 mol) in ether (100 ml) was added over 4.5 hr at −40° to $\Delta^{9,10}$-hexahydrocoumarin[13] (**20**) (15.2 g, 0.10 mol) in ether (100 ml). The diketone product of this reaction was refluxed under argon for 12 hr with KOH (14 g) in methanol (200 ml). Standard ether work-up, followed by chromatography over neutral grade I alumina (100 g), while eluting with hexane–ether mixtures, then bulb-to-bulb distillation (oven temperature 110° at 1.1 nm) yielded pure 1-methyl-$\Delta^{1(9)}$-2-octalone (**16**) (4.50 g, 28%): nmr δ 1.69 (*d*, $J \simeq$ 1 Hz, CH_3); ir λ_{max} (film) 6.00 (C=O), 6.18 (C=C); mass spec *m/e* (relative intensity), 164 (M^+, 71), 122 (100); uv λ_{max} (MeOH) 246 mμ (ϵ 11,900).

Lithium dimethylcopper, prepared at 0° under a dry nitrogen atmosphere from cuprous iodide (1.16 g, 6.1 mmol) in ether (15 ml) and 1.8 *M* methyllithium (6.8 ml, 12.2 mmol) in ether (20 ml), was treated with 1-methyl-$\Delta^{1(9)}$-2-octalone (0.50 g, 3.05 mmol) in ether (15 ml). After 2 hr at 0°, the reaction mixture was poured into 1.2 *N* HCl (150 ml) and stirred rapidly for 15 min. After standard ether work-up, the crude product was filtered through a short alumina column with ether as the eluent to yield **14** (0.25 g, 46%) as a colorless oil. Vpc analysis (12 ft SE30, 190°) revealed two components (retention times 27.4 and 29.4 min) in a ~5:1 ratio: ir λ_{max} (film) 5.84 μ (C=O); nmr ($CDCl_3$) 0.75–2.5 (m), (0.77 (s, C_9CH_3), 0.85 (d, J = 6.8 Hz, C_1CH_3)) (0.89 (d, J = 6.9 Hz, C_1CH_3), 1.15, C_9CH_3)) *in a 1:5 ratio.*

These two compounds are epimeric at C_1 as evidenced by the fact that equilibration occurred after 3 days in 0.2 *N* sodium ethoxide–ethanol with minor isomer (originally) now predominating to the extent of 85% by nmr analysis. This equilibrated mixture was essentially identical with **14** isolated from the trifluoroacetolyses: mass spec *m/e* (rel intensity) 180 (M^+, 25%), 108 (100), The semicarbazone of **14,** after three recrystallizations from ethanol–water, had mp 212–214° dec, as heavy white clusters.

Anal. Calcd for $C_{13}H_{23}N_3O$: C, 65.78; H, 9.76. Found: C, 65.75; H, 9.74.

1-(3-Hexynyl)-$\Delta^{1(9)}$-2-octalone (21). 1-Iodo-4-heptyne was prepared by refluxing a mixture of 1-chloro-4-heptyne (13.06 g, 0.10 mol) and sodium iodide (75 g, 0.50 mol) in acetone (350 ml) under nitrogen for 12 hr in the absence of light. After acetone was distilled off, 150 ml of water was added and the product taken up in ether and worked up as usual. Distillation yielded 20.3 g (91% yield) of pure iodide (by vpc on a 6 ft SE-30 column), bp 94–8° (23 mm).

The Grignard reagent prepared from 40.6 g (0.184 mol) of 1-iodo-4-heptyne and 8.94 g (0.368 g-atom) of magnesium turnings in ether was filtered through glass wool, under nitrogen pressure, into an addition funnel and added during 4.5 hr to **20**[13] (11.25 g, 0.074 mol) in ether at −40°. The diketone product resulting from hydrolysis was cyclized by refluxing with KOH (13.9 g) in methanol (210 ml) for 12 hr. Crude octalone was chromatographed over neutral grade 3 alumina (450 g). Nonpolar components were elut-

ed with hexane, after which the desired product was removed with ether. Bulb-to-bulb distillation (oven temperature 130° at 0.05 mm) then yielded 10.9 g (64%) of pure 1-(3-hexynyl)-$\Delta^{1(9)}$-2-octalone (**21**), showing a single vpc peak (6 ft SE-30, 210°): nmr (CCl_4) δ 2.38–0.83 (*c*, including δ 1.08 (t, J = 7 Hz, CH_3)); ir λ_{max} (film) 7.00 (C=O), 6.19 (C=C); mass spec *m/e* (relative intensity) 230 (M^+, 100%), 215 ($M^+ - CH_3$, 72); λ_{max} (MeOH) 248 (ϵ 11,300). The semicarbazone derivative of **21** had mp 184–190° dec after three recrystallizations from ethanol–water.

Anal. Calcd for $C_{17}H_{25}N_3O$: C, 71.04; H, 8.77. Found: C, 71.00; H, 8.74.

1-(3-Hexynyl)-*trans*-2-decalone (22). In a three-necked flask equipped with a Dry Ice condenser and mechanical stirrer was placed **21** (1.31 g, 5.70 mmol) in a mixture of ether (75 ml) and dry ammonia (75 ml). A solution of lithium (0.107 g, 15.4 mmol) in ammonia (40 ml) was added dropwise with stirring at −75°. After 10 min, ammonium chloride (10 g) was cautiously added, and the ammonia was then evaporated. Normal work-up followed by bulb-to-bulb distillation (120° at 0.05 mm) yielded 1-(3-hexynyl)-*trans*-2-decalone (**22**) (1.07 g, 77%), pure by vpc (6 ft SE30, 120°): nmr (CCl_4) δ 2.50–0.67 (*c*, including δ 1.08 (J = 7 Hz, CH_3)); λ_{max} (film) 5.85 (C=O); mass spec *m/e* (relative intensity) 232 (M^+, 14%), 217 ($M^+ - CH_3$, 8), 152 ($M^+ - C_6H_8$, 100). The semicarbazone derivative had mp 165–167° after three recrystallizations from ethanol–water.

Anal. Calcd for $C_{17}H_{27}N_3O$: C, 70.54; H, 9.40. Found: C, 70.57; H, 9.43.

1-(3-Hexynyl)-2-methyl-*trans*-2-decalol (17). Using a syringe, 1.8 *M* ethereal methyllithium solution (3.9 ml) was added dropwise to a solution of 1-(3-hexynyl)-*trans*-2-decalone (0.327 g, 1.41 mmol) in ether (10 ml) while stirring under argon at 0°. Normal work-up and purification by bulb-to-bulb distillation (130° at 0.05 mm) yielded 1-(3-hexynyl)-2-methyl-*trans*-2-decalol (**17**) (0.318 g, 91%), pure by vpc (6 ft SE30, 220°): nmr (CCl_4) δ 2.30–0.70 (*c*, including δ 1.09 (t, J = 7 Hz, CH_3CH_2)), 1.17 (s, carbinol CH_3); λ_{max} 2.89 (O–H); mass spec *m/e* (relative intensity) 248 (M^+, 3%), 233 ($M^+ - CH_3$, 17), 230 ($M^+ - H_2O$, 13), 150 (100).

1-(3-Hexynyl)-2-(α-thioanisyl)-*trans*-2-decalol (36). Diazabicyclo[2.2.2]octane (2.24 g, 20 mmol) and thioanisole (2.51 g, 20.6 mmol) were dissolved in dry THF (120 ml) and cooled to 0° under argon. *n*-Butyllithium–hexane solution (1.9 *M*) was added dropwise with stirring until aliquots of the reaction mixture just gave a positive Michler's ketone test, then additional *n*-butyllithium solution (9.5 ml, 18 mmol) was added. 1-(3-Hexynyl)-*trans*-2-decalone (**22**) (2.78 g, 12 mmol) was added dropwise at 0° and the reaction mixture was stirred at room temperature overnight. Standard ether work-up yielded the crude product (7.5 g) which was chromatographed on neutral alumina (Brockman No. 1, 124 g), eluting first with pentane to obtain recovered thioanisole and then with chloroform. Evaporation of the chloroform fractions yielded the product **36** as a colorless oil (3.70 g 87%), pure by tlc, which decomposed on attempted bulb-to-bulb distillation: nmr (CCl_4) δ 7.5–7.0 (*c*, 5 H, aromatic), 3.13 (AB q, J = 13 Hz, $\Delta\nu$ = 20.8 Hz, CH_2–S), 2.4–0.6 (*c*, 25 H) including 2.08 (q), 1.06 (t, J = 7.5 Hz, CH_2CH_3), 1.84 (bs OH); ir λ_{max} (film) 2.82 (O–H).

Anal. Calcd for $C_{23}H_{32}OS$: mol wt 356.2173; M^+ (obsd),[41] 356.2184.

Oxidation of 36 to Sulfoxides 37a and 37b. 1-(3-Hexynyl)-2-(α-thioanisyl)-*trans*-2-decalol (**36**) (1.836 g, 5.15 mmol) was dissolved in methylene chloride (30 ml) and cooled to 0°. *m*-Chloroperbenzoic acid (85% purity, 1.036 g, 5.11 mmol) in methylene chloride (35 ml) was added dropwise with stirring under argon during 1 hr, and the reaction mixtue was stirred at room temperature for 3 hr. Standard work-up yielded the crude oily product (2.138 g), seen by tlc to contain two components. The product was chromatographed on silica gel (30 g, Grade 62), eluting with chloroform and taking fractions at 40-ml intervals. Fractions 3–6 yielded mainly the early component as a colorless oil 1.422 g) and fractions 7–9 contained mainly the oily second component (0.380 g). Spectroscopic evidence (see below) indicated that the two components were isomers of the desired sulfoxide product (**37**) (total yield 1.802 g, 94%). Trituration of the oil from fractions 3–6 with pentane yielded a solid which was further crystallized from pentane to yield the major sulfoxide isomer (0.814 g) as white crystals, mp 110–111°: nmr (CCl_4) δ 7.8–7.3 (*c*, 5 H, aromatic), 3.70 (bs, 1 H, OH), 2.84 (AB q, J = 14 μ = 68.6 Hz, CH_2SO), 2.6–0.4 (*c*, 24 H) including 0.87 (t, J = 7 Hz, CH_3CH_2); ir λ_{max} (CCl_4) 2.90 (OH), 9.6 and 9.8 (S→O).

Anal. Calcd for $C_{23}H_{32}O_2S$: mol wt 372.2122; M^+ (obsd)[41] 372.2113. As above, trituration with pentane of the oil from fractions 7–9 yielded the minor sulfoxide isomer (0.147 g) as white crystals, mp 145–8°: nmr (CCl_4) δ 7.8–7.4 (*c*, SH, aromatic), 3.40 (bs, 1 H, OH), 2.97 (ABq, J = 14, $\Delta\nu$ = 34.3 Hz, CH_2SO), 1.5–0.6 (*c*, 24 H) including 0.92 (t, J = 7 Hz, CH_3CH_2); ir λ_{max} (CCl_4) 2.97 (OH), 9.6 and 9.75 (S→O).

Anal. Calcd for $C_{23}H_{32}O_2S$: mol wt 372.2122; M^+(obsd),[41] 372.2136. Chromatographic behavior, relative melting points, and spectroscopic evidence[42] indicate that the sulfoxide oxygen in the major isomer is intramolecularly hydrogen bonded.

Solvolysis of 17. Typical Cyclization and Hydrolysis Procedures. (a) One-Stage Formic Acid Cyclization of 1-(3-Hexynyl)-2-methyl-*trans*-2-decalol, 17. 1-(3-Hexynyl)-2-methyl-*trans*-2-decalol (**17**) (0.680 g, 2.7 mmol) was added to refluxing formic acid (97%, 15 ml), and the reaction mixture was refluxed under argon for 1 hr. After work-up the crude reaction mixture was refluxed with 10% KOH solution (20 ml) for 15 hr and worked up to afford, after bulb-to-bulb distillation (120° at 0.05 mm), the mixture of ketones **23** and **24** (0.490 g, 73%). Vpc analysis (6 ft SE30, 200°) showed three peaks (components A, B, C) of retention times 8.0, 9.0, and 10.4 min in a ratio of 7:28:65. Infrared analysis of each of these components showed absorption at 5.84 μ. Spectroscopic evidence and chemical degradation (see below) indicated that component A consisted of the cis-fused ketone **24** (with β-propionyl), component B contained the major cis-fused isomer **24** (α-propionyl) together with the minor trans-fused isomer **23** (α-propionyl), and component C was the major trans-fused ketone **23** (β-propionyl): nmr **23**, β-propionyl, δ 2.50 (bt, $CHCOCH_3$), 2.34 (q, CH_2CH_3), 1.00 (t, CH_2CH_3, J = 7 Hz), 2.2–0.5 (*c*), 0.60 (*s*, CH_3); **23**, α-propionyl, δ 2.70 (bt, $CHCOCH_3$), 2.34 (g, CH_2CH_3), 0.98 (t, CH_2CH_3, J = 7 Hz), 2.2–0.5 (c), 0.91 (s, CH_3); **24**, α-propionyl, δ 2.98 (bt, $CHCOCH_3$), 2.38 (q, CH_2CH_3), 1.01 (t, CH_2CH_3, J = 7 Hz), 2.2–0.5 (c), 0.79 (s, CH_3); **24**, β-propionyl, δ 2.5–0.5 (c), 1.18 (s, CH_3); ir (mixture) λ_{max} (film) 5.84 μ; mass spec *m/e* (relative intensity), component A 248 (M^+, 35%), 230 ($M^+ - H_2O$, 12), 149 (100); component B 248 (M^+, 49%), 230 ($M^+ - H_2O$, 12), 149 (100); component C 248 (M^+, 29%), 230 ($M^+ - H_2O$, 17), 95 (100). The semicarbazone of a mixture of **23** and **24** had mp 195–206° after three recrystallizations from ethanol–water.

Anal. Calcd for $C_{18}H_{31}N_3O$: C, 70.78; H, 10.23. Found: C, 70.80; H, 10.30.

The ratio of trans/cis-fused material was seen, by chemical degradation, to be **23/24** = 71/29.

(b) Three-Stage Trifluoroacetic Acid Cyclization of 17. 1-(3-Hexynyl)-2-methyl-*trans*-2-decalol (**17**) (0.407 g, 1.64 mmol) was added portionwise with stirring under argon to a mixture of trifluoroacetic acid (20 ml) and trifluoroacetic anhydride (8 ml) at −10°. The reaction mixture was stirred at −15 to 0° for 1 hr, when a portion of the mixture (9 ml) was withdrawn and subjected to standard ether work-up to yield a colorless oil (0.173 g). The reaction mixture was stirred at room temperature for 5.5 hr after which time a second aliquot (8 ml) was withdrawn and worked up to yield a dark oil (0.189 g). The remaining reaction mixture was refluxed for 16 hr and then worked up as usual to afford a dark oil (0.142 g). The crude enol esters from work-up of each of the three aliquots were refluxed overnight with 10% KOH solution (25 ml) and worked up to yield the appropriate ethyl ketones (0.108, 0.122, and 0.091 g, respectively); total combined yield from starting alcohol is 0.321 g (79%). Vpc and equilibration studies (see below) indicated that the ratio of trans/cis-fused material (**23/24**) was 81/19, 78/22, and 76/24, respectively.

Procedures for single stage cyclization and hydrolysis of the sulfur-containing carbinols **36** and **37** were similar to those described above. In the cases of **36** and **37** the colorless oils so obtained had spectroscopic characteristics appropriate for the expected ethyl ketones: nmr (CCl_4) **38** δ 7.4–6.9 (*c*, 5 H, arom), 3.4–0.5 (c), including 2.34 (q, CH_2CH_3), 1.00 (t, CH_2CH_3, J = 7 Hz); **39** δ 7.7–7.3 (*c*, 5 H, aromatic), 3.28 (bt, $CHCOCH_3$), 3.07–0.7 (c), including 1.02 (t, CH_2CH_3, J = 7 Hz).

Typical Raney Nickel Desulfurization. 38 to 23 and 24. The mixture of isomeric ethyl ketones **38** (0.135 g, 0.379 mmol), formed from cyclization and hydrolysis of **36**, was refluxed for 18 hr with 1

ml of settled Raney nickel catalyst[43] and methanol (20 ml). The reaction mixtue was cooled and allowed to settle, the methanol was decanted, the catalyst was washed with $CHCl_3$, and standard work-up with $CHCl_3$ was proceeded with. Removal of solvent yielded the product as a colorless oil (0.088 g, 94%) shown by vpc and nmr to contain only a mixture of the isomeric ketones **23** and **24.** After equilibration (see below), the trans/cis-fused ratio was determined to be 9/91.

Typical Degradation Procedures[12,17] (as applied to mixtures of **4** and **5** (see Scheme IV) and **23** and **24** (see Scheme VI)). Approximately 7.5 mmol of peroxytrifluoroacetic acid was prepared by dropwise addition of trifluoroacetic anhydride (1.30 ml, 7.5 mmol) to 90% hydrogen peroxide (0.20 ml, 9.0 mmol) in methylene chloride (5 ml) at 0° under argon. The reaction mixture was stirred for 45 min, and the reagent so formed was added dropwise with stirring to a solution of the ketone mixture, **23** and **24** (0.252 g, 1.01 mmol) in methylene chloride (12 ml) at 0° under argon. The reaction mixture was stirred at room temperature for 48 hr, and then subjected to standard work-up. The mixture of esters (verified by infrared absorption at 5.78 μ and loss of carbonyl absorption at 5.84 μ) was then quantitatively reduced with LAH in ether to a mixture of alcohols (ir) which was then oxidized with Jones reagent[44] in 6 ml of acetone to yield a mixture of **25** and **26** in a ratio of 71:29. Coinjection of this mixture with authentic **25** gave the expected peak enhancement of the larger, longer RT peak:[17] nmr (mixture) δ 2.50–0.60 (c), including δ 0.84 (s), 50.93 (s), CH_3 of trans- and cis-fused isomers, respectively; ir **25** and **26** λ_{max} (film) 5.75 (C=O); mass spec **25** *m/e* (relative intensity) 206 (M^+, 54%), 191 ($M^+ - CH_3$, 16), 188 ($M^+ - H_2O$, 11), 124 (100); **26** *m/e* (relative intensity) 206 (M^+, 72%), 191 ($M^+ - CH_3$, 7), 162 (100). The semicarbazone derivative prepared from the mixture of **25** and **26** had mp 237–238° after three recrystallizations from ethanol–water. Apparently, at this stage, the derivative of **26** had been effectively removed. No melting point depression was observed when mixed with the semicarbazone of authentic **25.**

Anal. Calcd for $C_{15}H_{25}N_3O$: C, 68.40; H, 9.57. Found: 68.41; H, 9.60.

Degradation of Enone 27 to Authentic *trans*-Hydrindanone 25. A solution of **27** (1.00 g, 4.54 mmol) in THF (50 ml) was added dropwise with stirring to a solution of lithium (0.113 g, 16.3 mmol), in a mixture of THF (60 ml) and ammonia (150 ml), under argon, in a three-necked flask equipped with a Dry Ice condenser. The reaction mixture was stirred for 1 hr, after which solid ammonium chloride (5 g) was added, and the ammonia was then evaporated and the THF removed at reduced pressure. Standard ether work-up yielded the product as an oil which crystallized on standing (1.01 g, 100%), pure by vpc (6 ft SE30, 220°): ir λ_{max} (film) 2.85 (O—H), 5.86 (C=O); mass spec *m/e* (relative intensity) 222 (M^+, 53%), 204 ($M^+ - H_2O$, 29), 163 (100).

The ketone (1.01 g, 4.54 mmol) was converted to its semicarbazone (1.18 g, 93%), which was used without further purification. The semicarbazone (1.18 g, 4.21 mmol), hydrazine hydrate (85%, 1.44 ml, 17.4 mmol), KOH (1.24 g, 21.8 mmol), and diethylene glycol (20 ml) were heated at 205° under argon, while stirring, for 1 hr. The reaction mixture was cooled and subjected to standard work-up to afford the desired alcohol (0.84 g, 96%), pure by vpc (11 ft SE30, 198°), which crystallized on standing: nmr δ 2.10–0.65 (c), including δ 3.55 (s, OH), 0.74 (s, CH_3).

The alcohol was oxidized using Jones reagent[44] to afford the desired ketone **25** after purification by bulb-to-bulb distillation (90° at 0.05 mm) (0.130 g, 87%), pure by vpc (11 ft SE 30, 190°): nmr δ 2.45–0.67 (c), including δ 0.88 (s, CH_3): ir λ_{max} (film) 5.75 (C=O); mass spec *m/e* (relative intensity) 206 (M^+, 68%), 188 ($M^+ - H_2O$, 27), 162 (100). The semicarbazone derivative had mp 237–238° after three recrystallizations from ethanol–water.

Anal. Calcd for $C_{15}H_{25}N_3O$: C, 68.40; H, 9.57. Found: C, 68.38; H, 9.54.

Acyl Side-Chain Equilibration of 23 and 24. Pure trans ketone **23,** β-propionyl (36 mg, obtained by preparative vpc, 6 ft SE 30, 210°) was refluxed with a solution of sodium (850 mg) in absolute methanol (45 ml) for 3 hr. The reaction mixture was subjected to standard work-up to afford the product as a colorless oil (31 mg, 86%) which was shown by vpc (6 ft SE 30, 210°) to consist of a mixture of **23,** β-propionyl, 75% and **23,** α-propionyl, 25%. The product was subjected to a further 3 hr of equilibration conditions which did not appreciably change the ratio of isomers. Similarly, samples of cis ketones only yielded equilibration mixtures of **24,** α-propionyl, 98% and **24,** β-propionyl, 2%. Accordingly, any mixture of the four isomeric ketones could be equilibrated and the amounts of **23,** α-acyl, and **24,** α-acyl, present under the overlapping vpc peak ("component B") could be deduced from the areas of the peaks corresponding to **23** β-acyl and **24** β-acyl. Trans/cis ratios so determined were in excellent agreement with the ratios obtained from the three-stage degradation procedure (see above).

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(4) (a) This assumes that the side chain in **6-R**$^+$ does not epimerize by deprotonation–reprotonation *via* tetrasubstituted double bonds. In the latter event, *axial* protonation would simply regenerate **6-R**$^+$ (*cf.* R. E. Ireland, S. W. Baldwin, and S. C. Welch, *J. Amer. Chem. Soc.* **94,** 2056 (1972)). (b) Another possible route to cis-fused product could be concerted trans addition of a proton and the cyclizing side chain to cycloalkene resulting from dehydrated carbinol, as postulated by G. A. Stork and A. W. Burgstahler, *J. Amer. Chem. Soc.*, **77,** 5068 (1955), for polyene cyclizations leading to cis-fused 6/6 systems. For a recent review on stereochemistry of polyene cyclizations, see K. E. Harding, *Bioorg. Chem.*, **2,** 248 (1973).
(5) Irreversible cyclization was expected to provide the best chance for high trans/cis ratios because equilibration would likely favor the more stable C/D cis compounds. Indeed, the trend toward more cis-fused product **8** was demonstrated by extended anhydrous formolysis experiments.
(6) For a recent review of vinyl cations in these and other reactions, see P. J. Stang, *Prog. Phys. Org. Chem.*, **10,** 205 (1973).
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(9) Usually the epimeric carbinol mixture was used without separation, especially when it was found that the separate diastereomers of **9** gave essentially comparable results.
(10) We are grateful to Professor R. Coates for an authentic sample of **15.**
(11) With methyl resonances appearing in part from within the methylene envelope, integrations are only qualitative and the percentage of each component is accurate to ±5% at best.
(12) Further results with **9** and related carbinols are found in T. R. Demmin's thesis, State University of New York, Buffalo, 1972.
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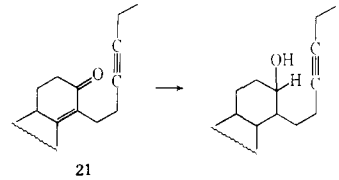
(15) Furthermore, in an experiment where *wet* ether was inadvertently used as cosolvent during lithium–ammonia reduction, the hydrolyzed lithium enolate underwent further reduction to a carbinol group *without* alkynyl reduction (G. E. DuBois, unpublished observations). This finding is at



21

variance with conclusions of Stork, *et al.* (G. Stork, S. Malhotra, H. Thompson, and M. Uchibayashi, *J. Amer. Chem. Soc.*, **87,** 1148 (1965)), and Weiler (B. J. Balf, B. Rao, and L. Weiler, *Can. J. Chem.*, **49,** 3135 (1971)), who suggest that alkynyl radical anions attack carbonyls during reductive cyclization. Our finding suggests that the ketyl derived from one-electron reduction of the carbonyl would add nucleophilically to the alkyne.
(16) The same material resulted when dimethylsulfonium methylide was added to **22** and the oxirane reduced with lithium aluminum hydride (G. E. DuBois, unpublished observations). The ambiguity concerning the stereochemistry of **17** arises from the general trend for equatorial addition of organometallics to cyclohexanones *vs.* axial addition of sulfonium ylides. In the case of **22,** it is not clear or readily predictable which reaction (→ **17**) is "abnormal."
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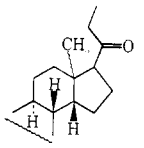
(18) The choice of a 3-hexynyl side chain in **17,** rather than a 3-pentynyl one, as in **9,** is now clear; the α-ethyl substituent allows **28,** if present, to fragment predictably *via* the McLafferty rearrangement whereas α-CH_3 would not (D. G. I. Kingston, J. T. Bursey, and M. M. Bursey, *Chem.*

Rev., **74**, 219 (1974)). Several small vpc peaks (*ca.* 2–4% of the total) were trapped and examined; since **28** was not present, it was assumed that they were diastereomers of **23** and **24** in which the cyclizing side chain had epimerized, *e.g.*



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Effect of Aromatic Cations on the Tertiary Structure of Deoxyribonucleic Acid[1]

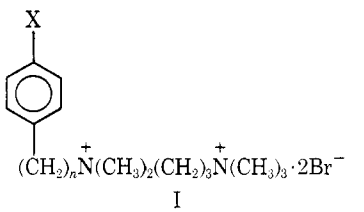
Lou Kapicak and E. J. Gabbay*[2]

Contribution from the Department of Chemistry, University of Florida, Gainesville, Florida 32601. *Received April 29, 1974*

Abstract: The synthesis of several aromatic substituted diammonium cations and their interaction specificity with DNA have been examined. The results of the temperature-dependent proton magnetic resonance (pmr), viscometric, and melting temperature studies are presented. It is found that significantly different effects on the tertiary structure of DNA may be caused by slight modifications in the aromatic substituted diammonium cations. A "wedge" model is proposed whereby the aromatic ring of the latter is either "partially" or "fully" inserted between base pairs thus leading to either a decrease or increase, respectively, in the effective length of the DNA helix.

The mechanism(s) by which histone and nonhistone proteins influence(s) the tertiary structure of DNA in condensed chromatin has been the subject of considerable interest in many laboratories.[3-10] Hanlon and coworkers[6] have suggested that supercoiling of DNA may occur in nucleohistone *via* alternating B and C conformations of the DNA duplex whereby the latter conformation is induced *via* histone binding. Recently, Bartley and Chalkley[3] have proposed that the histone proteins may act as a spring, *i.e.*, an α-helical segment of the polypeptide chain may be involved in connecting the protein to two or more binding sites along the DNA helix, thus causing the latter to bend and assume a supercoil condensed form. Recent work from this laboratory[11,12] on the interactions of oligopeptides with DNA has shown that the peptides which contain aromatic amino acids at the C terminus cause a dramatic decrease in the specific viscosity, η_{sp}, of the DNA solution. The above data together with the proton magnetic resonance studies of oligopeptides–DNA complexes led Gabbay, *et al.*,[11,12] to propose a nonclassical model of intercalation whereby the aromatic residue of the oligopeptides is partially inserted between base pairs of DNA thus leading to a bend of the helix at the point of intercalation.

In order to investigate the effect of partial and/or total insertion of an aromatic residue between base pairs on the tertiary structure of DNA, the following compounds were synthesized. It is reasoned that at low values of *n*, total insertion of the aromatic ring of I may not occur. On the



$(CH_2)_n\overset{+}{N}(CH_3)_2(CH_2)_3\overset{+}{N}(CH_3)_3 \cdot 2Br^-$

I

X = H; **1**($n = 1$); **2**($n = 2$); **3**($n = 3$); **4**($n = 4$)
X = NO_2; **5**($n = 1$); **6**($n = 2$); **7**($n = 3$); **8**($n = 4$)
X = CH_3; **9**($n = 2$)

other hand, at higher values of *n* and in the presence of para substituents, *i.e.*, NO_2 and/or CH_3 groups, the aromatic ring may fully insert itself between base pairs of DNA to cause a net increase in the helix length (Figure 3). The results of our studies are consistent with the above interpretation.