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Formation of Six-Membered Aromatic Rings by Cyclialkylation of Some Aldehydes and Ketones

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Contents

Charles K. Bradsher was born in Petersburg, VA, in 1912 and graduated from Duke University in 1933. His Ph.D. in organic chemistry was granted by Harvard University in 1937, based upon a dissertation entitled "The Reactions of Some β-Naphthoquinones" and done under the direction of Prof. L. F. Fieser. After postdoctoral fellowships at the University of Illinois with Prof. R. C. Fuson, he joined the chemistry faculty of Duke University, reaching the rank of James B. Duke Professor in 1965 and retiring from both teaching and research in 1979. His publications (over 200) deal principally with cyclization, cycloaddition, and the chemistry of analogues and benzologues of the quinolizinium ion.

I. Introduction

Alkenes and arenes having a carbonyl group, either aldehydic or ketonic, in a suitable relationship to an sp^2-bonded carbon atom, may undergo acid-catalyzed cyclialkylation. If the carbonyl group is five atoms removed from the target sp^2-linked carbon, and if the connecting chain has a fused aromatic ring, a double bond, or a substituent eliminated to form a double bond, cyclialkylation can afford a benzene or benzenoid ring.[1] Those cyclizations in which the target carbon is aromatic were summarized in an earlier review,[2] entitled *Aromatic Cyclodehydration*, which was broader in scope in that it included the formation of aromatic five-membered as well as six-membered rings.

Since the appearance of the earlier review, Barclay[3] has written a comprehensive chapter on cyclialkylation of aryl-substituted alkenes, alcohols, and alkyl halides, as well as aldehydes and ketones, with no restriction as to ring size or aromaticity of the product. Another review, even one of limited scope, seemed justified by the need to focus on an important application of the cyclialkylation of aldehydes and ketones as well as to

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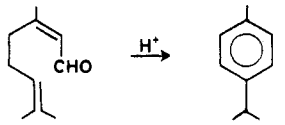

provide a report of developments in the 22 years since Barclay's chapter appeared.

Despite some important work on the formation of aromatic six-membered rings through the cyclialkylation of carbonyl compounds, as a synthetic tool the reaction has been underutilized. A number of reports, to be cited later, describe the synthesis of systems that should undergo aromatic cyclodehydration, without indication that such an application was contemplated or attempted. Perhaps this neglect arises because the cyclization reaction lacks analogy to a simple clearcut intermolecular reaction like that to be found in the alkylation of arenes by alcohols or alkyl halides. The intermolecular reaction of aldehydes and ketones with arenes rarely affords the primary product,[4] the best known examples being the formation of triphenylmethanes, bisphenol A, or DDT, in each of which 2 mol of the arene substrate react. The intramolecular reaction of aryl aldehydes and ketones has been used in the synthesis of rings having five, six, or seven members,[3] but it is clear that in the armamentarium of the synthetic organic chemist this method of forming a carbon–carbon bond occupies an unjustifiably insignificant place. For example, it has been proven possible to write otherwise creditable monographs on the carbonyl group[5] or the alkylation of arenes[6] without reference to such carbonyl alkylations.

In extending the discussion of the cyclization of carbonyl compounds to the parallel reactions of derivatives such as acetals, ketals, and oximes, *there is no intention to imply that an aldehyde or ketone is always involved in any such cyclization observed.* For other functional groups that are not carbonyl derivatives, but might yield a carbonyl group under the conditions used in the cyclization, for example the epoxide or acetylenic group, the inclusion may owe more to mnemonics than to mechanism. As may be seen in the Table of Contents, the ring systems being formed will be considered more or less in the order of complexity, with a final discussion of the reaction mechanism.

II. Intramolecular Attack at an Alkene

The systematic synthesis of benzene derivatives by carbonyl cycloalkylation at an alkene rather than an arene carbon is an important recent development, but there was at least one example dating from the last century. It was known that citral (**1**), in the presence of hydrochloric acid,[7] potassium bisulfate,[8] or even refluxing acetic acid[9] underwent cyclialkylation to afford cymene (**2**; Scheme 1) through what we today would characterize as the acid-catalyzed attack of an aldehyde group on an sp^2-carbon.

In a related reaction, the trimer **3a** (Scheme 2), produced when cyclohexanone was self-condensed in the presence of sodium hydroxide, was identified as a dihydroxy ketone.[10] The trimer could be dehydrated stepwise to afford a (cyclohexenylcyclohexylidene)-cyclohexanone (**4a**) and a dodecahydrotriphenylene

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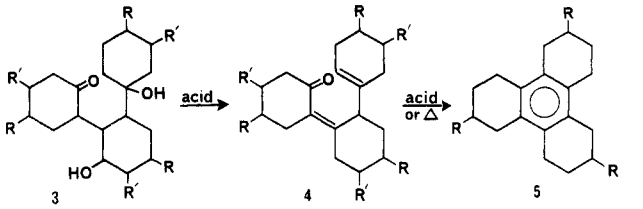
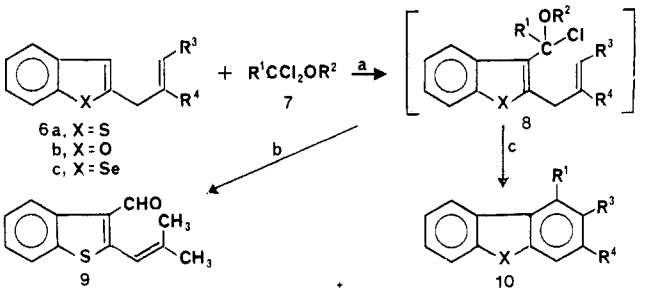


3a,4a, R = R′ = H; 3b,4b, R = CH_3, R′ = H; 3c,4c, R = H, R′ = CH_3; 5a, R = H; 5b, R = CH_3

SCHEME 3



a. $SnCl_4$, −50°. b. 20°, X = S, R^1 = R^3 = H, R^2 = C_4H_9, R^4 = CH_3. c. 20°.

TABLE 1. Synthesis of Benzothiophene (10, X = S) and Its Analogues (Scheme 3)

X	R^1	R^2	R^3	R^4	R^5	yield, %	ref
S	H	Me				55	12, 13
S	COOEt	Et				61	12, 13
S	H	Bu		Me		10[a]	12, 13
S	COOEt	Et		Me		41	12, 13
S	COOEt	Et	Me			*b*	15
O	COOEt	Et				32	13
O	COOEt	Et	Me			*b*	15
Se	COOEt	Et				*c*	15
Se	COOEt	Et			Me	*c*	15

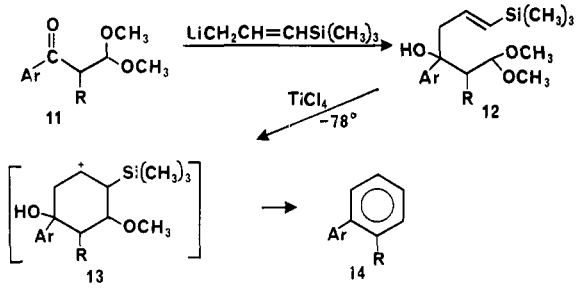
[a] In addition, **9** was obtained in 14% yield. [b] Yield "assez bon". [c] Yield not reported.

(**5a**). Both steps in the dehydration appeared to be acid catalyzed, although at 350 °C dehydration could occur without a catalyst. Similar results were obtained[11] starting with trimers (**3b, 3c**) prepared from 4-methyl- and 3-methylcyclohexanones. Support for the structures assigned the intermediates (**4a, 4c**) was afforded by the isolation of only a single cyclization product (**5b**) from the two intermediates.

The first systematic effort to make synthetic use of the acid-catalyzed cyclialkylation of acylalkenes to create a benzene ring appears to have been made by the Meth-Cohn group[12,13] as an extension of their work on the combined acylation and cyclialkylation of certain diarylmethanes (Part III.C2). If, in the place of the diarylmethane, 2-allylbenzothiophene (**6a**) was used, acylation in the presence of stannic chloride with Rieche's reagent[14] (a formyl chloride equivalent) was accompanied by cyclization to afford dibenzothiophene (**10a**). A parallel reaction leading to the formation of ethyl dibenzothiophene-1-carboxylate (**10a**: R^1 = COOEt, R^3 = R^4 = H) was carried out using ethyl ethoxydichloroacetate (**7**: R^1 = COOEt, R^2 = Et), an equivalent of the acid chloride of oxalic acid monoethyl ester (Scheme 3).

The proposal that the initial alkylation takes place on the aromatic ring rather than on the allyl group is supported by the isolation of **9**, and there is no evidence to controvert the belief[13] that cyclization proceeds

SCHEME 4



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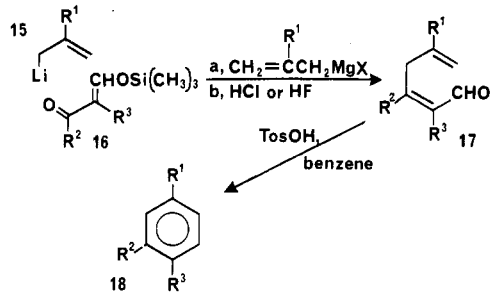


TABLE 2. Synthesis of Biaryls 14 from β-Hydroxyacetals 12 (Scheme 4)

12, aryl	R	yield, %	12, aryl	R	yield, %
p-tolyl		59	2-naphthyl		53
phenyl	Me	44	4-ethylphenyl		49

without the formation of a carbonyl intermediate. Results of similar reactions with allyl and methylallyl derivatives of benzofuran and benzoselenophene may be found in Table 1.

The biaryl synthesis devised by Tius[16] (Scheme 4) and based on cationic cyclialkylation involves the initial reaction of [3-(trimethylsilyl)allyl]lithium with the acetal of a β-keto aldehyde (11)[17] to afford a tertiary alcohol (12). For the cyclization (Table 2), which is believed to occur through 13, rather than the corresponding aldehyde, titanium chloride proved superior to a number of protic and Lewis acids.

A second and more general synthetic approach made by Tius[18,19] to the preparation of benzene derivatives involves protection of the β-hydroxymethylene ketone by silylation rather than acetal formation (16; Scheme 5). The new approach also differs from the first in that an aldehyde (17) is clearly an intermediate, with either a protic acid (p-toluenesulfonic acid) or boron trifluoride found to be effective cyclizing agents. Reminiscent of the cyclialkylation of citral (Scheme 1) better yields were observed (Table 3) when the target allyl group had a substituent on the β-carbon atom (15: R^1 = Me, Ph, Me_3Si), suggesting the importance of stabilizing the intermediate carbenium ion.

III. Condensed Aromatics by Intramolecular Attack at an Arene

A. Naphthalene and Its Analogues by Cyclialkylation of Carbonyl-Bearing Side Chains

1. A Chain Having a Double Bond

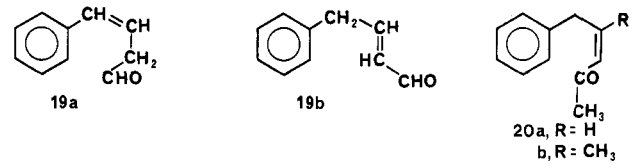
In the majority of carbonyl cyclialkylations leading to an aromatic six-membered ring, the attack of the carbonyl group is upon an aromatic nucleus (rather than upon an alkene), with the result that the product contains *at least two* fused aromatic rings. If a naphthalene derivative is sought, the minimum requirements are a benzene compound having a side chain with an actual or potential double bond and an actual or potential carbonyl group as the fourth carbon atom of that chain.

TABLE 3. Synthesis of Benzene Derivatives 18 by Cyclization of Aldehydes 17 (Scheme 5)

R^1	R^2	R^3	cyclizn[a]	yield, %	ref
Me	$-(CH_2)_3-$		A	58	18
Me	$-(CH_2)_2CH(CMe_3)CH_2$		A	77	18
Me	$-(CH_2)_5-$		A	81	18
Me	Et	Me	A	87	18
Me	$-CH_2CH(i\text{-}Pr)(CH_2)_2-$		A	76	18
Me	$-(CH_2)_{10}-$		A	84	18
H	$-(CH_2)_{10}-$		A	12	18
Me_3Si	$-CH_2CH(CMe_3)CH_2-$		A	53[c]	18
Ph	Ph	H	B	41	19
Ph	Ph	Me	A	58	19
Ph	p-$EtOC_6H_4$	H	A	90	19
Ph	4-$C_6H_5C_6H_4$	H	B	55	19
Ph	2-$C_{10}H_7$	H	B	55	19

[a] Cyclizing agent: A = TosOH; B = BF_3. [b] Overall yield from 2-hydroxymethylene ketone. [c] Yield includes some desilylated product.

Prototypes for naphthalene synthesis would appear to be the two 4-phenylbutenals **19a** and **19b**. One of

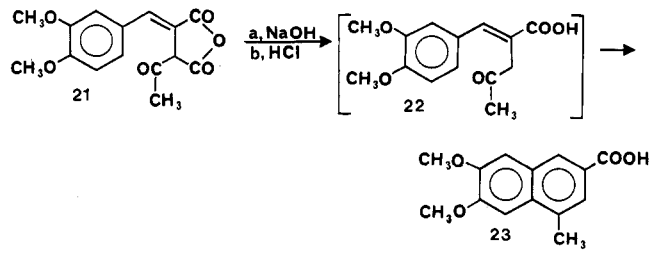


these two, first thought to be 4-phenylbut-3-enal (**19a**), but now known to be *trans*-4-phenylcrotonaldehyde (**19b**),[20,21] was shown[22] to undergo acid-catalyzed cyclodehydration to naphthalene in 25% yield. Although **19b** has since been prepared by at least eight groups,[23-30] there are no reports of attempts to cyclize it or the isomer **19a**.[31] There is a similar lack of information concerning the ability of the methyl ketone **20a**[32] to undergo cyclization, but it is known[33] that the action of perchloric acid on a homologue, 5-phenyl-4-methyl-3-penten-2-one (**20b**), affords 1,3-dimethylnaphthalene in 43% yield.

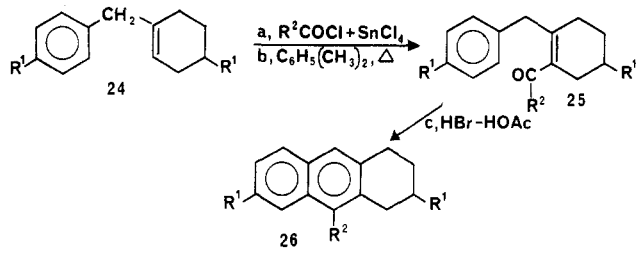
When the acetylation product (21; Scheme 6) of (3,4-dimethoxyphenyl)itaconic acid was dissolved in alkali and then strongly acidified and allowed to stand, it afforded 1-methyl-6,7-dimethoxy-3-naphthoic acid (**23**),[34] evidently via the keto acid **22**. No means were found for the improvement or extension of the reaction.

Through an ingenious extension of the cyclialkylation of unsaturated ketones, Colonge and Bonnard[35,36] devised a convenient synthesis of 1,2,3,4-tetrahydroanthracenes **26** (Scheme 7). The desired ketones **25**

SCHEME 6



SCHEME 7



SCHEME 8

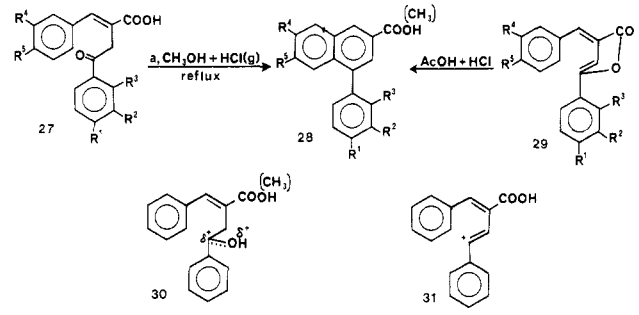


TABLE 4. Synthesis of 1,2,3,4-Tetrahydroanthracenes from 1-Benzylcyclohexenes (Scheme 7)

R^1	R^2	ketone	yield, %	overall
	Me	38	80	30.4
	Et	43	74	31.8
	Pr	45	69	31.1
	i-Pr	45	30[a]	13.5[a]
	Me_3C	44	*b*	*b*
	Ph	25	64	16
Me	Me	*c*	30	30
Me	Et	*c*	41	41

[a] The product was 1,2,3,4-tetrahydroanthracene. [b] No pure product isolated. [c] The dimethyltetrahydrodiphenylmethane (**24**, R = Me) underwent cyclization concurrently with acylation, and the mixture of ketone and product was not separated at this stage.

were prepared by an $SnCl_4$-catalyzed Friedel–Crafts reaction between acyl halides and the readily available 1-benzylcyclohexenes **24**. The good yields usually observed in the cyclization step (Table 4) must be favorably influenced by the enforced cis configuration of the ketones **25**.

The earlier review[2] summarized examples of the cyclization of α-benzylidene-β-benzoylpropionic acids **27** (Scheme 8) by the action of methanolic hydrogen chloride to yield methyl 4-phenyl-2-naphthoates **28**. Subsequently it was reported[37,38] that better yields of the corresponding acids could be obtained by the isomerization in boiling hydrochloric–acetic acid of the lactone **29** derived from the keto acid **27**. The results of such lactone cyclizations are summarized in Table 5. Despite the superior yields obtained by the acid-catalyzed cyclization of lactones, it is still necessary that there be a strong electron-releasing group para to the position at which cyclization is to occur. Undoubtedly El-Assal et al.[37] are correct in proposing that a vinyl carbonium ion (31) is an intermediate, but whether the rate of hydration of the ion is sufficiently high to make the conjugate acid (30) an intermediate also remains unknown.

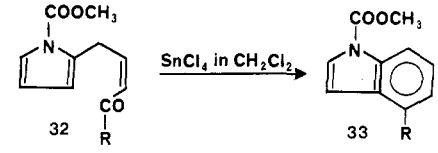
It is significant that when the cyclialkylation of the lactones **29** is carried out in a hydrocarbon solvent using anhydrous aluminum chloride as a catalyst,[39,40] thus excluding the possibility of the formation of a conjugate

TABLE 5. Synthesis of 4-Phenyl-2-naphthoic Acids 28 (Scheme 8) via Hydrochloric Acid Catalyzed Cyclization of the Lactone 29 of β-Benzoyl-α-benzylidenepropionic Acids

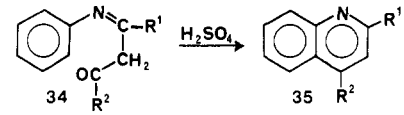
R^1	R^2	R^3	R^4	R^5	yield, %	ref
					a	37
MeO					*a*	37
			MeO		89	38
				MeO	*a*	37
MeO			MeO		100	38
			MeO	MeO	80	37
MeO				MeO	*a*	37
			OCH_2O		89	38
Cl			MeO		100	38
Me			MeO		96	38
		MeO	MeO		90	38
MeO			MeO	MeO	100	37
MeO	MeO		MeO		100	38
Cl			MeO	MeO	95	37
Me			MeO	MeO	100	37
MeO			OCH_2O		98	37
Me			OCH_2O		90	37
Cl			OCH_2O		100	38
MeO	MeO		OCH_2O		95	38

[a] No cyclization product could be isolated.

SCHEME 9

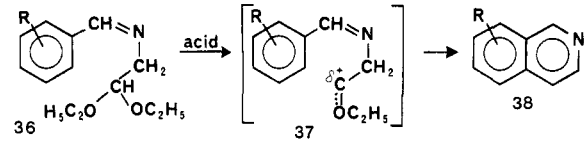


SCHEME 10



COMBES SYNTHESIS

SCHEME 11



POMERANZ-FRITSCH SYNTHESIS

acid such as **30**, the reaction is sufficiently vigorous to permit cyclization at a position not activated by a para substituent.

Natsume et al.[41,42] have made use of aldehyde or ketone cyclialkylation as the last step in the benzologation of 2-carbomethoxypyrrole to yield indoles that may have a substituent at the 4-position (**33**; Scheme 9). Satisfactory yields were obtained with stannic chloride as a catalyst, which, in trial experiments, proved superior to $HClO_4$ or boron trifluoride etherate (Table 6).

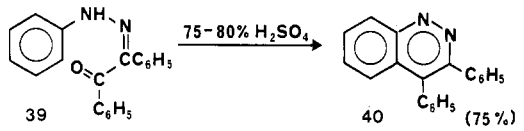
As indicated in the Table of Contents, it is possible to create a new aromatic ring by the cyclialkylation of γ-aryl carbonyl compounds which bear on the chain a group that is to be eliminated. Usually the cyclization and elimination occur under the same conditions and the products provide no clue as to the sequence in which the reactions occur. A major exception was encountered by Kröhnke[43] and by Curtze[44] who found that the elimination of a quaternary pyridinium group occurred much more rapidly than the cyclization step, making it possible to isolate the intermediate unsaturated ketone (**86**; Scheme 26).

TABLE 6. Indoles through Cyclialkylation of α,β-Unsaturated γ-(1-Carbomethoxypyrrol-2-yl)carbonyl Compounds (Scheme 9)

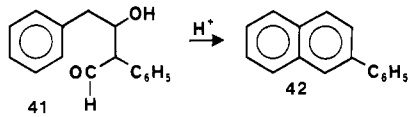
R	yield 33, %	recovered 32, %	ref
H	69		41
Me	51	27	41
Bu	44	23	41
i-Am	46	15	41
CH_2=$CH(CH_2)_2$	14	0	41
cyclohexyl	*a*		41
2-(1,3-dioxolan-2-yl)ethyl	44[b]	0	41
2-(2-methyl-1,3-dioxolan-2-yl)ethyl	52	22[b]	41
2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl	58[b]		42

[a] Trace. [b] Cleavage of dioxolane ring.

SCHEME 12



SCHEME 13



Probably the first important application of carbonyl cyclialkylation was in the Combes synthesis of quinolines (Scheme 10). Although interest in the reaction continues,[45,46] no effort will be made to update the tables of the earlier review.[2]

Interest has continued[45,47,48] also in the preparation of isoquinolines by the Pomeranz-Fritsch synthesis (Scheme 11). A recent improvement, but one that does not remove the need for a strongly activating group in the aromatic ring, is the use of boron trifluoride in trifluoroacetic anhydride as the cyclizing medium.[49] The suggestion that the ethoxy cation **37** is the intermediate is plausible.

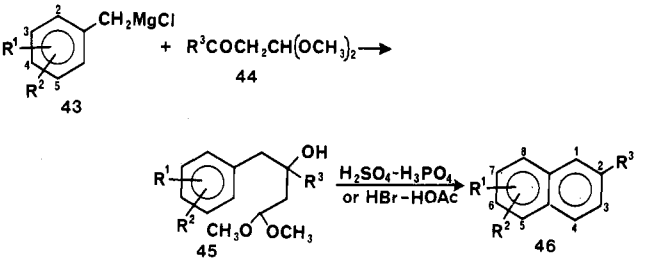
Perhaps most closely related to the Combes synthesis is the cyclization of the monophenylhydrazone of benzil (**39**; Scheme 12) to yield 3,4-diphenylcinnoline (**40**).[50]

2. A Chain Having a Group That May Be Eliminated

a. Hydroxyl. As a tool for the synthesis of naphthalene derivatives the cyclialkylation of γ-aryl carbonyl compounds having a double bond in the chain was limited by a tendency of such aldehydes and ketones to exist in an unfavorable (trans) configuration[2] as well as by difficulties in their preparation. Both of these problems have been addressed by having in the system, instead of the double bond, a substituent that would be eliminated during the cyclization, thus forming a double bond. By far the favorite group for such an elimination is the hydroxyl. Almost 100 years ago Zincke[51] proposed that 3-hydroxy-2,4-diphenylbutanal (**41**; Scheme 13) was an intermediate in the acid-catalyzed self-condensation of phenylacetaldehyde to 2-phenylnaphthalene (**42**), but at the time there was no way to test the hypothesis.

Much later Kochetkov et al.[17] found that the carbinols **45** (Scheme 14) formed by the reaction of the methyl acetals **44** of α-acyl aldehydes with benzyl Grignard reagents **43** can be cyclized in acid, affording

SCHEME 14



SCHEME 15

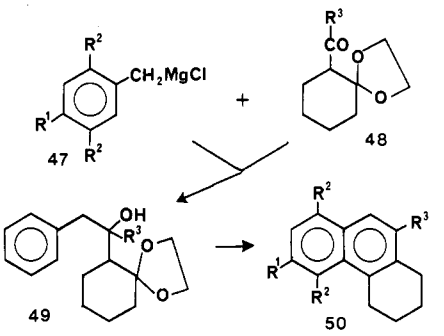


TABLE 7. Synthesis of 2-Alkylnaphthalenes (Scheme 14)

				46			
R^1	R^2	R^3	acid[a]	R^1	R^2	overall, %	ref
		Me	A			25	17
		Et	A			25.5	17
		Am	A			30	17
3-Me		Me	B	7-Me		57.5[b]	52
4-Me		Me	A	6-Me		26.5	17
4-Me		Pr	A	6-Me		35	17
2-F		Me	C	8-F		good	54
3-F		Me	C	7-F		80	53
4-F		Me	B	6-F		80	53
2-Me	4-Me	Me	A	6-Me	8-Me	11	17

[a] Key: A = 3:2 H_2SO_4–H_3PO_4; B = HBr–HOAc; C = refluxing 10% H_2SO_4. [b] The intermediate carbinol **45** was isolated pure (70%).

TABLE 8. 1,2,3,4-Tetrahydrophenanthrenes by the Kochetkov Synthesis (Scheme 15)

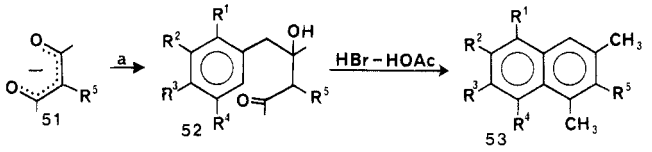
R^1	R^2	R^3	yield **50**,[a] %
		Me	22[b]
		Et	41
		i-Bu	53
Me		Me	14
	Me	Me	*c*

[a] Yield from **48** when cyclization was in H_2SO_4–H_3PO_4. [b] The intermediate **49** was isolated in 70.5% yield and cyclized in HBr–HOAc in 31.5% yield. Use of PPA or a mixture of sulfuric and phosphoric acids gave lower yields. [c] Yield not specified.

modest yields of 2-substituted naphthalenes **46**. Subsequent workers[52–54] have found the synthesis advantageous and with slight modifications have produced good overall yields of naphthalene derivatives (Table 7).

The first steps of the Kochetkov synthesis[55] of 1,2,3,4-tetrahydrophenanthrenes **50** (Scheme 15) resembles that for naphthalenes in that a benzyl Grignard reagent **47** was allowed to react with an unsymmetrical 1,3-dicarbonyl compound with one carbonyl group protected. The required 2-acetylcyclohexanone ketals **48** were prepared from cyclohexanone in only two steps. The crude carbinols **49** obtained by the Grignard ad-

SCHEME 16



a. Substituted or unsubstituted $C_6H_5CH_2MgCl$

SCHEME 17

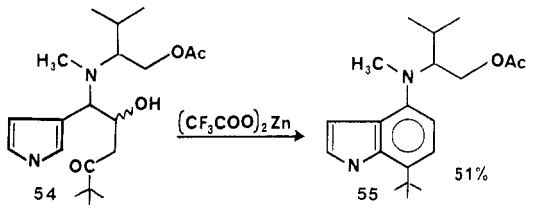


TABLE 9. 1,3-Dimethylnaphthalenes by the Method of Canonne et al. (Scheme 16)

					yield, %		
R^1	R^2	R^3	R^4	R^5	**52**	**53**	ref
					60–75	87–90	60, 56
Me					60–75	80–90	60, 56
Me		Me			50	80–90	60, 56
	Me		Me		60–75, 81	80–90, 80	60, 56, 59
Me			Me		60–75	80–90	60, 56
				Me	57	52	57
		Me		Me	46	54	57
Me	Me	Me		Me	19	31	57

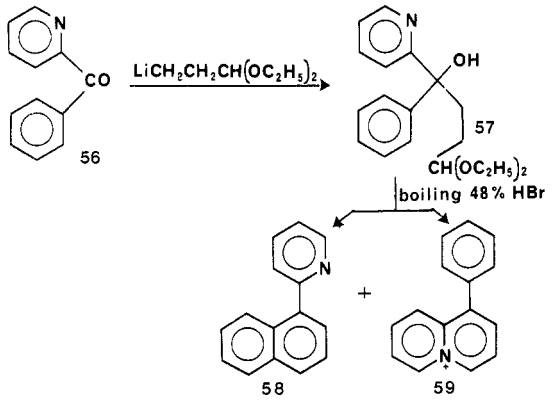
dition were usually cyclized in a sulfuric–phosphoric acid mixture (Table 8).

The naphthalene synthesis introduced by Canonne and co-workers[56,57] avoids the need for protection of one carbonyl group of the 1,3-diketone by employing a symmetrical diketone and as a consequence is limited to the preparation of naphthalenes having like substituents at positions 1 and 3. To call attention to another synthetic problem involved, the pentane-2,4-dione in Scheme 16 is represented as the anion **51** formed immediately as the benzyl Grignard reagent was added.[33,58] The first strategy applied was to employ a 200% excess of the reagent, which left a mixture from which it was difficult to isolate the pure hydroxy ketone **52**. The need for excess Grignard reagent appears to be avoided by first creating a lithium salt.[59] Although it was found possible to introduce a methyl group at position 2 (in addition to 1 and 3) by the use of 3-methylpentane-2,4-dione, lower yields were obtained (Table 9).

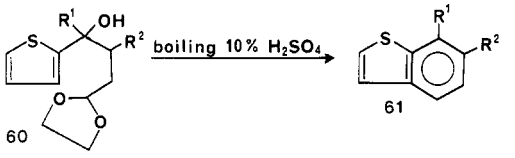
Recently a related cyclization[61] leading to a substituted indole (**55**) has been observed (Scheme 17). The cyclodehydration involving attack on a reactive pyrrole nucleus occurred at room temperature (zinc triflate catalyst) indicating that a β-hydroxyl will be eliminated in preference to a γ-amino group.

Although Zincke's[51] conclusion that a β-hydroxy aldehyde (Scheme 13) was an intermediate in the self-condensation of phenylacetaldehyde led him to try cross-aldolization of the aldehyde with acetaldehyde or acetone as a route to naphthalene derivatives other than **42**, he met with no success. The development of new methods for cross-aldolization,[62] and the evidence that at least one such method[63] can be used to produce hydroxy ketones that give every promise of being cyclizable, suggests that further research in this area should provide useful intermediates for naphthalene synthesis.

SCHEME 18



SCHEME 19



SCHEME 20

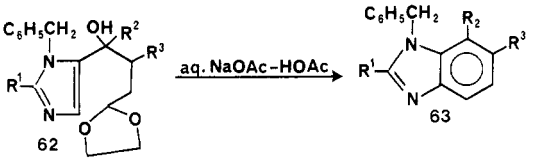


TABLE 10. Synthesis of Benzothiophenes by the Method of Loozen and Godefroi (Scheme 19)

R^1	R^2	overall yield, %	R^1	R^2	overall yield, %
H	H	68	*t*-Bu	H	*a*
Me	H	61	Me	Me	42
Et	H	70	Et	Me	44
i-Pr	H	64	2-(1,3-dioxolan-2-yl)ethyl	H	90[b]

[a] Gave a complex mixture. [b] The product was the corresponding aldehyde ($R^1 = (CH_2)_2CHO$), and the yield was calculated for the cyclization step only.

An alternate, and later, approach to naphthalene synthesis involved the use of systems in which the hydroxyl to be eliminated was located γ to the real or potential carbonyl group. It seems probable that the first example of such a cyclization was encountered accidentally by Glover and Jones[64] (Scheme 18) in an effort to prepare 1-phenylquinolizinium ion (**59**) by the cyclization of a γ-hydroxy acetal (**57**) in boiling hydrobromic acid. The major product proved to be 1-(2-pyridyl)naphthalene (**58**) although in only 16% yield.

The first to put this cyclization to practical use were Loozen and Godefroi[65] who used it to prepare 7-substituted and a few 6,7-disubstituted benzo[*b*]thiophenes **61** (Scheme 19). Cyclialkylation of the carbinol **60** gave good to satisfactory yields except where R^1 = *t*-Bu (Table 10). The same approach made possible a novel synthesis of benzimidazoles from imidazoles (Scheme 20).[66] Initial attempts to cyclize the intermediate hydroxy acetal **62** were frustrated by the tendency of the 10% sulfuric acid, used as the cyclizing medium in the benzothiophene synthesis, to protonate the imidazole ring, rendering it inactive toward the attack of a protonated aldehyde group. The difficulty was overcome by using as a cyclizing medium—dilute acetic acid

TABLE 11. Benzimidazoles from Imidazoles (Scheme 20)

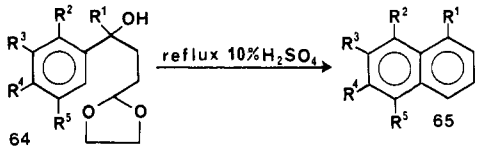
R¹	R²	R³	yield, % carbinol 62	yield, % product 63
Me	H	H	66	77
Et	H	H	85	70
i-Pr	H	H	68	92
t-Bu	H	H	79	33
Et	H	Me	80	94
Me	Me	H	51[a]	75
Me	*i*-Pr	H	61[a]	62

[a] Prepared by oxidation of 62 (R¹ = Me, R² = R³ = H) followed by addition of the appropriate Grignard reagent.

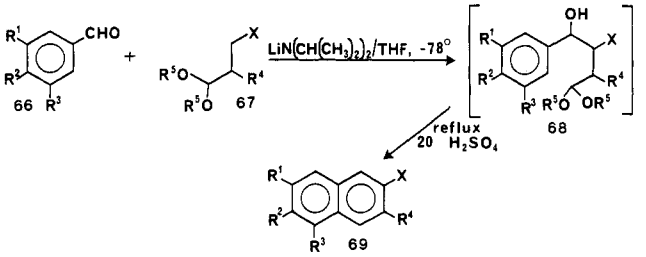
TABLE 12. Naphthalenes by the Loozen Synthesis (Scheme 21)

R¹	R²	R³	R⁴	R⁵	overall yield, %
					31
		Me			84
		OH			52
		OMe			84
	OH	OMe			54
Me		OMe			84
		O–CH_2–O			91
		OMe		OMe	62

SCHEME 21



SCHEME 22



containing sodium acetate as a buffer (Table 11). Attempts to extend the benzologation reaction to pyrrole or furan were defeated by the instability of those heterocycles toward the conditions needed for cyclization.[67]

Loozen[67] has shown that the same synthetic scheme provides a useful route to many substituted naphthalenes (Scheme 21). The only yield below 50% (Table 12) was that for the preparation of naphthalene (31%), evidence of the need for activating groups on the ring to undergo cyclialkylation. The synthesis of hydroxy ketones related in structure to the hydroxy acetals 64 of Loozen has been described,[68,69] but there has been no report of attempts to cyclize such ketones to form naphthalene derivatives.

Teague and Roth[70] have modified the Loozen naphthalene synthesis, replacing the Grignard reagent by the anion of 3-substituted 4,4-dialkoxybutanoates, -butanenitriles, or -butanamides (Scheme 22). The expected naphthalenes were obtained in excellent yields (Table 13).

It seems probable that the intermediate in the intermolecular reaction of veratrole (70; Scheme 23) with 2,5-diethoxytetrahydrofuran (71), a succindialdehyde

TABLE 13. Substituted Naphthalenes by the Teague and Roth Modification of the Loozen Synthesis (Scheme 22)

R¹	R²	R³	R⁴	R⁵	X	yield 69, %
	OCH_2O			Et	CN	82
	OCH_2O			*a*	COOMe	74
OMe	OMe			Me	CN	80
OMe	OMe			*a*	COOMe	78
	OCH_2O		Me	Me	CN	82
	OCH_2O		Me	Me	COOMe	83
OMe	OMe		Me	Me	COOMe	84
OMe	OMe	OMe	Me	Me	COOMe	82
	OCH_2O		Me	Me	$CONMe_2$	90
OMe	OMe		Me	Me	$CONMe_2$	90

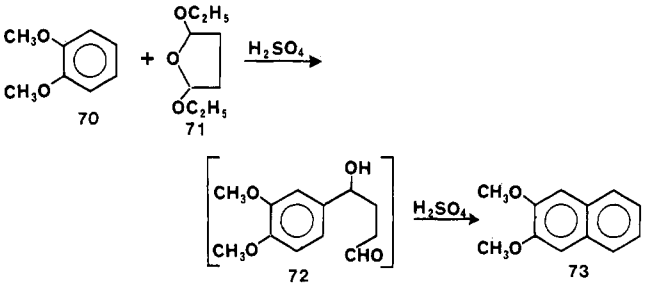
[a] One terminus of a $(CH_2)_3$ bridge.

TABLE 14. Synthesis of Triphenylenes (Scheme 24)

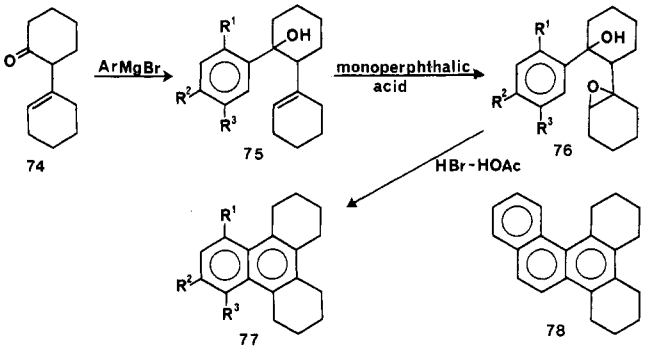
R¹	R²	R³	yield, %	ref
			50[a]	73
	Me		32[a]	73
		Me	35[a]	73
Me			15[a]	73
Me		Me	50[b]	73
	Ph		98[a]	75
MeO			*c*	73
	MeO		97[d]	72

[a] Yields are from the alcohol 75 to the dehydrogenated triphenylene. [b] Yield of 77 (R¹ = R³ = Me, R² = H). [c] Crude 77 (R¹ = MeO, R² = R³ = H) was dehydrogenated and gave only a trace of unsubstituted triphenylene. [d] Yield of unpurified 77 (R¹ = R³ = H, R² = OCH_3), which was dehydrogenated to 2-methoxytriphenylene in unspecified yield.

SCHEME 23



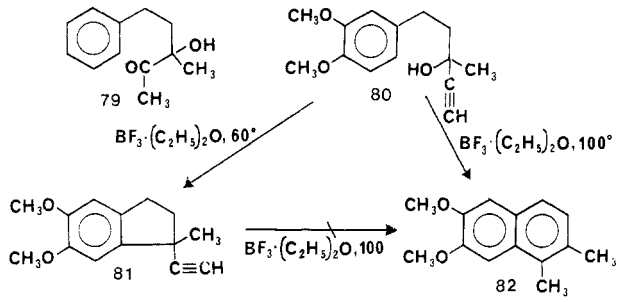
SCHEME 24



equivalent, is the hydroxy aldehyde 72, which may also be the intermediate in the Loozen synthesis (Scheme 21) of 2,3-dimethoxynaphthalene.[71]

Whether oxiranes cyclize directly, or are first isomerized under the influence of acids to form a cyclizable carbonyl compound, they may be regarded as carbonyl equivalents in devising cyclization reactions.[2] Barker et al.[72,73] made an early application of such an oxirane cyclization to what may be properly regarded as a naphthalene synthesis although the products were octahydrotriphenylenes 77 (Scheme 24). The easily

SCHEME 25



prepared[74] 2-cyclohexenylcyclohexanone (74) was allowed to react with an aryl Grignard reagent and the resulting alkenol 75 oxidized to the epoxide 76 which was cyclized in a hydrobromic–acetic acid mixture to yield an octahydrotriphenylene (77). If instead of phenyl a 1- or 2-naphthyl Grignard reagent was used, the product was octahydro-1,2-benzochrysene (78). While not explicit, the data (Table 14) suggest that the cyclization step takes place in satisfactory yields.

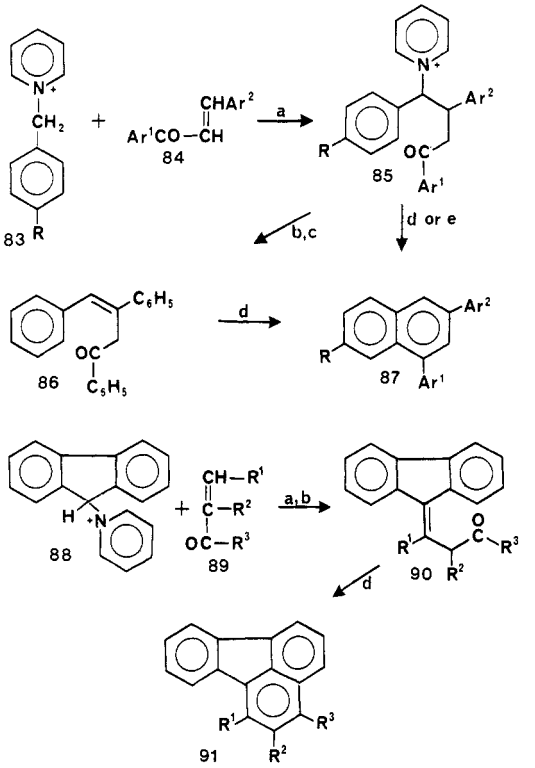
The cyclization of γ-aryl carbonyl compounds bearing hydroxyl groups at the β- or γ-positions met with success, which has not as yet found a parallel among the α-hydroxy isomers. Such α-hydroxy compounds should be easy to synthesize; indeed at least one (79; Scheme 25) is already known, but no report of their cyclization was found. A possible side reaction could be the formation of a five-membered ring, a problem encountered by Le Goffic et al.[76] in an effort to apply to the synthesis of naphthalenes the synthetic method developed by them for the synthesis of ellipticine.[77,78] The ethynyl carbinol 80 employed by Le Goffic in the model study appeared to cyclize exclusively to an indanyl derivative 81 when the boron trifluoride catalyzed reaction was carried out at 60 °C. Fortunately, in this example it proved possible to make the formation of 6,7-dimethoxy-1,2-dimethylnaphthalene (82) the major reaction by simply raising the reaction temperature to 100 °C. Despite the temptation to regard the ethynyl group as a potential acetyl, Le Goffic is probably correct in his assumption that the intermediate in his synthesis is a vinyl cation[76] rather than a protonated acetyl group.

b. Other Groups. The benzologation reactions discussed show that it is relatively easy to assemble γ-aryl carbonyl compounds (or their protected derivatives) having a hydroxyl group on the chain and that such a hydroxyl is eliminated under the conditions used for the cyclization. That at least one alternative for the hydroxyl group exists was made clear by Kröhnke[43] and Curtze[44] who showed that the Michael addition of the anion derived from the *N*-benzylpyridinium cation (83; Scheme 26) afforded a betaine (85), which in molten $ZnCl_2$ cyclized with the loss of the *pyridinium* group to yield 1,3-diphenylnaphthalene (87; R = H, Ar^1 = Ar^2 = Ph). Since the betaine (85) on heating in a hydrobromic–acetic acid mixture gave an unsaturated ketone (86), which on cyclization in $ZnCl_2$ produced 1,3-diphenylnaphthalene, the unsaturated ketone was assumed to be an intermediate in the direct cyclization of the betaine. Additional examples of the cyclization were provided by Tewari and Nagpal[79] (Table 15).

By use of the anion from the 9-fluorenyl-*N*-pyridinium cation (88) in a Michael reaction with several α,β-unsaturated ketones, Curtze et al.[44] were able to prepare fluoranthenes 91 with substituents at the 1-, 2-, and 3-positions (Table 16). With benzylidene derivatives of cyclic ketones (hydrindone, tetralone, acenaphthalenone, etc.) as substrates in the Michael reaction step, more complex polycyclic hydrocarbons were prepared.

Loozen et al.[67] reported that they had failed in an effort to apply their benzologation reaction to pyrrole derivatives. Trost et al.[80] have introduced modifications that make it possible to carry out such a reaction successfully. A thioketal (92; Scheme 27) was used in place of an acetal, and the hydroxyl group γ to the potential carbonyl group was replaced by a *p*-toluenesulfonyl group prior to cyclization. The yield of the indole 95b from 93b was 61%, but a parallel cyclization of 93a,

SCHEME 26



a. $NaOCH_3$. b. Boiling HBr–HOAc. c. R=H, Ar^1=Ar^2=C_6H_5. d. Molten $ZnCl_2$. e. Anhydrous $ZnCl_2$ in refluxing HOAc.

TABLE 15. 1,3-Diarylnaphthalenes 87 by the Method of Kröhnke and Curtze (Scheme 26)

R	Ar^1	Ar^2	yield, %	ref
	C_6H_5	C_6H_5	80[a]	43, 44
NO_2	4-$MeOC_6H_4$	4-ClC_6H_4	*b*	79
NO_2	4-MeC_6H_4	4-ClC_6H_4	*c*	79
NO_2	1-$C_{10}H_7$	5-Br-2,4-$Me_2OC_6H_2$	*c*	79
NO_2	1-(2-C_4H_3S)	3,4-$OCH_2OC_6H_3$	*c*	79

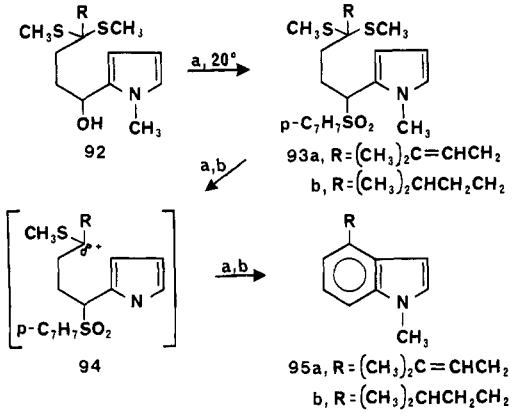
[a] Cyclization step only. [b] "Good yield" (overall). [c] "Fair yield" (overall).

TABLE 16. Synthesis of 1-, 2-, and 3-Substituted Fluoranthenes 91 by the Method of Kröhnke and Curtze (Scheme 26)

R^1	R^2	R^3	cyclizing agent[a]	yield, %
Ph		Ph	B	75
Me		Me	A	12[b]
Ph		Me	A	28[b]
Me		Ph	B	12
Ph	Me	Me	A	26[b]

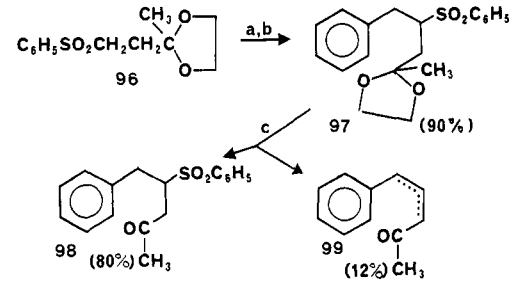
[a] Key: A = boiling HBr–HOAc; B = fused zinc chloride. [b] Overall yield including Michael reaction.

SCHEME 27



a. p-$C_7H_7SO_2H$,CH_3CN. b. 50° or reflux.

SCHEME 28



a. C_4H_9Li, -70°. b. $C_6H_5CH_2Cl$, HMPT.
c. H_2O, acetone, $(COOH)_2$, reflux.

which has a double bond in the side chain afforded only a 35% yield. From their experience with other thioketal cyclizations Trost et al. concluded that a thionium ion (**94**) was the intermediate in the cyclization.

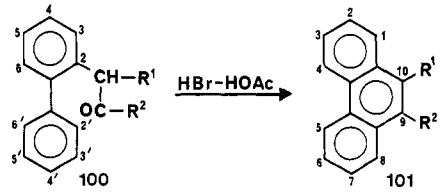
This successful use of a sulfonyl group as the leaving group in a benzologation reaction suggests a hitherto unexplored application of the Julia and Badet[32] synthesis of sulfones. It was shown that the sulfone **96** (Scheme 28) could be alkylated with benzyl chloride in 90% yield and that the alkylation product **97**, on hydrolysis with a catalytic quantity of oxalic acid in acetone–water solution, yielded a mixture of the expected keto sulfone **98** and unsaturated ketones **99**. The apparent ease with which elimination of the sulfonyl group occurs may indicate that **97** or perhaps some congener with activating groups on the benzyl ring could be cyclized to 1-methylnaphthalene (or a derivative) by the action of a suitable strong acid.

B. Phenanthrene and Its Analogues by Cyclialkylation of γ-Aryl Carbonyl Compounds with an Additional Aromatic Ring Fused to the β- and γ-Positions

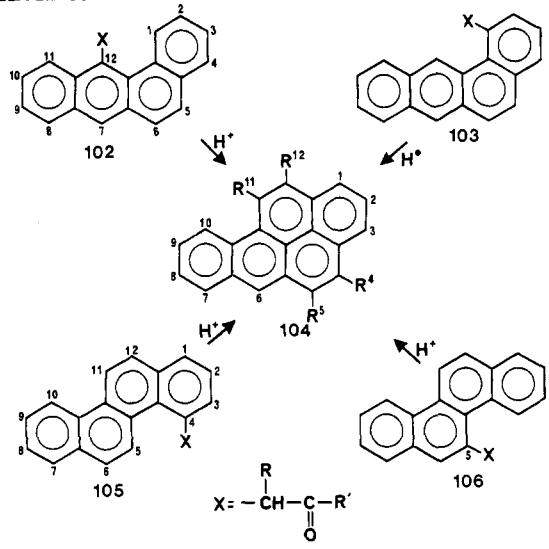
1. Homocyclic Systems

Just as γ-aryl carbonyl compounds having a double bond in the chain may afford naphthalene on cyclialkylation, a γ-aryl carbonyl compound having an aromatic ring fused to the chain may yield a fused tricyclic aromatic system. If the aryl groups are benzenoid, and the phenylene group is fused to the chain at the β- and γ-positions, the product is phenanthrene or a derivative (Scheme 29). Although carbonyl compounds had been postulated[2] as intermediates in the acid-catalyzed cyclization of epoxides and glycol ethers to form phen-

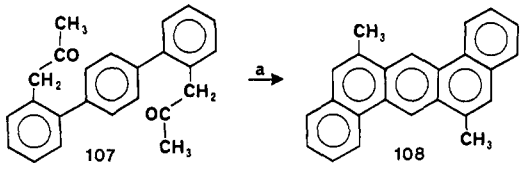
SCHEME 29



SCHEME 30



SCHEME 31

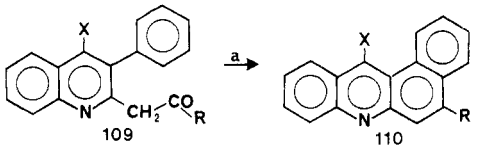


a. polyphosphoric acid.

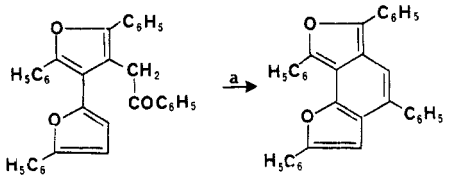
anthrenes, at the time of the earlier review there were only two simple ketones (**100**, $R^1 = R^2$ = Ph and a chlorinated analogue) that had been cyclized to phenanthrene derivatives. Since then, phenanthrene and a number of 9-, 10-, and 9,10-derivatives have been prepared by the acid-catalyzed cyclization of aldehydes and ketones (Table 17). Most of the ketones and aldehydes in the table were prepared from α-(2-biphenylyl)-acetonitrile. The cyclization of keto nitriles and keto esters frequently gave mixtures containing not only the expected cyclodehydration product but others in which the functional group had been hydrolyzed and/or undergone decarboxylation. More recent work by others with benzologs (vide infra) suggests that milder conditions can be found that might lead to cyclialkylation without modification of the functional groups.

An important extension of the phenanthrene cyclization (Scheme 29) has been the formation of benzo[*a*]pyrenes **104** by the cyclialkylation of 12- or 1-substituted benz[*a*]anthracenes **102** or **103** or 4- or 5-substituted chrysenes **105** or **106** (Scheme 30). The first such extension, by Blum and Bergmann,[92] involved the polyphosphoric acid catalyzed ring closure of an arylacetaldehyde (**102**, R = R′ = H, 5-F). The aldehyde was prepared by the following sequence: $ArCH_2CN$, $ArCH_2COOH$, $ArCH_2COOMe$, $ArCH_2CH_2OH$, $ArCH_2CHO$. The introduction of diisobutylaluminum hydride has made possible a more direct approach to the aldehyde

SCHEME 32



SCHEME 33



by reduction of either the ester[93] or the nitrile.[94a]

Another interesting application of the phenanthrene-type cyclization was in the dual cyclization of diacetonyl-*p*-terphenyl (**107**; Scheme 31) to afford 6,13-dibenz[*a*]anthracene (**108**) in 92% yield.[94b]

2. Heterocyclic Systems

Several ketone and aldehyde cyclizations parallel to the phenanthrene type have been observed in the heterocyclic series. Hauser and Murray[95] observed that some acylation products (**109**; Scheme 32) of 2-methyl-3-phenylquinoline and its 4-phenoxy derivative could be cyclized in polyphosphoric acid to afford good yields of benz[*a*]acridines **110**.

Another example of the formation of a phenanthrene analogue is the cyclization of a phenacylbifuryl (Scheme 33) in a refluxing mixture of hydrobromic and acetic acids to form a furoisobenzofuran.[96]

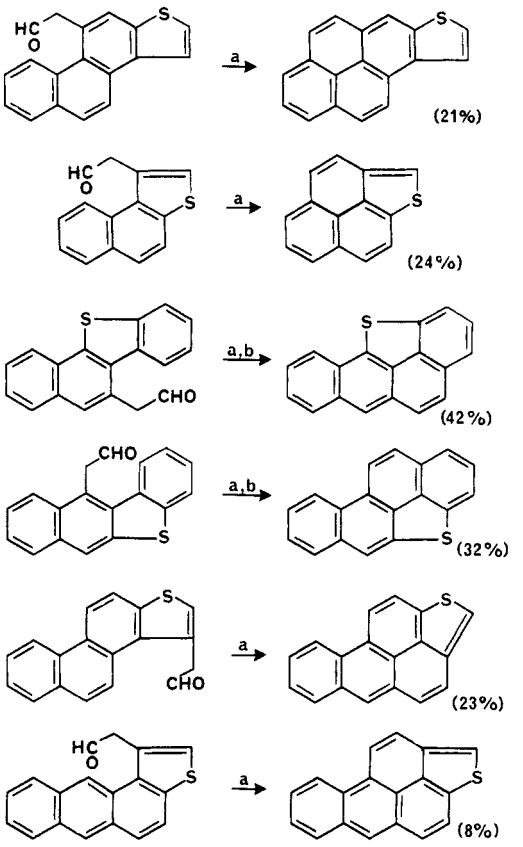
Castle et al. have undertaken the synthesis of analogues of the common fused polycyclic aromatic hydrocarbons, each characterized by having at least one fused thiophene ring. One approach has been the cyclization of arylacetaldehydes, and six such cyclizations are shown in Scheme 34.[97-101] The yields in parentheses are for reduction of the nitrile, hydrolysis of the imine, and cyclization. In general these yields are inferior to those reported in the synthesis of benzo[*a*]pyrenes (Table 18).

The general method for the synthesis of benzo[*a*]-quinolizinium salts (**113**; Scheme 35) was based upon the earlier synthesis of phenanthrenes (Scheme 29). 2-Phenylpyridine (**111**) or a congener was quaternized with bromoacetaldoxime, or an α-halo ketone, and the resulting quaternary salt was cyclized, usually in boiling hydrobromic acid. A recent review[102] lists 20 examples of such cyclizations, with an average yield of 48%.

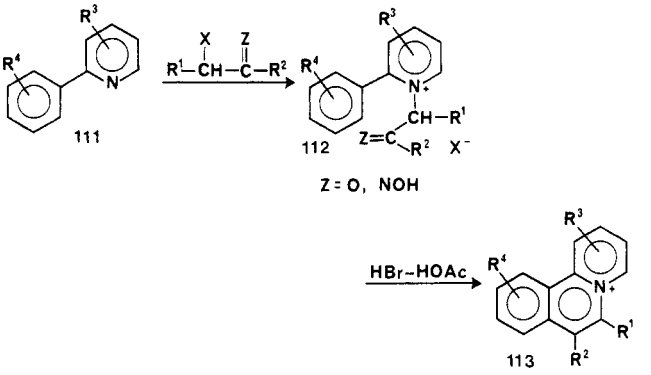
3. Phenanthrene Derivatives by Cyclization of Epoxides and Glycol Ethers

The earlier review[2] reported 20 examples of the formation of phenanthrenes by the cyclodehydration of epoxides. Aside from the ingenious application of Barker et al.[72,73] of epoxide cyclization to the synthesis of octahydrotriphenylenes (Scheme 24), the past 40 years appear to have produced only three examples of phenanthrenes produced by cyclization of epoxides.[107,108] The synthesis by Martin and Vassart[108]

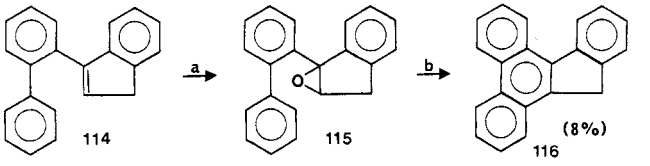
SCHEME 34



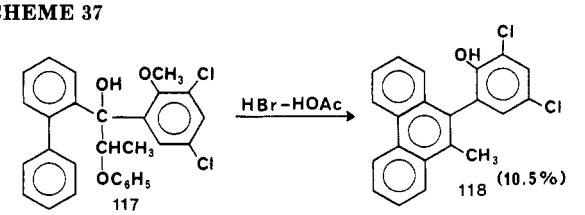
SCHEME 35



SCHEME 36



SCHEME 37



of dibenzo[*a*,*b*]fluorene (**116**; Scheme 36) starting with 1-(2-biphenylyl)indene (**114**) was accomplished in only 8% yield.

TABLE 17. Phenanthrenes 101 (Scheme 29)

a. By Cyclization of Aldehydes and Ketones

R^1	R^2	other subst	yield,[a] %	ref
			78	82
Me			93	82
Et			100	82
Me		3-OH[a]	92	82
	Me		68	82
	i-Bu		32	82
	p-C_6H_4OH[b]		45	83
Me	Me		87	84
Me	Me		*c*	85
Me	Et		86	84
Me	Pr		100	84
Me	Bu		92	84
Et	Et		91	84
Pr	Pr	3-OH[a]	89	84
C_9H_{19}	C_9H_{19}		70	86
C_9H_{19}	$C_{14}H_{29}$		34	86
$C_{14}H_{29}$	$C_{14}H_{29}$		23	86
Me	*p*-C_6H_4OH[b]		82	87
Et	*p*-C_6H_4OH[b]		82	87
Et	*p*-C_6H_4OH[c]	3-OH[d]	51	88
Me	C_6H_5	2,7-dibromo	83.5[e]	89
Et	*p*-$C_6H_4OCH_3$	2,7-dimethoxy	65.5[e]	89

b. By Cyclization of Keto Nitriles

100 (R^1 = CN) R^2	101 R^1	101 R^2	reflux, h	yield, %	ref
Me	CN	Me	1.5	56	82
Me		Me	168	22[f]	82
Et	$CONH_2$	Et	31.5	24[g]	82
Et		Et	168	73[h]	82
Ph		Ph	17	29	90
p-$CH_3OC_6H_4$		*p*-HOC_6H_4	1	96	90

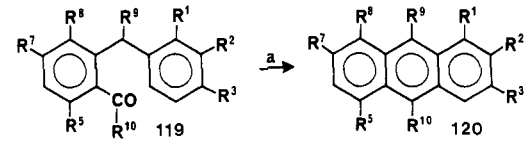
c. By Cyclization of Keto Esters

100 R^1	100 R^2	100 other	101 R^1	101 R^2	101 other	yield, %	ref
COOEt	CH_3	3,5-$(NO_2)_2$		CH_3	1,3-$(NO_2)_2$	54	91
COOEt	COOEt	3′-OCH_3	COOCO		3-OCH_3	53[i]	85
COOEt	COOEt	4′-OCH_3	COOCO		2-OCH_3	18[j]	85

[a] From methoxy derivative of **100**. [b] From **100** (R^2 = *p*-$CH_3OC_6H_4$). [c] Not reported. [d] From 5-methoxy derivatives of **100** (R = Et, R^2 = *p*-$CH_3OC_6H_4$). [e] Cyclized in PPA. [f] Plus 16% of **101** (R^1 = $CONH_2$, R^2 = Me). [g] Plus 12% of **101** (R^1 = $CONH_2$, R^2 = Et). [h] Plus 20% of **101** (R^1 = $CONH_2$, R^2 = Et). [i] By cyclization in 80% H_2SO_4, 100 °C; also yielded 20% of 1-MeO isomer. [j] Plus 45.5% of 2-methoxy-10-phenanthroic acid.

The cyclization by Tarbell and Sato[109] of the biphenylylglycol ether (**117**; Scheme 37) afforded the desired 9-methyl-10-arylphenanthrene **118** in 10.5% yield.

SCHEME 38



a. Usually refluxing HBr–HOAc mixture.

C. Anthracene and Its Analogues by Cyclialkylation of γ-Aryl Carbonyl Compounds Having an Additional Aromatic Ring Fused to the α- and β-Positions

1. Homocyclic Systems

Just as phenanthrene can be formed by the cyclodehydration of a γ-aryl carbonyl compound having an aromatic ring fused to the β- and γ-positions on the chain, anthracene and its analogues are formed if the fusion is instead at the α- and β-positions. Scheme 38 represents such an anthracene-type cyclodehydration.

a. Ketones. To learn more about the limitations and kinetics (see Mechanism) of such cyclialkylations, Vingiello and others have synthesized a great number of o-benzylphenones **119** and submitted them to the action of a hot mixture of hydrobromic and acetic acids. Many of the resulting cyclizations have been recorded in a previous review[110] and will not be reproduced here. In Table 19 are collected some later cyclialkylation results that justify comment. The first examples (1–8) show the effect of substitution in the benzyl ring. In every example in which the substituent was alkyl, aromatic cyclodehydration did afford the expected product, although the yield of 6-methylaceanthrene (example 5) was unsatisfactory, and loss of the methyl group from 3-ethyl-10-methylanthracene (example 4) was only avoided by use of polyphosphoric acid rather than hydrobromic as the cyclization medium. Deactivating groups such as trifluoromethyl or fluoro (examples 7 and 8) in effect prevented cyclization. Finally examples 9–11 indicate that a methyl in the ortho position of the benzoyl group impedes the reaction, probably via steric hindrance.

A dual application of the anthracene cyclization to a diketone, 1,4-bis(2-benzylbenzoyl)benzene (**121**; Scheme 39) has made possible the preparation of 1,4-bis(9-anthryl)benzene (**122**).[117] The method has been extended to benzologs of **121**.[117,118]

TABLE 18. Synthesis of Benzo[*a*]pyrene (Scheme 30)

compound cyclized, side chain: aryl group	R	R′	other group	benzopyrene: R^4	R^5	R^{11}	R^{12}	other group	yield, %	ref
102			5-F	F					25[a]	92
102			11-F					10-F	47[b]	103
102			9-F					8-F	48[b]	94[a]
102			10-F					9-F	42[b]	94[a]
102	COOEt					COOEt			59[c]	104
103									82[d]	93
103		Me				Me			74[d]	105
103	COOEt						COOEt		77[d]	104
103	CN						CN		86[d]	106
105									85[d]	93
105		Me			Me				65[d]	105
105	COOEt			COOEt					66[c]	104

[a] Plus 14% yield of 8-fluorobenz[1]aceanthrylene. [b] Overall yield for reduction of nitrile (DIBAL), hydrolysis of imine, and cyclization of aldehyde in PPA. [c] Overall yield for formylation and cyclization in $MeSO_2OH$ in CH_2Cl_2. [d] Cyclized in methanesulfonic acid.

TABLE 19. Cyclodehydration of Some *o*-Benzylphenones (Scheme 38)

no.	R^1	R^2	R^3	R^5	R^7	R^8	R^9	R^{10}	yield, %	ref
1	Me							Et	65	111
2	Me				Me			Me	60	111
3	Me			Me				Me	45	111
4			Et					Me	*b*	112
5					$-CH_2CH_2$			Me	6	113
6			Me					Ph	88	114
7		CF_3						Ph	*c*	114
8			F					Ph	*d*	114
9								$2\text{-}MeC_6H_4$	10	115
10								$2,6\text{-}Me_2C_6H_3$	*e*	116
11								$2,4\text{-}Me_2C_6H_3$	18[e]	116

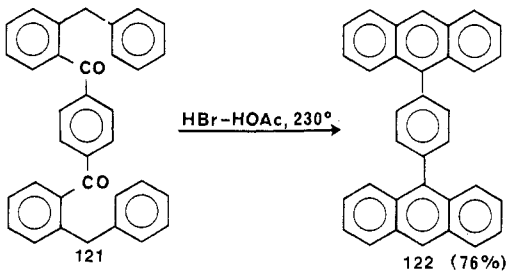
[a] Except as noted all cyclizations were in refluxing HBr–HOAc. [b] Cyclized in unspecified yield by heating in PPA at 130 °C. [c] Failed to cyclize in 10 days. [d] Failed to cyclize in 3 days. [e] By heating in a sealed tube.

TABLE 20. Effect of Reagents and Conditions on the Aromatic Cyclodehydration of *o*-Benzylphenyl Naphthyl Ketones 123 and 126 (Scheme 40)

		% yields of products obtained with							
		HBr[a]		Heat[b]		Al_2O_3[c]		HF[d]	
no.	R	AC	Elbs	AC	Elbs	AC	Elbs	AC	Elbs
123	H	11[e]	11		32		14		
123	Me	29[e]			11		14	28	
123	CF_3	*e*							
126	H	86			11		7	14	
126	Me	93		29			55	72	
126	CF_3	*e*							

[a] Except as noted, the ketone was refluxed for about 15 h in a mixture of HBr and glacial HOAc. [b] The ketone was heated with zinc dust for 3 h at 450 °C. [c] The ketone was mixed with alumina and heated at 250 °C for 2.5 h. [d] The ketone was mixed with liquid HF and allowed to stand at room temperature until the acid had evaporated. [e] The acid mixture was heated for 3 h at 200 °C in a sealed tube.

SCHEME 39

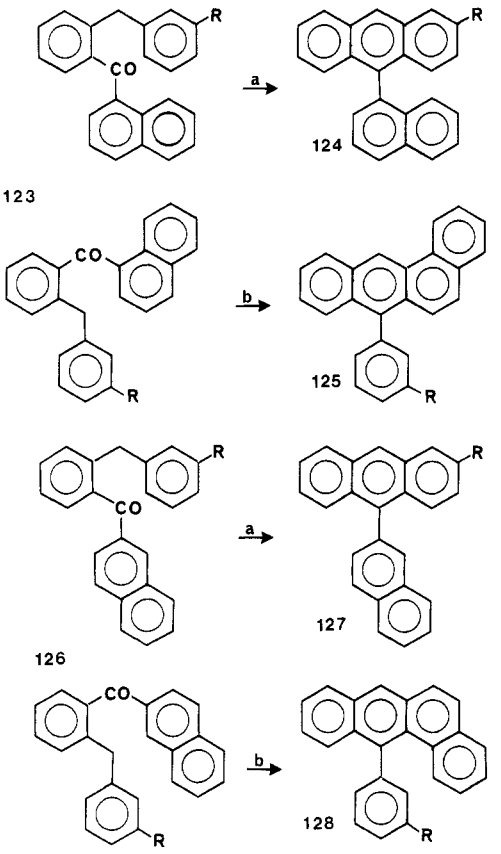


A discovery made by Vingiello et al.[119] was that an Elbs-type reaction[120] can occur under the acidic conditions usually used in aromatic cyclodehydration and that aromatic cyclodehydration, like the Elbs, can occur in the absence of acids.[119,121] Examples of both phenomena may be seen in Table 20. When 2-benzylphenyl 1-naphthyl ketone (**123**; Scheme 40) was heated in a sealed tube with a hydrobromic–acetic acid mixture, not only the expected 9-(1-naphthyl)anthracene (**124**, R = H) but an equal amount of 7-phenylbenz[*a*]anthracene was obtained.

The reactive 2-(3-methylbenzyl)phenyl 2-naphthyl ketone (**126**, R = Me) on heating at 430 °C without acid produced the product **127** (R = Me) which would be expected from acid-catalyzed cyclialkylation. Another example of a purely thermally activated ketone cyclialkylation was encountered later by Svetozarskii et al. (Scheme 2).[10,11]

Although it was believed[119] that yields in the Elbs reaction were not improved by use of a catalyst, a good yield of the Elbs product, 12-(3-methylphenyl)benz[*a*]anthracene (**128**, R = Me) was obtained when ketone **126** (R = Me) was heated with alumina while none was obtained under the usual Elbs conditions.

SCHEME 40

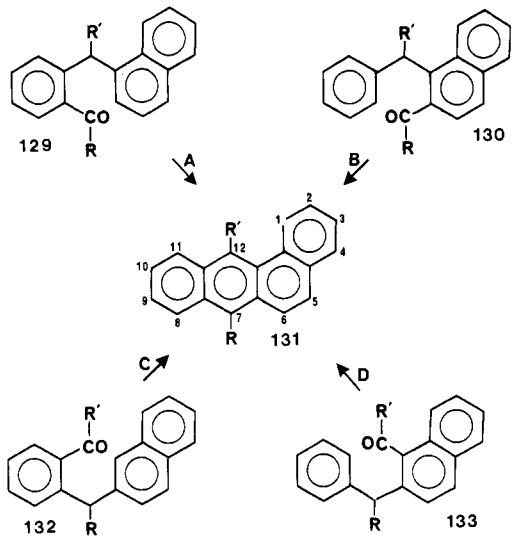


a. Aromatic cyclodehydration. b. Elbs reaction.

If an *o*-benzylphenyl ketone (**119**) is modified by having an aromatic ring fused to it, cyclodehydration produces a benzolog of anthracene, the most important of which is benz[*a*]anthracene. In Scheme 41 are shown two approaches to the synthesis of a 7-substituted benz[*a*]anthracene and two to a 12-substituted isomer. Vingiello et al. used ketone cyclialkylation to prepare many 7- and 12-arylbenz[*a*]anthracenes, and some examples too recent to be included in Barclay's chapter[3] are in Table 21.

Two alkyl analogues, **129** (R′ = H, R = isopropyl or cyclohexyl), which underwent dealkylation, afforded unsubstituted benz[*a*]anthracene as the major product. Detailed kinetic analysis of the cyclohexyl ketone cyclization showed that observed yields were the consequence of a relatively rapid cyclodehydration followed

SCHEME 41



Routes to meso-substituted benz[a]anthracenes

TABLE 21. 7- or 12-Substituted Benzo[*a*]anthracenes by Cyclialkylation of Aryl Ketones in HBr and HOAc (Scheme 41)

	at position 7[a]		at position 12[b]	
ketone	yield, %	ref	yield, %	ref
2-carboxyphenyl	100	154		
3-carboxyphenyl[c]	50	123a		
4-carboxyphenyl[c]	60	123a		
2-chlorophenyl	42	123b	91	123[b]
2-fluorophenyl	87	123b	79	123[b]
2-pyridyl	80	123c	45, 14[e-g]	124
3-pyridyl	69[d]	123c	48, 67[e,f]	124
4-pyridyl	96[d]	123c	83, 87[e]	124
2-thienyl	70[g]	125	71[g]	125
3-thienyl	54	125	52	125
2-benzo[b]thienyl	100[h]	126	97[h]	126
3-benzo[b]thienyl	66[h]	126	*h*	126
cyclohexyl	26[i]	123d		
isopropyl	*j*	123d		

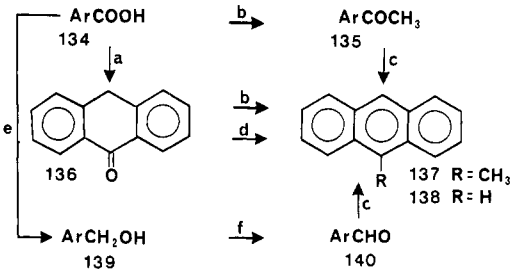
[a] From **129** (R′ = H) via route A. [b] Except as noted, from **132** (R = H) via route C. [c] Acid produced by cyclization of the keto nitrile, which hydrolyzed under the cyclization conditions. [d] By heating at 190 °C with phenyl hydrogen phosphate. [e] Yield from **133** (R = H) via route D. [f] Cyclized at 180 °C. [g] The ketimine rather than the ketone was the starting material. [h] Cyclized at 188 °C. [i] Plus 57% of unsubstituted benz[a]anthracene. [j] Plus 19% of unsubstituted benz[a]anthracene.

by a slower dealkylation reaction.[122]

Despite an early[127] demonstration that the cyclization of 2-(naphthylmethyl)acetophenones offered a convenient route to the synthesis of *meso*-methylbenz[*a*]anthracenes, and despite the existence of a continuing interest in the synthesis of related hydrocarbons, nearly two decades elapsed before the cyclialkylation scheme was first used by workers in the field. The delay in its application seemed to arise from the apparent failure of the new method to be easily related to classical approaches to the synthesis of *meso*-methylbenz[*a*]anthracenes.

To conserve space, the traditional method will be shown as applied to the synthesis of 9-methylanthracene (Scheme 42). The cyclization of *o*-benzylbenzoic acid (**134**) by the action of HF, H_2SO_4, or other dehydrating agent yields anthrone (**136**), which, when treated with methylmagnesium iodide in boiling benzene, produced 9-methylanthracene. Problems encountered in extending this simple reaction scheme to the preparation of derivatives of *meso*-methylbenz[*a*]anthracenes appear to have centered around the properties of the required benzanthrones. Some of these have proved unstable, either by themselves[128-130] or in the presence of organometallic reagents,[131,132] while others showed a greater tendency to exist as the tautomeric benzanthrol form.[133]

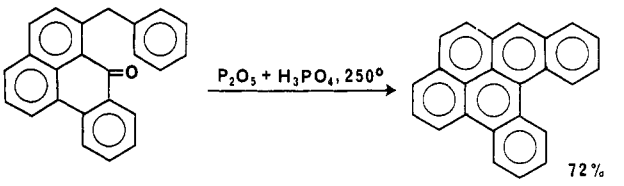
SCHEME 42



Ar = o-Benzylphenyl

a. H_2SO_4 or HF. b. CH_3Li. c. HBr or PPA. d. Zn + NaOH. e. $LiAlH_4$. f. $(C_5H_5N)_2 \cdot CrO_3$.

SCHEME 43



A simple alternative[134] to the anthranol route was the treatment of the *o*-benzylbenzoic acid with an excess of methyllithium to yield the methyl ketone **135** (79% yield), which could be cyclized to 9-methylanthracene in 80% yield.[135]

Newman and co-workers made extensive use of the cyclialkylation of methyl ketones in the synthesis of *meso*-methylbenz[*a*]anthracenes having halogen or methoxyl substituents (Table 22), a route that usually appears preferable to that via the benzanthrone. A notable exception occurs in the cyclization leading to 3-methoxy-7,12-dimethylbenz[*a*]anthracene where the route via the benzanthrone gave the better yield.[136] Failures of the cyclialkylation method included attempts to prepare 8-fluoro-7-methylbenz[*a*]anthracene[137] (loss of fluorine) and 9-(trifluoromethyl)-7,12-dimethylbenz[*a*]anthracene, in which the target position was too deactivated to permit attack.

Another extension of the anthracene synthesis through aromatic cyclodehydration of ketones was that leading to dibenzo[*a*,*l*]pyrene (Scheme 43). 6-Benzylbenzanthrone, prepared from benzanthrone by the action of benzylmagnesium bromide, was cyclized in 72% yield.[152]

An innovation by Newman[142] was the use of polyphosphoric acid (PPA) in place of the usual[2] mixture of hydrobromic and acetic acids. PPA, used earlier[95,89] in aromatic cyclodehydration of the phenanthrene type, offers the advantages that conditions can be selected leading to a more rapid, and sometimes cleaner, reaction. Newman[136] found that PPA gave better yields than hydrogen fluoride or a solution of zinc chloride in trifluoroacetic acid. For the cyclization of ketones to form *meso*-arylanthracenes (Table 19) and benz[*a*]anthracenes (Table 21), Vingiello et al. made frequent

TABLE 22. *meso*-Methylbenz[*a*]anthracenes by Aromatic Cyclodehydration of Methyl Ketones (Scheme 41)

R′	other subst	yield,[b] %	ref
	7-Methyl[a] from **129** (R = Me) via Route A		
H	none	91	138
Me	none	87	139, 138
H	1-Br	48	140
Me	1-MeO	47[c]	141
Me	2-F	57	144c
Me	2-Cl	74	144b
Me	2-MeO	94	141
H	3-Br	70	140
H	4-F	33[d]	142
Me	4-F	92	139
Me	4-MeO	94	141
H	5-F	40[e]	142
H	5-Br	80	143
H	5-OMe	81	144a
Me	5-F	66	139
Me	5-Br	83[f]	145
Me	5-OMe	70	144a
H	6-F	44[g]	94c
Me	6-OMe	*h*	144a
H	8-F	*i*	137
H	10-MeO	77	143
Me	10-MeO	>27[j]	150
H	11-MeO	76	143
Me	11-F	50	146
	7-Methyl from **130** (R = Me) via Route B		
H	2-F	20[j]	147
H	9-F	35[j]	148
H	9-OMe	50[j]	148
	12-Methyl from **132** (R = Me) via Route C		
Me	3-MeO	65[k]	136
H	6-F	12	149
Me	6-F	14[l]	149
Me	8-F	41[m]	146
Me	9-MeO	>33[i]	150
Me	$9\text{-}CF_3$	*n*	151

[a] Numbering of substituent positions corresponds to *Chemical Abstracts* practice for benz[*a*]anthracene (see **131**). [b] Yield is for the cyclization of the ketone **129** and, except as noted, was carried out in hot PPA. [c] Cyclized in a boiling benzene solution of *p*-toluenesulfonic acid. [d] In refluxing HBr–HOAc the yield was 27%. [e] An alternate route via the anthrone yielded about 1%. [f] Cyclized in sulfolane containing PPA. [g] Overall yield from ArCOOH. [h] Not reported. [i] Loss of fluorine. [j] Overall yield from 2-(2-lithio-4-methoxyphenyl)-4,4-dimethyl-2-oxazoline. [k] Alternate reagents: HF (37%), Cl_3COOH + zinc chloride (42%). The route via the methyl ketone gave less satisfactory yield than that via the benzanthrone. [l] Not obtained in a pure state. [m] 12% Yield was obtained via the anthrone. [n] Recovered 70% after heating with PPA at 70 °C. Decomposed when refluxed with zinc chloride in propionic anhydride.

use of hydrobromic–acetic acid mixtures, either under reflux or in a sealed tube, as well as phenyl hydrogen phosphate[153] or alumina.[121] Both research groups used hydrogen fluoride[154] or benzenesulfonic acid[153,141] successfully.

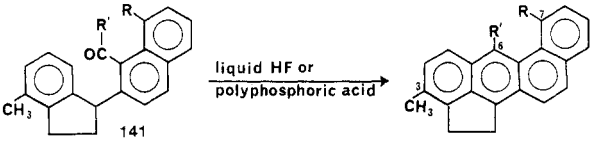
b. Aldehydes. Although it had been known for some time that *o*-benzylbenzaldehyde[155,156] would undergo acid-catalyzed cyclialkylation to afford anthracene **138**, the preparative use of this type of cyclialkylation was introduced in 1962 by Newman and Sheshadri[157] as an improvement over the classical route to benz[*a*]anthracenes via the related benzanthrone. Again for simplicity's sake, the two routes will be compared in terms of a possible synthesis of anthracene (Scheme 42). From the aromatic acid **134** the classical route is via the anthrone **136**, which on reduction with zinc and sodium hydroxide undergoes transannular dehydration to give anthracene **137**.[158] In addition to the drawbacks cited earlier (III.C.2) concerning the use of anthrone (or benzanthrones), reduction using a dissolving metal might effect hydrogenolysis of any halogen substituents present. In Newman's procedure the aromatic acid is first reduced with lithium aluminum hydride to the primary alcohol **139**, then oxidized to the aldehyde **140** by the action of $(C_5H_5N)_2CrO_3$, and cyclized using PPA. Good yields of benz[*a*]anthracenes by this method have been reported (Table 23).

TABLE 23. Benz[*a*]anthracenes by Cyclization of Aldehydes by Scheme 41

aldehyde R	aldehyde R′	other subst[a]	yield,[b] %	ref
		Reaction Type A (**129**)		
H	Me	5-Br	81	143
H	H	5-OMe	85[c]	144b
H	Me	5-OMe	>95[d]	144b
H	Me	6-OMe	73	144b
H	H	$6,8\text{-}Me_2$	62	159
		Reaction Type C (**132**)		
H	H	1-F	50[e]	157
Me	H	1-F	56[e]	157

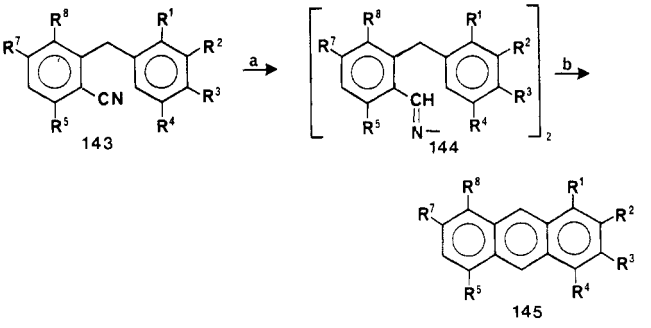
[a] Numbers refer to *Chemical Abstracts* numbering of benz[*a*]anthracene (see **131**). [b] Unless otherwise indicated, yields are from the aldehyde. [c] Yield from $ArCH_2OH$. [d] "Practically quantative". [e] From ArCOOH.

SCHEME 44



141 142a R=H, R′=CH_3 (49%) b R=OCH_3, R′=H (30%) c R=OCH_3, R′=CH_3 (32%)

SCHEME 45



143 144 145

a. $NH_2\text{-}NH_2\cdot H_2O$, Ni. b. HBr–HOAc.

The aldehyde cyclization was also used in the preparation of 7-methoxy-3-methylcholanthrene (**142b**; Scheme 44). 6-Methyl analogues **142a** and **142c** were prepared by cyclialkylation of the corresponding methyl ketones **141** in hydrogen fluoride.[160]

c. Azines. *o*-Benzylbenzonitrile (**143**; Scheme 45) and its congeners were used as starting materials for the preparation of the *o*-benzylphenyl ketones first cyclized to meso-substituted anthracenes.[135,127] Zajac and Denk[161] recognized that the reduction of the same nitriles by hydrazine hydrate[162] should give azines **144** capable of yielding cyclizable[135,127] aldehydes upon acid hydrolysis. Indeed, conditions for the hydrolysis were

TABLE 24. Cyclization of Azines (Scheme 45)

R^1	R^2	R^3	R^4	R^5	R^7	R^8	yield (143→145), %	ref
							85.5	161
Me	Me						79	161
	Me	Me	Me	Me			45	111
	Me	Me	Me		Me		50	111
	Me	Me	Me			Me	45	111
benzo							90	111
		benzo					86.5	111

TABLE 25. Acylation-Cyclization of Some Thienyl Derivatives (Scheme 48)[a]

Ar^1	Ar^2	acyln agent	cyclizn product	yield, %	ref
5-chloro-2-thienyl	5-chloro-2-thienyl	R	**153c**	8	167
5-chloro-2-thienyl	5-chloro-2-thienyl	M	**153e**	30	167
5-chloro-2-thienyl	5-chloro-2-thienyl	A	**153b**	16	166
3-thienyl	3-thienyl	V	**153a**	33	166
3-thienyl	3-thienyl	A	**143d**	NR	166
2-thienyl	3-thienyl	R	F		167
2-benzothienyl	2-benzothienyl	R	**155a**	96	166
2-benzothienyl	3-thienyl	R	**154**	25	167
2-benzothienyl	3-benzothienyl	R	**156a**	24	167
5-methyl-2-benzothienyl	3-benzothienyl	R	**156c**	77	167
2-benzothienyl	3-benzothienyl	M	**156d**	25	167
2-benzothienyl	benzyl	R	**157a**	15	167
2-benzothienyl	*p*-methylbenzyl	R	**157b**	50	167
3-benzothienyl (+2-isomer)	benzyl	R	**157a**	13	167
2-benzothienyl	2-naphthyl	R2	**158a**	63	101
2-benzothienyl	2-naphthyl	A2	**158b**	35	101
2-benzothienyl	1-naphthyl	R2	**159**	60	101

[a] Key: R = Cl_2CHOBu (Rieche's reagent) + $SnCl_4$; M = $CH_3C(Cl_2)OC_2H_5$ + $SnCl_4$; A = HOAc + PPA; V = $POCl_3$ + $HCON(Me)_2$ (Vilsmeier–Haack); NR = not reported; F = formylated starting material recovered; R2 = Cl_2CHOMe + $SnCl_4$; A2 = acetic anhydride + $SnCl_4$.

selected such that cyclization occurred affording the expected anthracene derivative **145** in good-to-excellent overall yields (Table 24).

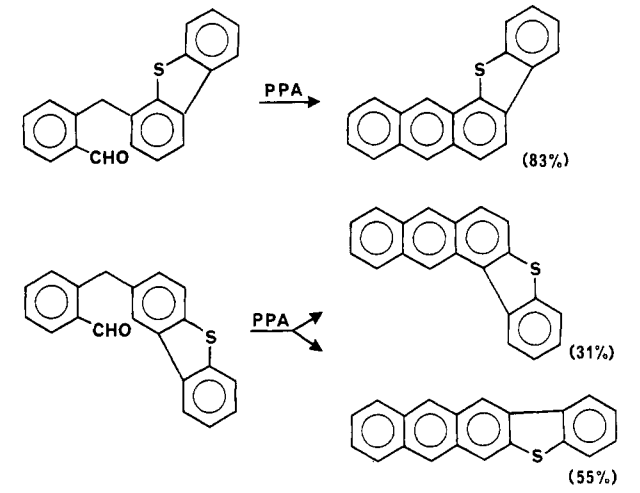
2. Heterocyclic Systems

A method by which heterocyclic isosteres of benz- and naphthanthracenes can be assembled is by creation of the anthracene ring through aromatic cyclodehydration of an *o*-benzylbenzaldehyde (or ketone) having a heterocyclic ring fused to it. Castle et al.[101] used this approach to synthesize the three possible anthrabenzo-[*d*]thiophenes (Scheme 46). A strategy for creating nitrogen-containing isosteres of anthracene is to replace the methylene bridge of the diarylmethane by NH. The earlier review[2] summarized 30 examples of the acid-catalyzed cyclization of 2-(arylamino)benzaldehydes **146a** (Scheme 47) or phenyl ketones **146b** to afford acridine derivatives **147**. Two subsequent books on acridine chemistry[163,164] plus a recent chapter on the synthesis of pyridine and its benzologs[45] has made redundant any update of this cyclialkylation.

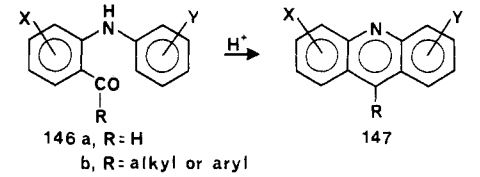
Meth-Cohn et al.[165–167] demonstrated that a diarylmethane **148** (Scheme 48), which undergoes acylation at a site adjacent to the methylene bridge will usually undergo concomitant cyclialkylation to afford an isostere of anthracene (**150**) or of an anthracene benzolog. To date, the diarylmethanes used successfully in the Meth-Cohn procedure have each had at least one thienyl or benzothienyl group to provide a reactive site for the acylation necessary to cyclization.

A drawback of the method is that the product can undergo further, perhaps unwanted, acylations. In the first acylation–cyclization of this type encountered, tetrathienyl derivative **151** (Scheme 49) on heating with acetic acid and polyphosphoric acid afforded product

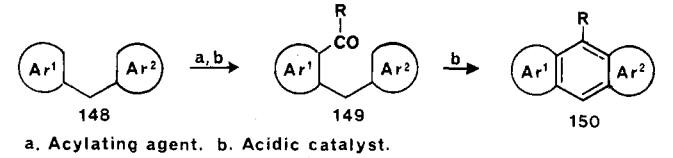
SCHEME 46



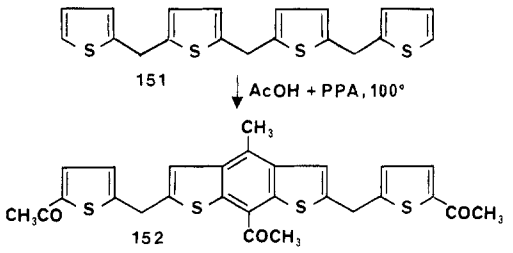
SCHEME 47



SCHEME 48

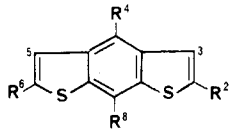


SCHEME 49

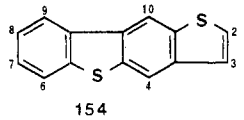


152, having three acetyl groups beyond that required for cyclodehydration.

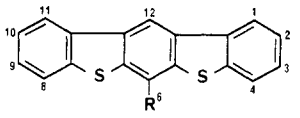
With other less vulnerable diarylmethanes, conditions have been found that provide useful yields of the primary cyclization products (Table 25), although some examples of further acylation were noted (e.g., **153b**, **155b**, and **156b**). Acetylations (Scheme 48) were carried out in an acetic acid–polyphosphoric acid mixture while formylation was best achieved with Rieche's reagent (Cl_2CHOBu) and carboethoxylation with CH_3OCCl_2C-OOH. The last two were used with a $SnCl_4$ catalyst. The Meth-Cohn procedure has been used by Castle et al.[101] for the synthesis of isosteres of carcinogenic hydrocarbons.



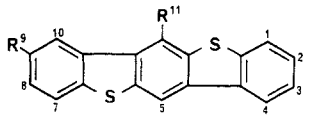
153a, $R^2 = R^4 = R^6 = R^8 = H$
b, $R^2 = R^6 = Cl$, $R^4 = CH_3$, $R^8 = Ac$
c, $R^2 = R^6 = Cl$, $R^4 = R^8 = H$
d, $R^2 = R^6 = Cl$, (X,Y = diacetyl)
e, $R^2 = R^6 = Cl$, $R^4 = COOC_2H_5$, $R^8 = H$



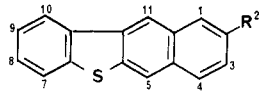
154



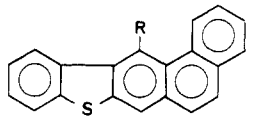
155a, $R^6 = H$
b, $R^6 = CHO$



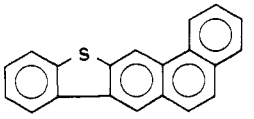
156a, $R^9 = R^{11} = H$
b, $R^9 = H$, $R^{11} = CHO$
c, $R^9 = CH_3$, $R^{11} = H$
d, $R^9 = H$, $R^{11} = COOC_2H_5$



157a, $R^2 = H$
b, $R^2 = CH_3$



158a, R = H
b, $R = CH_3$



159

Essentially the same procedure was used in the preparation of benzanthracene isosteres through formylation–cyclization of some 2-(arylmethyl)benzo-

SCHEME 50

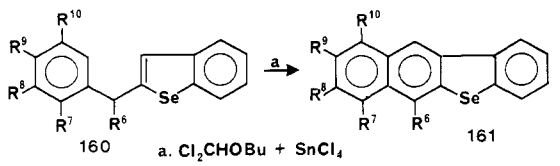


TABLE 26. Benzo[*b*]naphtho[2,3-*d*]selenophenes by Formylation–Cyclization (Scheme 50)

R^6	R^7	R^8	R^9	R^{10}	method[a]	yield 161, %
H	H	H	H	H	A	90
H	Me	H	H	H	B	79
H	H	H	Me	H	B	80
H	Me	H	Me	H	B	82
Me	H	H	H	H	B	*b*
Me	H	H	Me	H	B	54
CH_2CH_2		H	H	H	B	*b*
H	benzo		H	H	A	89
H	H	H	benzo		A	69
Me	H	H	benzo		B	*b*

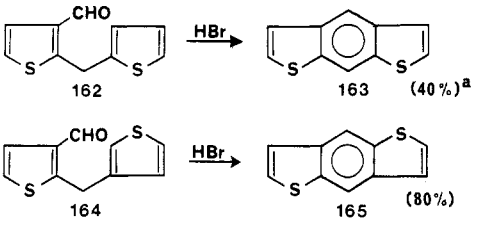
[a] Key: A = cyclization found complete at end of formylation reaction; B = cyclization found incomplete and completed by action of PPA. [b] Not reported.

TABLE 27. Benzanthracene Isosteres by Cyclization of Aldehydes and Methyl Ketones (Scheme 48; 149 → 150)

Ar^1	Ar^2	cyclizn product	yield,[a] %	ref
3-formyl-2-thienyl	2-naphthyl	**166**	56[b]	171
3-formyl-2-thienyl	1-naphthyl	**167**	57[b]	171
3-aceto-2-benzothienyl	phenyl	**168**	*c*	99
2-acetophenyl	2-thienyl	**168**	53[d]	99
2-formyl-3-naphthyl	2-thienyl	**169**	51[b]	172
2-formylphenyl	2-benzothienyl	**170**	58[b]	172

[a] All cyclizations were in PPA. [b] Overall yield from ArCOOH. [c] The starting material underwent deacylation. [d] Yield from ketone. Additional hydrocarbon was formed in the preparation of the ketone, evidently by an anionic cyclization observed earlier.[134]

SCHEME 51

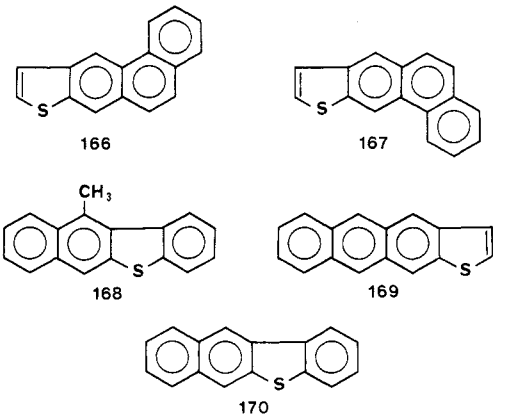


[a] Overall yield from ArBr

selenophenes **160** (Scheme 50; Table 26).[168]

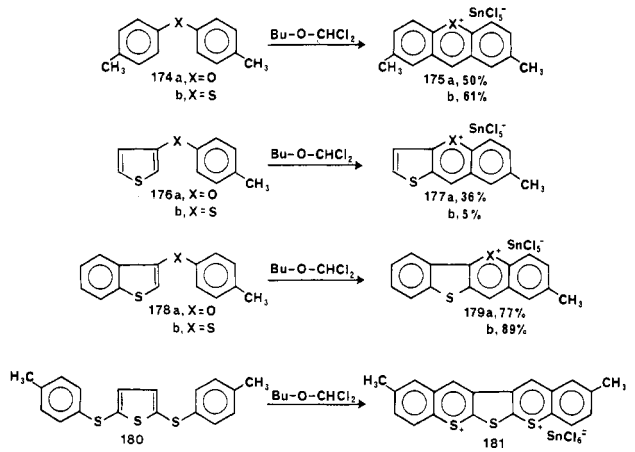
By a more conventional approach, anthracene isosteres in which both of the terminal rings have been replaced by thiophene rings[169,170] (Scheme 51), as well as a number of isosteres of benzanthrenes[171,99,172] (Table 27), were prepared.

Good yields were obtained in the cyclization except with (3-aceto-2-benzothienylphenyl)methane where the rate of hydrolysis of the acetyl group was high relative to that for cyclodehydration.

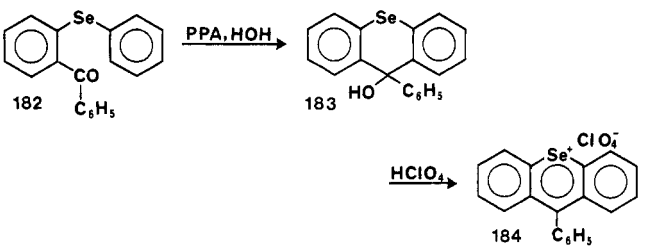


SCHEME 52

SCHEME 53



SCHEME 54

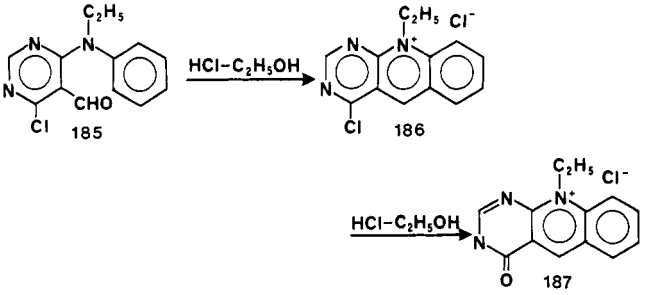


3. Cationic Heterocyclic Systems

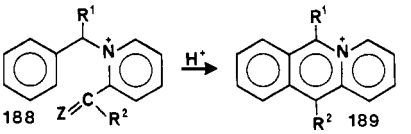
In the previously examined aromatic cyclodehydrations leading to anthracene, its benzologs, and isosteres, the bridge connecting the two aryl groups has always had at least one hydrogen on it, i.e. CH_2, CHR, or NH. This section deals with bridges with no attached proton, specifically O, S, Se, and NR and, as a consequence, lead to the formation of a cationic aromatic system (**172**; Scheme 52). Such aromatic cations undergo hydrolysis readily; hence, in early experiments, the products actually isolated from the cyclialkylation of carbonyl derivatives **171** were xanthydrols **173** (X = O) or analogues. Rather than a historic survey of the field, recent examples of the synthesis of each of the four types of cationic aromatic heterocycle will be presented.

As an extension of the acylation–cyclization method developed with thienyl- or benzothienyl- arylmethanes (preceding section), the Meth-Cohn group[166,173] carried out experiments using related ethers and thioethers. Some of the xanthylium and thioxanthylium systems obtained are shown in Scheme 53. Easy isolation of the cationic salts was made possible by the use of anhydrous conditions and tin(IV) chloride as a catalyst. The low yield obtained with the 3-thienyl sulfide **176b** reflects the high probability that initial (and unproductive) acylation will occur at the reactive 5-position. With **180** it was possible to effect a double acylation, leading, on cyclization, to a condensed aromatic system with two cationic centers.

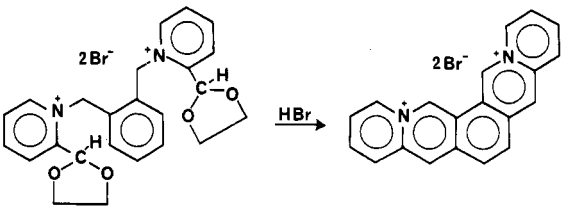
SCHEME 55



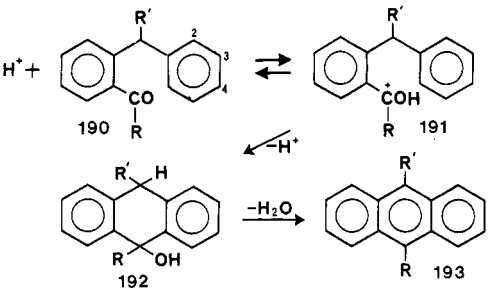
SCHEME 56



SCHEME 57



SCHEME 58



The synthesis of 9-(phenylseleno)xanthylium perchlorate (**184**; Scheme 54) was achieved by the cyclization of *o*-(phenylseleno)benzophenone (**182**) in PPA followed by hydrolysis to yield the (phenylseleno)-xanthol (**183**), which, on treatment with perchloric acid, yielded the salt **184**.[174] As pointed out earlier, there is reason to believe that **184** was an intermediate in the formation of **183**.

It was conjectured[175] that the action of ethanolic hydrogen chloride on 4-chloro-6-(*N*-ethylamino)pyrimidine-5-carboxaldehyde (**185**; Scheme 55) to yield a dihydropyrimidoquinoline (**187**) occurs via the aromatic salt **186**.

In 1954[176] aromatic cyclodehydration was used to produce a cationic anthracene analogue having a quaternary nitrogen at a bridgehead position. The new system (**189**, $R^1 = R^2 = H$; Scheme 56), known as the acridizinium or benzo[*b*]quinolizium system, was prepared by the acid-catalyzed cyclization of the benzyl salt of pyridine-2-carboxaldehyde (**188**, $R^1 = R^2 = H$, Z = O). The synthesis, which has recently been reviewed,[102] is very general and has been used for the preparation

of a large number of derivatives and benzologs. One application was the first synthesis of a condensed polycyclic system having two cationic centers[177] (Scheme 57).

D. Mechanism

The focus of studies directed toward understanding the process by which an aromatic ring may be formed through cyclialkylation of aldehydes or ketones has been the anthracene synthesis (Scheme 58). It was early recognized[2,178,179] that the first step was the reversible addition of a proton to the carbonyl group,[178,179] followed by an electrophilic cyclialkylation with rapid loss of water to give the hydrocarbon **193**.

1. Reaction Kinetics

Investigations of the kinetics of aromatic cyclodehydration have apparently been confined to the anthracene synthesis and the Combes synthesis of quinolines. First Berliner[180] showed that, in acid solution, *o*-(1-phenylethyl)phenyl ketones **190** (R = Me; Scheme 58) gave pseudo-first-order kinetics and that the reaction rate was somehow related to the hydrobromic acid concentration in the cyclizing mixture. The lack of direct proportionality to acid concentration was made understandable by Brice and Katstra[181] who showed that a dramatic increase in the rate of cyclization can be achieved if the hydrogen bromide concentration is held constant but the mole ratio of acetic acid to water in the mixture is increased, a consequence of the greater basicity of water relative to the ketone **190** or acetic acid.

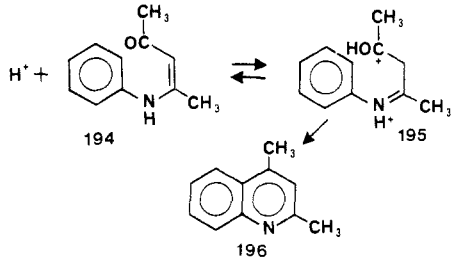
The majority of the *o*-benzylphenyl ketones studied have been phenyl ketones **190** (R′ = H, R = Ph) in which the phenyl group has a substituent. The cyclization rates of the ketones, especially those para and meta substituted, might be expected to correlate in some simple way with the electron release (or attraction) of the substituents (perhaps by a significant Hammett relationship), but they do not.[182] It was pointed out[156] that substituents that release electrons should make the positive center of the conjugate acid **191** less positive and, hence, *slow* the reaction, while the same substituent by increasing the basicity of the ketone **190** should increase the concentration of the conjugate acid **191** and tend to *accelerate* the reaction. When the substituents on the benzoyl group were in the para position and were methyl, hydrogen, chlorine, or bromine, all gave rates within experimental error of each other, but when the substituent was fluorine, a significantly lower rate was obtained. Subsequent experiments by the Vingiello group,[183] in particular with meta-substituted phenyl ketones and the 2-benzylphenyl 2-, 3-, and 4-pyridyl ketones, suggest that electronic effects on the positive nature of the conjugate acid **191** are more important in determining the overall rate (**190** → **193**) than are those affecting the acid–base equilibrium (**190** → **191**).

That steric hindrance impedes cyclization was seen[115] in the relatively large differences in rates of 2-benzylphenyl phenyl ketones having a substituent at the ortho position of the benzoyl ring (**190**, R′ = H, R = *o*-XC_6H_4): H, 55; Me, 9.5; F, 38.6; Cl, 6.9; Br, 3.3. The major factor in the large decrease in rate of cyclization with increasing chain length (to butyl) of *o*-(1-phenylethyl)-

TABLE 28. Activation Parameters for the Cyclodehydration of Some 2-Benzylphenyl Benzo[*b*]thienyl Ketones (Scheme 58; 188 → 191 (R′ = H, R = benzo[*b*]thienyl))

ketone R	E_a, kcal/mol	H^*, kcal/mol	S^*, eu
2-benzo[*b*]thienyl	20.6	19.9	−28.8
3-benzo[*b*]thienyl	16.0	15.3	−44.3

SCHEME 59



phenyl alkyl ketones **190** (R′ = Me, R = alkyl)[180] is most likely the steric factor.

In contrast with the small rate changes seen in modifying the electronic environment of the carbonyl group of *o*-benzylphenyl aryl ketones, large changes can be made by modifying the availability of electrons at the target ortho position of the benzyl group. The introduction of a methyl group at position 3 on the benzyl ring of **190** (R′ = H, R = Ph) makes the cyclization 55 times as rapid as with an unsubstituted ring, while replacing the methyl group with a trifluoromethyl group gives a compound that does not cyclize.

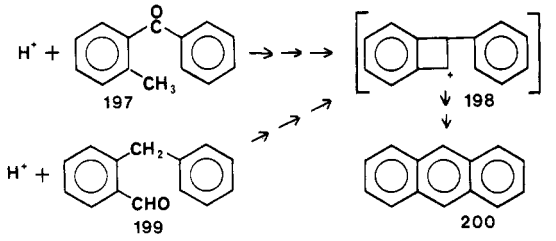
Measuring the rates of aromatic cyclodehydration at several different temperatures makes possible the calculation of the usual activation parameters[184] (Table 28). While both the isomeric 2-benzylphenyl benzo[*b*]thienyl ketones show rather large negative entropies of activation, that for the 3-benzo[*b*]thienyl ketone is significantly greater than that for its 2-isomer, which cyclizes 4 times as rapidly. The difference suggests that the entropy factor has an important effect on the cyclization rate.

Less extensive, but significant kinetic data have been reported for the Combes synthesis of quinolines. These data indicate that the cyclization of 4-anilinopent-3-en-2-one (**194**) in sulfuric acid to yield 2,4-dimethylquinoline occurs via a diprotinated intermediate **195**.[185,186a,b] The first-order rate constants are related to the acidity function $H°$ by the Hammett equation.[185] From a comparison of the cyclization rates of deuteriated 4-anilinopent-3-en-2-one with those of the undeuteriated counterpart, it was concluded[187] that some weakening of the C–H bond occurs in the rate-determining step. The cyclodehydration of each of three *m*-halogeno-4-anilinopent-3-en-2-ones occurs more rapidly than for the unsubstituted system **194**, as would be predicted from the electron release of the halogen atoms[186b] (Scheme 59).

2. Aromatic Cyclodehydration and the Elbs Reaction

As was reported earlier[155,2] the formation of a small amount of anthracene **200** (Scheme 60) in the acid-catalyzed hydrolysis of the acetal of *o*-benzylbenzaldehyde (**199**) was ascribed by Bergmann[155] to an Elbs reaction. The classical Elbs synthesis of anthracene is by pyrolysis (usually without a catalyst) of 2-methylbenzophenone (**197**). The two synthetic methods re-

SCHEME 60



Lupes' mechanism

semble each other in that a carbonyl group is present, and in both the loss of water leads to the formation of an aromatic ring. They differ in that aromatic cyclodehydration is definitely acid catalyzed while any indication of such catalysis in the Elbs reaction seems to have escaped the attention of those who have discussed the reaction mechanism[120,188-190] earlier. Although Fieser,[120] in his review of the Elbs reaction, made a clear distinction between the two types of cyclization, others[191,192] have found it more difficult to do so. The distinction might appear to be further clouded by the observation of the Vingiello group[119] (Scheme 40) that, under the strenuous conditions needed to bring about the aromatic cyclodehydration of some sterically hindered *o*-benzylphenyl naphthyl ketones, the Elbs reaction can occur as an alternative.

Recently Lupes et al.[193] reviewed the Elbs reaction with the thought that the side reactions might provide a clue to the mechanism. They concluded that the Elbs reaction must be acid catalyzed and that an important intermediate was a benzocyclobutenyl carbonium ion, in this example **198**. A further conclusion, more germane to the present review, is that **198** is the intermediate in the acid-catalyzed cyclization of *o*-benzylbenzaldehyde and, with suitable modification, of its congeners. What is known[4] about the alkylation of aromatic nuclei by aldehydes and ketones, and the demonstration that ketones structurally incapable of forming a cyclobutene can still be cyclized,[178-179] make it unlikely that a cyclobutenyl intermediate plays a part in aromatic cyclodehydration.

3. Cyclization of Derivatives of Ketones and Aldehydes

It is convenient to classify as carbonyl cyclialkylations the ring closure of such derivatives as acetals, ketals, thioacetals, oximes, and azines, but it is likewise inaccurate, there being no evidence that hydrolysis to a carbonyl compound must always occur more rapidly than cyclization. In the cyclization of acetals in aqueous acid (e.g., Schemes 21–23), prior hydrolysis to the aldehyde probably does occur. On the other hand, where cyclizations are carried out under anhydrous conditions using Lewis acid catalysts, such a route seems less probable. For example, there is reason to believe that under anhydrous conditions at −78 °C the electrophilic species generated from an acetal is the $-CH^+OCH_3$ ion (Scheme 4). A parallel reaction has been postulated for thioacetals (Scheme 27). Since the cyclization of oximes (Schemes 35 and 55) and azines (Scheme 45) is carried out in the presence of aqueous acid, it has been assumed that cyclization is preceded by hydrolysis, but the possibility remains that some or all of the derivatives cyclize directly. The possibility that carbonyl compounds are intermediates in the cyclization of epoxides was considered in the earlier review.[2]

Acknowledgments. I am grateful to a colleague, Prof. Richard Polniaszek, and to Prof. Frank A. Vingiello of Northeast Louisiana University for reading the manuscript and making helpful suggestions. Also, I am indebted to my wife, Dorothy, for her tireless efforts with the structural formulas, tables, and references.

Registry No. Naphthalene, 91-20-3; phenanthrene, 85-01-8; anthracene, 120-12-7.

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