THE ACYLOIN CONDENSATION AS A CYCLIZATION METHOD

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I. INTRODUCTION

During the sixteen years since its introduction as a promising method for the preparation of large and medium carbocyclic systems, the acyloin condensation has been used in an impressive variety of cyclizations. Its uses in ring closure have been reviewed by McElvain as one aspect of the over-all reaction (85).

Several papers dealing with various chemical subjects have reviewed specialized applications of the acyloin condensation without attempting to be comprehensive (6, 8, 60, 63 82, 91, 109, 113, 114, 125).

In this review special emphasis has been placed on those papers which introduce new modifications of the reaction or apply it to the preparation of new compounds. In cases where the same procedures have been used by more than one author, all have been included. Only those acyloins which result from cyclization are of interest in this survey, and no attempt has been made to present or discuss the reactions or physical properties of them or the compounds for which they serve as precursors.

In order to make the nomenclature as uniform and clear as possible, all compounds are named as derivatives of the parent ketone. While this is perhaps a deviation in the case of very simple acyloins, it is more consistent when a wide variety of compounds are to be included. The common names of the simplest cyclic systems have also been mentioned to avoid confusion.

It has been necessary to include a few papers dealing with open-chain compounds since these are all that are available concerning the mechanism of the reaction. An effort has been made to report any observations noted in the preparation of cyclic systems which bear on mechanistic detail and these are discussed in the appropriate section.

The literature has been covered through *Chemical Abstracts* and current chemical papers for 1963. In addition to these sources, the following journals have been completely searched through December, 1963: *Journal of the American Chemical Society, The Journal of Organic Chemistry, Journal of the Chemical Society, Tetrahedron,* and *Helvetica Chimica Acta.*

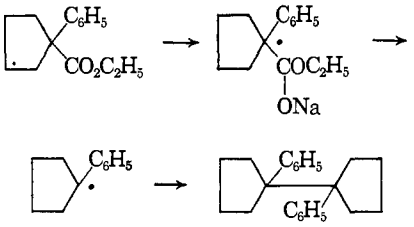
II. MECHANISM OF THE REACTION

Mechanistic studies of the acyloin condensation are very limited and include neither kinetics nor work of any kind involving cyclization reactions. At present the best that can be done is to cite those few cases studied along with such yield data as are available for cyclic systems. The information from these two sources is of marginal value since there are several unwarranted assumptions implicit in its interpretation. Perhaps one of the chief reasons for this review is to show the unsatisfactory state of our knowledge concerning the scope, limitations, and mechanism of this important synthetic tool.

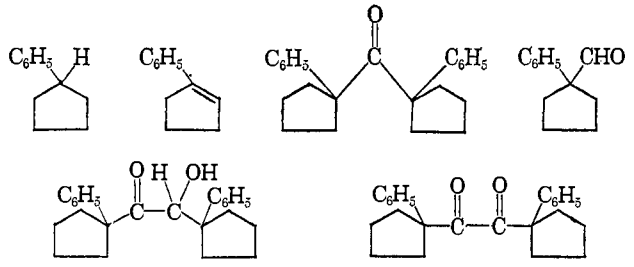
The various mechanisms which were first proposed for the condensation are well presented in McElvain's earlier review and will not be repeated here (85). Several later studies provide interesting evidence relating to these mechanistic pathways especially in regard to the possibility of a free-radical intermediate.

Long before the use of the reaction as a cyclization method, it had been suggested that in liquid ammonia an intermediate free radical would explain the formation of diketones and acyloins. Very careful product analyses have shown that in two noncyclization reactions the heterogeneous acyloin condensation may also involve a radical reaction (126, 127).

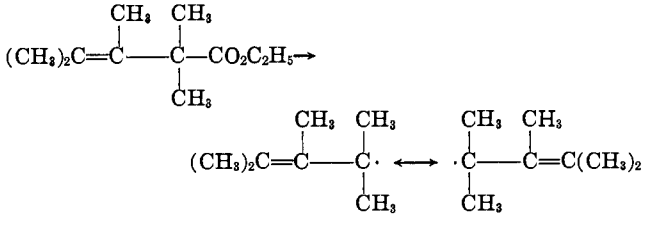
The first reaction studied attracted attention because under acyloin conditions a hydrocarbon was obtained, and its structure suggested a radical coupling (126).



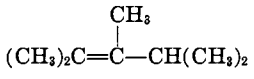
If this mechanism is correct, smaller amounts of those products which would be expected from the usual reactions of the intermediate radicals should be found. These products would result from reduction, disproportionation, and interaction between the radicals, and all were found with the exception of the aldehyde and its reduction product. The expected products were

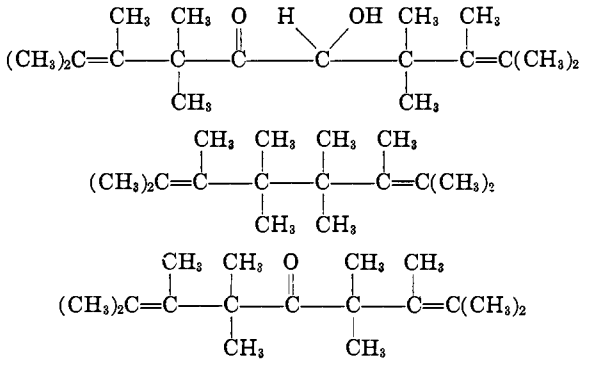


In order to extend this work to a completely aliphatic system and yet to limit the number of possible products, a potential tertiary, resonance-stabilized radical was chosen (127).



On the basis of the CO lost, 68% of the ester decomposed in this manner. As in the earlier work, analysis showed the presence of several of the expected products resulting from the intermediate radicals





There were very small amounts of other products which were not isolated.

The experiments reported in these two papers provide very convincing evidence for the free-radical mechanism being applicable in both heterogeneous and homogeneous media. They do not provide any direct evidence as to the mechanism in cases of cyclization although there would seem to be no reason to require a very different path.

The question of greatest interest for ring closure reactions is why the acyloin condensation is so uniquely effective in the case of medium rings. Since there is a total lack of kinetic studies or complete product analyses, very little can be said beyond simple speculation. The currently accepted rationale is that first advanced by Prelog in the original work on the method and is illustrated in Fig. 1 (91, 93).

This speculation without experimental evidence shows our very inadequate understanding of the mechanism of the acyloin cyclization. The situation may be improved somewhat by a careful consideration of the yield of various cyclic systems and the factors which affect the yields. This kind of information, which will be considered after a survey of the synthetic applications of the reaction, at least will point out possible fruitful areas for future investigation.

III. Scope of the Reaction

The purpose of this section is to present as complete a picture as possible of the extensive use of the acyloin condensation in the preparation of cyclic systems. The yields and conditions of these reactions are summarized in tabular form at the end of each subsection but the implications of these data are deferred until a later section dealing with factors affecting yields. The addition time is reported only in the case of the heterogeneous reactions, since all reported uses of the homogeneous system have employed normal rates of addition and have not used any high dilution cycle. In most cases the temperature of the reaction was that of the boiling point of the solvent system and these are not explicitly stated.

In the interest of clarity and completeness two rather arbitrary practices have been followed: (1) studies

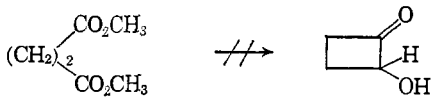
which include rings of more than one size are cited in each appropriate subsection, and (2) references which merely repeat earlier work are included. The equation numbers correspond to citations in the tables.

A. SMALL AND NORMAL RINGS

The only successful application of the heterogeneous acyloin reaction to the preparation of small rings is the synthesis of the bicyclo[2.4.0]octane system containing a four-membered acyloin (28).

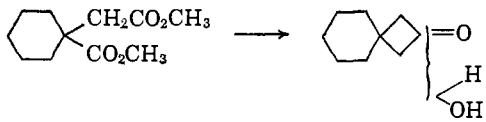
(Eq.1)

The application of the homogeneous liquid ammonia method to the preparation of small and normal rings produced interesting results in the four-membered case (49). The use of dimethyl succinate to form the parent compound, 2-hydroxycyclobutanone, gave only a few milligrams of distillable product, which was not characterized.



(Eq.2)

When the starting diester included a cyclohexane ring, a product was obtained which gave indications of being the spiro compound, but the structure was not proven.



(Eq.3)

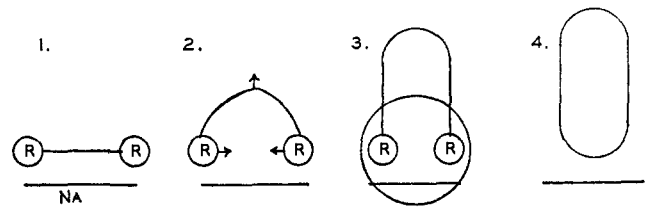
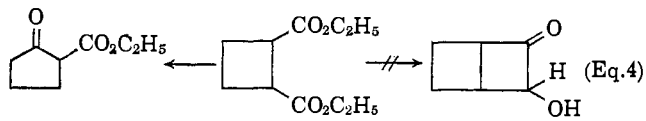


Fig. 1.—Rationale for acyloin cyclization: (1) the electrophilic carbon atoms of the α,ω-diester are attracted to the sodium surface; (2) the lowest energy translational motion available is sliding on the metal surface; (3) the collisions of other molecules finally bring the terminal groups close enough for ring closure; (4) after ring closure, the electrophilic character is no longer sufficient to hold the cyclic system to the metallic surface.

An unsuccessful attempt to prepare a four-membered acyloin in the bicyclo[2.2.0]hexane system has been reported (23).

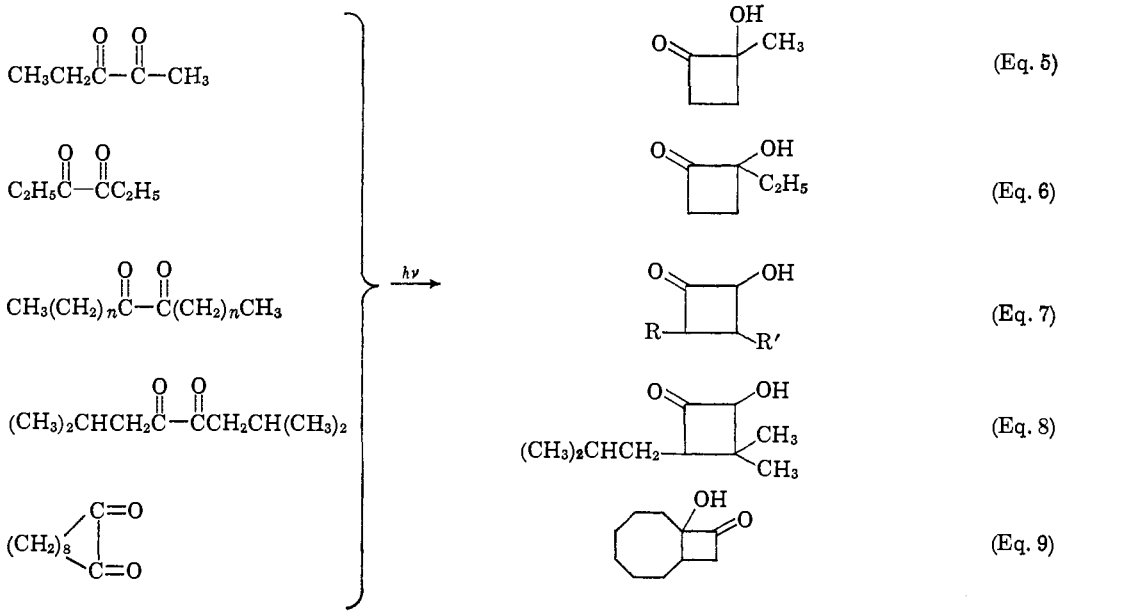


(Eq.4)

The reaction was tried using both xylene and liquid ammonia as solvents and while the yield of cyclic (ring opening and Dieckmann) product varied, in neither case was there any indication of acyloin.

In recent studies of the photochemistry of α-diketones, a new and promising synthetic approach to the small rings has been found (123, 124).

Examples of the formation of five-membered rings using the acyloin reaction are much more numerous and include both simple and fused ring systems. The earliest successful preparation was of the parent compound, 2-hydroxycyclopentanone (glutaroin) (66, 108). This was closely followed by the synthesis of a mix-



(Eq. 5)

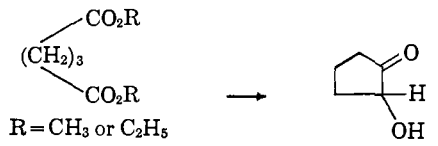
(Eq. 6)

(Eq. 7)

(Eq. 8)

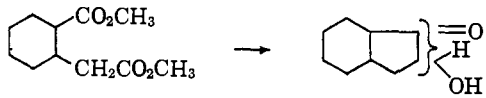
(Eq. 9)

n = 2, R = $CH_3CH_2CH_2$; R′ = CH_3
n = 3, R = CH_3CH_2: R′ = $CH_3CH_2CH_2CH_2$



(Eq. 10)

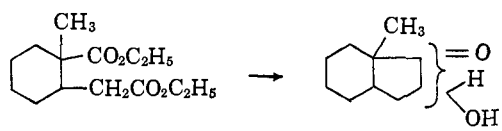
ture of acyloins in the bicyclo[4.3.0]nonane system (107).



(Eq. 11)

The unsubstituted compound has been reported by three laboratories using the same methods and obtaining approximately the same yields with one exception (49). In an application of the homogeneous liquid ammonia technique the yield was significantly higher.

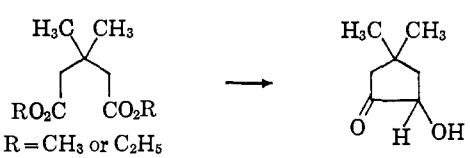
The work with five-membered rings was extended to the preparation of a bicyclic system with an angular methyl group as a model compound for future work in the steroid field (102). Both the homogeneous and the heterogeneous reaction conditions were used and other variations were introduced which will be described



(Eq. 12)

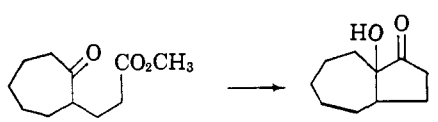
in detail in a later section.

Several different laboratories have prepared 4,4-dimethyl-2-hydroxycyclopentanone employing slightly different procedures and starting materials (49, 68, 86, 99).



(Eq. 13)

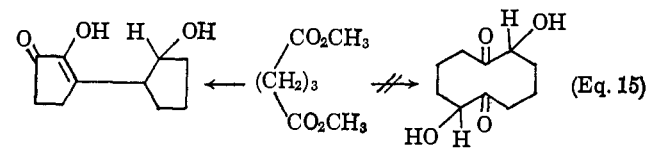
A rather unusual acyloin cyclization has been reported recently (57).



(Eq. 14)

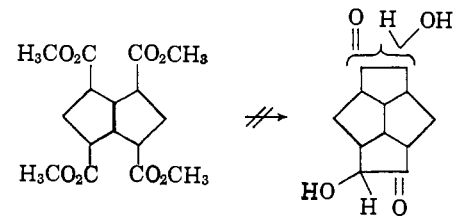
When liquid ammonia was employed as solvent, the product was also a bicyclo[5.3.0]decane, but the 8-keto or hydroxy derivative instead of the acyloin.

Using higher concentrations in an attempt to prepare a ten-membered ring by dimerization, the unexpected product actually obtained was one consisting of two covalently bonded five-membered rings (30).



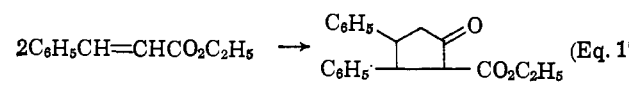
(Eq. 15)

No acyloin product was obtained in efforts to prepare a tetracyclic carbon system (58).



(Eq. 16)

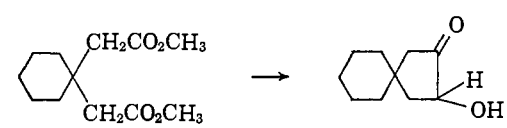
A very interesting example of Dieckmann product obtained under acyloin conditions has been found in the preparation of acyclic acyloins (120).



(Eq. 17)

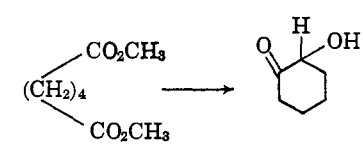
This reaction as well as that of the dihydrocinnamate was carried out in several solvents. The saturated ester gave the expected carbon chain, but only the dione with no indication of acyloin.

A final successful example of the use of the acyloin condensation as a means of closing five-membered rings involves the preparation of an acyloin which was isolated as spiro[4.5]decanedione-2,3 (49).



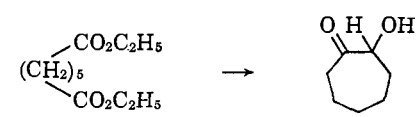
(Eq. 18)

The large number of synthetic methods available for the preparation of six-membered carbon rings has limited the application of the acyloin reaction to their synthesis. The notable exceptions are in the case of the steroids which will be discussed in a separate section. As preliminary work in that field 2-hydroxycyclohexanone (adipoin) has been prepared (108).



(Eq. 19)

The scarcity of examples of the use of the acyloin ring closure for seven-membered rings is more surprising. The parent seven-membered acyloin, 2-hydroxycycloheptanone (pimeloin), has been reported (66).



(Eq. 20)

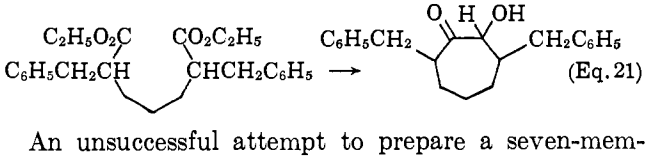
TABLE I

SUMMARY OF SMALL AND NORMAL RING ACYLOINS

Equation	Solvent[a]	Addition time, hr.	Yield of acyloin, %	Ref.
1	X	45.5	12[b]	28
2	A		...	49
3	A		...	49
4	T or A	1.5	0	23
5	B		49	124
6	Propanal		23	123
	Cyclohexane		60	123
7, n = 2	B		92	123
n = 3	B		89	123
8	B		89	123
9	B		74	124
10	T	1	15.5[b]	108
	T	65	13.4[b]	66
	A		50	49
11	T	4.5	41[b]	107
12	X	...	42[b]	102
	X	...	30	102
	A		50	102
13	A		80	68
	A-E		52[c]	86
	A-E		81	99
	A		75[d]	49
14	THF-naphthalene	...	20	57
15	T	3	30	30
16	A		0	58
17	E	2	0	120
	B	2	0	120
	T	2	0	120
18	A		78[d]	49
19	T	1	57[b]	108
	A		38	108
20	X	65	40–52.5[b]	66
21	X	13	87[b]	77
22	X	...	0[b]	52
	A		0[e]	52
23, n = 1	E	...	0[b]	71
n = 2	E	48	91[b]	71
n = 3	E	48	69[b]	71

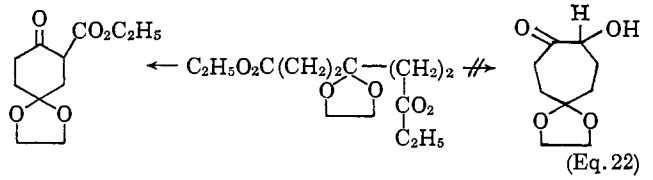
[a] Solvents: A, ammonia; B, benzene; E, ether; T, toluene; X, xylene. [b] High dilution cycle. [c] Ethyl ester used as starting material. [d] Obtained as ketone. [e] Perhaps a small amount, but no characterization.

The synthesis of the seven-membered cyclic acyloin with both adjacent positions substituted by one benzyl group has been carried out (77).



(Eq. 21)

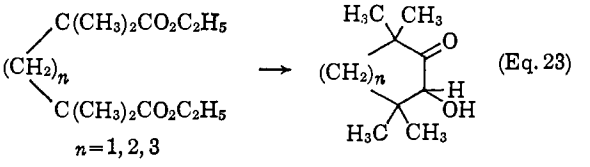
An unsuccessful attempt to prepare a seven-membered ring acyloin has also been observed (52).



(Eq. 22)

The use of very high dilution and the lactone of ethyl γ-hydroxypimelate also produced a β-keto ester rather than an acyloin. This compound was also shown to be the Dieckmann product. A careful and thorough reinvestigation of earlier acyloin condensations which result in seven- and eight-membered rings produced some interesting results which will bear on the mechanism of the reaction.

A series of tetramethyl cyclic acyloins which include one medium and one large ring compound is included here since three of the structures contain normal rings (71).



(Eq. 23)

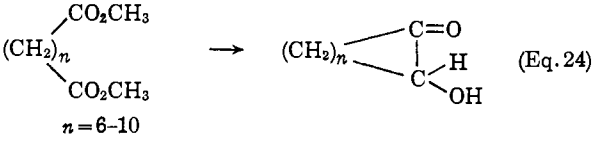
The preparation of this series of normal rings is interesting in that it employed ether as the solvent and produced the six- and seven-membered rings in yields higher than the unsubstituted cases, while none of the five-carbon system was obtained.

A summary of small and normal ring acyloins is given in Table I.

B. MEDIUM RINGS

The use of the acyloin condensation for the closure of medium rings (8–11 members) still represents the method of choice and practically the only choice in most cases. It is not surprising, therefore, that a rather large number of applications of the reaction involve rings of these sizes. Since many of the studies, concerned mainly with medium rings, include the twelve-membered compound, it will be found in this section although it is no longer considered to be a medium ring.

Except for the eight-membered case, these rings were reported by Prelog and Stoll in their original work and the yields obtained are summarized by McElvain (85).



(Eq. 24)

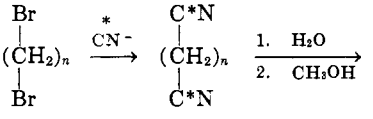
More recently the yields of cyclic acyloins in medium rings using laboratory scale procedures have been greatly improved. The same basic methods were employed, but with modifications which will be discussed in a later section (12, 17, 24, 61, 65, 67, 131).

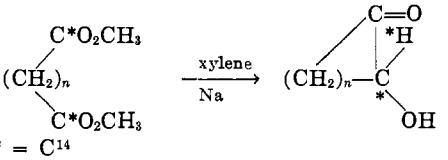
Just prior to these developments, Stoll obtained patents which described larger scale preparations with very significant improvements (115, 116). The main application of this work was to rings classed as large and will be included in that section and in the section deal-

ing with factors affecting yields. The exception was the preparation of 2-hydroxycyclodecanone (sebacoin) from dimethyl sebacate (Eq. 24, $n = 8$).

The synthesis of medium rings has been reported by other laboratories with no significant modifications or improvement in yield (3, 13, 20, 25–27, 29a, 59, 80, 96, 98).

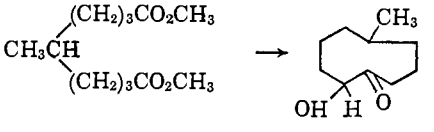
Additional use of the reaction for the preparation of required medium rings reflects (in increased yields) the further refinement of technique (2, 16). Of particular interest is the application to the syntheses of compounds in which the carbons of the acyloin linkage were labeled with C^{14} (67, 94, 97, 122).





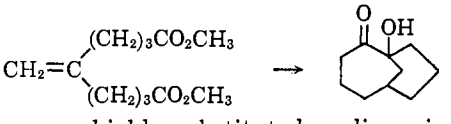
n = 7, 8, and 10; * = C^{14}

A number of substituted medium ring systems have been prepared in attempts to resolve optical isomers of these constrained molecules. The simplest such compound, 2-hydroxy-6-methylcyclononanone, has been reported (18, 90). One attempted preparation of the corresponding 6-methylene compound yielded a mixture of products, the major one of which seemed to be bicyclo[4.3.1]decan-1-ol-2-one although no structure



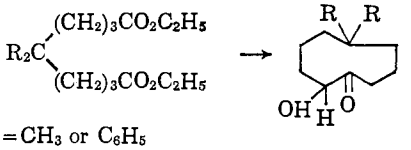
(Eq.25)

proof was obtained (90).



(Eq. 26)

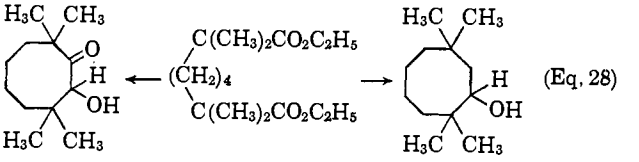
Other more highly substituted medium ring acyloins have been prepared and most have involved cyclononane (11, 14, 22).



(Eq. 27)

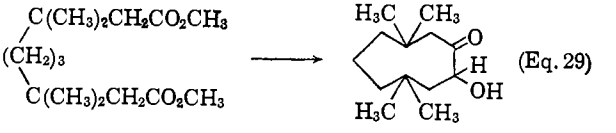
R = CH_3 or C_6H_5

Medium ring acyloins with four methyl groups as substituents have been prepared (71). Those in the α-positions are of special interest because conditions which produced good yields of the six- and seven-membered rings gave an eight-carbon ring which contained only a hydroxy group and was assigned the structure below. Higher temperatures resulted in the expected acyloin.



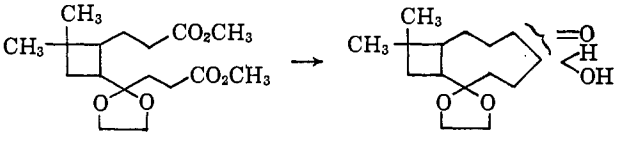
(Eq. 28)

With methyl groups in the β-positions, the expected product was obtained in very high yield (19).



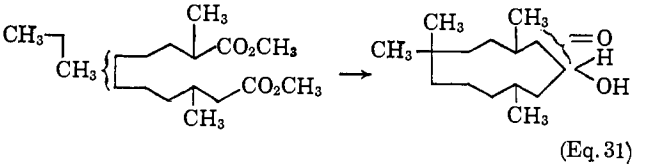
(Eq. 29)

The synthesis of natural products has provided some examples of highly substituted medium rings through the use of the acyloin condensation. For example, in an attempted preparation of caryophyllene the following reaction was carried out (31).



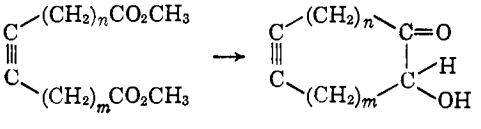
(Eq. 30)

Two different laboratories have reported the use of the acyloin ring closure in the preparation of humulene (48, 110).



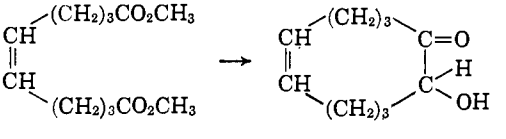
(Eq. 31)

A very important new method for the inclusion of triple bonds in carbon rings is the use of the acyloin reaction in cases of at least four methylene groups in each bridge (34, 40). The reaction involving a triple bond and three methylene groups resulted only in the recovery of the starting diester. When the unsaturation



(Eq.32)

was reduced to a simple olefin, both the *cis* and *trans* isomers were readily cyclized (40).



(Eq.33)

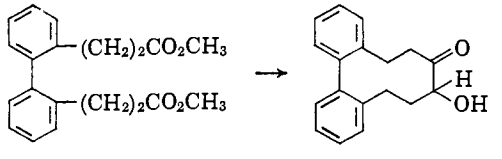
Two substituted medium carbocyclic systems have been prepared for use in other studies (46, 87).

TABLE II

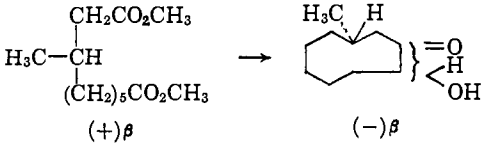
SUMMARY OF MEDIUM RING ACYLOINS

Equation	Solvent[a]	Addition time, hr.	Yield of acyloin, %	Ref.
24, n = 6	X	7	47[b]	61
n = 7	X	10	41.6	65
n = 8	X	15	65	24
n = 9	X	...	71	131
n = 10	X	...	63.5	67
25	X	7.5	60	18
26	X	60	...[c]	90
27, R = CH_3	X/T	...	66–70	22
R = C_6H_5	X	9	40	14
28	E	...	0	71
	X	...	33	71
29	T	12	84	19
30				31
31	X	...	49	110
32, n = m = 4				
alkyne	X	3.5	73	34
alkene *cis*	X	18	78–81	34
n = 3, m = 4				
alkyne	X	9	0	40
33, alkyne	X	6	0	34
alkene *cis*	X	9	80	40
alkene *trans*	X	9	51	40
34	X	...	25[d]	87
35	T	17	33.2[b]	46
36	X	5	63.5	92
37, x = 2				
R = C_6H_5	X	4–6	10	69
x = 3				
R = CH_3	X	4–6	75	69
C_2H_5	X	4–6	73	69
$(CH_3)_2CH$	X	5	60[b]	72
$(CH_3)_3C$	X	4.5	...[b]	72
$(CH_3)_2CHCH_2$	X	4–6	48[b]	75
C_6H_{11}	X	4–6	50[b]	75
C_6H_5	X	4–6	3[b]	73
p-$CH_3C_6H_4$	X	4–6	38[b]	73
p-C_5H NC_6H_4	X	4–6	37[b]	73
C_3H_5	X	4–6	45[b]	74
x = 4				
R = CH_3	X	4–6	64	69
C_2H_5	X	4–6	85	69
37a	X	24	0	29b

[a] Solvents: E, ether; T, toluene; X, xylene; X/T, xylene or toluene. [b] High dilution cycle. [c] Bicyclic acyloin; no structure proof. [d] Obtained as the diketone.



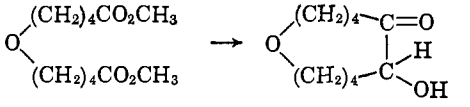
(Eq.34)



(Eq. 35)

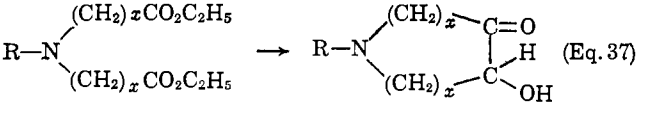
(+)β (−)β

The preparation of medium rings which contain heteroatoms has been carried out in a few cases and involves oxygen and nitrogen. The case of oxygen is represented by only a single example (92).



(Eq. 36)

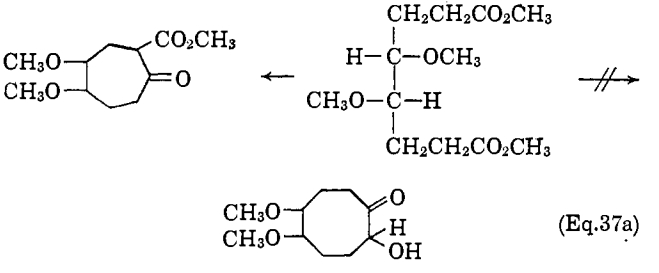
A far more extensive series of N-substituted cyclic amino acyloins has been prepared which includes both variation of substituent and ring size (69, 70, 72–75).



(Eq. 37)

R = CH_3, C_2H_5, $(CH_3)_2CH$, $(CH_3)_3C$, $(CH_3)_2CHCH_2$, C_6H_{11}, C_3H_5, C_6H_5, p-$CH_3C_6H_4$, and p-$C_5H_5NC_6H_4$; x = 2–4

An interesting example of the failure of eight-membered ring formation under acyloin conditions has been reported (29b). As was observed in the seven-membered case containing ketal linkages, the sole product was Dieckmann cyclization.



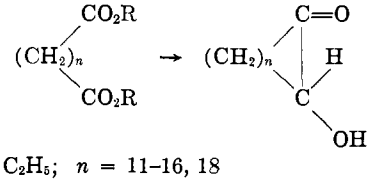
(Eq. 37a)

A summary of medium ring acyloins is given in Table II.

C. LARGE RINGS

Many of the applications of the acyloin reaction to cyclization problems have resulted in the synthesis of macrocyclic systems which include structural features for the uses intended; in several cases, the work is extensive enough to warrant a separate tabulation. In the present subsection only those unsubstituted or very simply substituted rings which are composed of 12 or more atoms will be included (see Table III).

As was the case with the medium rings, the large carbocycles were prepared by Prelog and Stoll and reported in an earlier review (85).



(Eq. 38)

R = CH_3 or C_2H_5; n = 11–16, 18

Stoll's later patents represent a very slight improvement in yield, but the increase does not approach that

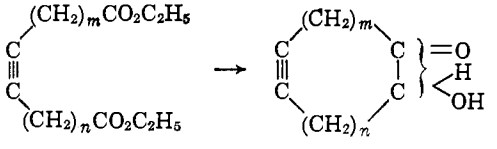
cited in the medium rings (115, 116). The inclusion of a few substituted compounds will be discussed in the section devoted to the musks.

Later use of the acyloin condensation for the preparation of large rings has not resulted in any modifications, new compounds, or improvement in yield and are included only for completeness (7, 25, 59, 62, 95).

One exception is the preparation of the 34-membered carbocyclic acyloin in connection with the demonstration of the existence of the catenanes (see Eq. 38, $n = 32$) (128).

A large ring with four methyl substituents in the α-position has been prepared by the usual methods, and no pure product was obtained free of the diketone (see Eq. 23, $n = 14$) (71).

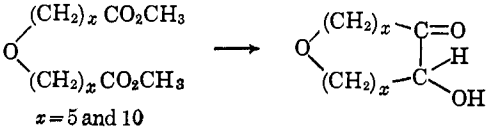
It has been possible to prepare large rings containing a triple bond just as it was in the case of the 12-carbon system (47, 81).



(Eq. 39)

$m=5, n=9; m=n=7$

A few compounds with a heteroatom (oxygen and nitrogen) included as a member of the ring have been prepared (69, 92).



(Eq. 40)

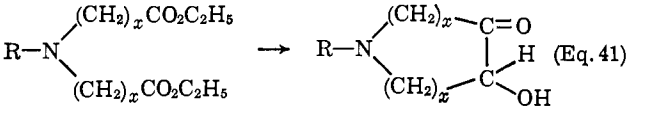
$x=5$ and 10

TABLE III

SUMMARY OF LARGE RING ACYLOINS

Equation	Solvent[a]	Addition time, hr.	Yield of acyloin, %	Ref.
38[b], $n = 32$	X	...	5-20[c]	128
23, $n = 14$	X	...	...[d]	71
39, $m = 5, n = 9$	X	...	71	81
$m = n = 7$	X	...	...	47
40, $x = 5$	X	7	71	92
$x = 10$	X	6	56	92
41, R = CH_3				
$x = 5$	X/T	4-6[e]	86	69
$x = 6$	X/T	4-6[e]	83	69
$x = 7$	X/T	4-6[e]	84	69
$x = 8$	X/T	4-6[e]	83	69
R = C_2H_5				
$x = 5$	X/T	4-6[e]	77	69
$x = 6$	X/T	4-6[e]	88	69
$x = 10$	X/T	4-6[e]	72	69

[a] Solvents: T, toluene; X, xylene; X/T, xylene or toluene. [b] Yields and conditions are reported in earlier review (85). [c] Reported only the second preparation in the presence of the macrocycle. [d] No pure sample obtained. [e] High dilution cycle.



(Eq. 41)

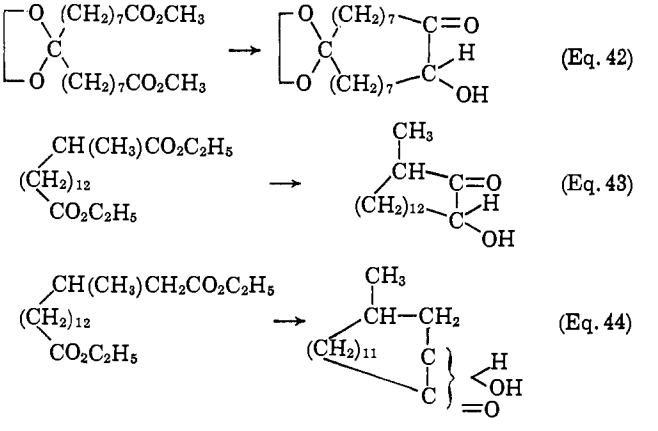
$R=CH_3$ or C_2H_5; $x=5$-8 or 10

D. MACROCYCLIC MUSKS

Macrocyclic ketones are much sought for their pleasant fragrance. This represented one of the very important reasons for the early development of methods of ring closure, especially the use of the acyloin condensation. A significant number of later papers, including some very recent ones, are concerned with the preparation of compounds of this type and are presented in this separate subsection although they clearly are closely related to the large rings previously treated (see Table IV).

Many of the partial reviews of the acyloin cyclization are specifically devoted to its application to synthetic perfume problems (6, 8, 60, 113, 114, 125).

In the years immediately following the introduction of the acyloin condensation as a useful means of preparing large rings, several compounds noted for their musk odor were obtained (112, 117, 118). These, as well as the unsubstituted large rings, have been described by Stoll in an American and a British patent for industrial scale operation (115, 116).

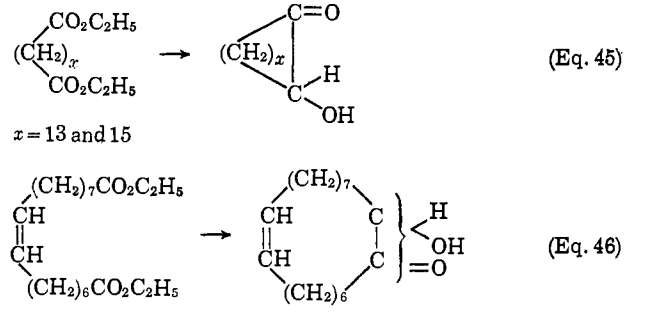


(Eq. 42)

(Eq. 43)

(Eq. 44)

Very recently another group has begun to apply the acyloin condensation to the preparation of musks.



(Eq. 45)

$x=13$ and 15

(Eq. 46)

The compounds first described in a series of brief communications were subsequently included in complete papers (9, 10, 45, 53, 54, 83, 84).

Isolated reports of the preparation of acyloins for use in various aspects of perfume chemistry have been made with no significant improvements (119, 130).

TABLE IV

SUMMARY OF MUSK ACYLOINS

Equation	Solvent[a]	Addition time, hr.	Yield of acyloin, %	Ref.
42	X	0.5	83	118
43	X	2.5	72	112
44	X	1.5	73.8	117
45, x = 13	X	1	72	84
x = 15	X	2	70	45
46[b]	X	1.5	72	83

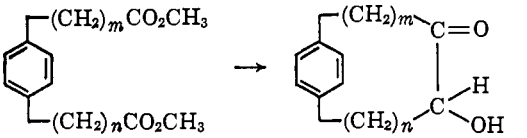
[a] X = xylene. [b] Mixture of isomers.

E. PARACYCLOPHANES

Perhaps no other single application of the acyloin condensation has been as extensive as that of its use as the key step in the preparation of the paracyclophanes. This is the generic name of a group of hydrocarbons consisting of one or more aromatic nuclei joined by *para*-substituted methylene bridges (see Table V).

A few early efforts in this field have been completely overshadowed by the work of Cram and his students (51, 64, 129). The initial publications of this group have been reviewed (32) but will be included here in so far as they concern the acyloin cyclization.

In repeating and extending the first successful work in this field, a modest improvement in yield was also obtained (37–39). In cases where one of the bridges was much shorter than the other, the aromatic ring



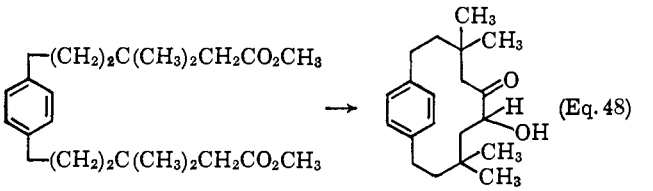
(Eq. 47)

m	6	5	4	3	2	1
n	6	5	4	4	5	6

had to be reduced to obtain intramolecular acyloins, and even the reduced compound failed to close with $m = 2$, $n = 5$ as did the one with six methylene groups in each bridge (35, 41). The latter failed to close when the diacid chloride was subjected to acyloin conditions (35). Another study, in which $n = 0$, gave no acyloin product (121). This later work involved an *ortho*-disubstituted aromatic ring.

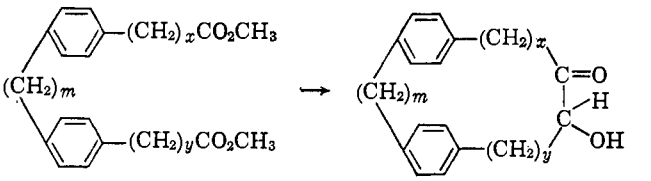
These same preparations have been carried out in other laboratories with no significant modifications or improvement in yield (5, 21).

One new compound of interest is the [10]paracyclophane in which four methyl groups occupy the β-positions (15).



(Eq. 48)

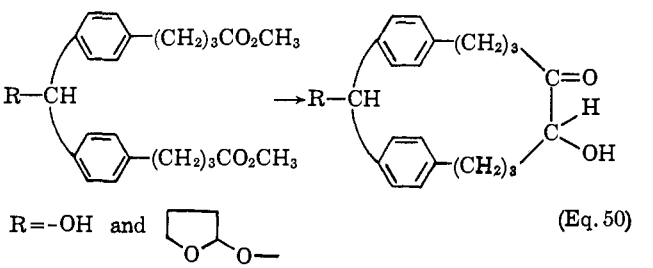
Even more extensive researches have been performed on those paracyclophanes which contain two aromatic rings (1, 4, 35, 36, 43, 111).



(Eq. 49)

m	x	y	m	x	y
1	2	2	2	1	1
1	2	3	3	0	2
1	3	3	3	1	1
			3	2	2
1	3	4	4	2	2
1	4	4	5	2	2
1	4	5	6	2	2
1	5	5			

The compound in which one bridge consists of a single substituted methylene group has been reported (42).

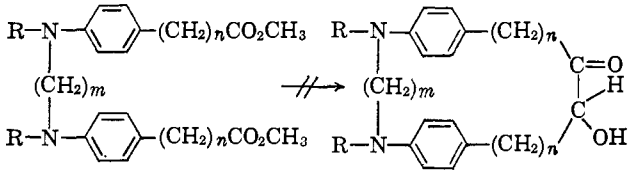


(Eq. 50)

For the preparation of certain members of this series it was necessary to reduce the aromatic rings as had been done with those containing only a single nucleus. The resulting compound could subsequently be aromatized, but usually in very low yield [see Eq. 49 where the following values of m, x, and y, are used (1, 4, 33, 35, 36, 44)].

m	x	y	
1	2	2	see Eq. 49
1	2	3	
3	0	1	
3	1	1	
4	1	1	
5	1	1	
5	1	2	

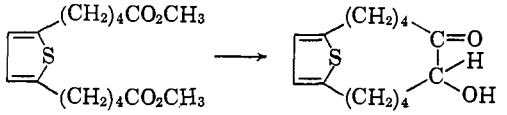
The inclusion of nitrogen in the paracyclophane ring system has been attempted and failed in all cases investigated (50).



(Eq. 51)

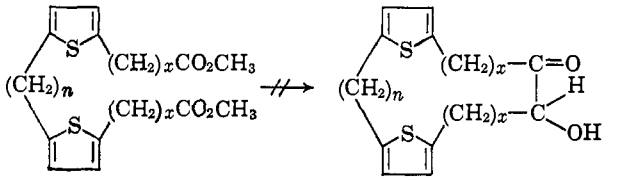
R = C_6H_5CO $m = 4$; $n = 1, 2$
R = H $m = 4$; $n = 2$
R = $C_6H_5CH_2$ $m = 4, 3$; $n = 2$

A very interesting and potentially useful synthetic method involves the use of thiophene rather than benzene as the aromatic ring upon which the cyclic bridge is built. The earliest report of this involves a single unsubstituted thiophene ring and produced rather low yields of the acyloin (55).



(Eq. 52)

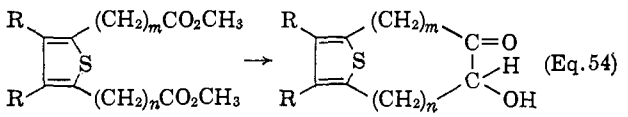
Attempts to carry out the reaction with two thiophene rings have not resulted in any useful product, but only a high recovery of starting material (101).



(Eq. 53)

$n = 1$, $x = 3, 5$
$n = 3$, $x = 2, 3$

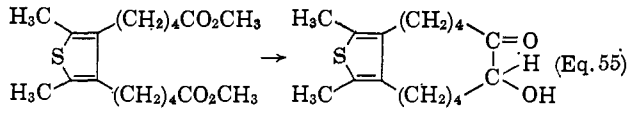
Under similar conditions, but somewhat lower temperature, a linear acyloin containing two thiophene rings was obtained showing that the ring itself does not prevent reaction. Later work has increased the yields of systems containing a single thiophene ring by modifying the conditions and the substrate (56). The dimethyl-substituted compound in which the positions of the alkyl and ester groups is reversed has also been



(Eq. 54)

R = H, CH_3
$m = n = 4$; $m = 4$, $n = 5$

prepared by acyloin ring closure (56).



(Eq. 55)

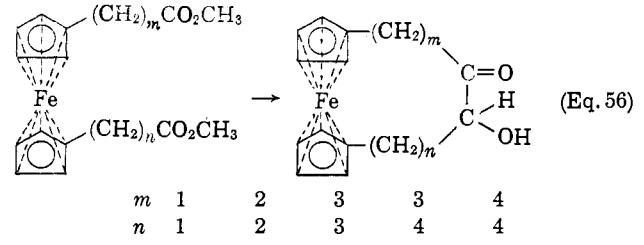
TABLE V

SUMMARY OF PARACYCLOPHANE ACYLOINS

Equation	Solvent[a]	Addition time, hr.	Yield of acyloin, %	Ref.
47, m n				
6 6	X	...	0[b,c]	35
5 5	X	...	70	35
4 4	X	44	76	38
3 4	X	60	36	85
2 5	X	...	0[b]	85
1 6	X	...	75[b]	85
48	T	11	31.4[d]	15
49, m x y				
1 2 2	X	50	0	36
1 2 3	X	50	0	36
1 3 3	X	50	28	36
1 3 4	X	50	46	36
1 4 4	X	50	62	36
1 4 5	X	50	51	36
1 5 5	X	50	80	36
2 1 1	X	60	0	43
3 0 2	X	79	0	4
3 1 1	X	60	0	43
3 2 2	X	60	52.8	43
4 2 2	X	60	37	1
5 2 2	X	46	71	111
6 2 2	X	60	70	1
50, R = OH	X	50	23	42
R = $C_4H_7O_2$	X	60	62	42
49,[b] m x y				
1 2 2	X	50	0	36
1 2 3	X	50	2[e]	36
3 0 1	X	...	1[e]	35
3 1 1	X	34	26	4
4 1 1	X	74	25	33
5 1 1	X	16	47	4
5 1 2	X	12	62	4
51, R = C_6H_5CO	...	...	0	50
R = H	...	...	0	50
R = $C_6H_5CH_2$	...	...	0	50
52	X/E	...	4.5	55
53, n x				
1 3	X	14	0	101
1 5	X	14	0	101
3 2	X	14	0	101
3 3	X	14	0	101
54, R = H				
m n				
4 4	X/E	...	10.3[f]	56
4 5	X/E	...	10.4[f]	56
R = CH_3				
m n				
4 4	X/E	...	42.5[f]	56
55,	X/E	...	72[f]	56
56,[g] m n				
1 1	X	3	20	100
2 2	X	3	50	100
3 3	X	3	58	100
3 4	X	3	55	100
4 4	X	3	75	100

[a] Solvents: E, ether; T, toluene; X, xylene; X/E, xylene and ether. [b] With reduced aromatic rings. [c] Also tried as the diacid chloride. [d] Required a twofold excess of sodium. [e] Overall hydrocarbon yield. [f] Na–K alloy. [g] No high dilution.

A final example related to bridge compounds of the paracyclophane type is a series of ferrocene derivatives (100).

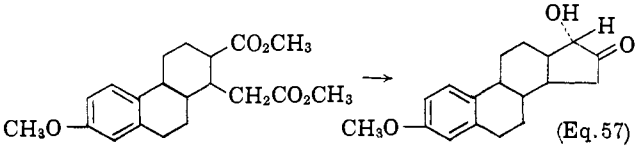


(Eq. 56)

m	1	2	3	3	4
n	1	2	3	4	4

F. STEROIDS

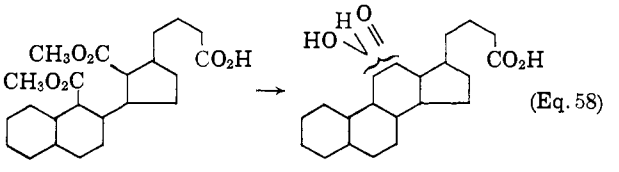
A very interesting start, which does not seem to have been followed, has been made in the application of the acyloin condensation to cyclization problems in the synthesis of steroids (see Table VI). The use of the homogeneous liquid ammonia method for the preparation of normal rings has been especially successful in this field. The earliest reports indicated a complete failure of the usual acyloin conditions, *i.e.*, refluxing xylene (103).



(Eq. 57)

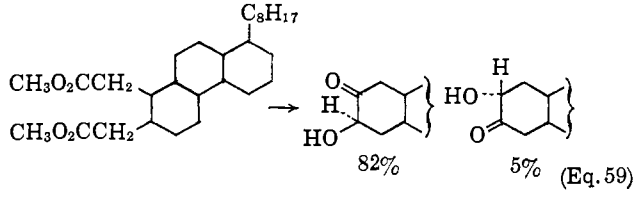
The very selective nature of the reaction is noteworthy; of the four possible isomers only one was obtained and that in quite high yield. It was later found that the isomer obtained was β- rather than α-hydroxy, and the yield has been made nearly quantitative (104). This work was later repeated with the same results and in one case was the means of including C^{14} at the 16-position (79, 106).

An application of this method for the closure of the C-ring showed the same selectivity and resulted in a single isomer although the structure was not determined (103).



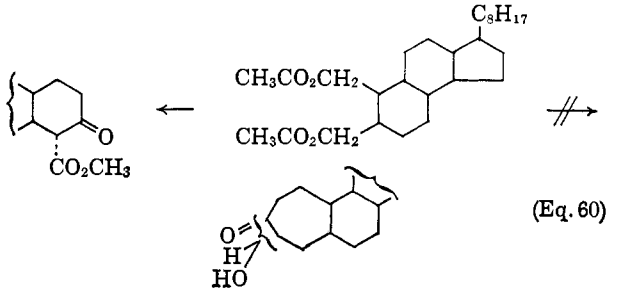
(Eq. 58)

This method has also been applied to the closure of the A-ring and once again very selective results have been observed (105).



82% 5% (Eq. 59)

One report of an attempt to prepare a seven-membered A-ring of a steroid using the acyloin method under the usual conditions of refluxing xylene produced only Dieckmann product (88). The reaction was also carried out in liquid ammonia with sodium or lithium and resulted only in oily, inseparable products.



(Eq. 60)

TABLE VI

SUMMARY OF STEROID ACYLOINS

Equation	Solvent[a]	Addition time, hr.	Yield of acyloin, %	Ref.
57	X[b]	..	0	103
	A/E		96	104
58	A/E		75–80	103
59	A/E		87	105
60	X[b]	11	0	88
	A[c]		0	88

[a] Solvents: A, ammonia; E, ether; X, xylene; A/E, ammonia and ether. [b] High dilution cycle. [c] Attempted with lithium as well as sodium.

IV. FACTORS INFLUENCING EASE OF CYCLIZATION

In view of the complete lack of kinetic data for the acyloin condensation as a cyclization reaction, it is necessary to discuss these factors in terms of the yields obtained. In very few cases has any systematic attempt been made to obtain really comparable values, and in most instances the data are obtained by different laboratories in synthetic problems which involved no search for optimum conditions. Even with limitations of this kind, yield data can provide important indications as to the relative ability of various systems to cyclize and of different conditions to promote the reaction.

The various subsections will be concerned with the heterogeneous reaction on which more data are available, and a separate subsection will be devoted to what is known about the homogeneous reaction.

A. THE EFFECT OF CHAIN LENGTH

The discussion of a cyclization reaction demands at the very least some knowledge of the ability of various unsubstituted open-chain compounds to close. For information of this kind some progress has been made, and at least one set of consistant yield data is available

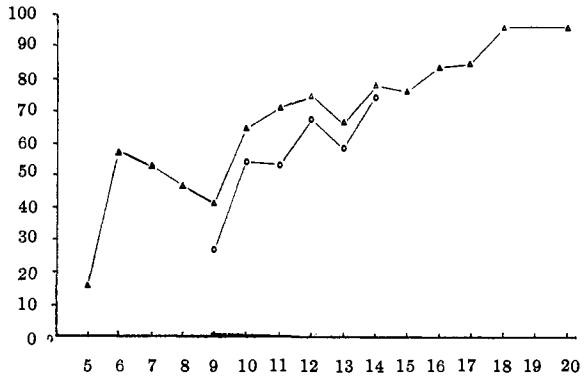


Fig. 2.—Variation of yield with ring size: vertical axis, per cent yield; horizontal axis, ring size; Δ, highest yield of acyloin obtained under heterogeneous reaction conditions regardless of the date or laboratory (see Tables I–IV for references); O, reproducible yields of cyclic monoketones by the acyloin cyclization (76, 78).

in the very important medium ring compounds as shown in Fig. 2 (76, 78).

The yields reported in this study are over-all values of the diester to the corresponding cyclic ketone, and an attempt was made to obtain optimum, reproducible yields. For both of these reasons, the numbers as such are not comparable with the others presented in Fig. 2, which represent the widest range of unsubstituted cyclic structures known to have been prepared by the acyloin condensation. These values are yields of more or less impure acyloins obtained in the course of a synthetic sequence.

In spite of the fundamental difficulties of interpreting these data the general trends are clear. At very large ring size the reaction becomes nearly quantitative, and even the formerly inaccessible medium rings are obtained in very respectable yields. The situation with small and normal rings is complicated by the fact that most of the successful preparations of these systems make use of the homogeneous reaction. One obvious conclusion is that the acyloin condensation represents a reversal of the usual rule that medium rings are more difficult to prepare than normal rings.

B. THE EFFECT OF SUBSTITUENTS

Even the general trends are much less clear concerning the influence of substituents on the ease of ring formation, because of the scarcity of data. As can be seen in Table VII there does seem to be some indication of substitution facilitating cyclization. The few short series of compounds which represent changes only in degree of substitution strengthen this generalization. The effect of a fused ring is also interesting although limited to two cases.

Unfortunately there are, as indicated in Table VIII, cases of similar substitution causing either a decrease or no change in the yield of the ring closure product. In the cases involving very large rings this lack of influence is understandable, but with the normal and medium ring cases the reason for the observation is not obvious.

TABLE VII

EFFECT OF SUBSTITUENTS ON ACYLOIN YIELD

Ring size	Yield (unsubstd.), %	Substituent	Yield (substd.), %	Ref.
6	57	2,2,5,5-Tetramethyl	91	71
7	46	2,2,6,6-Tetramethyl	69	71
		2,6-Dibenzyl	87	77
9	37.5	6-Methyl	60	18
		6,6-Dimethyl	68	22
		6,6-Diphenyl	40	14
		3,3,7,7-Tetramethyl	84	19
5	15.5	Fused cyclohexane	41	107
		Fused cyclohexane and angular methyl group	42	102

TABLE VIII

EFFECT OF SUBSTITUENTS ON ACYLOIN YIELD

Ring size	Yield (unsubstd.), %	Substituent	Yield (substd.), %	Ref.
5	15.5	2,2,4,4-Tetramethyl	0	71
8	47	2,2,7,7-Tetramethyl	33	71
11	71	2,5,5,9-Tetramethyl	49	110
15	77	2-Methyl	72	112
		3-Methyl	73.8	117
5	15.5	Steroid system	0	103

The effect of the presence of a cyclic ethylene ketal is instructive. In the seven-membered ring with the ketal in the 3-position no acyloin product was obtained (52), but in the 17-membered ring with the ketal in the 9-position the yield was a very respectable 83% (115, 116, 118). The failure of the seven-membered ring to close was attributed by the authors to an interaction of the carbethoxy groups with the dioxalane ring, which is less likely in the much larger ring. Both this sytem and ethyl γ-hydroxypimelate lactone gave Dieckmann product under acyloin conditions.

A very similar situation, which also resulted in Dieckmann product under acyloin conditions, occurred in an attempt to close an eight-membered ring with two methoxy groups (29b).

Related to the question of the effect of substituents on the ease of cyclization is that of the influence of various ester alkyl groups. With a few exceptions [*n*-butyl (24) and phenyl (121)], only methyl and ethyl esters have been employed and in no case was any significant preference observed.

A final example of the effect of a substituent on acyloin cyclization is that cited in Eq. 21 (90). If the structure of the product is that suggested by the author, it illustrates the possibility of preparing bicyclic systems by combined acyloin cyclization and transannular interaction with unsaturated substituents.

C. THE EFFECT OF UNSATURATED AND AROMATIC SYSTEMS

The introduction of carbon atoms with other than sp^3 hybridization into the chain undergoing cyclization can have very definite effects on the yield of cyclic product.

TABLE IX

EFFECT OF CARBONS OF OTHER HYBRIDIZATION ON ACYLOIN YIELD

Ring size	Yield (all sp^3), %	Carbons of other hybridization	Yield, %	Ref.
10	65	5,6-Triple bond	0	34
		5,6-*cis*-Double bond	80	40
		5,6-*trans*-Double bond	51	40
11	71	5,6-Triple bond	0	40
12	63.5	6,7-Triple bond	73	34
		6,7-*cis*-Double bond	79.5	34
17	70	8,9-Mixture of double-bond isomers	72	83
18	96	7,8-Triple bond	71	81

The results presented in Table IX, although once again very meager, lend themselves to straightforward if tenuous interpretation. The linear acetylenic system prevents cyclization in the medium rings, but once the chain length is great enough it helps to promote closure by decreasing transannular hydrogen interaction. A pronounced *cis–trans* geometric influence is observed in the medium rings with the *cis* producing the expected high yield by both introducing a favorable geometry and reducing hydrogen compressions.

The lack of a strong effect in the 17-membered ring is not unexpected, but the significant decrease in yield of the 18-membered case should be repeated.

Much more data are available in cases where the change in hybridization is introduced by means of one or more aromatic rings. In Fig. 3 the variation of yield with ring size is presented. Once again it can be seen that while the general trends are as expected, *i.e.*, the yields increase with increasing size, there are obvious exceptions which demand an explanation. The most striking of these is the failure of the reaction in the case of the acyloin corresponding to [14]paracyclophane (35). After the high yields obtained with smaller systems, no simple justification is apparent.

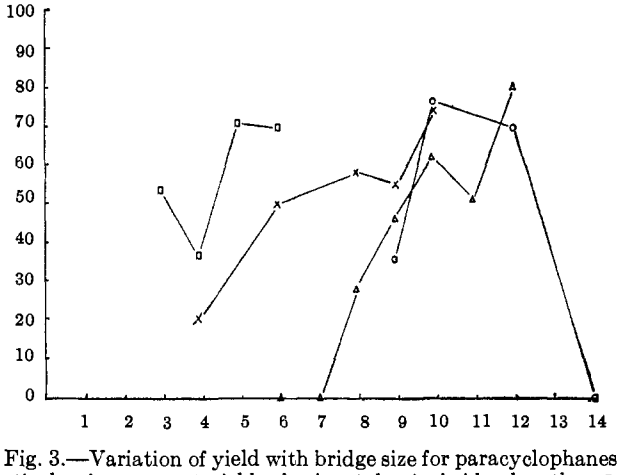


Fig. 3.—Variation of yield with bridge size for paracyclophanes: vertical axis, per cent yield; horizontal axis, bridge length; ○, paracyclophane with one aromatic ring (Eq. 47); △, paracyclophane with two aromatic rings and one bridge held constant at one methylene group (Eq. 49, $m = 1$); □, paracyclophane with two aromatic rings and one bridge held constant at six methylene groups (Eq. 4, $x = y = 2$); ×, bridged ferrocene (Eq. 56).

Another case which needs to be looked at carefully is that of the [10]paracyclophane in which the two β-positions are substituted by four methyl groups (15). In contrast to the usual observation of alkyl substituents increasing the ease of cyclization, the yield here drops sharply even when a twofold excess of sodium is used. This excess, it should be noted, has to be employed in order to carry out the reaction.

With one minor exception, the bridged ferrocenes show a steady increase in yield with increased length of the methylene chain (100). The yield that is low occurs at the nine-membered bridge and is not seriously out of line.

Two final instructive examples involving systems of the paracyclophane type are those with the inclusion of heteroatoms. The first of these, in which N-substituted anilines were employed, failed to give any useful product (50). In at least one instance, the polymeric material obtained was attributed to attack on the amide linkage.

The second and more productive example is the incorporation of a thiophene ring in place of benzene (55). While the yields are low in most instances and no extensive variation of ring size has been made, the reaction does show some promise for future development. The improvement of the yield when the remaining thiophene positions are substituted with alkyl groups is remarkable (56).

D. THE EFFECT OF HETEROATOMS

Another method by which the steric repulsions of internal hydrogens can be reduced is by including heteroatoms as part of the ring. As is shown in Fig. 4,

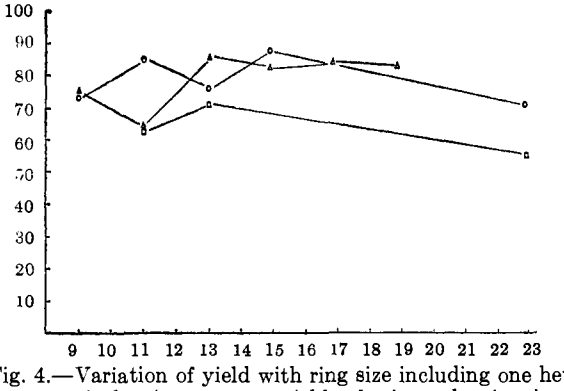


Fig. 4.—Variation of yield with ring size including one heteroatom: vertical axis, per cent yield; horizontal axis, ring size including heteroatom; □, oxygen (Eq. 36 and 40); △, nitrogen (Eq. 37 and 41, R = CH_3); ○, nitrogen (Eq. 36 and 41, R = C_2H_5).

the difference in yield between oxygen and nitrogen and the variations with the N-substituent are insignificant when the fact that they were obtained by different groups over a period of time is considered. This is also true of the comparison of all of these values with the carbocyclic rings of similar size. The range of ring sizes studied and the internal consistency of the data do not allow anything like definitive statements to be made concerning the effect of the heteroatoms.

E. THE EFFECT OF STEREOCHEMISTRY

There are several interesting pieces of evidence with regard to the part that stereochemistry plays in promoting or retarding cyclization. This is in addition to those already cited in the case of double bonds.

A four-membered ring fused to a six-membered ring (Eq. 1) was obtained in much higher yields from the *cis*-diester than from a *cis–trans* mixture indicating that only the *cis* cyclizes as would be expected (28). In the case of a five-membered ring fused to a six-membered ring both the *cis*- and *trans*-diesters appear to undergo ring closure, since both ring fusion products are obtained (102, 107).

In an attempt to prepare a system of four fused five-membered rings (Eq. 11), no acyloin product was obtained, and it was later shown that the method of preparation of the tetraester resulted in the least favorable stereochemical orientation of the groups (58).

Several of the paracyclophanes could be prepared only by cyclizing those systems in which the aromatic rings were reduced (4, 33, 35). In some cases the yields of products indicated that only one isomer was closing. When the chains of aliphatic carbons were long enough, both the *cis–cis* and the *cis–trans* isomers underwent ring closure.

F. THE EFFECT OF REACTION CONDITIONS

At least from a practical point of view, somewhat greater progress has been made in this area than in those discussed thus far. Those cases which have been studied so as to show clearly a contrast between different conditions are reported in Table X.

TABLE X

EFFECT OF REACTION CONDITIONS ON ACYLOIN YIELD

Equation	Original yield, %	Change in procedure	New yield, %	Ref.
10	15.5	Addition time increases from 1 to 65 hr.	13.4	66, 108
12	30	Employed high dilution cycle	42	102
24, $n = 6$	37	As above	47	61
24, $n = 8$	43	High purity nitrogen (oxygen less than 0.2%)	65	24
52	0	Lower temperature using xylene–ether mixture	4.5	55
54, R = H	4.5	Liquid Na–K alloy	10.4	56
28	33	Solvent changed from xylene to ether	0	71
10	15.5	Homogeneous reaction in liquid ammonia instead of heterogeneous method	50	49, 108
12	42	As above	50	102
19	57	As above	38	108
57	0	As above	96	103, 104
60	0	As above	0	88

In addition to these reports of the actual yield before and after the change, there are a number of reports in which only the direction of the change is given.

The influence of small amounts of oxygen in the covering atmosphere is quite clear and well documented. Substantial increases in the acyloin yield are cited in a variety of examples including most of the various applications of the reaction. It is especially important to notice that the reaction must be kept under nitrogen as long as it is basic and not simply during the addition and reflux time.

Using high dilution cycles and extended addition times does not in every instance raise the yield. It seems clear that the best results are obtained using a high dilution apparatus in the case of medium-sized rings. It should be especially noted that in the large cyclic systems reasonably high concentrations can be employed to produce excellent yields, while in the small and normal rings only high dilution methods have been successfully carried out.

An interesting, but little studied, modification is the use of a lower reaction temperature and the liquid Na–K alloy. In the case of the thiophene analogs of the paracyclophanes, this technique produced substantially improved yields.

Finally, although the conclusion is based on quite fragmentary evidence, there emerges no pattern that can be related to changes in solvent. For the small and normal rings, the homogeneous reaction in liquid ammonia seems to be markedly superior, but until many more examples have been studied under both conditions, little can be concluded.

Two points concerning the homogeneous modification are worth pointing out. First, the reaction appears to be nearly instantaneous as indicated by the disappearance of the deep blue sodium color. Hence, the usefulness of slow addition and high dilution appears to be very limited in this reaction although they are unstudied.

Second, the preparation of the strained spiro systems, the highly stereospecific nature of steroid syntheses, and the general tendency to favor small and normal ring formation should be noted. All of these effects promise many more exciting possibilities than would be indicated by their study thus far.

G. BY-PRODUCTS OF THE CONDENSATION

One very important factor in understanding the theory and practice of the acyloin condensation is the other products which result from the reaction and the amount of recovered starting material. Unfortunately, few authors have investigated and/or reported the nature or yield of by-products. The usual statement is that the by-products appear to be diketone and polymers. While this is almost certainly true in view of the yellow solution and insoluble material, it would be much more helpful to know how much of each is present and, in fact, to be sure that they are correctly identified. Those cases where the nature of the by-product was given are listed in Table XI.

TABLE XI

NATURE OF BY-PRODUCTS OF ACYLOIN CONDENSATION

Equation	By-products	Ref.
11	Diketone and bimolecular acyloins	107
24	Polymer and polymeric acid	115
48	Diacyloin (?)	15
49	Diketone	1

In only one case was a complete study of the by-products reported (80). A preparation of 2-hydroxycyclodecanone gave the following distribution of products other than acyloin.

Neutral products	Yield, %
Cyclononanone and cyclodecanedione	14
1,10-Decanediol	3
Cycloeicosanedioldione	0.5
Cyclononadecanol-1-dione-2,11	15
Acid products	
Sebacic acid	17
Polymer	49

The polymer gave an analysis which corresponds to

$$HO_2C(CH_2)_8—CHOH—(CH_2)_8—CO—(CH_2)_8—CHOH—(CH_2)_8—CO_2H$$

V. CONCLUSIONS

The free-radical mechanism for the acyloin condensation in both homogeneous and heterogeneous modifications seems firmly established although the number of cases studied is certainly minimal and includes no cyclization reactions. Aside from mechanistic considerations, the scope and limitations of the method are very inadequately understood, and the several observed cases of excellent stereospecificity are completely unexplained.

The relative importance of various structural factors and reaction conditions in promoting the reaction have been inadequately investigated. In several cases, even the direction of the influence has not been clearly determined.

For a reaction which has proven to be of such synthetic importance, is seems worthwhile to encourage fundamental study. Kinetic studies, while difficult in a heterogeneous system, would be most desirable for discussing questions posed by the data reported in this review.

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