VOLUME 40 OCTOBER 3, 1975 NUMBER 20 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

THE JOURNAL OF Organic Chemistry

Published by the
AMERICAN CHEMICAL SOCIETY
1155 16th Street, N.W.
Washington, D.C. 20036

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Published biweekly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second-class postage paid at Washington, D.C., and at additional mailing offices.

Editorial Processing Department, American Chemical Society, 20th and Northampton Sts., Easton, Pa. 18042: Department Head, Charles R. Bertsch; Associate Department Head, Marianne C. Brogan; Production Editor, Eileen B. Segal; Assistant Editor, Fern S. Jackson; Editorial Assistant, Andrew J. D'Amelio; Production Assistant, Jane U. Lutick.

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JOCEAH 40(20) 2853-3004 (1975)
ISSN 0022-3263

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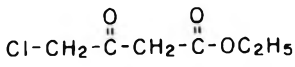

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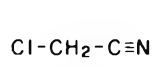

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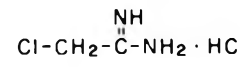

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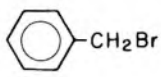

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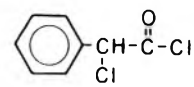
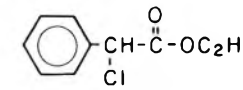
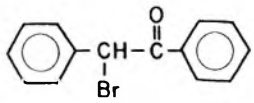


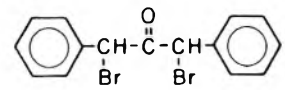
1935 α-Chlorophenylacetyl chloride
15.75/50g



1637 Ethyl α-chlorophenylacetate
9.75/25g



2072 Desyl bromide
16.80/10g



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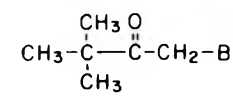
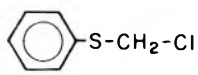


1100 1-Bromopinacolone
15.10/25g 46.50/100g



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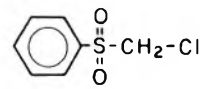
18.50/25g 56.95/100g



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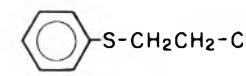

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THE JOURNAL OF Organic Chemistry®

VOLUME 40, NUMBER 20

OCTOBER 3, 1975

Arynic and SNAr Reactions of Polyhalogenobenzenes. IV.[1,2] Condensation of Ketone Enolates

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Received January 28, 1975

Condensations of aliphatic or alicyclic ketone enolates with miscellaneous dialkylaminochlorobenzenes in the presence of base and in aprotic media lead, chiefly, to corresponding amino chloro phenyl ketones and benzocyclobutenols. Relative ratios of these last two products depend mainly on experimental conditions and on the relative substituent positions in the starting halo compounds. In two cases, benzofuran formation, in low yields, is observed. Ring opening by bases of benzocyclobutenols thus synthesized was briefly studied. In all these reactions arynes seem to be the major reaction intermediates.

It is well known that condensations of amines with 1,2,4- and 1,2,3-trichlorobenzene as well as with dialkylaminochlorobenzenes, in the presence of bases, involve arynic (EA) and/or SNAr mechanisms.[2]

On the other hand, we have also shown that ketone enolates condense with arynes in aprotic media to lead to aromatic ketones, and, in some cases, to benzocyclobutenols.[3]

The results thus obtained prompted us to study the condensation of ketone enolates with some dialkylaminodichlorobenzenes. Our purpose was to investigate the behavior of these polyhalogeno compounds in these reactions and to synthesize some new derivatives with substituents on the aromatic ring, the properties of which we wanted to study. The present paper discloses the results obtained.

I. Condensation of Ketone Enolates with *N,N*-Diethylamino-3,4-dichlorobenzene. A. Condensation of Alicyclic Ketone Enolates. Scheme I gives a general summary of the results obtained in this series of reactions.

In fact, the results are much less complex than it might at first seem. By varying experimental conditions, it is possible to make these reactions fairly selective, and we report in Table I the essential results.

From this set of results, we can make some general remarks. Obviously, under our basic conditions, the chloro derivative **1** is converted into the aryne **7**.[2]

After the ketone enolate condensation, one obtains compounds **3**, **4**, and **5**, a result in agreement with our previous work.[2,3] The formation of the benzofurans **6** can be attributed only to further reaction, in basic medium, of the ketones **3**. We shall see in the next paper that this hypothesis is verified and that the "side" reaction (here) is in fact a good approach to the heterocycles **6**.

From Table I and from a systematic study, the following essential features can be pointed out.

Scheme I

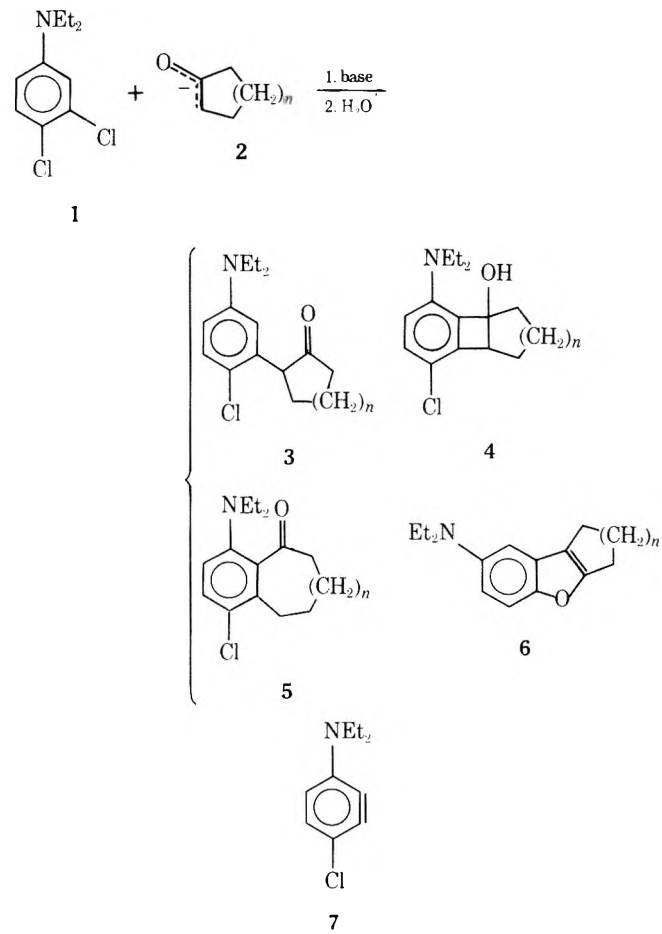
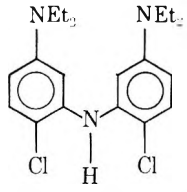


Table I
Condensation of Ketone Enolates 2 with *N,N*-Diethylamino-3,4-dichlorobenzene (1) in THF (Unless Otherwise Mentioned) in the Presence of a Base

No.	n	Temp, °C	Time, hr	Base	3, % [a]	4, % [a]	5, % [a]	6, % [a]	Total yield, % [b]
1	1	−15	16	Complex base[c]	88	5	7		85
2	1	22	2	Complex base	61-80	26-10	13-8		80-90
3	1	45-50	1.25	Complex base	63		37		90
4	2	25	7	Complex base	100				77
5	2	45	2	$NaNH_2$	87			13	61
6	3	−10	40	Complex base	45	55			70
7	3	55	1.25	Complex base	18	82			80
8	4	20	4	Complex base	54	46			70
9	4	48	1.25	Complex base	80	20			70
10[d]	4	40-45	2	Complex base	75			25	50

[a] Relative ratios as determined by VPC analysis. [b] Yields obtained after column chromatography of the crude product. [c] For a general review on complex bases, see ref 5. [d] The reaction solvent is DME.

(1) Amine formation, issuing from NH_2^- condensation, is sometimes observed.



(2) The use of the complex base $NaNH_2$–*t*-BuONa[5] often leads to greater total yields than does the use of $NaNH_2$ alone; however, this difference is markedly apparent only for $n = 1$ and 4.

(3) These condensations are a good approach to the aryl ketones **3** but not to the benzocyclenones **5**; however, the latter are sometimes accessible by ring opening of the alcohols **4** (see below).

As for the formation of the alcohols **4**, some marked differences are observed in comparison with the nonsubstituted arynes. Thus, for $n = 1$, yields are markedly better than those obtained with benzyne itself.[4] (Note: with $n = 1$ and below 20° the reactions are not always completely reproducible.) In contrast, with $n = 2$, it has not been possible to synthesize the corresponding alcohol, whereas it is obtained with a 45% yield in the nonsubstituted series.[4] This result does not seem due to some instability of the corresponding alcoholate, but rather to the fact that cyclization does not take place. A temperature lowering, indeed, only stops the condensation [without the appearance of **4** ($n = 2$)] and a temperature increase only leads to formation of the benzofuran **6** ($n = 2$) at the expense of **3**.

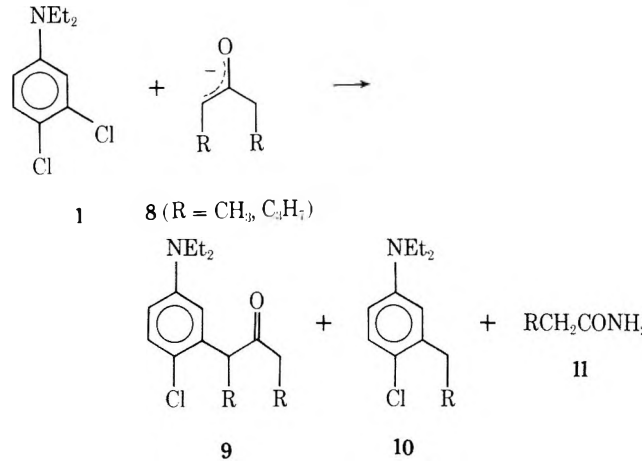
In the case where $n = 3$, observations are much the same as for those described for $n = 2$ in the nonsubstituted series[4] for which, in THF medium, only formation of the alcohol **4** is observed. Here, it has been impossible to avoid some formation of the ketone **3** ($n = 3$).

Lastly, with $n = 4$, we could never prove the existence of a benzocyclobutenol from benzyne itself.[6] Here, contrary to what we expected, the alcohol **4** ($n = 4$) can be obtained with a satisfactory yield.

For the moment, we have no ready rational explanation concerning these different observations. However, one point needs to be emphasized: after cyclization occurs, the alcoholates corresponding to **4** should be more stable than the unsubstituted ones.

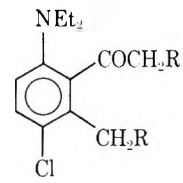
This led us to think that this particular stabilization could perhaps enable us to prepare benzocyclobutenols from aliphatic ketones, a reaction that is not possible with benzyne itself.[7] We shall see below that this hope has been only partially fulfilled.

Scheme II



B. Condensation of Aliphatic Ketone Enolates. Linear ketones condense with **1** according to the reaction of Scheme II.

Amide **11** and chloroaniline **10** are always obtained in equivalent quantities. These derivatives originate from a Haller–Bauer splitting,[8] met before in several cases.[3,9] We shall see in the next paper that the ketone **9**, put again into the reaction medium, undergoes no splitting. Thus we think that **12** is the degradate ketone (we never have been able to isolate it).



12

Various experiments showed us that the condensation results are not markedly dependent on the nature of the base used ($NaNH_2$ or $NaNH_2$–*t*-BuONa), nor on the solvent (THF or DME). We record the best two results we have obtained.

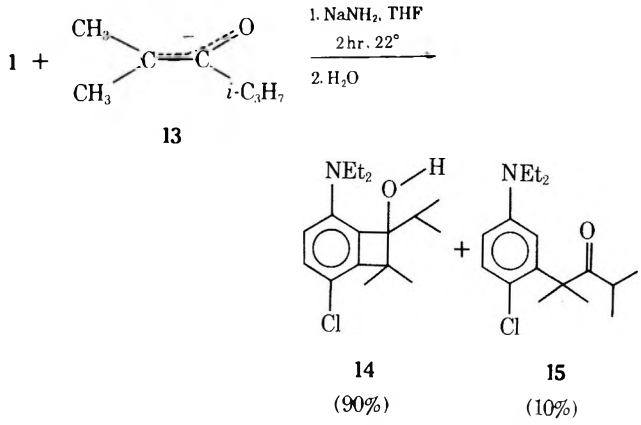
(1) With R = CH_3, in DME, and in the presence of $NaNH_2$–*t*-BuONa an 85% total yield is reached, with a ratio **9**:**10** = 65:35 (25°, 1 hr).

(2) With R = Pr, in THF and in the presence of $NaNH_2$

or $NaNH_2$–*t*-BuONa, an 80% total yield is reached, with **9:10** = 60:40 (25°, 2 hr).

The condensation of diisopropyl ketone enolate (Scheme III) leads to a quite different result shown in Scheme III.

Scheme III



13

14 (90%) 15 (10%)

total yield 60%

The temperature and the nature of the base have little effect upon the total yield and the ratio **14:15.**

The high proportion of alcohol **14** is certainly a consequence of the presence of the *gem*-dimethyl group which favors small ring closure and of the fact that the corresponding alcoholates should be particularly stable.

II. Condensation of Ketone Enolates with Various Aminochlorobenzenes. Taking into account the large variety of aminochloroaromatic compounds previously obtained,[2] it is clear that the applications of the condensations described above could lead to a large number of new products. As this kind of work offers no wide interest from a fundamental basic point of view, we limited ourselves to some typical condensations, in order to examine the generality of the method.

The Case of Morpholino-3,4-dichlorobenzene. Condensations of cycloheptanone and diisopropyl ketone enolates lead to the following results (Scheme IV).

It clearly appears that changes of substituents on the nitrogen atom do not modify the results obtained above, which can be considered as general.

The Case of Diethylamino-3,5-dichlorobenzene. Here we have modified the relative positions of the chlorine atom and the amino group. The results are summarized in Scheme V.

Qualitatively, the results agree with those we have described above; however, the propensity for benzocyclenol formation is much smaller. This may be due to several factors.

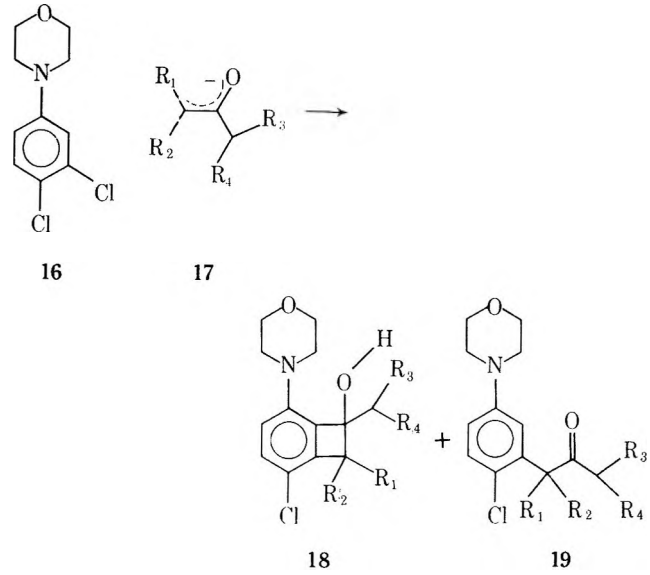
(1) A SNAr reaction may be involved in the formation of **22,** which precludes, of course, any subsequent cyclization.

(2) The stability of alcoholates corresponding to **21** is lower. This is particularly clear from examination of the nature of the products formed from diisopropyl ketone enolate. No alcohol is observed, but rather a transposed ketone **23,** coming from the intermediate alcoholate.

Furthermore, in the case of diisopropyl ketone, a new side reaction appears, namely, the condensation of the enolate with the product of Haller–Bauer splitting, **24,** leading to the alkylamino ketone **25.**

The Case of *N,N,N′,N′*-Tetraalkyl-1,3-diamino-4-chlorobenzene. We have condensed cycloheptanone (the ketone showing the greatest tendency to lead to benzocyclobutenols) with two amines of this type. The only observed reaction is depicted in Scheme VI.

Scheme IV

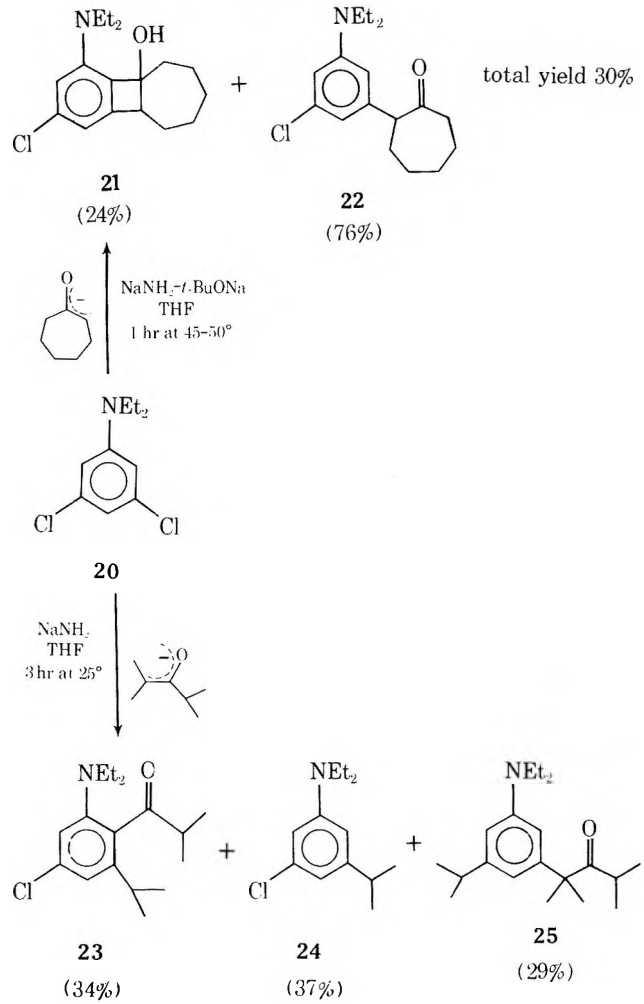


16 17

18 19

	Relative ratios, % 18	19	Total yield, %
$R_1 = R_3 = H$; $R_2, R_4 = (CH_2)_4$	80	20	80
$R_1 = R_2 = R_3 = R_4 = CH_3$	95	5	55

Scheme V



21 (24%) 22 (76%)

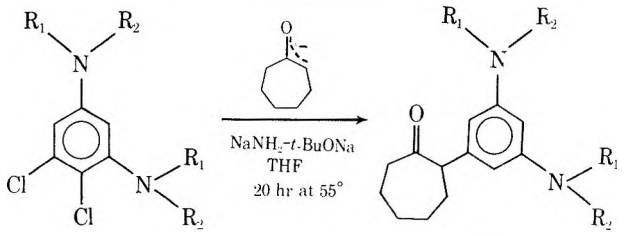
total yield 30%

20

23 (34%) 24 (37%) 25 (29%)

total yield 68%

Scheme VI

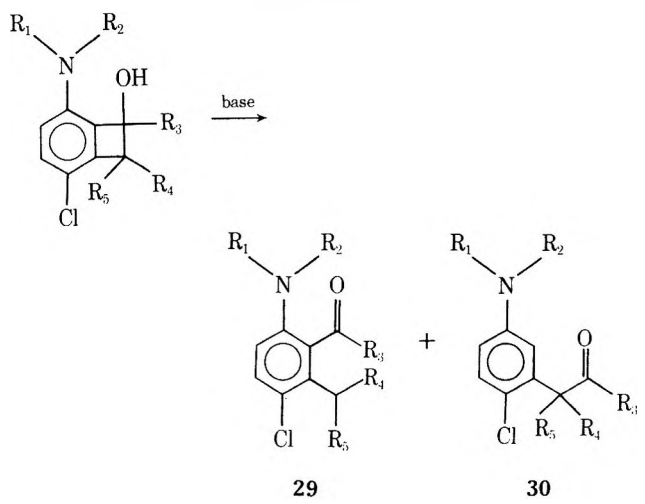


26 27 28

$R_1 = R_2 = Et$
$R_1, R_2 = (CH_2CH_2)_2O$

yield 75–83%

Scheme VII



29 30

An arynic pathway is followed, certainly, but the keto anion formed shows no propensity for cyclization.

Whatever the aminochlorobenzenes studied, condensation products of ketone enolates are always the result of one or several reactions described in Scheme I of the present work.

Taking into account the great number of parameters we cannot control for the moment, the nature of the product(s) formed and, much less, their relative ratios are not easy to predict.

III. Ring Opening of Benzocyclobutenols 4, 14 and 18 by Bases. In previous work[10] we have shown that benzocyclobutenols are opened by the action of bases, to lead to "normal" ketones **30** or "transposed" ketones **29** or their mixture.

We have subjected some of the alcohols described in the present work to the action of bases, in order to determine the reactivity of the new alcohols. Moreover, these reactions should allow us to obtain by an unequivocal way the ketones isolated from the arynic condensation, and, thus, complete their structural assignment. The results are given in Scheme VII and Table II.

the substituents on the aromatic ring. Therefore, in the present state of our knowledge, we can give no consistent explanation for our results.

Practically, this short study shows that the ring opening of these alcohols leads to transposed ketones (particularly benzocyclenones), which were not accessible by direct condensations. These ring openings enable us, too, to increase the yields of "normal" phenyl ketones obtained in the direct condensation. We shall see in the next paper that the latter are interesting starting materials.

Structural Elucidation. Taking into account the reactivity of 1,[2] the alcohols **4** can correspond to the structure shown in Scheme I only. This structure is confirmed by the aromatic part of the NMR spectrum (AB, J = 8–9 Hz) and by the ring opening in basic medium of the alcohols, leading to the α-phenylated ketones **3**. The structure of the latter is determined, too, long-range irradiation at the level of the methylenes of the diethylamino groups always showing a sharpening of the signals of two aromatic protons (ortho and ortho′).[2]

Table II
Ring Opening in Basic Medium of Benzocyclobutenols 4, 14, and 18 in HMPA and DME

Run	R_1	R_2	R_3	R_4	R_5	Solvent	Base	Temp, °C	Time, hr	Total yield, %	30, %	29, %
11	Et	Et	$(CH_2)_3$		H	HMPA	$NaNH_2$	25	1	80	100	0
12	Et	Et	$(CH_2)_3$		H	DME	NaH	25	2	80	0	100
13	Et	Et	$(CH_2)_5$		H	HMPA	$NaNH_2$	25	2	80	100	0
14	Et	Et	$(CH_2)_5$		H	DME[a]	NaH	50[a]	3	85	100	0
15	Et	Et	$(CH_2)_6$		H	HMPA	NaH	25	1	70	0	100
16	Et	Et	*i*-Pr	CH_3	CH_3	HMPA	$NaNH_2$	25	4	95	75	25
17	Et	Et	*i*-Pr	CH_3	CH_3	DME[a]	$NaNH_2$	50[a]	0.5	85	79	21
18	OC_4H_8		$(CH_2)_5$		H	HMPA	$NaNH_2$	25	2.5	80	75	25
19	OC_4H_8		*i*-Pr	CH_3	CH_3	HMPA	$NaNH_2$	25	2	90	55	45
20	OC_4H_8		*i*-Pr	CH_3	CH_3	DME[a]	$NaNH_2$	50[a]	0.6	80	95	5

[a] The ring opening does not occur at room temperature.

It is clear that the behavior of these alcohols is different from that which we have seen with the alcohols lacking substitution on the aromatic ring.[10] With the latter, indeed, HMPA greatly favors ring opening to give "transposed" ketones, whereas in the present work, run no. 15 excepted, the reverse is observed. On the other hand, if polarity of the solvent is decreased, the direction of the ring opening becomes strongly dependent on the nature of the starting alcohol. Let us remember that, in the nonsubstituted series, an increased yield of the "normal" ketone is observed.

The discussion we have given previously[10] about the direction of the ring opening of alcohols shows that many factors may be involved. Moreover, we have here the effects of

The structure of the transposed ketones **5** is deduced from that of the alcohols **4**, taking into account the ring cleavage reaction of the latter.

Conclusion

The present work shows that the observed reactions are satisfactorily explained by the mechanisms established previously, but that substitution in the aromatic ring brings some marked differences in the stability and the reactivity of the products formed, particularly for the benzo-

cyclobutenols. Moreover, we have observed, in two cases, the formation of small amounts of benzofurans.

We shall show in the next paper that the arylation products we have obtained here can be readily cyclized into aminobenzofurans, by what will be a new route to these heterocycles.

Experimental Section

Ir spectra were recorded with a Perkin-Elmer R-457 spectrophotometer; NMR spectra were carried out with Bruker HX 90 MHz, Varian A-60, or Jeol C-60 HL instruments. Chemical shifts are given in 10^{-6} δ units with respect to Me_4Si as internal standard. Analytical VPC analyses were carried out at 220° with a Carlo Erba GI 452 instrument, flame ionization detector, and SE-30 15% column (Chromosorb W DMCS). The silica gels used for liquid phase and thin layer chromatography were Kieselgel 0.05–0.2 mm and Kieselgel G (Merck), respectively, unless otherwise stated. Eluents were petroleum ether (bp 45–60°)–ether mixtures. We used Fluka brocken sodium amide, washed several times and ground in a mortar, under solvent. All reactions were carried out under a nitrogen atmosphere. Melting points are noninstantaneous and uncorrected.

All new compounds have satisfactory carbon, hydrogen, nitrogen and chlorine microanalyses and infrared spectra which were submitted to referees.

General Procedure. Reaction times and temperatures are indicated in Tables I and II and Schemes III, IV, VI, and VII. Reactions were carried out with magnetic stirring.

Reactions Carried Out in the Presence of the Complex Base $NaNH_2$–*t*-BuONa. To a suspension of $NaNH_2$ (125 mmol) in THF (30 ml), was added, dropwise, a solution of *t*-BuOH (25 mmol) in THF (10 ml); the mixture was heated at 40° for 2 hr; the ketone (50 mmol) in solution in THF (10 ml) was added at room temperature, and the mass was heated at 35–40° for 2 hr. To the mixture thus obtained, heated at the desired temperature, was added a solution of the halogenobenzene derivative (18 mmol) in THF (10 ml). After the end of the reaction, the mass was poured onto ice, extracted with ether, and dried over K_2CO_3. After evaporation of the solvents under reduced pressure, the different components of the mixture were separated by chromatography through a silica gel column (unless otherwise stated).

Reactions Carried Out in the Presence of $NaNH_2$. To a suspension of $NaNH_2$ (100 mmol) in THF (40 ml) the ketone (50 mmol) dissolved in THF (10 ml) was added at room temperature, and the mass was heated at 35–40° for 2 hr. The mixture was heated to the desired temperature and the halogeno derivative (18 mmol) dissolved in THF (10 ml) was added dropwise. After the end of the reaction, the mass was poured onto ice, etc. (see above).

Condensation of Ketone Enolates (50 mmol) with 1 in the Presence of a Base. Condensation of Cyclopentanone Enolates. The reaction mixture was fractionated by means of chromatography through a column filled with a 1:1 mixture of neutral alumina–silica gel. The following products were isolated successively.

5 (n = 1): NMR (CCl_4) 0.94 (t, J = 7 Hz, 6 H), 2.45 (m, 2 H), 2.92 (6 H, multiplet, including a q, J = 7 Hz), 1.72 ppm (4 H, multiplet); aromatic protons, AB spectrum, 6.87 (d, J = 9 Hz, 1 H), 7.20 ppm (d, J = 9 Hz, 1 H).

3 (n = 1): NMR ($CDCl_3$) 1.09 (t, J = 7 Hz, 6 H), 2.70–1.50 (6 H, multiplet), 3.00–3.60 ppm (5 H, multiplet including a quartet at 3.23, J = 7.5 Hz); aromatic H's, ABX spectrum, 7.03 (d, J = 8.75 Hz, 1 H), 6.40 (dd, J = 8.5, 3.0 Hz, 1 H), 6.24 ppm (d, J = 3.0 Hz, 1 H). Irradiation at 3.23 ppm results in the sharpening of the dd (6.40) and the d (6.24).

4 (n = 1): mp 122–123°; NMR ($CDCl_3$) 1.11 (t, J = 7 Hz, 6 H), 1.20–2.25 (6 H, multiplet), 3.38 (6 H, multiplet, becoming a 5 H after addition of D_2O), 3.38 ppm (q, J = 7 Hz); aromatic H's, AB spectrum, 6.30 (d, J = 9 Hz, 1 H), 6.99 ppm (d, J = 9 Hz, 1 H).

Condensation of Cyclohexanone Enolate. By means of chromatography through a silica gel column, the following products were isolated successively.

6 (n = 2): mp 25–26°; NMR ($CDCl_3$) 3.22 (q, J = 7 Hz, 4 H), 1.07 (t, J = 7 Hz, 6 H), 2.40–2.80 (4 H, multiplet), 1.65–2.0 ppm (4 H, m); aromatic H's, ABX spectrum, 7.08 (d, J = 9.5 Hz, 1 H), 6.40–6.70 ppm (four signals, 2 H). Irradiations at 3.22 and 2.60 ppm result in the sharpening of the peak (6.40–6.70).

3 (n = 2): NMR ($CDCl_3$) 3.91 (1 H, multiplet), 3.28 (q, J = 7.5 Hz, 4 H), 1.5–2.6 (8 H, multiplet), 1.14 ppm (t, J = 7.5 Hz, 6 H); aromatic protons, ABX spectrum, 7.03 (d, J = 9.5 Hz, 1 H), 6.30–6.50 ppm (multiplet, five signals, 2 H). Irradiation at 3.28 ppm results in the sharpening of the peak (6.30–6.50).

Condensation of Cycloheptanone Enolate. The reaction mixture was fractionned through a column filled with a 1:1 mixture of neutral alumina–silica gel. The following products were isolated successively.

3 (n = 3): NMR ($CDCl_3$) 1.13 (t, J = 7 Hz, 6 H), 1.20–2.90 (10 H, multiplet with strong resonance at 2.37 and 3.13), 3.31 (q, J = 7 Hz, 4 H), 4.22 ppm (multiplet, 1 H); aromatic protons, ABX spectrum, 7.12 (d, J = 9 Hz, 1 H), 6.40–6.60 ppm (multiplet with three peaks, 2 H). Irradiation at 3.31 ppm results in the sharpening of the peaks (6.40–6.60).

4 (n = 3): mp 89–90°; NMR (CCl_4) 1.09 (t, J = 7 Hz, 6 H), 1.20–2.5 (10 h, multiplet with strong resonance at 1.50 and 1.85), 2.48 (s, 1 H, disappears after addition of D_2O), 3.30 ppm (5 H, multiplet with q, J = 7 Hz); aromatic protons, AB spectrum, 6.19 (d, J = 9 Hz, 1 H), 6.84 ppm (d, J = 9 Hz, 1 H).

Condensation of Cyclooctanone Enolate. The reaction mixture was fractioned through a column filled with a 1:1 mixture of neutral alumina–silica gel. The following products were isolated successively.

6 (n = 4): $n^{24}D$ 1.5765; NMR ($CDCl_3$) 3.28 (q, J = 7 Hz, 4 H), 2.34 (multiplet with six peaks, 4 H), 1.10 (t, J = 7 Hz, 6 H), 1.20–1.90 ppm (two multiplets, 8 H); aromatic protons, ABX spectrum, 7.13 (d, J = 8 Hz, 1 H), 6.40–6.70 ppm (2 H, multiplet). Irradiations at 3.28 and 2.34 result in the sharpening of the peaks (6.40–6.70).

3 (n = 4): mp 52–54°; NMR ($CDCl_3$) 3.0–0.75 (18 H, multiplet including a triplet, J = 7.5 Hz at 1.18), 3.33 (q, J = 7 Hz, 4 H), 4.55 ppm (1 H, multiplet); aromatic protons, ABX spectrum, 7.02 (d, J = 8.5 Hz, 1 H), 6.75 (d, J = 3 Hz, 1 H), 6.40 ppm (dd, J = 9, 2.5 Hz). Irradiation at 3.31 ppm results in the sharpening of d (6.75) and dd (6.40).

4 (n = 4): NMR ($CDCl_3$) 1.10 (t, J = 7 Hz, 6 H), 1.20–2.60 (13 H, multiplet becoming a 12 H after addition of D_2O, with strong resonance at 1.58 and 2.30), 2.95 (m, 1 H), 3.38 ppm (split q, J = 7 Hz, 4 H); aromatic H, AB spectrum, 6.32 (d, J = 9 Hz, 1 H), 6.98 ppm (d, J = 9 Hz, 1 H).

Condensation of Diethyl Ketone Enolate. By means of chromatography on silica gel, the following products were isolated successively.

10 (R = CH_3): NMR ($CDCl_3$) 1.10 (t, J = 7 Hz, 6 H), 1.20 (t, J = 7 Hz, 3 H), 2.66 (q, J = 7.5 Hz, 2 H), 3.28 ppm (q, J = 7.5 Hz, 4 H); aromatic protons, ABX spectrum, 7.11 (d, J = 8.5 Hz, 1 H), 6.30–6.5 ppm (2 H, multiplet, three peaks). Irradiation at 3.28 ppm results in the sharpening of the peaks (6.30–6.55).

9 (R = CH_3): NMR ($CDCl_3$) 0.98 (t, J = 7 Hz, 3 H), 1.11 (t, J = 7 Hz, 6 H), 1.33 (d, J = 7 Hz, 3 H), 2.41 (q, J = 7 Hz, 2 H), 3.31 (q, J = 7 Hz, 4 H), 4.22 ppm (q, J = 7 Hz, 1 H); aromatic H, ABX spectrum, 6.35 (d, J = 3 Hz, 1 H), 6.49 (dd, J = 8.75, 3 Hz, 1 H), 7.16 ppm (d, J = 8.75 Hz, 1 H). Irradiation at 3.31 ppm results in the sharpening of d (6.35) and dd (6.49).

Condensation of Dibutyl Ketone Enolate. 10 (R = C_3H_7): NMR ($CDCl_3$) 0.6–2 (13 H, multiplet including a triplet at 1.15, J = 7 Hz), 2.70 (2 H, multiplet), 3.39 ppm (q, J = 7 Hz, 4 H); aromatic protons, ABX spectrum, 7.3 (d, J = 7.5 Hz, 1 H), 6.35–6.85 ppm (multiplet with three peaks, 2 H).

9 (R = C_3H_7): NMR ($CDCl_3$) 2.20–0.70 (20 H, multiplet), 2.33 (t, J = 7 Hz, 2 H), 3.26 (q, J = 7 Hz, 4 H), 4.24 ppm (t, J = 7 Hz, 1 H); ABX spectrum, 7.18 (d, J = 8.5 Hz, 1 H), 6.65–6.35 ppm (multiplet with four peaks, 2 H). Irradiation at 3.26 ppm results in the sharpening of the multiplet (6.65–6.35).

Condensation of Diisopropyl Ketone Enolate. By means of chromatography on silica gel, the following products were isolated successively.

15: mp 58–59°; NMR ($CDCl_3$) 1.05 (d, J = 7 Hz, 6 H), 1.20 (t, J = 7 Hz, 6 H), 1.55 (s, 6 H), 2.77 (septet, J = 7 Hz, 1 H), 3.38 ppm (q, J = 7 Hz, 4 H); aromatic protons, ABX spectrum, 7.12 (d, J = 9 Hz, 1 H), 6.78 (d, J = 3 Hz, 1 H), 6.52 ppm (dd, J = 9, 3 Hz, 1 H). Irradiation at 3.38 ppm results in the sharpening of d (6.78) and dd (6.52).

14: mp 65–66°; NMR ($CDCl_3$) 1.00 (d, J = 7 Hz), 1.05 (t, J = 7.5 Hz) (9 H), 1.22 (d, J = 7 Hz, 3 H), 1.41 (s, 3 H), 1.52 (s, 3 H), 2.10 (s, 1 H, disappears after addition of D_2O), 2.18 (septet, J = 7 Hz, 1 H), 3.13 (sextet, J = 7 Hz, 2 H), 3.55 ppm (sextet, J = 7 Hz, 2 H); aromatic protons, AB spectrum, 6.44 (d, J = 9 Hz, 1 H), 7.00 ppm (d, J = 9 Hz, 1 H).

Condensation of Ketone Enolates (50 mmol) with 16 (18 mmol). Condensation of Cycloheptanone Enolate (50 min at

45–50°). By means of chromatography on silica gel, the following products were isolated successively.

19 [$R_1 = R_3 = H$; $R_2 = R_4 = (CH_2)_4$]: NMR ($CDCl_3$) 0.8–2.4 (8 H, multiplet with strong resonance at 1.96), 2.70 (2 H, multiplet), 3.11 (4 H, multiplet), 3.76 (4 H, multiplet), 4.24 ppm (1 H, multiplet); aromatic protons, ABX spectrum, 7.18 (d, J = 8.5 Hz, 1 H), 6.8 (d, J = 3 Hz, 1 H), 6.69 ppm (dd, J = 8.5, 3 Hz, 1 H). Irradiation at 3.11 ppm results in the sharpening of d (6.8) and dd (6.69); irradiation at 4.24 ppm results in the sharpening of d(6.80).

18 [$R_1 = R_3 = H$; $R_2, R_4 = (CH_2)_4$]: mp 132–134°; NMR ($CDCl_3$) 1.00–2.6 (10 H, multiplet), 2.98 (s, 1 H, disappears after addition of D_2O), 3.00–3.60 (5 H, multiplet), 3.90 ppm (4 H, multiplet); aromatic protons, AB spectrum, 6.68 (d, J = 8.75 Hz, 1 H), 7.30 ppm (d, J = 8.75 Hz, 1 H).

Condensation of Diisopropyl Ketone Enolate (1.5 hr at 25°). **19** ($R_1 = R_2 = R_3 = R_4 = CH_3$): NMR ($CDCl_3$) 1.02 (d, J = 6.5 Hz, 6 H), 1.56 (s, 6 H), 2.71 (septet, J = 6.5 Hz, 1 H), 3.2 ppm (4 H, multiplet); aromatic protons, ABX spectrum, 7.22 (d, J = 8.5 Hz, 1 H), 7.08 (d, J = 2.75 Hz, 1 H), 6.77 ppm (dd, J = 8.5, 2.75 Hz, 1 H). Irradiation at 3.20 ppm results in the sharpening of d (7.08) and dd (6.77); irradiation at 1.56 ppm results in the sharpening of d (7.08).

18 ($R_1 = R_2 = R_3 = R_4 = CH_3$): mp 178–179°; NMR ($CDCl_3$) 1.02 (d, J = 7 Hz, 3 H), 1.27 (d, J = 7 Hz, 3 H), 1.4 (s, 3 H), 1.51 (s, 3 H), 2.20 (septet, J = 7 Hz, 1 H), 2.25 (s, 1 H, disappears after addition of D_2O), 2.96 (2 H, multiplet), 3.38 (2 H, multiplet), 3.78 ppm (4 H, multiplet), aromatic H's AB spectrum, 6.47 (d, J = 8.5 Hz, 1 H), 7.00 ppm (d, J = 8.5 Hz, 1 H).

Condensation of Ketone Enolates (50 mmol) with 20 (18 mmol). Condensation of Cycloheptanone. By means of chromatography on silica gel, the following products were isolated successively.

22: NMR ($CDCl_3$) 1.16 (t, J = 7 Hz, 6 H), 1–3 (10 H, multiplet with strong resonance at 2.02 and 2.60), 3.37 ppm (5 H, multiplet including a quartet, J = 7 Hz); aromatic protons, AB_2 spectrum, 6.53 (t, J = 2 Hz, 1 H), 6.63 (d, J = 2 Hz, 2 H).

21: NMR ($CDCl_3$) 1.15 (t, J = 7.5 Hz, 6 H), 1–2.5 (10 H, multiplet with strong resonance at 1.92 and 1.57), 3.40 ppm (6 H, multiplet, becoming 5 H after addition of D_2O, including quartet, J = 7 Hz), aromatic protons, AB spectrum, 6.60 (d, J = 3 Hz, 1 H), 6.68 ppm (d, J = 3 Hz, 1 H).

Condensation of Diisopropyl Ketone Enolate. By means of chromatography on silica gel, the following products were isolated successively.

24: NMR ($CDCl_3$) 1.14 (t, J = 6 Hz, 6 H), 1.24 (d, J = 7 Hz, 6 H), 2.85 (septet, J = 7 Hz, 1 H), 3.36 ppm (q, J = 7 Hz, 4 H); aromatic protons 6.50–6.75 ppm (3 H, multiplet).

23: NMR ($CDCl_3$) 0.99 (t, J = 7 Hz, 6 H), 1.12 (d, J = 7 Hz, 6 H), 1.21 (d, J = 7 Hz, 6 H), 2.69 (septet, J = 7 Hz, 1 H), 2.96 (q, J = 7 Hz, 4 H), 3.20 ppm (septet, J = 7 Hz, 1 H); aromatic H, AB spectrum, 6.94 (d, J = 2 Hz, 1 H), 7.06 ppm (d, J = 2 Hz, 1 H). Irradiation at 3.20 ppm results in the sharpening of d (6.94); irradiation at 2.69 ppm results in sharpening of d (7.06).

25: NMR ($CDCl_3$) 0.90 (split d, J = 7 Hz, 6 H), 1.16 (split t, J = 7 Hz, 6 H), 1.23 (d, J = 7 Hz, 6 H), 1.46 (s, 6 H), 2.74 (septet, J = 7 Hz, 2 H), 3.32 ppm (split q, J = 7 Hz, 4 H); aromatic protons 6.62–6.25 ppm (3 H, multiplet).

Condensation of Ketone Enolates (50 mmol) with 1.3-Bis(*N,N*-dialkylamino)-4-chlorobenzene (18 mmol) (26). Condensation of Cycloheptanone Enolate. After filtration through a silica gel column, the following products were isolated.

27 [α-3.5-bis(*N,N*-diethylamino)phenylcycloheptanone]: NMR (CCl_4) 1.11 (t, J = 7.5 Hz, 12 H), 2.8–1 (10 H, multiplet), 3.28 ppm (5 H, multiplet including quartet, J = 7.5 Hz); aromatic protons, A_3 spectrum, 5.87 ppm (s, 3 H).

28 [α-3.5-di(*N*-morpholino)phenylcycloheptanone]: mp 117–118°; NMR ($CDCl_3$) 1–3 (10 H, multiplet), 3.17 (8 H, multiplet), 3.5–3.7 (1 H, multiplet), 3.82 ppm (8 H, multiplet); aromatic protons, A_3 spectrum, 6.33 ppm(s, 3 H).

Basic Ring Cleavage of Benzocyclobutenols 4, 14, and 18. Solvents, reaction times, and temperatures are indicated in Table II. An excess of base was used.

Ring cleavage products were described above, except for the following.

29 [$R_1 = R_2$ = Et; $R_3, R_4 = (CH_2)_6$; R_5 = H]: mp 56–57°; NMR ($CDCl_3$) 0.95 (t, J = 7.5 Hz, 6 H), 2.5–0.6 (10 H, multiplet) 2.5–3.8 ppm (8 H, multiplet including quartet at 2.93, J = 7.5 Hz); aromatic H, AB spectrum, 6.93 (d, J = 8.75 Hz, 1 H), 7.30 ppm (d, J = 8.75 Hz, 1 H).

29 ($R_1 = R_2$ = Et; R_3 = *i*-Pr; $R_4 = R_5 = CH_3$): NMR ($CDCl_3$) 0.8–1.5 (18 H, multiplet including t at 0.98, J = 7.5 Hz, d at 1.17, J = 7.5 Hz, d at 1.40, J = 7.5 Hz), 2.5–3.5 (6 H, multiplet including a quartet at 2.90, J = 7.5 Hz); aromatic H, AB spectrum, 6.92 (d, J = 9 Hz, 1 H), 7.24 (d, J = 9 Hz, 1 H).

29 [$R_1, R_2 = OC_4H_8$; $R_3, R_4 = (CH_2)_5$; R_5 = H]: mp 114–116°; NMR ($CDCl_3$) 1–2 (10 H, multiplet), 2.2–3.5 (8 H, multiplet), 3.82 ppm (4 H, multiplet); aromatic H, 7.12 (d, J = 8 Hz, 1 H), 7.52 ppm (d, J = 8 Hz, 1 H).

29 ($R_1, R_2 = OC_4H_8$; R_3 = *i*-Pr; $R_4 = R_5 = CH_3$): mp 65–67°; NMR ($CDCl_3$) 1.21 (d, J = 7 Hz, 6 H), 1.32 (d, J = 7 Hz, 6 H), 2.3–4 ppm (10 H, multiplet with strong resonance at 2.95 and 3.80); aromatic protons, AB spectrum, 7.15 (d, J = 7.5 Hz, 1 H), 7.46 ppm (d, J = 7.5 Hz, 1 H).

Acknowledgments. We are grateful to K. G. Taylor, visiting Professor in Nancy University, and the referees for discussing this manuscript, to Produits Chimiques Ugine Kuhlmann for financial support, and to M. Dorme (Laboratoire de Microanalyse, Paris VI) for the microanalyses.

Registry No.—**1**, 55039-58-2; **2** (n = 1), 55886-83-4; **2** (n = 2), 55886-84-5; **2** (n = 3), 55886-85-6; **2** (n = 4), 55886-86-7; **3** (n = 1), 55887-02-0; **3** (n = 2), 55887-03-1; 3 (n = 3), 55887-04-2; **3** (n = 4), 55887-05-3; **4** (n = 1), 55887-06-4; **4** (n = 3), 55887-07-5; **4** (n = 4), 55887-08-6; **5** (n = 1), 55887-09-7; **6** (n = 2), 55887-10-0; **6** (n = 4), 55887-11-1; **8** (R = CH_3), 29263-72-7; **8** (R = C_3H_7), 55887-12-2; **9** (R = CH_3), 55887-13-3; **9** (R = C_3H_7), 55887-14-4; **10** (R = CH_3), 55887-15-5; **10** (R = C_3H_7), 55887-16-6; **13**, 55887-17-7; **14**, 55887-18-8; **15**, 55887-19-9; **16**, 55039-68-4; **18** [$R_1 = R_3 = H$; $R_2, R_4 = (CH_2)_4$], 55887-20-2; **18** ($R_1 = R_2 = R_3 = R_4 = CH_3$), 55887-21-3; **19** [$R_1 = R_3 = H$; $R_2, R_4 = (CH_2)_4$], 55887-22-4; **19** ($R_1 = R_2 = R_3 = R_4 = CH_3$), 55887-23-5; **20**, 55039-56-0; **21**, 55887-24-6; **22**, 55887-25-7; **23**, 55887-26-8; **24**, 55887-27-9; **25**, 55887-28-0; **26** ($R_1 = R_2$ = Et), 55039-60-6; **26** [$R_1, R_2 = (CH_2CH_2)_2O$], 55039-70-8; **27**, 55887-29-1; **28**, 55887-30-4; **29** [$R_1 = R_2$ = Et; $R_3, R_4 = (CH_2)_6$; R_5 = H], 55887-31-5; **29** ($R_1 = R_2$ = Et; R_3 = *i*-Pr; $R_4 = R_5 = CH_3$), 55887-32-6; **29** [$R_1, R_2 = OC_4H_8$; $R_3, R_4 = (CH_2)_5$; R_5 = H], 55887-33-7; **29** ($R_1, R_2 = OC_4H_8$; R_3 = *i*-Pr; $R_4 = R_5 = CH_3$), 55887-34-8; $NaNH_2$, 7782-92-5; *t*-BuOH, 75-65-0.

References and Notes

(1) Taken, with ref 2, from the Thèse de Doctorat d'Etat of L. Lalloz, University of Nancy, 1975.
(2) Previous paper: (a) P. Caubere and L. Lalloz, *Bull. Soc. Chim. Fr.*, 1983 (1974); (b) ibid., 1989 (1974); (c) ibid., 1996 (1974).
(3) P. Caubere, G. Guillaumet, and M. S. Mourad, *Bull. Soc. Chim. Fr.*, 3493 (1973), and references cited therein.
(4) P. Caubere, N. Derozier, and B. Loubinoux, *Bull. Soc. Chim. Fr.*, 302 (1971).
(5) P. Caubere, *Acc. Chem. Res.*, **7**, 301 (1974).
(6) P. Caubere, G. Guillaumet, and M. S. Mourad, *Tetrahedron*, **29**, 1857 (1973).
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Arynic and SNAr Reactions of Polyhalogenobenzenes. V.[1,2] Synthesis of Benzofurans

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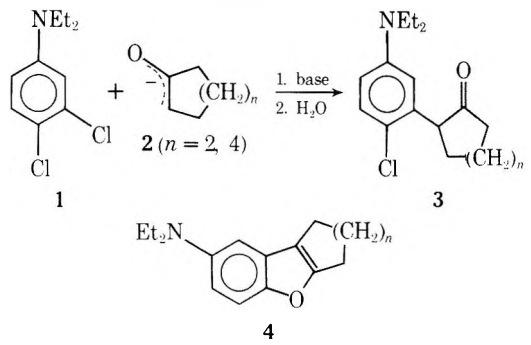
Received January 28, 1975

The formation of benzofurans during the condensation of ketone enolates on dialkylamino dichlorobenzenes in the presence of bases in aprotic medium was studied. It was shown that the dialkylamino monochloro phenyl ketones, formed during these condensations, are the intermediates. With suitable experimental conditions the heterocyclic compounds are easily synthesized from dialkylamino dichlorobenzenes in one or two steps. Furthermore, it is demonstrated that this new synthesis of benzofurans is general and applicable to polyhalogenobenzenes starting materials.

In the previous paper, we have observed the formation of small amounts of benzofurans (**4**) in the course of the condensation of cyclohexa- and cyclooctanone enolates with *N,N*-diethylamino-3,4-dichlorobenzene in the presence of bases (Scheme I).

Scheme I



In the present work, we study the mode of formation of these heterocycles, and we attempt to make such a reaction suitable for synthesis.

Results

It seemed reasonable to suppose that **4** originated from **3** under the influence of bases. After having verified this hypothesis by preliminary experiments, we have undertaken the study of these cyclizations. We shall further discuss their mechanism.

Cyclization of Phenylcyclanone Enolates 5 (Scheme II). Synthesis of 2,3-Polymethylene-5-diethylamino-benzofurans. We have carried out many systematic runs, varying time, temperature, base, solvent, and dilution. Table I reports only the most interesting results.

From many experiments, carried out in other instances, the following facts can be pointed out.

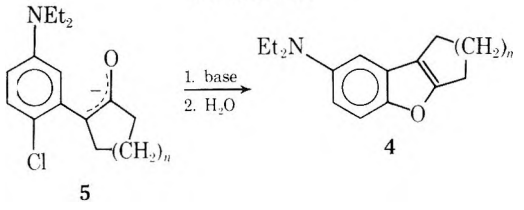
(1) Base and solvent should be properly chosen. In THF, complex base $NaNH_2$–*t*-$BuONa$[3] should be used. In HMPA–THF, $NaNH_2$ alone should be used; the required quantity of base and reaction time are then markedly decreased. However, for $n = 1$ in HMPA, it is not possible to carry out the cyclization of the arylcyclopentanone, unstable and destroyed in this solvent.[4]

(2) Dilution plays an important part, particularly for $n = 4$. A decrease of dilution, in regard to the values of Table I, generally results in a decrease of the yield, which likely may be attributed to some intermolecular reactions.

(3) Without base, considerable decrease of the yield is observed; thus, in the conditions of run 5, but without sodium amide, no benzofuran is obtained at all.

Practically, Table I shows that compounds **4** are readily accessible from ketones **3**. Taking into account the results of the previous paper, we can consider two pathways for the synthesis of benzofurans (Scheme III).

Scheme II



Scheme III

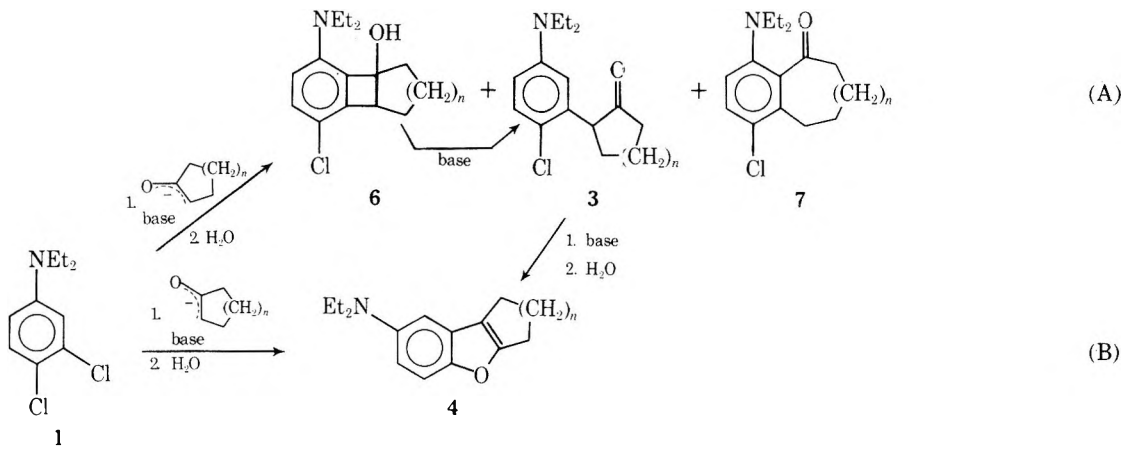


Table I
Cyclization of Enolates 5 into Benzofurans 4 in the Presence of a Base

Run	n	5, mmol	Base (mmol)[a]	Solvent (cm^3/mmol of 5)	Temp, °C	Time, hr	3 recovered, %	4, %
1	1	8	$NaNH_2$-*t*-BuONa (32–16)	THF (13)	47	64	4	76
2	2	9	$NaNH_2$-*t*-BuONa (27–13.5)	THF (3)	52	16	0	88
3	2	9	$NaNH_2$ (18)	THF–HMPA 3:1 (8)	50	1.5	0	79
4	3	4.6	$NaNH_2$-*t*-BuONa (20–10)	THF (13)	46	24	3	76
5	3	7	$NaNH_2$ (14)	THF–HMPA 3:1 (13)	65	0.75	0	79
6	4	6	$NaNH_2$-*t*-BuONa (24–12)	THF (13)	47	20	5	75
7	4	7.5	$NaNH_2$ (15)	THF–HMPA 3:1 (13)	65	2	0	45

[a] The quantity of $NaNH_2$ indicated is the leading sodium amide after formation of tertiobutylate and enolate. (See Experimental Section.)

Table II
Condensation of Enolates 2 (50 mmol) with 1 (18 mmol) in the Presence of Base in 240 ml of Solvent

Run	n	Base (mmol)	Solvent	Experimental conditions	4, %[a]
8	1	$NaNH_2$-*t*-BuONa (110–55)	THF	2 hr at 20° then 48 hr at 50°	40
9	2	$NaNH_2$-*t*-BuONa (110–55)	THF	2 hr at 20-25° then 17 hr at 52°	48
10	2	$NaNH_2$ (65)	THF then THF-HMPA 3:1	3 hr at 20-25° then 2.5 hr at 50°	53
11	3	$NaNH_2$ (65)	THF then THF-HMPA 3:1	2 hr at 20-25° then 2.5 hr at 50°	51
12	4	$NaNH_2$ (65)	THF then THF-HMPA 3:1	50 min at 45-50° then 2.5 hr at 50°	32

[a] Yields of isolated products, calculated with respect to the starting chloro amine.

Route B may be reasonably considered: in basic medium and in a suitable solvent, indeed, alcohols **6** are opened to lead mainly to **3**;[2] and moreover, the formation of **7** may be made very small or totally avoided.[2]

Table II summarizes the essential results of a study carried out with the purpose of realizing, in practice, route B.

It is clear that 5-(*N*,*N*-diethylamino)benzofurans may be directly obtained from the dichloro compound **1**, with quite satisfactory yields. Various runs, not reported here, show that the choice of experimental conditions, and especially of the "base–solvent" system, is important. Thus, for $n = 1$, use of $NaNH_2$ in THF–HMPA mixture led to formation of only traces of benzofurans, whereas for $n = 3$ and 4 this is the only efficient system. On the other hand, for $n = 2$, both media are suitable.

In conclusion, taking into account what we described in the preceding paper, it appears that, as far as yields are concerned, routes A and B are comparable. Route B is preferable since it is carried out in *only one* pot.

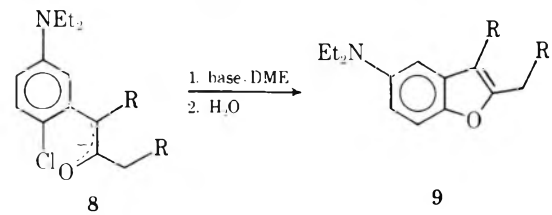
Cyclization of Phenyl Ketone Enolates 8 (Scheme IV). Ketones of this type can be prepared by means of the reactions described in the preceding paper. The conditions used for the cyclizations of arylcyclanones are not suitable here, and some preliminary runs led us to use the system $NaNH_2$–*t*-BuONa in DME. The results are summarized in Scheme IV and Table III.

Temperature and amounts of base lower than those mentioned in Table III strongly decrease the yields.

Table III
Cyclization of 8 (10 mmol) in the Presence of $NaNH_2$ (50 mmol)–*t*-BuONa (25 mmol) in DME (130 ml)

Run	R	Temp, °C	Time, hr	8-H recovered, %	9, %	9 + 8-H, %
13	CH_3	75	20	13	56	69
14	*n*-C_3H_7	80	21	0	55	55

Scheme IV



8 9

On the other hand, attempts at direct cyclization (route B of the preceding section) have been so far unsuccessful.

Cyclization of Phenyl Ketone Enolates 10. The starting ketone has no enolizable benzylic hydrogen atom. In basic conditions the formed enolate **10** is cyclized, following the reaction of Scheme V.

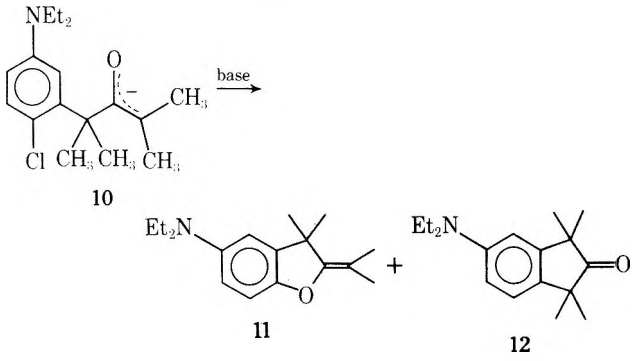
After short systematic studies, we have retained, as interesting for synthesis, the runs reported in Table IV.

Run 16 is satisfactory for the synthesis of **11** and run 15 is a way of formation of the ketone **12**.

Table IV
Cyclization of 10 (7 mmol) in the Presence of a Base in 90 ml of Solvent

Run	Base (mmol)	Solvent	Temp, °C	Time, hr	11, %	12, %	Total yield, %
15	$NaNH_2$-*t*-BuONa (28–14)	THF or DME	50–60	21–23	65	35	75–80
16	$NaNH_2$ (14)	THF–HMPA 3:1	57	3	82	18	75

Scheme V



Attempts at direct syntheses of 11 and 12 from the dichloro derivative 1 were synthetically unsuccessful.

Discussion

With 13 and 14 being the intermediates corresponding, respectively, to ketones enolizable or not enolizable at the benzylic position, two reaction paths (SNAr or AE) (Scheme VI) may be a priori considered.

We cannot discard the occurrence of some SNAr, particularly in the presence of HMPA, which favors, at the same time, these reactions[5] and O-alkylations of enolates.[6] However, we have seen that in the absence of base, cyclization yields were *strongly decreased*. It seems therefore quite reasonable to think that the arynic mechanism is markedly preponderant.

On the other hand, competition between O- and C-arylations is possible in all cases. When the ketone has a benzylic hydrogen atom, C-arylation would lead to an instable benzocyclopropene, and O-arlyation only is observed. If there is no benzylic hydrogen atom, competition becomes effective, and a mixture of ketone and oxygen heterocycle is obtained. According to what we expected,[6] O-arylation is favored in HMPA (cf. Table IV).

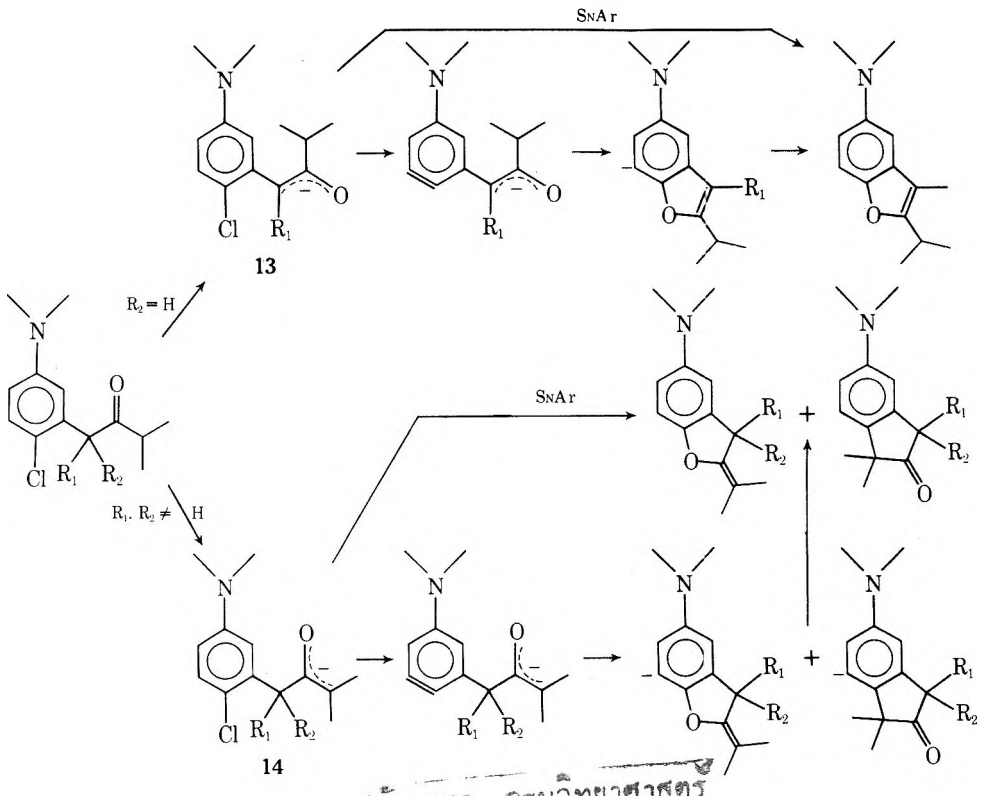
Lastly, we may compare these reactions with arynic heterocyclizations of amides and thioamides, carried out in liquid NH_3.[7-9] Curiously, in this solvent, aryl 2-ketones lead to an indolic heterocycle[7,8] rather than to a benzofuran.

Synthesis of 6-Morpholinobenzofurans. If the hypothesis about the intervention of an aryne in the formation of benzofurans 4 is true, it should be possible to carry out the synthesis of 6-aminobenzofurans from morpholino-2,3-dichlorobenzene (15) (Scheme VII). This chloro derivative has been prepared previously, by condensing morpholine with 1,2,3-trichlorobenzene,[10] and its reactivity is well known.[11]

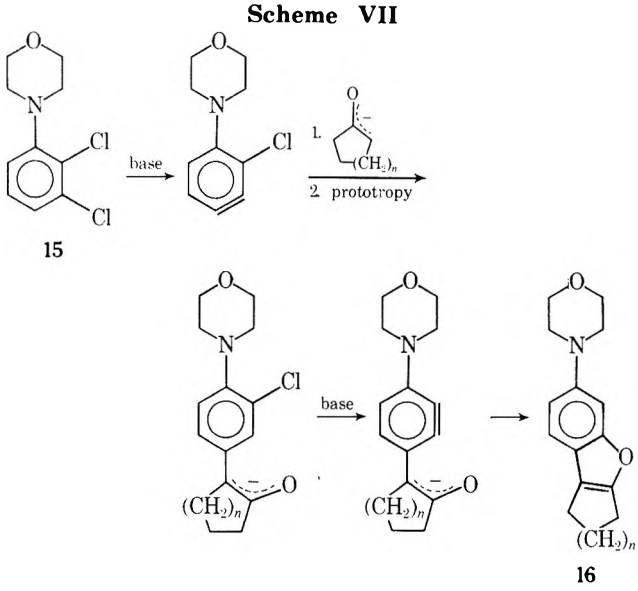
We have carried out the condensations of cyclohexa- and cycloheptanone enolates. We give, in Table V, the best results.

Here, the yields are lower than in the synthesis of 5-diethylaminobenzofurans. The observed difference may have its origin together in the lower reactivity of 15 compared with that of 1[11] and in the interference of some SNAr reaction of 1.

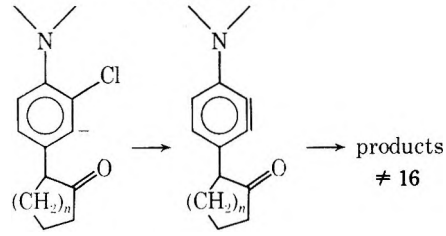
Scheme VI



Scheme VII



Scheme VIII



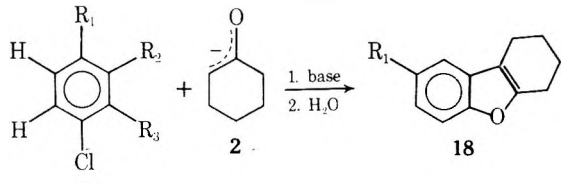
Moreover, a part of the ketocarbanionic intermediate may lose chloride ion more rapidly than prototropy occurs (Scheme VIII).

Formation of benzofuran **16** from the keto aryne thus generated is hardly likely.

Conclusion

These cyclizations into benzofurans are, in fact, quite general. As an example, we have condensed cyclohexanone with the three following chloro derivatives: 3,4-dichloroanisole, 1,2- and 1,3-dichlorobenzene. The results are summarized in Scheme IX and Table VI.

Scheme IX



We need not emphasize the fact that this new application of the condensation of ketone enolates with arynes, adding to those we have described before,[12] is an interesting source of synthesis for widely diversified aromatic oxygenated heterocycles.

From a more particular point of view, 1,2,4- and 1,2,3-trichlorobenzene being the starting material in the synthesis of many dichlorinated dialkylanilines,[10] it appears that these trichloro derivatives of benzene may find versatile applications in synthesis.

Experimental Section

Ir spectra were recorded with a Perkin-Elmer R 457 spectrophotometer; NMR spectra were carried out with Brucker HX 90 MHz, Varian A-60, or Jeol C-60 HL instruments; chemical shifts are given in 10^{-6} units with respect to Me_4Si as internal standard. Analytical VPC was carried out at 220° with a Carlo Erba GI 452 instrument, flame-ionization detectors, SE-30 15% column (Chromosorb W DMCS). The silica gels used for liquid phase and thin layer chromatography were Kieselgel 0.05–0.2 mm and Kieselgel G (Merck), respectively. Eluents were petroleum ether (bp 45–60°)–ether mixtures. We used Fluka sodium amide, washed several times, and finely ground with a mortar, under solvent. Melting points (uncorrected) were measured with a platine. All new compounds have satisfactory carbon, hydrogen, nitrogen, and chlorine microanalyses and were submitted to referees.

Table V
Cyclization of 15 (10 mmol) and 2 (27.5 mmol) in the Presence of Base in THF (130 ml)

Run	n	Base (mmol)	Conditions	16, %
17	2	$NaNH_2$-*t*-BuONa (35–17.5)	16 hr to 38° then 2 hr to 55°	30
18	3	$NaNH_2$-*t*-BuONa (35–17.5)	21 hr to 45–50°	11

Table VI
Condensation of 17 and 2 in THF in the Presence of $NaNH_2$-*t*-BuONa[a]

Run	R_1	R_2	R_3	Yield, % 18
19	CH_3O	H	Cl	29
20	H	Cl	H	27
21	H	H	Cl	25

[a] For experimental conditions, see Experimental Section.

General Procedure. The quantities involved, as well as reaction times and temperature, are indicated in Tables I–VI. Operations were carried out with magnetic stirring, under nitrogen atmosphere.

The general procedure is exemplified with the following examples.

Run 8 (Table II). *t*-BuOH (55 mmol) in THF (10 ml) was added dropwise to a suspension of 125 mmol of $NaNH_2$ in THF (30 ml); the mixture was heated at 45–50° for 2 hr; the ketone (50 mmol) diluted in THF (10 ml) was added at a temperature <20°, and the mass was heated at 40° for 2 hr. The mixture thus obtained was heated to the desired temperature, and, after addition of 170 ml of THF, the reagent (18 mmol) diluted in THF (20 ml) was added dropwise (total quantity of THF 240 cm^3). After the end of the reaction, the mass was poured on ice, extracted with ether, and dried over K_2CO_3. After evaporation of the solvents under reduced pressure, the mixture was simply filtered over a silica gel column.

Run 10. To a suspension of $NaNH_2$ (115 mmol) in THF (30 ml), the ketone (50 mmol) diluted in THF (10 ml) was added at a temperature below 20°, and the mass was heated at 40° for 2 hr. The mixture being heated at the desired temperature, the reagent (18 mmol) was added dropwise with 50 ml of THF. After a time mentioned in Table II (3 hr at 20–25°) 60 cm^3 of HMPA, diluted in 90 cm^3 of THF, was added. After the end of the reaction (25 hr at 50°), the mass was poured onto ice, etc. (see above).

Isolated Products. 5-(*N*,*N*-Diethylamino)-2,3-trimethylenebenzofuran (**4**, $n = 1$): mp 29–30°; $n^{24}D$ 1.5822; NMR ($CDCl_3$) aliphatic H's 3.29 (q, $J = 7$ Hz, 4 H), 1.11 (t, $J = 7$ Hz, 6 H), 2.71 ppm (m, 6 H); aromatic H's, ABX spectrum, 7.26 (dd, $J = 8.7$, 1 Hz, 1 H), 6.60–6.75 ppm (three signals, 2 H). Irradiations at 3.29 and 2.71 ppm result in the sharpening of the peaks (6.60–6.75).

5-(*N*,*N*-Diethylamino)-2,3-tetramethylenebenzofuran (**4**, $n = 2$): see previous paper.

5-(*N*,*N*-Diethylamino)-2,3-pentamethylenebenzofuran: NMR ($CDCl_3$) aliphatic H's 3.29 (q, $J = 7$ Hz, 4 H), 1.10 (t, $J = 7$ Hz, 6 H), 2.83 (m, 2 H), 2.61 (m, 2 H), 1.77 ppm (m, 6 H); aromatic H's, ABX spectrum, 7.21 (d, $J = 8.5$ Hz, 1 H), 6.65–6.80 ppm (m, four signals, 2 H). Irradiations at 3.29 ppm result in the sharpening of the peaks (6.65–6.80).

5-(*N*,*N*-Diethylamino)-2,3-hexamethylenebenzofuran (**4**, $n = 4$): see previous paper.

5-(*N*,*N*-Diethylamino)-2-ethyl-3-methylbenzofuran (**9**, R =

CH_3): NMR ($CDCl_3$) aliphatic H's 3.30 (q, J = 7.5 Hz, 4 H), 2.71 (q, J = 7.5 Hz, 2 H), 2.11 (s, 3 H), 1.27 (t, J = 7.5 Hz, 3 H), 1.11 ppm (t, J = 7.5 Hz, 6 H); aromatic H's 7.20 (d, J = 9.5 Hz, 1 H), 6.85–6.65 ppm (m, three signals, 2 H). Irradiations at 3.30 ppm result in the sharpening of the peaks (6.85–6.65).

5-(*N,N*-Diethylamino)-2-butyl-3-propylbenzofuran (**9**, R = *n*-C_3H_7): NMR ($CDCl_3$) aliphatic H's 2.0–0.65 (m, 18 H), 2.57 and 2.70 (2 t, J = 7 Hz, 4 H), 3.32 ppm (q, J = 7 Hz, 4 H); aromatic H's, ABX spectrum, 7.25 (d, J = 8 Hz, 1 H), 6.83 (d, J = 1.5 Hz, 1 H), 6.73 ppm (dd, J = 8.5, 2.5 Hz, 1 H). Irradiations at 3.32 ppm result in the sharpening of the d (6.83) and the dd (6.73).

5-(*N,N*-Diethylamino)-2-isopropylidene-3-dimethyldihydro-2,-3-benzofuran (**11**): NMR ($CDCl_3$) aliphatic H's 3.23 (q, J = 7 Hz, 4 H), 1.10 (t, J = 7 Hz, 6 H), 1.52 (s, 6 H), 1.79 ppm (s, 6 H); aromatic H's, ABX spectrum, 6.73 (d, J = 9.5 Hz, 1 H), 6.56 (d, J = 2.5 Hz, 1 H), 6.52 ppm (dd, J = 9.5, 2.5 Hz, 1 H); ir (film) $\nu_{C=C}$ 1705 cm^{-1}.

5-(*N,N*-Diethylamino)-1,3-tetramethylbenzo-3a,7a-cyclopentanone (**12**): NMR ($CDCl_3$) aliphatic H's 3.42 (q, J = 7 Hz), 1.18 (t), 1.26 (s), 1.33 ppm (s) (18 H); aromatic H's 7.17 (d, J = 8.25 Hz, 1 H), 6.85–6.50 ppm (m, three signals, 2 H); ir (film) 1750 cm^{-1}.

6-Morpholino-2,3-tetramethylenebenzofuran (**16**, n = 2): mp 122–123°; NMR ($CDCl_3$) aliphatic H's 1.82 (m, 4 H), 2.62 (m, 4 H), 3.10 (m, 4 H), 3.82 ppm (m, 4 H); aromatic H's 7.27 (d, J = 8.5 Hz, 1 H), 6.96 (d, J = 2 Hz, 1 H), 6.85 ppm (dd, J = 8, 2 Hz, 1 H). Irradiations at 3.10 ppm result in the sharpening of the d (6.96) and of the dd (6.85). Irradiations at 2.62 ppm result in the sharpening of the d (7.27).

6-Morpholino-2,3-pentamethylene-2,3-benzofuran (**16**, n = 3): mp 109–110°; NMR ($CDCl_3$) aliphatic H's 1.80 (m, 6 H), 2.66 (m, 2 H), 2.88 (m, 2 H), 3.13 (m, 4 H), 3.86 ppm (m, 4 H); aromatic H's, ABX spectrum, 7.27 (d, J = 8 Hz, 1 H), 7.0–6.8 ppm (m, AB part, three signals, 2 H). Irradiation at 3.13 ppm results in the sharpening of the AB part. Irradiation at 2.66 ppm results in the sharpening of the X part of the spectrum.

Condensation of 17 (20 mmol) and 2 (40 mmol) in THF (260 cm^3) with $NaNH_2$ (40 mmol) and *t*-BuONa (20 mmol). Experimental conditions. Run 19, 25 then 50°; 2.5 then 24 hr; runs 20 and 21, 25 then 50°; 1 then 3 hr.

5-Methoxy-2,3-tetramethylenebenzofuran (**18**, R_1 = CH_3O): NMR ($CDCl_3$) aliphatic H's 1.80 (m, 4 H), 2.60 (m, 4 H), 3.75 ppm (s, 3 H); aromatic H's, ABX spectrum between 6.60 and 7.35 ppm.

2,3-Tetramethylenebenzofuran (**18**, R_1 = H): NMR ($CDCl_3$) m between 1.5 and 1.2 (4 H), m (2.3–3, 4 H), m (7–7.75, 4 H).

Acknowledgments. We are grateful to K. G. Taylor, visiting Professor in Nancy University, and the referees for discussing this manuscript, to Produits Chimiques Ugine Kuhlmann for financial support, and to M. Dorme (Laboratoire de Microanalyse, Paris VI) for the microanalyses.

Registry No.—**1**, 55039-58-2; **2** (n = 1), 55886-83-4; **2** (n = 2), 55886-84-5; **2** (n = 3), 55886-85-6; **2**(n = 4), 55886-86-7; **4** (n = 1), 55886-87-8; **4** (n = 3), 55886-88-9; **5** (n = 1), 55886-89-0; **5** (n = 2), 55886-90-3; **5** (n = 3), 55886-91-4; **5** (n = 4), 55886-92-5; **8** (R = CH_3), 55886-93-6; **8** (R = *n*-C_3H_7), 55886-94-7; **9** (R = CH_3), 55886-95-8; **9** (R = *n*-C_3H_7), 55886-96-9; **10**, 55886-97-0; **11**, 55886-98-1; **12**, 55886-99-2; **15**, 55039-67-3; **16** (n = 2), 55887-00-8; **16** (n = 3), 55887-01-9; **17** (R_1 = CH_3O; R_2 = R_3 = H), 623-12-1; **17** (R_1 = R_3 = H; R_2 = Cl), 541-73-1; **17** (R_1 = R_2 = H; R_3 = Cl), 95-50-1; **18** (R_1 = CH_3O), 7291-77-2; **18** (R_1 = H), 13130-19-3.

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High-Dilution Cyclization of Polyoxapentacosanodinitriles[1]

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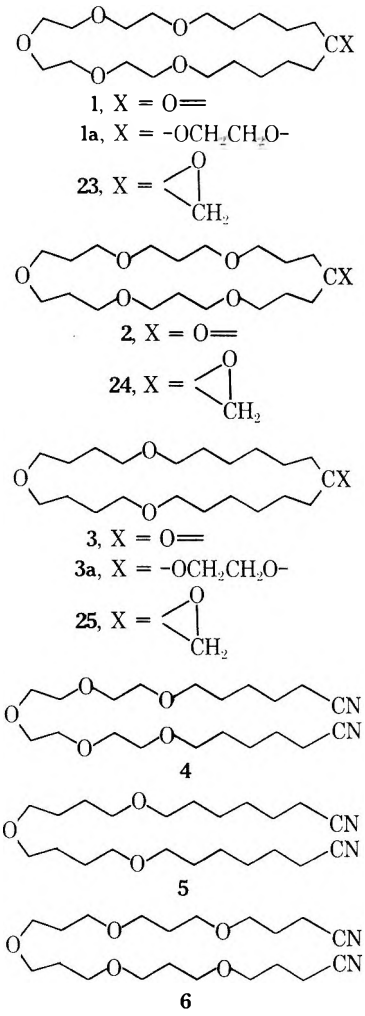
Received January 10, 1975

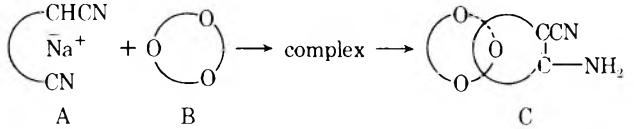
The syntheses of 7,10,13,16,19-pentaoxapentacosanodinitrile (**4**), 8,13,18-trioxapentacosanodinitrile (**5**), and 5,9,13,17,21-pentaoxapentacosanodinitrile (**6**), and the Ziegler-type cyclization of these nitriles by an improved method, are described. The cyclized products were converted into 7,10,13,16,19-pentaoxacyclotetracosanone (**1**), 8,13,18-trioxacyclotetracosanone (**3**), and 5,9,13,17,21-pentaoxacyclotetracosanone (**2**), respectively. From **1**, **2**, and **3** were prepared the amino alcohols 1-piperidinomethyl-7-10-13-16-19-pentaoxacyclotetracosanol (**26**), 1-piperidinomethyl-5,9,13,17,21-pentaoxacyclotetracosanol (**27**), and 1-piperidinomethyl-8,13,18-trioxacyclotetracosanol (**28**), respectively. By reduction of the ketonitrile obtained by the cyclization of **5**, there was obtained 2-aminomethyl-8,13,18-trioxacyclotetracosanol (**29**). The amino alcohols **26**–**29** were screened for biological activity with negative results.

In this paper the syntheses of 7,10,13,16,19-pentaoxacyclotetracosanone (**1**), 5,9,13,17,21-pentaoxacyclotetracosanone (**2**), and 8,13,18-trioxacyclotetracosanone (**3**), and derivatives thereof, are described. These compounds were desired as possible components of catena and rotaxane type compounds.[4] The novel catena compounds hoped for would be of interest for testing as to their pharmacological activity inasmuch as the two functional groups would be on different rings, e.g., hydroxyl on one ring, amino on the other, which by rotating could put the functions at different distances from each other. In previous examples of catena compounds, polymethylene chains were used almost exclusively in the construction of the desired large rings. We were interested in including oxygen atoms in the chain for three reasons: (a) the presence of oxygen atoms might make possible the attainment of yields of catenas and rotaxanes higher than those heretofore obtained by statistical methods;[5,6] (b) the resulting compounds would be more



likely to have solubility in aqueous biological systems than their polymethylene counterparts; and (c) the ability of oxygen atoms in cyclic ethers (crown ethers)[7] to complex with inorganic cations might make potential medicaments derived from such precursors of interest.

Thus, to elaborate on the function of the ether oxygens under (a) above, if one were to cyclize a long-chain dinitrile under Ziegler–Thorpe conditions the initial sodio derivative A might complex in the region of the oxygen atoms[7] of a suitably sized large ring B, so that when cyclization to the eneaminonitrile occurred a larger fraction of catena compound C would be formed than would be the case if the ring B did not contain any ether oxygens.



Although our attempts to prepare catena compounds by Ziegler–Thorpe cyclization of 7,10,13,16,19-pentaoxapentacosanodinitrile (**4**) and of 8,13,18,-trioxapentacosanodinitrile (**5**) in the presence of 7,10,13,16,19-pentaoxacyclotetracosanone ethylene ketal (**1a**) and 7,12,17-trioxacyclotetracosanone ethylene ketal (**3a**), respectively, failed, we made observations on the cyclization of the dinitriles, **4**, **5**, and 5,9,13,17,21-pentaoxapentacosanodinitrile (**6**), which are of interest in connection with high-dilution techniques. These dinitriles were chosen because each would result eventually in a 24-member ring ketone, a size which a study of molecular models indicated could comfortably include a catena or rotaxane insert.

In the classic studies from the Ziegler laboratory detailed directions for the cyclization of dinitriles by strong bases (e.g., sodium methylanilide) by a high-dilution technique are given.[8,9] An elaborate apparatus was used; lengthy reaction periods (often 3–14 days) and careful attention to concentration factors were required if yields in the range of 70–80% of iminonitriles were to be obtained. Hydrolysis and decarboxylation to ketones was generally effected by refluxing with 70% H_2SO_4.

We have simplified the apparatus as shown in Figure 1.

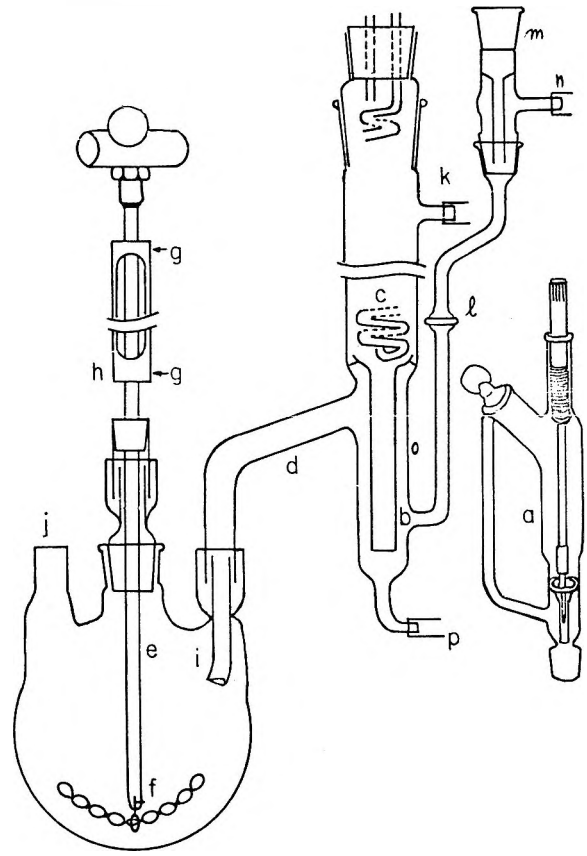


Figure 1.

The chief change lies in the replacement of the cumbersome mercury-controlled addition system[10] by a special addition funnel[11] a which delivers a dilute ethereal solution of the dinitrile as shown in b where it is further diluted with the ether condensed by the efficient copper-coiled condenser[12] c and swept into the reaction flask via return tube d. The use of mercury-sealed joints and stirrer was dictated by the experience of the Ziegler school in the publications of which such seals are always preferred to other methods of closure. The stirrer shaft e was constructed of $^{3}/_{16}$ in. stainless steel and was connected to a Hershberg wire stirrer[13] f (or a curved metal blade containing holes). The two ball bearings g which guide the shaft are contained in a one-piece hollowed metal holder h which ensures that the ball bearings remain firmly aligned during a lengthy reaction period. The ether returning to the reaction flask is delivered at i, a wide driptip which delivers the ether so that it does not first touch the walls of the flask. This device prevents the buildup of large clumps of insoluble complexes in this area as occurs when such a driptip is not used.[14]

For the cyclizations the main reaction flask was flamed and swept with dry nitrogen introduced through a tube at j and exited at opening k with a solid balljoint at l instead of the addition funnel a. After cooling under nitrogen, the solution of sodium *N*-methylanilide, prepared in another

Table I
Cyclization of Dinitriles

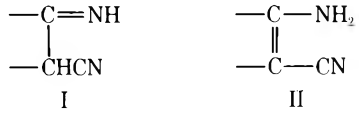
Expt	Dinitrile,[a] g	Ether,[b] ml	Total vol[c] of ether, l.	Time for addition[d]	EAN[e]	KN[f]
			4			
1	25.5	300	1.8	20	82.5	79
2	45.4	300	1.8	26	82	80[g]
3	61.4	400	2.8	24		82[g]
4	63.8	300	1.8	26	80	
5	61.4	400	2.8	6		82
6[h]	30.0	200	1.4	19	23	77[i]
7[h]	15.0	200	1.4	16	33	
8[h,j]	8.0	100	0.3	7	74	
			5			
9	59.3	400	2.5	36		79
10	55.5	500	3.0	72	83	
11	59.3	400	2.5	24	81	
12[h]	15.0	200	1.4	12	86	
13[h,k]	5.0	75		5[l]	60	
14[h,m]	12.0	80	0.3	6	86	
15[k]	6.3	200	2.0	16	78	
16[h,j]	8.0	100	0.3	5	44	
17[h,n]	15.0	100	0.385	10	79	
			6			
18	57.6	400	2.5	24	86	
19[h]	59.5	750	2.5	24	80	

[a] In all runs only redistilled dinitrile and about a tenfold excess of sodium *N*-methylanilide were used. [b] Milliliters of ether used to dissolve dinitrile. [c] The total final volume of ether includes the ether used for *b* and also that involved in making and transferring the condensing agent, sodium *N*-methylanilide. [d] Time in hours for addition of dinitrile. After addition complete refluxing continued for 1–5 hr. [e] Yield of crude ethyleneaminonitrile (EAN) usually was equal to the weight of starting dinitrile. Portions on vacuum distillation usually yielded 70–85% of pure distilled EAN. When percent is given this means distilled EAN. [f] The overall yield of distilled ketonitrile from dinitrile without purification of EAN. [g] Typical of several runs in which little variation in yield of KN was noted. [h] Run in appropriately sized conventional three-necked flask by direct addition of dinitrile solution (NHDA, not high dilution apparatus). [i] Percent of polymer. [j] Potassium *N*-methylanilide used. The preparation from KH[42] and *N*-methylaniline was more inconvenient than that for the sodio derivative. [k] NHDA experiment with about 3–4 equiv of $[(CH_3)_3SI]_2NNa$[43] as condensing agent. [l] Refluxed 10 hr after addition. [m] About one-half the concentration of sodium *N*-methylanilide was used, e.g., 4–5 mol/mol of dinitrile. [n] Only about 2 equiv of condensing agent per mole of **5** (about ⅕ of amount recommended earlier[16]).

conventional three-neck flask, was forced in by nitrogen pressure through a tube inserted at j. The addition funnel a (with flow rate previously calibrated) was then attached to an adapter m attached at l and the openings k and n connected by a T-tube (not shown) opening to the atmosphere through a drying tube (not shown). The ethereal solution of the dinitrile was added to a after a rapid rate of reflux of ether had been maintained for enough time to fill the body of the mixing chamber o to the overflow point. The opening p at the bottom of the mixing chamber was closed by a pinch clamp at q (not shown).

A solution of the dinitrile in ether was added slowly to a well-stirred rapidly refluxing solution of an excess of sodium methylanilide in ether freshly prepared by treating sodium with *N*-methylaniline in the presence of isoprene.[15,16] Much importance was attached to very slow addition (often 72 hr or more) of the solution of dinitrile in ether to the sodium *N*-methylanilide reagent solution in order that high yields might result.[15] We have found that **4, 5,** and **6** are cyclized in high yields even when addition of the dinitriles is made in as short a time as 6 hr (see Table I) and in certain cases when conventional apparatus is used instead of the high-dilution setup as outlined in Figure 1. Perhaps these results are due to conformational factors which make intramolecular cyclization more facile when oxygen atoms are present in the chains.[17,18]

In the work of Ziegler and coworkers[8] the cyclized products from dinitriles were assumed to have the β-iminonitrile structure I. In the cases of **4a, 5a,** and **6a,** we believe that the ethyleneaminonitrile structure II is at hand. Our



I II

evidence lies in the fact that the nitrile bands in the infrared for **4a, 5a,** and **6a** are sharp single lines near 4.6 μm[19] whereas the nitrile band in the starting dinitriles are sharp bands near 4.4 μm. If the structure I were at hand we would expect the CN band to occur near 4.4 μm.

The hydrolyses of the cyclized products to yield cyclic ketones had been carried out by refluxing with strong sulfuric acid solutions.[15,16] Because of the oxygen atoms in the rings of our compounds, we worked out an improved stepwise procedure under milder conditions, as shown in Scheme I (shown only for compounds derived from **4**).

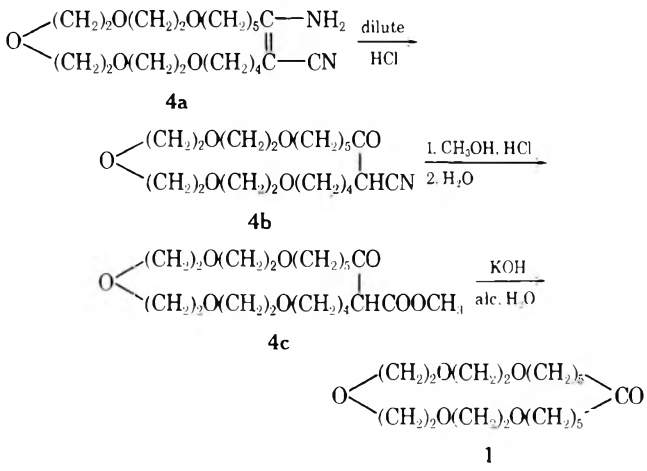
The syntheses of **4** and **5** were carried out as shown in Scheme II.

Interestingly, the best yields of **8** and **11** were obtained when the dimesylate **7** or the dichloride **10** was added to the solution (held near 100°) formed by treating 3 equiv of sodium with excess diol as solvent. The conversion of the dimesylates **9** and **12** to dinitriles **4** and **5** was better effected in benzene by using phase-transfer catalysis[20] than by reaction with potassium cyanide in aqueous DMSO.

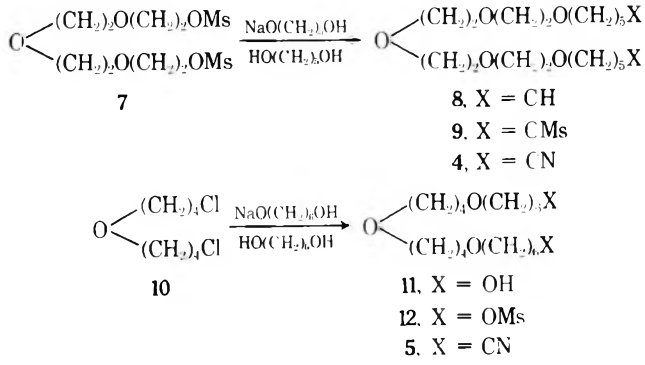
The synthesis of **6** was carried out as shown in Scheme III.

The conversion of 1,3-propanediol to **13** was carried out essentially as described.[21] Methanolysis of **13** using a cationic exchange resin afforded **14** in almost quantitative

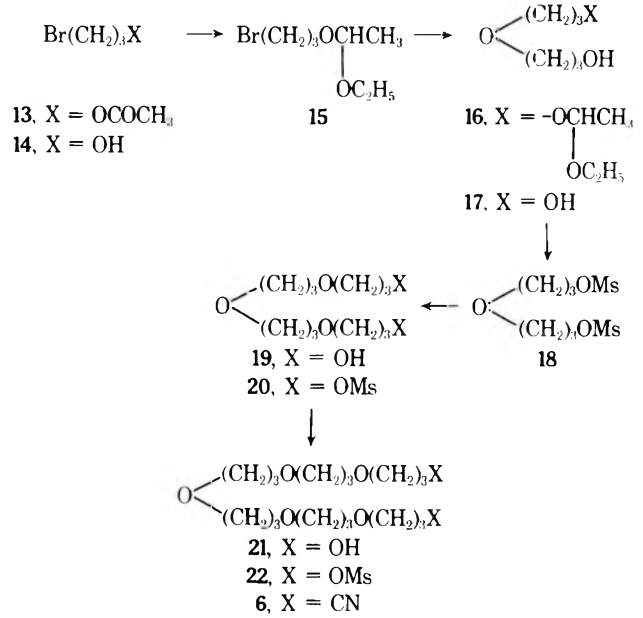
Scheme I



Scheme II

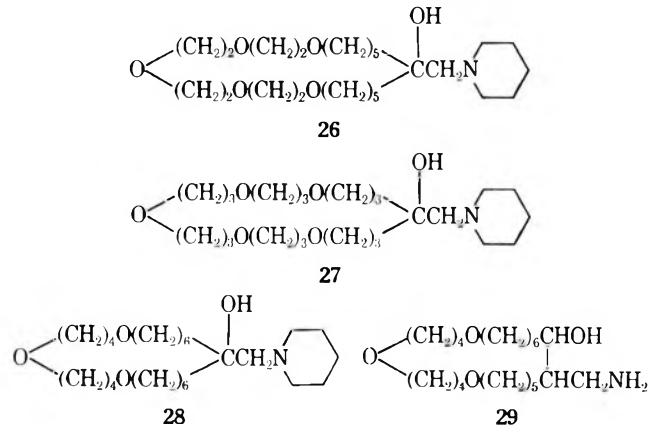


Scheme III



yield. The conversion of **14** to **17** has previously been accomplished in 57% yield.[22] We have improved this by proceeding through the intermediate[23] **15**, which was added to a solution formed by treating sodium with excess 1,3-propanediol to form **16**. Hydrolysis of **16** yielded **17** in 70% overall yield from **14**. The remaining steps were carried out essentially as in the syntheses of **4** and **5**.

In order to investigate the possibility that amino alcohols having a crown ether type[7] feature in a large ring might have interesting physiological activity, we prepared 1-piperidinomethyl-7,10,13,16,19-pentaoxacyclotetracosanol (**26**) from **1**, 1-piperidinomethyl-5,9,13,17,21-pentaoxacyclotetracosanol (**27**) from **2**, and 1-piperidinomethyl-8,13,18-trioxacyclotetracosanol (**28**) from **3**, by conversions of the ketones to epoxides[24] **23**, **24**, and **25**, respectively, followed by reaction of these with piperidine. In addition, 2-cyano-8,13,18-trioxacyclotetracosanone (**5b**) was reduced with $LiAlH_4$ to yield 2-aminomethyl-8,13-18-trioxacyclotetracosanol (**29**). The four compounds, **26**–**29**, were



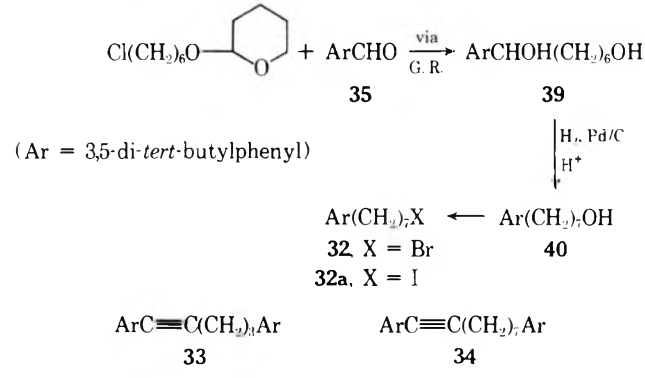
screened at the Upjohn Co.[25] Compounds **26**, **27**, and **29** were screened at Merck Sharp and Dohme.[26] Unfortunately, no activity was found in any of the tests used.[25,26]

A few experiments were run in which the sodium and lithium salts of 3,5-di-*tert*-butylphenylacetylene[27] (**30**) were condensed with 3-(3,5-di-*tert*-butylphenyl)propyl bromide (**31**) (and iodide, **31a**), and 7-(3,5-di-*tert*-butylphenyl)heptyl bromide (**32**) (and iodide, **32a**) in the presence of **1a**. Although the alkylation reactions proceeded well to yield 1,5-di(3,5-di-*tert*-butylphenyl)-1-pentyne (**33**) and 1,9-di(3,5-di-*tert*-butylphenyl)-1-nonyne (**34**), respectively, both in the presence and absence of **1a**, no evidence for the formation of appreciable amounts of rotaxanes was obtained.

The bromide **31** was prepared from the mesylate **36a** of 3-(3,5-di-*tert*-butylphenyl)propanol (**36**), which was prepared by the steps 3,5-di-*tert*-butylbenzaldehyde (**35**)[27] → methyl 3-(3,5-di-*tert*-butylphenyl)-3-hydroxypropanoate[27] → methyl 3-(3,5-di-*tert*-butylphenyl)acrylate (**37**) → methyl 3-(3,5-di-*tert*-butylphenyl)propanoate (**38**) → **36**.

The bromide **32** and the iodide **32a** were synthesized as shown in Scheme IV.

Scheme IV



Experimental Section[28]

Dimesylate of 3,6,9-Trioxa-1,11-undecanediol (7). To a cooled, stirred solution of 194 g (1 mol) of tetraethylene glycol[29] in 1 l. of benzene containing 253 g (2.5 mol) of distilled triethylamine in a 3-l. flask[30] was added dropwise during 2 hr a solution of 286 g (2.4 mol) of methanesulfonyl chloride in 50 ml of benzene. The

temperature during addition and for 3 hr more was held at 5–7°. The solid was suction filtered and washed twice with 300 ml of 1:1 benzene–CH_2Cl_2. The filtrate and washings were combined and concentrated to dryness on a rotary evaporator. A CH_2Cl_2 solution of the residue was washed with ice water (3 × 100 ml) and saturated salt solution (2 × 45 ml) and was dried over $MgSO_4$. After complete removal of the CH_2Cl_2 on a rotary evaporator there was obtained 325 g (93%) of crude dimesylate **7**. This crude product was further purified by stirring vigorously with dry ether (150 ml), which was then decanted to leave 320 g (91.6%) of **7** as a yellow oil suitable for conversion into 8.

6,9,12,15,18-Pentaoxa-1,23-tricosanediol (8).* To 1404 g (13.5 mol) of redistilled 1,5-pentanediol, bp 137–138° (12 mm), held at 95–100° under N_2 in a 3-l. flask[30] by a heating mantle was added 62 g (2.7 mol) of sodium in small clean chunks. The reaction temperature was maintained at 105–110° by the rate of addition of the sodium (about 2 hr needed without any external heating by the mantle which was kept in place). As soon as the last sodium had reacted, a solution of 315 g (0.9 mol) of **7** was added during 90 min without external heating (temperature in the 100–105° range) and the resulting viscous, homogeneous reaction mixture was held at 100° for 20 hr. This hot solution was poured into 1.5 l. of acetone and to the resultant cooled solution was added about 450 ml of dry ether saturated at room temperature with dry HCl until the pH was 6–7 (external testing). The solid was removed by filtration and washed with dry acetone (2 × 1 l.). The filtrate and washings were concentrated on a rotary evaporator and the residue was rapidly vacuum distilled in a modified Claisen flask[31] to yield 280 g (87.5%), bp 220–250° (0.5 mm), after recovery of the excess 1,5-pentanediol which was reused as obtained in other similar runs. Redistillation[32] afforded 230 g (74% overall) as a center cut, bp 235–240° (0.5 mm), of **8**.[33] This material was analytically pure.

7,10,13,16,19-Pentaoxapentacosanodinitrile (4).* By the same method as described above for **7**, 220 g of **8** was converted into 305 g (97%) of crude **9** [271 g (87%) of purified **9**]. A well-stirred mixture of 195 g of KCN, 300 ml of water, 300 ml of benzene, 5 g of Aliquat 336,[20] and 261 g of pure **9** was held at reflux for 5–6 hr, cooled, diluted with water to dissolve salts, and worked up as usual using CH_2Cl_2–benzene extraction. Distillation afforded 83% of **4**, bp 230–250° (1 mm). Redistillation yielded 70% (overall) of analytically pure **4**, bp 240–247° (1 mm), ir 4.42 μm. The boiling point recorded for various runs varied somewhat because it was advantageous to heat the Claisen neck externally in order to expedite distillation of the high-boiling material.[32]

7,12,17-Trioxa-1,23-tricosanediol (11).* In a typical run the solution at 80–90° formed by treating 75.9 g of sodium with 2124 g of 1,6-hexanediol, bp 132° (9 mm), at 100° was treated with 299 g of **10**,[34] bp 92–94° (1 mm), during 1 hr. After stirring at 80–90° for 14 hr the mixture was diluted with sufficient acetone and ether to facilitate filtration (in this case 400 ml of acetone and then 300 ml of ether). After a work-up similar to that for **8** there was obtained 365 g (67%) of **11**, bp 215–225° (0.3 mm). A center cut was taken for analysis.

8,13,18-Trioxapentacosanodinitrile (5).* In a manner similar to that described for the preparation of **7**, 385 g of **11** in 800 ml of benzene containing 260 g of triethylamine was treated with 283 g of methanesulfonyl chloride in 300 ml of benzene to yield crude mesylate **12*** in 98% yield. A small portion was crystallized from hexane–ether to yield pure **12**, mp 50–51°. Conversion of 600 g of **12** into **5** was carried out as described for **4** by heating at reflux with 390 g of KCN, 200 ml of water, and 400 ml of benzene containing 10 g of Aliquat 336[20] for 5 hr. After two distillations there was obtained 300 g (68%) of a center cut of **5**, bp 244–249° (0.3 mm), ir 4.44 μm, as a pale yellow oil.

3-Bromo-1-propanol (14). 3-Bromo-1-propyl acetate (**13**), bp 55–60° (1 mm), was obtained in 67% yield essentially as described.[21] A solution of 120 g of **13** in 600 ml of methanol containing 50 g of ion exchange resin[35] was held at reflux for 6 hr. The resin was removed by filtration and the filtrate was distilled to yield 92 g (98%) of **14**, bp 60–64° (1 mm).

4-Oxa-1,7-heptanediol (17). To a stirred solution at 100–105° formed by treating 17.7 g of sodium with 380 g of 1,3-propanediol, bp 110° (12 mm), was added during 1 hr 148 g of **15** formed from 104 g of **14** as described.[23] The mixture was held at 100–105° for 10 hr and then acidified with concentrated HCl until neutral (pH 7, external testing). After adding 50 g of resin[35] and 81 g of water the mixture was refluxed for 24 hr. The solids were removed by filtration and rinsed with ethanol. Distillation of the combined filtrate and washings yielded 100.5 g (70% from **14**) of **17**, bp 90–95° (0.5 mm).[36]

4,8,12-Trioxa-1,15-pentadecanediol (19).* The diol **17** was converted into its dimesyl derivative **18** essentially as described for the preparation of **7**. Then **18** was converted, in 77% overall yield from **17**, into **19**, bp 158–165° (0.5 mm), by adding to excess 1,3-propanediol containing its sodium salt as described for the preparation of diols **8** and **11**.

4,8,12,16,20-Pentaoxa-1,23-tricosanediol (21).* The diol **19** was converted via its dimesyl derivative **20** into **21** essentially as described above in analogous examples. Overall yields of **21**, bp 220–228° (0.5 mm), were about 78%.

5,9,13,17,21-Pentaoxapentacosanodinitrile (6).* The dimesylate **22** was prepared as described above for **7** and the crude product was converted in 82% overall yield to **6**, bp 230–238° (0.5 mm) (twice distilled), ir 4.45 μm.

General Description of Ziegler-Type High-Dilution Cyclizations. Sodium sand was prepared in a 3-l. flask[30] by melting clean sodium under freshly distilled xylene and then stirring rapidly while cooling. In general about 10 g-atom of sodium was used per mole of dinitrile. The xylene was forced out with pure dry nitrogen and the sodium sand was rinsed with dry ether (all ether was freshly distilled from Grignard reagent[37]). In a typical run a solution of 102 g (1.5 mol) of distilled isoprene (undistilled isoprene was also used) and 209 g (1.95 mol) of distilled *N*-methylaniline in 50–300 ml of dry ether was added dropwise during 1 hr to a *gently* stirred suspension of the sand prepared from 34.5 g (1.5 g-atom) of sodium under 300 ml of ether. To the resulting suspension of sodium *N*-methylanilide was added about 2 l. of ether to effect solution. This was then transferred by N_2 pressure into the high-dilution apparatus (Figure 1).[38] To this *vigorously* (about 3 l. of ether per hour) refluxing solution was added a solution of 57.6 g (0.15 mol) of **4** in 400 ml of ether during 24 hr.[39] After addition of **4**, the refluxing was continued for 2 hr. Water[40] was then added until the exothermic reaction was over and then 300 ml more to aid in obtaining clean layers.[41] After the usual work-up[28] (no acid wash) the *N*-methylaniline, bp ca. 65° (0.2 mm), was removed by distillation (heating bath in the range 100–200°) and the residue was weighed. In a typical case the weight of crude residue equaled the weight of starting dinitrile. Small amounts were vacuum distilled to yield analytical samples. In the present case a center cut of 2-amino-8,11,14,17,20-pentaoxacyclotetracosenonitrile (**4a**),* bp 235–240° (0.5 mm), ir 4.58 μm, was taken for analysis and spectral data.

The remainder of crude **4a** was shaken with 2 l. of 6 *N* HCl for 30 min. After dilution with 2 l. of water, the ketonitrile was isolated as usual to yield 49.3 g (85.6% based on **4**) of 2-cyano-7,10,13,16,19-pentaoxacyclotetracosanone (**4b**),* bp 210–213° (0.5 mm). In general conversions of crude ethyleneaminonitriles (EAN) to pure distilled ketonitriles (KN) ran well over 90%. In the preferred procedure, the crude EAN were converted directly into KN.

By similar procedures **5** was converted into 2-amino-9,14,19-trioxacyclotetracosenonitrile (**5a**),* bp 225–230° (0.3 mm), ir 5.62 μm, and 2-cyano-8,13,18-trioxacyclotetracosanone (**5b**),* bp 205–210° (0.2 mm), and **6** into 2-amino-6,10,14,18,22-pentaoxacyclotetracosenonitrile (**6a**),* bp 235–240° (0.6 mm), ir 4.58 μm, and 2-cyano-5,9,13,17,21-pentaoxacyclotetracosanone (**6b**),* bp 210–213° (0.5 mm).

Perusal of Table I allows a number of observations to be made regarding Ziegler-type cyclizations. Evidently the presence of oxygen atoms makes the yield of cyclized product less sensitive to dilution factors and to time of addition of the dinitrile solution to the condensing agent (expt 1–5 for **4** and 9–11 for **5**) than is the case with dinitriles of the general formula $NC(CH_2)_nCN$.[16] Experiments 5 and 14 show that even if the time of addition is cut to 6 hr high yields of eneaminonitriles can be obtained. Indeed, experiments in which solutions of dinitrile were added directly to solutions containing condensing agent without use of high-dilution apparatus afforded acceptable yields of EAN in the cases of **5** and **6** (expt 12, 14, 19). However, this technique did not work well in the case of **4**; as much polymer was obtained under these conditions (expt 6, 7). A few experiments demonstrated that condensing agents (expt 8, 16, $C_6H_5NKCH_3$,[42] expt 13, 15, $[(CH_3)_3Si]_2NNa$[43]) other than sodium *N*-methylanilide can be used successfully.

Conversion of β-Ketonitriles 4b, 5b, and 6b into Cyclotetracosanones, 1, 2, and 3. In the best of many experiments, 147.5 g of distilled **4b** was stirred with 2740 ml[44] of methanol saturated with dry HCl at 25–30° for 4 hr. Most of the methanol was removed on a rotary evaporator and 500 ml of water was added to the residue. An ether–CH_2Cl_2 extract of the product was washed with saturated salt solution, and the crude residue, after removal of organic solvents, weighed 144.6 g. This crude keto ester was held at reflux

in a solution containing 217 g of KOH and 720 ml of water in 720 ml of ethanol for 17 hr. After a conventional work-up, vacuum distillation afforded 109 g (88%) of **1**,* bp 192–210° (0.4 mm). The use of phosphoric acid in dilute acetic acid, which proved successful in a previous case,[19a] did not work nearly as well with our ethyleneaminonitriles, nor did any of several other hydrolytic methods mentioned.[19a]

In a typical experiment, 98.4 g of **6b** and 2 l. of saturated methanolic HCl were stirred for 5 hr and worked up as described above to yield 106 g of crude keto ester. A portion was distilled to yield pure methyl 2-keto-6,10,14,18,22-pentaoxacyclotetracosanylcarboxylate (**6c**),* bp ca. 225° (0.4 mm). A solution of the remaining crude **6c** in 1 l. of 50% alcohol containing 160 g of KOH was refluxed for 20 hr and worked up as usual to yield 65 g (71% from **6b**) of **2**,* bp 190–198° (0.5 mm).

The ketonitrile **5b** was converted into methyl 2-keto-9,14,19-trioxacyclotetracosanylcarboxylate (**5c**) as described above for **4c**. A portion of **5c**,* bp 232–235° (0.3 mm), was taken for analysis. A solution of 105 g of crude **5c** in 1.1 l. of 50% alcohol containing 159 g of KOH was refluxed for 8 hr. After the usual work-up there was obtained 69 g (76%) of pure **3**,* bp 195–197° (0.3 mm).

Ethylene Ketals of 1 and 3. In a typical experiment a solution of 10.8 g of **1**, 2.8 g of ethylene glycol, and 200 mg of *p*-toluenesulfonic acid in 250 ml of benzene was held at reflux for 5 hr with removal of water by azeotropic distillation. Solid K_2CO_3 (20 g) was stirred in for 2 hr. After a conventional work-up there was obtained 11.0 g (91%) of **1a**,* bp 230–235° (0.5 mm). In a similar experiment involving 10.5 g of **3** and 3.0 g of ethylene glycol there was obtained 10.6 g (90%) of **3a**,* bp 202–205° (0.3 mm)

1-Piperidinomethyl-8,13-18-trioxacyclotetracosanol (28).* In a 250-ml flask[30] was placed 1.6 g of a sodium hydride suspension (57%) in mineral oil. By washing several times under N_2 with petroleum ether the mineral oil was removed. To the NaH was added 20 ml of THF and 20 ml of dimethyl sulfoxide (DMSO). Heating at 65–70° was maintained until no more hydrogen was evolved (45–55 min). About 20 ml of THF was added and the mixture was cooled to −5°, when 6.6 g of trimethylsulfonium iodide in 20 ml of DMSO was added during 2 min followed by a solution of 5.6 g of **3** in 25 ml of DMSO. After stirring at −5° for 15 min the solution was held at 20–25° for 45 min. After a conventional work-up there was obtained 5.5 g (94.5%) of the epoxide of 1-methylene-8,13,18-trioxacyclotetracosane (**25**),* bp 190–193° (0.4 mm). A solution of 5.4 g of **25** in 70 ml of freshly distilled piperidine was held at reflux for 24 hr. Most of the piperidine was vacuum distilled, the brown residue was distilled, and the distillate was treated with about 1 g of activated charcoal (Darco G-60) in CH_2Cl_2. Distillation afforded 5.7 g (86%) C of **28** as a pale yellow oil, bp 215–220° (0.4 mm).

1-Piperidinomethyl-7,10,13,16,19-pentaoxacyclotetracosanol (26).* In a similar way 5.04 g of **1** was converted into 4.25 g (81%) of the epoxide of 1-methylene-7,10,13,16,19-pentaoxacyclotetracosane (**23**),* purified by molecular distillation[45] at 125–135° for analysis, bp 205–207° (0.2 mm). On heating with piperidine as above there was obtained 3.1 g (63%) of twice distilled[45] center cut of **26**, bath temperature about 140°, pressure not accurately recorded.

1-Piperidinomethyl-5,9,13,17,21-pentaoxacyclotetracosanol (27).* In a manner entirely similar to that described for the synthesis of **28**, 14.4 g of **2** was converted into the epoxide **24**, which was converted directly into 13.0 g (75% overall) of **27**, bp 225–230° (0.3 mm).

2-Aminomethyl-8,13,18-trioxacyclotetracosanol (29).* In a typical experiment a solution of 8.0 g of **5b** in 100 ml of 1:1 ether–THF was added to a suspension of 2 g of $LiAlH_4$ in 100 ml of 1:1 ether–THF. After stirring for 15 hr the mixture was worked up (including 20% sodium potassium tartrate in the aqueous phase) to yield 5.0 g (62%) of **29**, bp 225–227° (0.2 mm).

3-(3,5-Di-*tert*-butylphenyl)propanol (36).* Methyl 3-(3,5-di-*tert*-butylphenyl)-3-hydroxypropanoate was prepared from **35** and methyl bromoacetate as described.[27] In the best of several experiments a solution of 29.2 g of β-hydroxy ester in 100 ml of benzene containing 5 g of resin[35] was refluxed into a Dean-Stark trap for about 19 hr, when the formation of a cloudy distillate had ceased. A conventional work-up afforded 23.6 g (86%) of methyl 3-(3,5-di-*tert*-butylphenyl)acrylate (**37**),* bp 134–137° (0.5 mm). In another experiment similar to this except that boron trifluoride etherate (2 ml) replaced the resin and 10 g of molecular sieves[46] was included in the reaction mixture, a 44% yield of **37** was obtained and a 28% yield of dimethyl 3,5-di-(3,5-di-*tert*-butylphenyl)-4-oxaheptanedioate (**41**),* mp 157.5–158.5°. Catalytic hydrogenation of the acrylate over 5% Pd/C in ethyl acetate for 90 min produced methyl 3-(3,5-di-*tert*-butylphenyl)propanoate (**38**),* bp 121–124° (0.5 mm), in 92% yield. Reduction of **38** (undistilled product from reduction of **37**) in THF yielded **36**, bp 119–121° (0.4 mm), in 93% overall yield from **37**. The mesylate **36a**,* mp 69–72°, was obtained in 94% yield. By treatment of 19.8 g of **36a** in toluene containing Aliquat 336[20] with aqueous sodium bromide there was obtained 20.3 g (82%) of **31**,* bp 120–121° (0.4 mm). This bromide, **31**, was also produced in high yield by reaction of **36** with CBr_4 and $(C_6H_5)_3P$ as described.[47] The iodide **31a**, bp 124–129° (0.4 mm), *m/e* 358, was also similarly prepared in high yield but was not analyzed because of rapid discoloration. The **31a** used in chemical reactions was always freshly prepared.

1,5-Di-(3,5-di-*tert*-butylphenyl)-1-pentyne (33).* The sodium hexamethyldisilazane prepared from 1.69 g of hexamethyldisilazane[48] and sodium amide in 75 ml of dry benzene was treated with a solution of 2.14 g of **30** in 10 ml of diglyme and 15 ml of benzene. During the addition of **30** a white precipitate appeared. A solution of 3.11 g of **31** in 15 ml of benzene was then added during 25 min and the mixture was refluxed for 12 hr. The product, 4.41 g, isolated as usual, was chromatographed over 60 g of silica gel to yield 3.1 g (72%) of **33**, mp 114–116°, using Skellysolve B. The analytical sample, obtained with little loss by recrystallization from ethanol, melted at 118.5–119.5°. In a similar preparation, except that **31a** was used instead of **31**, a 74% yield of **33** was obtained.

Attempts to Prepare a Rotaxane. In several similar experiments about 12 g of **1a** was added after the preparation of the sodium salt of **30** and the benzene was removed by distillation. Freshly distilled iodide **31a** was then added to the viscous residue during 5 min at 25°. Then about 2 ml of benzene was added whereupon an exothermic reaction occurred (40°). The benzene was then distilled and the mixture was heated at 70° for 66 hr. After isolation as usual the entire product was chromatographed over 350 g of silica gel. From the fractions eluted with Skellysolve B there was recovered appreciable amounts of **30**, **31a**, and **33**, followed by 1.1 g of a fraction which on mass spectrographic analysis showed a peak at *m/e* 849, that expected for the rotaxane. However, further attempts at chromatography of this fraction failed to yield a pure rotaxane. When the lithium salt of **30** was used (prepared with butyllithium) results similar to those described above were obtained.

1-(3,5-Di-*tert*-butyl)phenyl-1,7-heptanediol (39).* A solution of 45 g of 6-(tetrahydropyranyloxy)hexyl chloride, bp 125–128° (4.5 mm), prepared in 85% yield essentially as described,[49] in 50 ml of THF was added during 1 hr to 6.8 g of Mg in 100 ml of THF after about 2 g of ethylene dibromide[50] had been used to activate the Mg. After refluxing for 2 hr and cooling to room temperature a solution of 25 g of **35**[25] in 50 ml of THF was added rapidly and the resulting mixture was held at reflux for 2 hr. After the usual work-up 30 g (80%) of **39**, bp 204–206° (0.5 mm), suitable for further work, was obtained. After a small sample had stood for 2 weeks it crystallized to yield the analytical sample, mp 79–80°, on recrystallization from petroleum ether (bp 90–100°).

7-(3,5-Di-*tert*-butylphenyl)heptanol (40).* A mixture of 62 g of **39**, 300 ml of pure methanol, 1 ml of concentrated H_2SO_4, and 0.5 g of 5% Pd/C was hydrogenated under 50 psi of H_2 for 10 hr to yield 56 g (95%) of **40**, bp 158–160° (0.9 mm). When pure **39** was used the major part of the reduction was complete within 30 min.

7-(3,5-Di-*tert*-butylphenyl)heptyl Bromide (32) and Iodide (32a). The mesylate of 30 g of **40** was prepared in a conventional way in benzene using triethylamine and converted into **32**, bp 160–162° (0.5 mm), in 91% overall yield by using phase transfer catalysis[18] and aqueous sodium bromide. Similarly the iodide **32a**, bp 188–194° (1.5 mm), was obtained in 82% overall yield. Because both the bromide and iodide discolored on standing no analyses were performed. However, NMR data [$CDCl_3$, $(CH_3)_4Si$, δ 0] were consistent with data expected from **32**, δ 1.29 [s, 28, $(CH_3)_3C$ and $(CH_2)_5$], 2.50 (t, 2, J = 7 Hz, $ArCH_2$), 3.25 (t, 2, J = 7 Hz, CH_2Br), 6.68 (d, 2, J = 2 Hz, ArH), and 7.12 (t, 1, J = 2 Hz, ArH); and **32a**, δ 1.29 [s, 28, *t*-Bu and $(CH_2)_5$], 2.50 (t, 2, J = 7 Hz, $ArCH_2$), 3.10 (t, 2, J = 7 Hz, CH_2I), 6.85 (d, 2, J = 2 Hz, ArH), and 7.12 (t, 1, J = 2 Hz, ArH). Freshly distilled samples of **32** and **32a** were used in all alkylation experiments.

1,9-Di-(3,5-di-*tert*-butylphenyl)-1-nonyne (34).* In the best of several experiments in which solvent (DMSO, diglyme, HMPA) and cation (Na, Li) were varied, a solution of 2.14 g of **30** in 10 ml of hexane at 0° was treated with 5.3 ml of 1.9 *M* butyllithium in hexane. The white precipitate which formed dissolved after adding 10 ml of THF. To this solution was added 3.67 g of **32** in 20 ml of hexamethylphosphoramide, freshly distilled from CaH_2. The mixture was held at room temperature and worked up as usual to yield 3.6 g (72%) of **34**, isolated by chromatography as an oil. Hydroge-

nation over 5% Pd/C in ethyl acetate afforded 1,9-di(3,5-di-*tert*-butylphenyl)nonane (**42**),* mp 45–46°. In all attempts to obtain a rotaxane compound by treating Na and Li salts of **30** with **32** or **32a** in the presence of **1a**, no fractions were obtained which showed the presence of a rotaxane when subjected to mass spectrographic analysis.

Registry No.—**1**, 55333-55-6; **1a**, 55333-56-7; **2**, 55333-79-4; **3**, 55333-80-7; **3a**, 55333-81-8; **4**, 55333-82-9; **4a**, 55333-83-0; **4b**, 55333-84-1; **5**, 55333-85-2; **5a**, 55333-86-3; **5b**, 55333-87-4; **5c**, 55333-88-5; **6**, 55333-89-6; **6a**, 55333-90-9; **6b**, 55333-91-0; **6c**, 55333-92-1; **7**, 55400-73-2; **8**, 55333-93-2; **9**, 55400-71-0; **10**, 6334-96-9; **11**, 55333-94-3; **12**, 55333-95-4; **13**, 592-33-6; **14**, 627-18-9; **15**, 34399-67-2; **17**, 2396-61-4; **18**, 55333-96-5; **19**, 30242-05-8; **20**, 55333-97-6; **21**, 55333-98-7; **22**, 55333-57-8; **23**, 55333-58-9; **24**, 55333-59-0; **25**, 55333-60-3; **26**, 55333-61-4; **27**, 55333-62-5; **28**, 55333-63-6; **29**, 55333-64-7; **30**, 36720-94-2; **31**, 55333-65-8; **31a**, 55333-66-9; **32**, 55333-67-0; **32a**, 55333-68-1; **33**, 55333-69-2; **34**, 55333-70-5; **35**, 17610-00-3; **36**, 55333-71-6; **36a**, 55333-72-7; **37**, 55333-73-8; **38**, 55333-74-9; **39**, 55333-75-0; **40**, 55333-76-1; **41**, 55333-77-2; **42**, 55333-78-3; methanesulfonyl chloride, 124-63-0; 1,5-pentanediol, 111-29-5; 1,6-hexanediol, 629-11-8; 1,3-propanediol, 504-63-2; 6-(tetrahydropyranyloxy)hexyl chloride, 2009-84-9.

References and Notes

(1) This work was supported by Grant GM 17264 from the National Institute of General Medical Sciences and by Grant AFOSR-72-2237 from the Air Force Office of Scientific Research.
(2) Postdoctoral Research Associate.
(3) Graduate Assistant.
(4) G. Schill, "Catenanes, Rotaxanes, and Knots", Academic Press, New York, N.Y., 1971.
(5) Reference 4, Chapter 8.
(6) I. T. Harrison, *J. Chem. Soc., Chem. Commun.*, 231 (1972).
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(9) K. Ziegler in Houben-Weyl, "Methoden der Organischen Chemie", Vol. IV, Georg Thieme Verlag, Stuttgart, 1952, pp 758–764.
(10) K. Ziegler, H. Eberle, and H. Ohlinger, *Justus Liebigs Ann. Chem.*, **504**, 94, 123 (1933).
(11) A pressure equalizing funnel, based upon the controlled capillary flow system of the Hershberg dropping funnel, was used as described in L. F. Fieser, "Experiments in Organic Chemistry", 2nd ed, D. C. Heath, Boston, Mass., 1941, p 312.
(12) The importance of rapid distillation of ether is stressed[10] in order that high dilution of the dinitrile be obtained. Our condenser consisted of an outer and an inner helix of 0.25-in. copper tubing about 18 in. high. In practice this condenser was more efficient than necessary so that smaller similar condensers would undoubtedly suffice. See c, Figure 1.
(13) Reference 11, p 308.
(14) A referee pointed out that an alternate apparatus has been described: D. W. Karle, Ph.D. Thesis, University of South Carolina, 1965, CU Microfilms No. 65-7233.
(15) In early work, K. Ziegler, L. Jakob, H. Wolltham, and A. Wenz, *Justus Liebigs Ann. Chem.*, **511**, 64 (1934), prepared sodium *N*-methylanilide by reaction of powdered sodium with styrene in the presence of methylaniline and mention that 1,3-butadiene or isoprene might also be used. We prefer the use of isoprene.
(16) K. Ziegler and R. Aurnhammer, *Justus Liebigs Ann. Chem.*, **513**, 43 (1934).
(17) K. Ziegler and H. Holl, *Justus Liebigs Ann. Chem.*, **528**, 143 (1937), mention that the presence of oxygen atoms appeared to facilitate ring closure in the cyclodecane series. However, insufficient evidence was adduced to make a strong point of this factor.
(18) The influence of nitrogen atoms in facilitating ring closures is commented on by J. E. Richman and T. J. Atkins, *J. Am. Chem. Soc.*, **96**, 2268 (1974), as pointed out by a referee.
(19) The band for an unsaturated nitrile occurs at a slightly greater value (4.59 μm) than does a saturated nitrile (4.46 μm): (a) S. Baldwin, *J. Org. Chem.*, **26**, 3280 (1961). See also C. F. Hammer and R. A. Hines, *J. Am. Chem. Soc.*, **77**, 3640 (1955); S. S. Kulp, V. B. Fish, and N. R. Easton, *Can. J. Chem.*, **43**, 2512 (1965), and references cited therein.
(20) C. M. Starks, *J. Am. Chem. Soc.*, **93**, 195 (1971). Aliquat 336 is methyltricaprylylammonium chloride, now obtainable from the McKerson Corp., Minneapolis, Minn.
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(25) The screening tests were the following.

Acute Hypotensive. Two rats are given a single dose of the test compound orally. Mean arterial pressure is measured directly from the aorta through a chronic indwelling cannula, prior to and 4 and 24 hr after dosing. Variations in average pressure at the three time periods are evaluated statistically.

Antidiabetic. The test compound is administered orally to rats at a dosage of 100 mg/kg. Immediately prior to giving the test material the animals are injected subcutaneously with 100 mg of glucose. The rats are bled two hours later via the jugular vein and blood sugar concentrations determined. Results are expressed as a ratio (T/C) of blood glucose values of test animals to controls. [See G. C. Gerritsen and W. E. Dulin, *J. Pharmacol. Exp. Ther.*, **150**, 491 (1965)].

Anti-Inflammatory Hind Paw Edema. The test compound is administered orally, and ts effect on the reduction of the local inflammatory edema produced by injection of carageenin in the right paw of the rat is expressed as per cent inhibition of edema formation and as potency relative to a standard such as aspirin. [See E. M. Glenn, B. J. Bowman, W. Kooyers, T. Koslowske, and M. L. Myers, *J. Pharmacol. Exp. Ther.*, **155**, 157 (1967)].

Antiviral-Cell Culture. Test compounds are added to infected (RNA and DNA viruses) and control cell cultures which are subsequently examined for cell toxicity and/or antiviral activity, scored in terms of relative diameter of cell lysis protection.

Antiviral In Vivo. The compound is administered to mice, intraperitoneally, 100 mg/kg before and after intranasal infection with encephalomyocarditis (EMC) virus. A three-stage sequential system is used to classify the compound as active or inactive on the basis of mortality in groups of animals.

CNS Preliminary Screen. The compound is administered intraperitoneally to a group of mice at a dose of 100 mg/kg. Observations, 30 min after dosing, are made on spontaneous effects and autonomic symptoms. Then nicotine sulfate is injected intravenously and observations on convulsions and lethality are recorded.

Apomorphine Antagonism. The ability of the test compound administered intraperitoneally to inhibit cage climbing in mice induced by 2.5 mg/kg dose of apomorphine is expressed in terms of seconds (out of a 60-sec test period) in which the mice did show the climbing response.

Diuretic. Fasted male rats are given a 40 mg/kg oral dose of the test compound, and urine volume is measured for 5 hr after administration. [See L. L. Skaletzky, B. E. Graham, and J. Szmuszkovicz, *J. Med. Chem.*, **12**, 977 (1969)].

Serum Lipids. The test compound is administered orally in two divided doses in a 20-hr period following the injection of Triton WR-1339 to fasted rats. At 43 hr after the Triton injection, blood is collected, and serum cholesterol and triglycerides are determined. Values are reported in relation to those in 30 control animals. [See P. E. Schurr, J. R. Schultz, and T. M. Parkinson, *Lipids*, **7**, 68 (1972)].

Cholesterol–Lipoprotein. The test compound is administered orally to groups of rats prefed a diet which elevates blood lipids. After four days of compound treatment, the animals are fasted overnight, blood collected, and individual serum samples analyzed for total cholesterol and heparin-precipitable lipoprotein. Values are reported in terms of ratios to corresponding levels in control animals. [See A. Tinsho, I. Shimizu, T. Takenawa, H. Hikuchi, and T. Rukjo, *J. Pharm. Soc. Jpn.*, **92**, 879 (1972)].

Signed by Paul W. O'Connell, Ph.D., Head, Biological Screening Office, the Upjohn Co., Kalamazoo, Mich.

(26) The screening tests were as follows.

Compounds **26**, **27**, and **29** were screened rather extensively in a series of in vitro tests for antimicrobial activity. These include a standard in vitro assay, by an agar tube dilution method, for an assortment of gram-positive and gram-negative bacteria and fungi considered important in human disease; plus other antibacterial and antifungal activities in vitro for organisms of industrial significance, e.g., for the pulp, paper, and paint industries.

These compounds were also tested in a standard anthelmintic assay in which they were administered for varying periods of time to laboratory rodents harboring commonly available parasites (flukes, nematodes, etc.) of specific ages. They were tested for coccidiosis activity by administering mixed with feed to groups of chickens harboring an infection of *Eimeria* over a standard length of time.

In vitro antiviral testing was carried out by adding the compounds to cells infected with a representative of DNA or RNA virus such as herpes, adeno, polio, para-influenza, or rhinovirus.

Compound **29** was examined in a special in ova procedure against a transplantable tumor, the assay being designed to pick up activity against both the primary tumor and metastasis of the tumor.

As you know, of all the testing mentioned above, the single positive result was with **26**, which showed some in vitro activity against rhinoviruses. We have attached no significance to the finding.

Signed by Norman G. Brink, Ph.D., Director of University Relations, Merck Sharp and Dohme Research Laboratories, Rahway, N.J.

(27) M. S. Newman and L. F. Lee, *J. Org. Chem.*, **37**, 4468 (1972).
(28) (a) All melting and boiling points are uncorrected. Melting points were taken with a Thomas-Hoover capillary melting apparatus. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich., and Galbraith Laboratories, Knoxville, Tenn. Infrared (ir) absorption spectra were recorded on a Perkin-Elmer Infracord spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on an A-60 NMR spectrophotometer, Varian Associates, Palo Alto, Calif. A Varian Aerograph A90-P3 was used for gas–liquid chromatographic (GLC) analyses. Silica gel, 100–200 mesh, purchased from Matheson Coleman and Bell and Woelm activity grade I alumina were used for column chromatography. The phrase "worked up as usual" means that the reaction mixture was extracted with ether–benzene and the organic solution was washed successively with water and saturated sodium chloride solution and dried by filtering through a bed of anhydrous magnesium sulfate, and the solvent was removed in vacuo on a rotary evaporator. (b) All compounds marked with an asterisk gave analytical results within 0.3% of the theoretical. Ed.
(29) Tetraethylene glycol (Aldrich Chemical Co.) was fractionated to yield a constant-boiling fraction, bp 198° (14 mm).
(30) All reactions were carried out in three-necked flasks fitted with pressure

equalizing addition funnels, reflux condenser, and appropriate mechanical stirrers.
(31) The side arm of such flasks varied from 6 to 8-in. depending on the size of the flask. All parts were at 0.5–0.75 in. i.d.
(32) Heating of the pot in such distillations was best accomplished by means of a molten salt bath (equimolar $NaNO_2$, KNO_3) with the external liquid level up to the narrow neck of the Claisen flask. Near the end of the distillation the refluxing distillate in the side arm was easily forced over by use of a heat gun or a Bunsen burner played gently over the side arm.
(33) The conditions described led consistently to better yields than others in which lower temperatures and other solvents were used.
(34) K. Alexander and L. E. Schniepp, *J. Am. Chem. Soc.*, **70**, 1839 (1948).
(35) Analytical grade cation exchange resin, AG-50W-X_4, 200–400 mesh, obtained from Bio-Rad Laboratories.
(36) A boiling point of 148–162° (15 mm) is given in ref 20.
(37) A suitable apparatus is described in M. S. Newman, "An Advanced Organic Laboratory Course", Macmillan, New York, N.Y., 1972, p 110.
(38) Any unreacted sodium was not transferred to the high-dilution flask. In many runs an undetermined amount of sodium failed to react. However, since such a large excess of sodium *N*-methylanilide was used, the yield of product did not seem to be affected.
(39) To determine the setting of the plunger in the addition funnel[11] the drop rate (in this case, 1 drop in 3–3.5 sec) was determined by calibration.
(40) In larger runs (and when much solid was present on walls in some runs) it was preferable to use 50% alcohol during the first stages of quenching.
(41) If polymer had formed in a reaction, it separated at this stage and could be removed by filtration.
(42) A suspension of KH in mineral oil was used as obtained from AlFA Products, Beverly, Mass. No isoprene was used.
(43) The use of sodium bis(trimethylsilyl)amide for preparation of sodio derivatives of nitriles has been described by C. Kruger, *J. Organomet. Chem.*, 9, 125 (1967), and references cited therein.
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(45) For a description of the apparatus used see ref 36, p 102.
(46) Linde 4A, Ventron, Beverly, Mass.
(47) J. Hooz and S. S. H. Giliani, *Can. J. Chem.*, **46**, 86 (1968).
(48) U. Wannagat and H. Niederprum, *Chem. Ber.*, **94**, 1540 (1961).
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Mechanism and Stereochemistry of Oxetane Reactions. II. High Syn Stereoselectivity in the Oxetane Ring Opening of 6-Phenyl-7-oxabicyclo[4.2.0]octane under Acidic Conditions. Comparison with the Analogous Reactions of the Corresponding Oxirane

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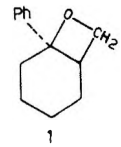
Received April 5, 1975

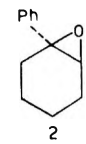
The direction and the stereochemistry of some oxetane ring opening reactions of 6-phenyl-7-oxabicyclo[4.2.0]octane (1) have been determined and compared with those of the corresponding oxirane (2). The reactions of 1 give mixtures of the syn and anti addition products, of the olefin 6 and of the unsaturated alcohol 9. Unexpectedly, some of the addition products are not stable under the reaction conditions and show facile epimerization at the tertiary carbon. The true kinetic product ratios were therefore obtained by extrapolation. The results reveal significant variation in the stereoselectivity and in the yields and ratios between the trichloroacetolysis and the solvolysis reactions of 1. A comparison of the reactions of 1 and 2 shows a much larger amount of nonaddition products in the case of oxetane 1 and marked differences in the syn stereoselectivity. The observed data can be explained by means of a mechanism involving transition states or intermediates with a high degree of carbocation character.

Whereas the stereochemistry of the ring opening of oxirane derivatives has received much attention and has been extensively investigated,[1,2] almost no data are available on that of their higher homologs, the oxetanes.[3] Although the structure and hybridization of orbitals in oxetanes and oxiranes are fundamentally different, the reactivity of the two systems is similar, especially under acidic conditions: the lesser degree of ring strain in oxetanes can be compensated by the greater electron donor capability of the ring oxygen atom.[3]

Previous work carried out in these laboratories on the stereochemistry of the ring opening of substituted oxiranes in acidic media has shown that these reactions are strongly influenced by several factors, such as structure, conformation, and configuration of the epoxide, solvent, type of reagent, etc. In order to get a better insight into the reactivity of the oxetane system and to establish how the stereochemical behavior of the ring opening of small-ring heterocycles can be modified depending on the size of the ring, we have undertaken a study of 6-phenyl-7-oxabicyclo[4.2.0]octane (1), a homolog of the oxirane 2 which has been thoroughly investigated and characterized.[2a,b,g,4,5] Furthermore, protonated oxetanes have been often suggested as intermediates in the Prins reaction,[6] so that a knowledge of the stereochemistry of oxetane ring opening under acidic conditions could offer a good tool for a better understanding of the debated mechanism of the Prins reaction.



1



2

Oxetane 1 has been prepared by conversion of the cis diol 3 into the tosylate 4, which on treatment with potassium *tert*-butoxide afforded 1 (Chart A). The structure of 1 was confirmed by its ir and NMR spectra: presence of an ir band at 10.3 μ[7] and a NMR signal at δ 4.45 due to the methylene protons of the oxetane ring.[8]

It was first necessary to define the regiochemistry of the ring opening of 1. In fact, whereas the attack of the nucleophile on the benzylic carbon of 1 can afford both cis and trans products, the attack on the oxetane methylenic carbon can give, evidently, only cis products. The acid-catalyzed solvolysis of 1 in anhydrous methanol gave mixtures of the two methyl ethers 7 and 8 and of small amounts of the olefin 6 and the unsaturated alcohol 9; the methyl ether 5 arising from a nonbenzylic attack of the nucleophile was not detected and less than 0.2% of it could have been present. The conversion of 1 was very rapid (it had com-

Chart A

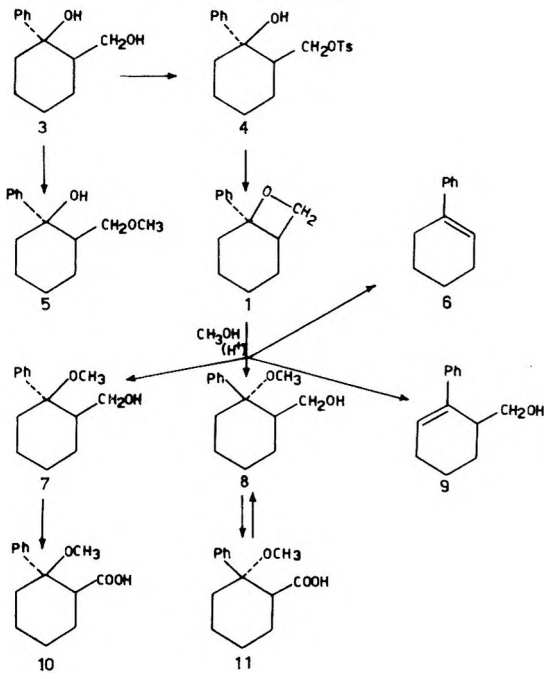
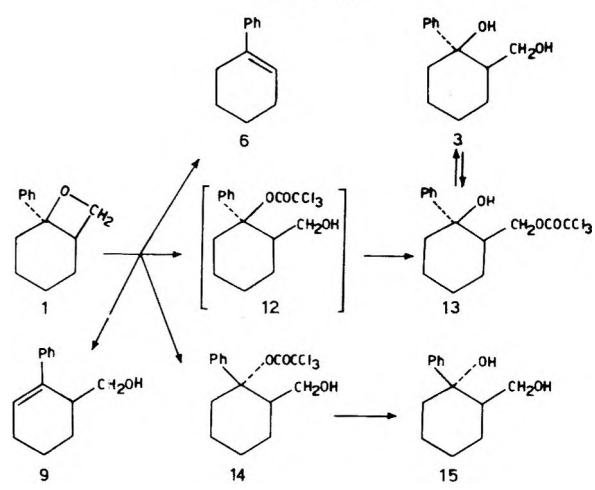


Chart B



pletely disappeared after 10 min). When the reaction mixture was stored for longer times, the amounts of **6** and **9** increased only slightly owing to a very slow conversion of **7** and **8**; the ratio between **7** and **8**, however, slowly changed to reach a constant value of ca. 72.5:27.5 because of a slow epimerization of the two ethers **7** and **8**. After short reaction times (10 min) the trans isomer **8** clearly prevailed (see Table I) and it could be purified by crystallization of the crude reaction mixture. The cis ether **7** was obtained by crystallization of a crude, obtained by longer contact times (3 days), in which it was the main product. Oxidation of **7** and **8** with Jones reagent[9] gave the corresponding acids **10** and **11**, respectively. Reduction of **11** with $LiAlH_4$ afforded the pure ether **8**. When the methanolysis of **1** was carried out in aqueous methanol the reaction was equally regiospecific but the ratio of the products **6**, **9**, **8**, and **7** was slightly different and small amounts of the diols **3** and **15** were also formed (see Table I). In the latter case the rearrangement and the epimerization of **7** and **8** was markedly slower then in the case of the reaction in anhydrous methanol. The relative configurations of the methyl ethers **7** and **8** were indicated by their ir spectra in the 3-μ range in dilute solution of CCl_4. The spectrum of the cis methyl ether **7** shows only a band at 3533 cm^{-1} indicative of a strong intramolecular OH···O bond;[10] such a band is possible in both chair conformers of **7**. On the other hand, compound **8** shows two strong absorptions at 3639 and 3601 cm^{-1} and a weak one at 3507 cm^{-1}, which can be attributed respectively to the free OH, to the OH bonded to the phenyl group and to an OH···O interaction.[10] This suggests that compound **8** should exist preferentially in a chair conformation in which the methoxy and the hydroxymethyl groups are axial with only a small contribution of the other chair conformer, the only one in which an intramolecular OH···O bond is possible. The configurations of **7** and **8** were confirmed by examining the NMR spectra of the corresponding acids **10** and **11**. Since the phenyl group should occupy an equatorial position in the preferred conformation of **10** and **11**, the half-band widths of the methinic proton (17.0 Hz for **10** and 9.0 Hz for **11**) are consistent with the assigned configurations.[2c,e,11]

Also the hydrolysis of **1** in 0.2 *N* aqueous H_2SO_4 was rapid (complete in less than 30 min) and gave mixtures of the cis (**3**) and of the trans diol **15**, the latter predominating, accompanied by minor amounts of **6** and **9**. However, whereas the total amounts of **6** and **9** did not change significantly with the reaction time, a fast pseudo-first-order epimerization of the trans diol **15** into the cis isomer **3** was observed (see Table II); the true kinetic product ratio between **3** and **15** was obtained by extrapolation.

The reaction of **1** with trichloroacetic acid in CH_2Cl_2 was very rapid (complete in less than 1 min) and led to a mixture of **6**, **9**, and the trichloroacetates **13** and **14** (Chart B) from which **6**, **9**, and **13** were separated by preparative TLC. On reduction with $LiAlH_4$ **13** afforded the cis diol **3**, which was reconverted to **13** by esterification with trichloroacetyl chloride; this confirmed the structure of the trichloroacetate **13**, since trichloroacetyl chloride should react preferentially with the primary, rather than with the tertiary, hydroxyl. It may be pointed out that the isolation of **13** from the reaction mixture of **1** with trichloroacetic acid

Table I
Initial Product Compositions for the Oxetane Ring Opening of 1 under Acidic Conditions

Solvent	Acid	6	9	Syn adduct	Anti adduct	Syn:anti ratio
Cyclohexane	CCl_3COOH	24.5	22.0	36.0[a,b]	17.5[b,c]	67.5:32.5
CCl_4	CCl_3COOH	23.0	24.0	35.0[a,b]	18.0[b,c]	66.0:34.0
Benzene	CCl_3COOH	24.5	20.0	40.0[a,b]	15.5[b,c]	72.0:28.0
$CHCl_3$	CCl_3COOH	22.0	25.5	42.0[a,b]	10.5[b,c]	80.0:20.0
CH_2Cl_2	CCl_3COOH	20.0	21.0	49.5[a,b]	9.5[b,c]	84.0:16.0
H_2O[d]	H_2SO_4	1.0	4.5	17.5[a,b]	77.0[b,c]	18.5:81.5
MeOH	H_2SO_4	5.5	9.0	15.0[e]	70.5[f]	17.5:82.5
MeOH–H_2O (9:1 v/v)	H_2SO_4	1.0	4.5	12.0[e]	72.5[f]	14.0:86.0
				1.0[a]	9.0[c]	10.0:90.0

[a] Cis diol **3**. [b] After $LiAlH_4$ reduction. [c] Trans diol **15**. [d] Extrapolated initial composition. [e] Cis methyl ether **7**. [f] Trans methyl ether **8**.

Table II
Production Compositions for the Acid-Catalyzed Reaction of Oxetane 1 in Water at Different Contact Times

Time	6	9	3	15
30 min	1.0	4.5	22.0	72.5
1 hr	1.0	5.0	27.0	67.0
3 hr	1.0	6.0	45.0	48.0
6 hr	1.0	6.5	61.5	31.0
1 day	1.0	8.0	86.5	4.5
2 days	1.0	8.5	87.5	3.0

does not imply that it is the primary reaction product; the tertiary ester **12** is very probably initially formed and rapidly transformed into **13** through an acyl shift involving a six-membered cyclic intermediate, favored by the decrease in steric crowding connected with the shift. Analogous behavior was observed in the reactions of 1,2-epoxides with trichloroacetic acid.[2a,c,12,13] Table I summarizes the product compositions of the crude mixtures resulting from the $LiAlH_4$ reduction of the reaction products of oxetane **1** with trichloroacetic acid in different solvents. The reaction products, **6**, **9**, **13**, and **14**, were stable under the appropriate reaction conditions for times (10 min) longer than the reaction times used (1 min). However, much longer contact times led to partial conversion of **13** and **14** into **6** and **9**.

The facile epimerization of the tertiary alcohols and ethers obtained from **1**, under mild reaction conditions in which the corresponding addition products of the oxirane **2**[1g] were completely stable, is somewhat surprising. The differences in reactivity between the two classes of compounds may be justified on the assumption that the ionization of the tertiary C–O bond should be easier in the adducts from **1** than in those from **2** because the nonbenzylic OH in the former is farther from the developing carbenium ion and should therefore exert to a much smaller degree its electron-withdrawing inductive effect.

The practically complete regiospecificity which is observed in the methanolysis of **1** and very probably is present also in the other reactions for which a direct proof is still lacking, is in accordance with previous results on the acid-catalyzed methanolysis[14] and on the reaction with HCl[15] of 2-aryloxetanes. After the protonation of the oxetane oxygen the rupture of the ring will occur between the oxygen and the tertiary benzylic carbon atom, in accordance with an intermediate stage with a high degree of carbocation character.

An interesting point in the reactions of **1** is the very significant difference in the stereoselectivity of the ring opening and in the yield and ratios of elimination products found between the trichloroacetolysis reactions on one hand and the solvolysis ones on the other. Some interesting differences also result from a comparison of the reactions of **1** with the analogous ones of epoxide **2**.

The stereochemistry of the reactions of **1** can be accounted for through a mechanism, analogous to the one admitted for aryloxiranes,[2,16] involving transition states in which bond breaking has proceeded more than bond formation[14] (A1 or "borderline A2" type mechanism) (see Scheme I) in agreement with kinetic results.[14] In aprotic solvents the protonated oxetane **16** can evolve through an incipient carbocation **17** to an intimate ion pair **19**[2,16] in which the anion and the cation are probably held together by hydrogen bonding.[2,13] Attack of the nucleophile on **17** could only give the anti adduct **18**, since the C–O bond is not yet completely broken. On the other hand, the collapse of the ion pair **19** should afford preferentially the syn adduct **20**. Also the formation of the olefin **6** and of the unsaturated alcohol **9** can be justified by this mechanism: intermediate **17** and **19** could easily undergo a retro-Prins fragmentation[3] to **6** and formaldehyde or they can eliminate H^+ to give **9**. Any factor tending to favor one of the intermediates may change the course of the reaction.

Scheme I

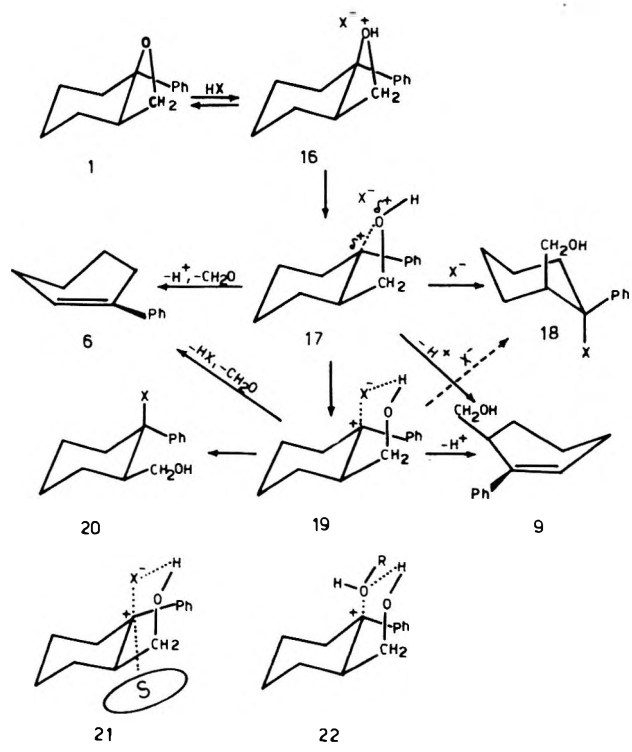


Table I reveals a very definite dependence of the product composition on the nature of the solvent in the trichloroacetolysis of **1** in nonprotic solvents. This effect can be accounted for, as previously pointed out for oxiranes,[2c,f,16] by a nucleophilic back-side solvation of the benzylic carbenium ion which can stabilize the ion pair **19** as shown in **21**. In such a way the intermediate **19** is more favored and consequently products arising from it should be preferentially formed. In fact, when the solvent is changed from cyclohexane (which has very low solvating power) to the chlorinated solvents (which can solvate the center of charge by means of the polarized chlorine atoms) the syn stereoselectivity increases and the increments parallel the order of polarization of the C–Cl bond in the solvents (CCl_4 < $CHCl_3$ < CH_2Cl_2), and therefore their solvating capability. Also benzene[2c,f,16] can solvate the intermediate carbenium ion by its π system in accordance with the results.

When the reactions of **1** are carried out in protic solvents, strong solvation effects and the large availability of attacking molecules can modify the picture of the opening process. The low amount of nonaddition products obtained in protic solvents must be likely due to the large excess of nucleophilic molecules (H_2O or MeOH)[2f] which can make the elimination paths leading to **6** and **9** less competitive. The benzylic carbenium ion formed can be selectively solvated to intermediates like **22**. The collapse of the solvent–carbenium ion complex **22** should also in this case afford the syn adducts. On the other hand, the nucleophilic solvation of the incipient carbenium ion **17** from the anti side should clearly favor the attack of the solvent on **17** before the complete rupture of the C–O bond and therefore should favor the formation of the anti adducts. An analogous higher anti stereoselectivity in the reactions carried out in pro-

Table III
Product Compositions for the Trichloroacetolysis and Hydrolysis of Oxetane 1 and Oxirane 2

Compd	Acid	Solvent	Syn adduct	Anti adduct	Other products
1	CCl_3COOH	Benzene	40.0	15.5	44.5
2[a]	CCl_3COOH	Benzene	95.0	<0.2	5.0
1	H_2SO_4	H_2O	17.5	77.0	5.5
2[a]	H_2SO_4	H_2O	60.0	40.0	<0.2

[a] Reference 18.

tic solvent has been also observed in the acid-catalyzed ring opening reactions of aryloxiranes.[2,16]

A further point of interest is in the differences in the reactions of 1 and of oxirane 2. Table III gives the relative amounts of syn and anti adducts and nonaddition products obtained in the reactions of 1 and 2 in H_2O and benzene under acidic conditions. The reactions of epoxide 2,[2a,f,g,4,17,18] when compared with those of oxetane 1 show a markedly higher syn stereoselectivity and much lower amounts of nonaddition products. If the mechanistic proposals discussed above are correct the differences in the amounts of nonaddition products should point to a higher degree of carbocationic character in the reactions of 1 in agreement with the statement (see above) that the carbenium ion derived from 1 is more stable than that from 2. On the other hand, the same effect should also favor the syn stereoselectivity of the reactions of 1 with respect to that of 2, in contrast with the obtained results. Evidently other factors, such as the lower stability of the intermediates 19 and 22, compared with that of the corresponding intermediates derived from 2, because of the higher steric repulsion, or different values of the differences between the entropic contents of the transition states leading to the syn and to the anti adducts,[17] could be responsible for the different stereoselectivity of the ring-opening reactions of oxetane 1 and oxirane 2 in acid media.

Experimental Section

Melting points were determined on a Koller apparatus and are uncorrected. Ir spectra for comparison between compounds were taken on paraffin oil mulls on a Perkin-Elmer Infracord Model 137 and those for the determination of OH stretching bands with a Perkin-Elmer Model 257 double beam grating spectrophotometer in dried (P_2O_5) CCl_4, using the indene band at 3110 cm^{-1} as a calibration standard; a quartz cell of 2-cm optical length was employed, and the concentration of the solutions was 5×10^{-3} *M* or lower to prevent intramolecular association. NMR spectra were determined on ca. 10% $CDCl_3$ solutions with a Jeol C-60 HL spectrometer using Me_4Si as an internal standard. GLC analyses were run on a Carlo Erba Fractovap apparatus with a flame ionization detector, using a dual columns system with glass columns. The relative percentages of compounds 3, 6, 7, 8, 9, and 15 were obtained from two or more separate runs on each experiment and were determined using columns packed with 10% Carbowax 20M on 80–100 mesh silanized Chromosorb W (2 mm × 1.0 m); temperatures, low isotherm 135° (3 min), high isotherm 210° (increase 6°/min), evaporator 200°, detectors 200°, nitrogen flow 35–40 ml/min. The order of increasing retention times follow: 6, 9, 7, 8, 3, and 15. Preparative TLC was performed on 2 mm layer silica gel plates (Merck F_{254}) containing a fluorescent indicator; spots were detected under uv light (245 nm). All comparison between compounds were made on the basis of ir and NMR spectra and GLC. Magnesium sulfate was always used as drying agent. Evaporations were made in vacuo (rotating evaporator). Petroleum ether refers to the fraction boiling at 40–70°; cyclohexane, CCl_4, $CHCl_3$, and CH_2Cl_2 were refluxed over P_2O_5 and rectified; benzene was washed with concentrated sulfuric acid, refluxed over sodium, and rectified.

1-Phenyl-*c*-2-hydroxymethyl-*r*-1-cyclohexanol (3)[6f,19] **and 1-phenylcyclohexene (6)**[20] were prepared as previously described.

1-Phenyl-*c*-2-tosyloxymethyl-*r*-1-cyclohexanol (4). Tosyl chloride (36.8 g, 0.193 mol) was slowly added to a solution of 3 (9.2 g, 0.044 mol) in dry pyridine (100 ml), left 4 days at room temperature, treated with ice, and extracted with $CHCl_3$. The organic extracts were washed with dilute H_2SO_4 and water and evaporated to give a crude product (15.3 g) which crystallized from CCl_4 to yield pure 4 (12.2 g): mp 108–109°; ir λ_{OH} 2.82 μ; NMR δ 3.73 (d, 2, J = 5.5 Hz, CH_2O), 2.39 ppm (s, 3, CH_3). Anal. Calcd for $C_{20}H_{24}O_4S$: C, 66.66; H, 6.66; Found: C, 66.71; H, 6.75.

6-Phenyl-7-oxabicyclo[4.2.0]octane (1). A. A solution of 4 (4.8 g, 13.4 mmol) in anhydrous *tert*-butyl alcohol was treated with potassium *tert*-butoxide (2 g, 17.8 mmol), while keeping the temperature at about 5°. After 20 hr at room temperature the reaction mixture was diluted with petroleum ether, filtered, and evaporated to dryness to yield crude 1 (2.0 g). Distillation of crude 1 (2.0 g) from powdered KOH (0.050 g) gave pure 1 (1.6 g): bp 117° (1.5 mm); ir λ_{CCC} 10.3 μ; NMR δ 4.45 ppm (m, 2, CH_2O). Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.77; H, 8.37.

B. A solution of KOH (0.140 g) in 2-propanol (3 ml) was added to a solution of 4 (0.200 g) in *tert*-butyl alcohol (6 ml), left for 20 hr at room temperature, diluted with petroleum ether, and filtered. Evaporation of the organic solution gave crude 1 (0.090 g).

Reaction of 1 with Sulfuric Acid in Anhydrous Methanol. A solution of 1 (0.400 g) in 0.2 *N* H_2SO_4 in anhydrous methanol (40 ml) was stirred at 25° for 10 min, then treated with $NaHCO_3$, diluted with water, and extracted with ether. Evaporation of the washed (H_2O) and dried ether extracts yielded an oily residue (0.410 g), consisting of 6, 9, 7, and 8 in the ratio of 5.5:9.0:15.0:70.5 (see Table I). The mixture was crystallized twice from petroleum ether (bp 30–50°) to yield pure (GLC). **1-phenyl-*t*-2-hydroxymethyl-*r*-1-methoxycyclohexane (8)** (0.080 g): mp 79–81°; ir ν_{OH} (CCl_4) 3639 (s, free OH), 3601 (s, OH···π), and 3508 cm^{-1} (w, OH···O); NMR δ 2.90 ppm (s, 3, CH_3). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.36; H, 9.09. Found: C, 76.21; H, 9.19. Reactions of 1 carried out under the same conditions stopping after relatively longer reaction times (0.5 hr) yielded the same product compositions within the experimental error, but much longer contact times showed a partial rearrangement of 7 and 8 into 6 and 9 and a marked epimerization of 8 into 7. Separate reactions quenched after 3 and 6 days yielded the following product compositions, respectively: 6, 11.0; 9, 23.5; 7, 46.0; 8, 19.5 and 6, 11.5; 9, 28.0; 7, 44.0; 8, 16.5. Analogous results were obtained when pure 7 or 8 were put under the same reaction conditions as 1. Crystallization of a crude mixture (0.210 g) obtained from 1 (0.200 g) after a contact time of 3 days from petroleum ether (bp 30–50°) at 5° gave **1-phenyl-*c*-2-hydroxymethyl-*r*-1-methoxycyclohexane (7)** (0.040 g): mp 95–97°; ir ν_{OH} (CCl_4) 3553 cm^{-1} (OH···O); NMR δ 3.25 ppm (s, 3, CH_3). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.36; H, 9.09. Found: C, 76.49; H, 9.05.

Reaction of 1 with Sulfuric Acid in Methanol–Water. A solution of 1 (0.100 g) in methanol (9 ml) was treated with aqueous 2 *N* H_2SO_4 (1 ml) and stirred for 24 hr at 25°. Treatment with $NaHCO_3$, dilution with water, extraction with ether, and evaporation of the washed (saturated aqueous $NaHCO_3$ and H_2O) and dried extracts gave an oily mixture (0.118 g) of 6, 9, 7, 8, 3, and 15 in the ratio of 1.0:4.5:12.0:72.5:1.0:9.0 (see Table I). Reactions carried out under the same conditions but stopping after 3 and 6 days yielded the same products in the following relative percentages, respectively: 6, 2.0; 9, 5.5; 7, 23.5; 8, 62.5; 3, 3.5; 15, 3.0 and 6, 2.5; 9, 8.0; 7, 27.5; 8, 56.0; 3, 4.0; 15, 2.0.

2-Phenyl-*c*-2-methoxy-*r*-1-cyclohexanecarboxylic Acid (10). A solution of 7 (0.030 g, 0.14 mmol) in acetone (1.5 ml) was treated with Jones reagent[9] (0.07 ml). After 10 min at room temperature the mixture was diluted with water and extracted with ether and the ether layer was extracted with 10% aqueous Na_2CO_3. Acidification of the alkaline solution with 10% aqueous HCl, extraction with ether, and evaporation of the washed (H_2O) and dried extract yielded 10 (0.028 g) which crystallized from petroleum ether: mp 146–148°; NMR δ 3.32 (s, 3, CH_3), 2.70 ppm (m, 1, $W_{1/2}$ = 17 Hz, CHCOO). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.52; H, 7.86.

2-Phenyl-*t*-2-methoxy-*r*-1-cyclohexanecarboxylic Acid (11). Oxidation of 8 (0.090 g), as described for the oxidation of 7, gave 11 (0.085 g) which crystallized from petroleum ether at −5°, mp 131–132°, NMR δ 2.82 ppm (s, 3, CH_3). Anal. Calcd for $C_{14}H_{18}O_3$ C, 71.77; H, 7.74. Found: C, 71.40; H, 7.92.

Reduction of 11 with Lithium Aluminum Hydride. A solution of 11 (0.110 g, 0.47 mmol) in ether (10 ml) was added dropwide to a stirred suspension of $LiAlH_4$ (0.300 g, 7.9 mmol) in ether (5 ml). After completion of the addition, the mixture was refluxed

for 6 hr and then treated with H_2O and 2 *N* aqueous NaOH. Evaporation of the dried ether yielded pure (GLC) **8** (0.100 g).

2-Phenyl-3-hydroxymethylcyclohexene (9). A solution of **2-phenyl-3-acetoxymethylcyclohexene**[6f] (0.500 g, 2.77 mmol) in ether (20 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.500 g, 13.1 mmol) in ether (20 ml); the mixture was then refluxed for 7 hr and treated with H_2O and 2 *N* aqueous NaOH. Evaporation of the dried ether yielded crude **9** (0.400 g) which was purified by preparative TLC (eluent, a 7:3 mixture of petroleum ether and ether) giving pure **9**[6f] as an oil (0.360 g): ir λ_{OH} 2.98 μ; NMR δ 6.02 (m, 1, CH=), 3.50 ppm (d, 2, J = 5.25 Hz, CH_2O).

1-Phenyl-*c*-2-methoxymethyl-*r*-1-cyclohexanol (5). A solution of **3** (0.800 g) in DMFA (40 ml) and CH_3I (3.4 g) was stirred for 24 hr at room temperature with freshly prepared silver oxide (from 2.7 g of $AgNO_3$), then diluted with water and extracted with ether. Evaporation of the washed (H_2O) ether extracts gave an oily residue of crude **5** (0.800 g) which was purified by preparative TLC (85:15 mixture of petroleum ether and ether was used as the eluent) yielding pure **5** (0.530 g) as an oil: ir λ_{OH} 2.88 μ; NMR δ 3.12 ppm (s, 3, CH_3). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.36; H, 9.09. Found: C, 76.25; H, 9.18.

Compound **5** was recovered unchanged after treatment of its acetone solution with Jones reagent[9] for 10 min.

1-Phenyl-c-2-trichloroacetoxy-*r*-1-cyclohexanol (13). A. A solution of **3** (0.467 g, 2.25 mmol) in dry benzene (25 ml) and dry pyridine (0.355 g, 2.70 mmol) was treated with trichloroacetyl chloride (0.490 g, 2.70 mmol), left for 1 hr at room temperature, then diluted with water and extracted with ether. Evaporation of the washed (diluted aqueous HCl, 10% aqueous Na_2CO_3, H_2O) and dried ether layer yielded crude **13** (0.720 g) which crystallized from petroleum ether: mp 48–49°; ir λ_{OH} 2.77 μ; NMR δ 4.12 ppm (d, 2, J = 5.5 Hz, CH_2O). Anal. Calcd for $C_{15}H_{17}O_3Cl_3$: C, 51.10; H, 4.82. Found: C, 51.21; H, 4.69.

B. A solution of **1** (0.300 g, 1.59 mmol) in dry CH_2Cl_2 (30 ml) was added to 1 *N* trichloroacetic acid in dry CH_2Cl_2 (1.75 ml), left for 1 min at room temperature, washed with saturated aqueous $NaHCO_3$ and H_2O, and evaporated to give a mixture (0.370 g) of **6, 9, 13,** and **14** which was subjected to preparative TLC, a 7:3 mixture of petroleum ether and ether being used as the eluent. Extraction of three main bands with ether (the fastest moving band contained **6** and the slowest one contained **9**) yielded **6** (0.054 g), **13** (0.120 g), and **9** (0.060 g).

Reaction of 1 with Sulfuric Acid in Water. A suspension of **1** (0.100 g) in 0.2 *N* aqueous H_2SO_4 (10 ml) was stirred at 25° for the time shown in Table III, treated with $NaHCO_3$, and then extracted with ether. Evaporation of the washed (saturated aqueous $NaHCO_3$ and H_2O) and dried ether extracts gave mixtures of **6, 9, 3,** and **15** (see Table III). The epimerization of **15** into **3** was shown to follow pseudo-first-order kinetics and the initial ratio between **3** and **15** was obtained by extrapolation. When pure **7** or **8** were treated under the same reaction conditions as **1**, a similar epimerization was obtained. Reactions of **1** carried out under the same conditions using more dilute (0.02 *N*) aqueous H_2SO_4 showed slower epimerization of **15** into **3**, but an almost identical extrapolated initial ratio between **3** and **15**.

A crude mixture (0.420 g), obtained from **1** (0.400 g) as described above after a reaction time of 30 min, was subjected to preparative TLC; a 7:3 mixture of petroleum ether and ether was used as the eluent and elution was repeated two times. Extraction of the two bands with ether (the slowest moving band contained **15**) afforded a mixture of **9** and **3** (0.070 g) and the trans diol **15**[21] (0.280 g) as an oil: ir λ_{OH} 2.90 μ; NMR δ 3.37 ppm (m, 2, CH_2O).

Reaction of 1 with Trichloroacetic Acid in Different Solvents. The reactions were carried out in dry benzene, cyclohexane, CCl_4, $CHCl_3$, and CH_2Cl_2 in carefully dried apparatus in the following way. To a solution of **1** (0.100 g, 0.53 mmol) in the solvent (10 ml) was added trichloroacetic acid (0.60 mmol) using a ca. 1 *M* solution of the acid in the same solvent. The mixture was allowed to stand for 1 min at room temperature, washed with saturated aqueous $NaHCO_3$ and H_2O, dried, and evaporated to dryness. The crude residue was dissolved in ether (20 ml) and added dropwise to a stirred suspension of $LiAlH_4$ (0.100 g) in ether (20 ml). When the addition was complete, the mixture was refluxed for 10 min and then treated with H_2O and 2 *N* aqueous NaOH. Evaporation of the dried ether yielded mixtures of **6, 9, 3,** and **15** which were analyzed by GLC (see Table I). Reactions of **1** carried out for each solvent under the same conditions stopping after relatively longer times (10 min) yielded the same product composition within the experimental error. However, much longer contact times showed partial rearrangements to **6** and **9**.

Acknowledgment. This work was supported in part by a grant from the Consiglio Nazionale delle Ricerche. We thank Dr. P. L. Barili for the NMR spectra and Dr. V. Nuti for the elemental analyses.

Registry No.—**1**, 56086-93-2; **2**, 4829-01-0; **3**, 56086-94-3; **4**, 56086-95-4; **5**, 56086-96-5; **6**, 771-98-2; **7**, 56086-97-6; **8**, 56086-98-7; **9**, 27831-78-3; **10**, 56086-99-8; **11**, 56087-00-4; **13**, 56087-01-5; **15**, 37545-87-2; tosyl chloride, 98-59-9; sulfuric acid, 7664-93-9; 2-phenyl-3-acetoxymethylcyclohexene, 27831-79-4; trichloroacetyl chloride, 76-02-8; trichloroacetic acid, 76-03-9.

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1,3-Dipolar Addition of an Oxazolium 5-Oxide to Cyclopentadienequinone and to Anthracenequinone

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Received April 4, 1975

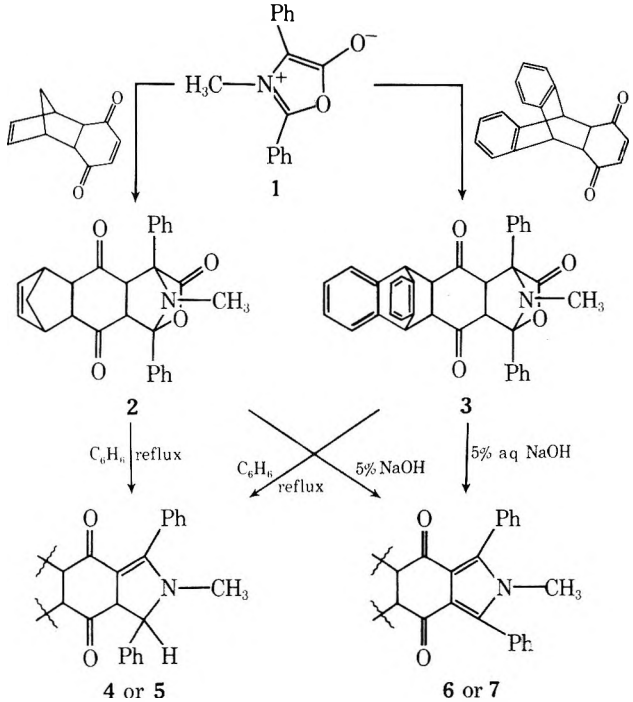
Reaction of 3-methyl-2,4-diphenyloxazolium 5-oxide (1) with cyclopentadienequinone and anthracenequinone, respectively, gave 1:1 adducts **2** and **3** in which the elements of carbon dioxide have been retained. The N-bridged lactone structures assigned to **2** and **3** are based on the spectral analyses and chemical decompositions. Conversions of **2** and **3** into the corresponding pyrrolines **4** and **5** and pyrroles **6** and **7** are described. Formation of a novel cage-type compound, 8-aza-7,9-diphenyl-8-methyltetracyclo[4.3.0.0^{3,9}.0^{4,7}]nona-2,5-dione (**9**), during thermal decomposition of **2** is also discussed.

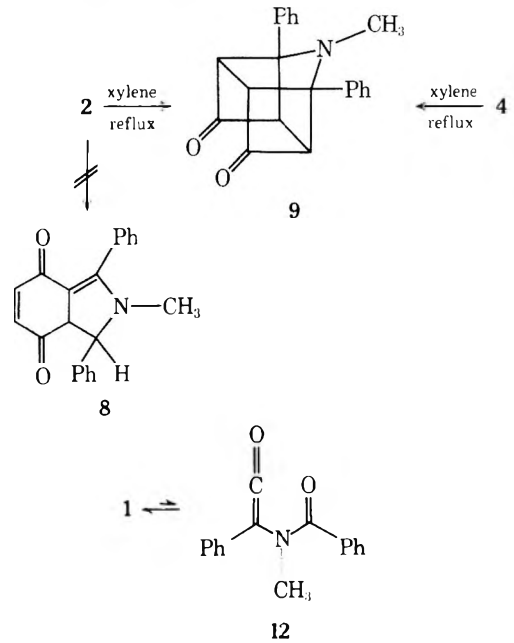
Oxazolium 5-oxides have recently been utilized in the synthesis of a variety of heterocyclic systems, for example pyrroles,[1] 2-pyrrolines,[2] 4-pyridones,[3] and polymers.[4] The accepted pathway[1-4] to each product involves a 1,3-dipolar cycloaddition of the oxazolium 5-oxide with a suitable dipolarophile to give an unstable, N-bridged intermediate which rapidly loses a molecule of carbon dioxide and forms the product. In this paper is described the isolation of two stable 1:1 adducts from analogous reactions in which the elements of carbon dioxide are retained. Each adduct decomposes thermally losing carbon dioxide and giving products which correspond to ones observed in previous work. Formation of an interesting cage-type compound during thermal decomposition of one of the adducts is also described.

The reaction of 3-methyl-2,4-diphenyloxazolium 5-oxide (**1**)[5] with cyclopentadienequinone[6] and anthracenequinone[7] gave stable 1:1 adducts as evidenced by their elemental analyses. The adduct from **1** and cyclopentadienequinone revealed a very weak molecular ion in its electron-impact mass spectrum, while only the field-desorption[8] mass spectrum of the adduct from **1** and anthracenequinone showed the molecular ion. This is in agreement with an N-bridged lactone structure for each adduct which could readily lose carbon dioxide. The NMR spectrum of each adduct, when compared with that of its starting quinone, revealed a disappearance of two vinylic hydrogens and a corresponding increase in the relative integration area for the hydrogens α to a carbonyl of two. This supports 1,3 addition across the quinone carbon–carbon double bond. Therefore, the 1:1 adducts were assigned the N-bridged lactone structures **2**, 1-carboxy-1,3,3a,4,4a,5,8,8a,9,-9a-decahydro-4,9-dioxo-1,3-diphenyl-3-hydroxy-5,8-methano-2-methyl-2*H*-benz[*f*]isoindole-1,3-lactone, and **3**, 1-carboxy-1,3,3a,4,4a,5,8,8a,9,9a-decahydro-4,9-dioxo-1,3-diphenyl-3-hydroxy-5,8-benzethano-6,7-benzo-2-methyl-2*H*-benz[*f*]isoindole-1,3-lactone, respectively.

Thermal decomposition of lactones **2** and **3** in refluxing benzene released carbon dioxide and yielded the Δ^2-pyrrolines **4** and **5**, respectively. Huisgen and coworkers[2] had previously obtained Δ^2-pyrrolines from the reaction of **1** with olefinic dipolarophiles. Lactone **3** in refluxing xylene was converted to a mixture of pyrroline **5** and the corresponding pyrrole **7**. Huisgen had obtained similar mixtures from certain alkenes.[2] Treatment of lactones **2** and **3** with aqueous base afforded the pyrroles **6** and **7**, respectively.

Decomposition of lactone **2** in refluxing xylene did not produce pyrrole **6**. Instead, a dark red, crystalline compound, which revealed a molecular ion at *m/e* 315 in the mass spectrum, was obtained. Obviously, cyclopentadiene has been lost along with carbon dioxide. However, a concerted loss of the two fragments is apparently not required, since it was observed that pyrroline **4** also afforded the product under the same conditions. Simple cleavage of the cyclopentadiene fragment from **4** in a reverse Diels–Alder reaction[9] to give pyrroline **8** would not be in agreement





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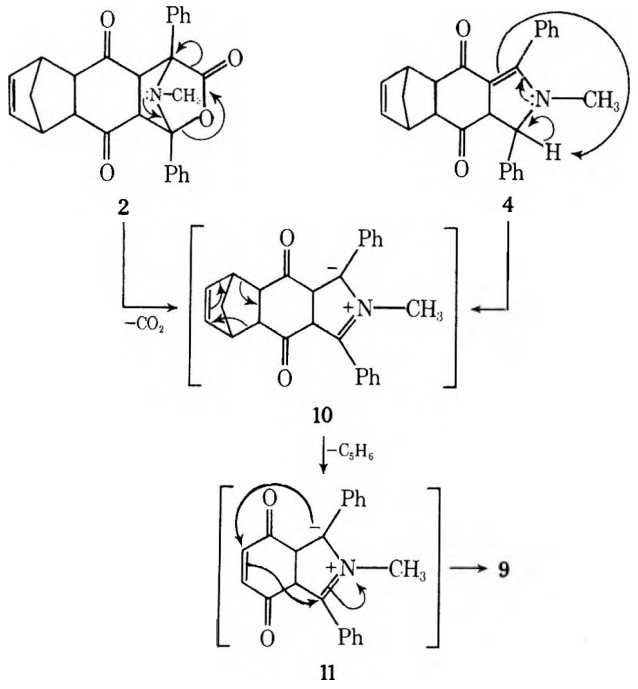
with the NMR spectrum. The proton NMR spectrum was very simple, having three singlets at δ 2.85, 3.30, and 7.47 in a ratio of 4:3:10. The structure assigned to the red solid is that of the novel tetracyclic diketone **9**, 8-aza-7,9-diphenyl-8-methyltetracyclo[4.3.0.0^{3,9}.0^{4,7}]nona-2,5-dione.

A possible mechanism for the formation of **9** from **2** or **4** is presented in Scheme I. The 1,3 dipole **10** suggested in

Scheme I



this mechanism is the same intermediate anticipated[2] in the conversion of **2** to **4**. Hydrogen migration in **4** could result in the reversible formation of **10**. Reverse Diels–Alder cleavage of the cyclopentadiene fragment from **10** would produce a quinone-type double bond in **11**. Intramolecular cycloaddition of the 1,3 dipole to the activated double bond in **11** would afford **9**. The reverse Diels–Alder cleavage of cyclopentadiene could actually precede formation of the 1,3 dipole from **4**.

The 1:1 adducts **2** and **3** appear to be the first N-bridged lactone intermediates isolated from the 1,3-dipolar addition of an oxazolium 5-oxide (munchnone) to a dipolarophile. However, similar 1:1 adducts have been isolated from the reaction of a Reissert salt (munchnone imine) with acetylenic dipolarophiles,[10] from the reaction of an oxazolium 4-oxide (isomunchnone) with dimethyl fumarate,[11] and from the reaction of 4-hydroxythiazolium hydroxides (thiocarbonyl ylides) with olefinic dipolarophiles.[12] Formation of 1:1 adducts from the reaction of a tautomeric form of **1**, the ketene imine **12**, with the dipolarophile acting as a ketenophile as reported by Huisgen[13] is not observed.

Experimental Section

General. The uv, NMR, and mass spectral analyses and microanalyses were performed at the Burroughs-Wellcome Research Laboratories, Research Triangle Park, N.C. Certain mass spectra were also furnished by the Center for Mass Spectrometry at the Research Triangle Institute. Melting points are uncorrected. NMR absorptions are relative to Me_4Si as internal standard. The following spectrometers were used: NMR, Varian T-60; ir, Beckman IR-10; uv, Bausch and Lomb Spectronic 505; mass spectra, Varian CH-5[8b] (electron impact and field desorption) and AEI MS-902. Cycloadditions were carried out under nitrogen, and a barium hydroxide trap was attached to measure any carbon dioxide gas evolution.

Addition of 3-Methyl-2,4-diphenyloxazolium 5-Oxide (1) to Cyclopentadienequinone. Five grams (0.020 mol) of **1**[5] was added to a solution of 3.48 g (0.026 mol) of cyclopentadienequinone[6] in 50 ml of benzene. After stirring for 2 hr at 55–60°, only a small amount of precipitate was observed in the trap. A yellow precipitate was filtered from the reaction mixture and washed with 50 ml of benzene. The yield was 7.4 g (88%) of **2**: mp 158–160°; ir (Nujol) 1755, 1590, 1525, 1160, 1150, 1110, 1045, 790, 690, and 675 cm^{-1}; uv (EtOH) 248 nm (ε 9090) and 363 (11,420); NMR (Me_2SO-d_6) δ 1.32 (2 H, broad s), 2.40 (3 H, s), 2.6–3.0 (2 H, m), 3.0–3.3 (4 H, m), 6.0–6.35 (2 H, m), 7.20–7.65 (10 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 425 (2), 381 (29), 379 (19), 353 (21), 325 (39), 315 (100), 233 (75).

Anal. Calcd for $C_{27}H_{23}NO_4$: C, 76.22; H, 5.45; N, 3.29. Found: C, 76.48; H, 5.62; N, 3.13.

Addition of 1 to Anthracenequinone. To a suspension of 8.00 g (0.028 mol) of anthracenequinone[7] in 100 ml of benzene was added 7.10 g (0.028 mol) of **1**. The thick, yellow suspension was maintained at 55–60° with stirring for 30 min. No precipitate was observed in the $Ba(OH)_2$ trap. A bright yellow precipitate was filtered from the reaction mixture and washed with 50 ml each of benzene and ether. The yield was 13.5 g (89%) of **3**: mp 205–208°; ir (Nujol) 1700, 1525, 1220, 1180, 1165, 750, 700, and 695 cm^{-1}; NMR (Me_2SO-d_6) δ 2.35 (3 H, s), 2.8–3.5 (4 H, m), 4.60 (2 H, broad s), 6.9–7.7 (18 H, m); uv (EtOH) 245 nm (ε 8510) and 372 (14,040); electron-impact mass spectrum (70 eV) *m/e* (rel intensity) 493 (80), 315 (95), 287 (58), 233 (90), 178 (100); field-desorption mass spectrum[8] (3 kV, field anode voltage, and −5.9 kV cathode voltage, 25 and 26 mA through emitter) *m/e* (rel intensity) 537 (29), 493 (100), 491 (27).

Anal. Calcd for $C_{36}H_{27}NO_4$: C, 80.43; H, 5.06; N, 2.61. Found: C, 80.41; H, 5.34; N, 2.38.

Lactones **2** and **3** were prepared in similar yields at room temperature in xylene or tetrahydrofuran. Reaction times much longer than those specified or attempted recrystallization decreased the yield.

Decomposition of Lactone 2 in Refluxing Benzene. A suspension of 5.00 g (0.012 mol) of **2** in 50 ml of benzene was refluxed for 24 hr. Carbon dioxide was liberated. The resulting orange solution was evaporated to an orange solid residue. Recrystallization from warm petroleum ether–ether gave 3.95 g (86%) of the yellow-orange pyrroline **4**: mp 156–159°; ir (Nujol) 1695, 1660, 1620, 1600, 1530, 1345, 1335, 1225, 1165, 1020, 785, 750, 735, 715, and 690 cm^{-1}; NMR ($CDCl_3$) δ 1.43 (2 H, m), 2.47 (3 H, s), 2.8–3.5 (4 H, m), 3.72 (1 H, d, J = 11 Hz), 5.02 (1 H, d, J = 11 Hz), 5.85–6.15 (1 H, m), 6.25–6.55 (1 H, m), 7.3–7.6 (10 H, m); uv (EtOH) 245 nm (ε 13,770) and 361 (10,990); mass spectrum (70 eV) *m/e* (rel intensity) 381 (6), 379 (13), 315 (100), 313 (51), 258 (33), 118 (71), 77 (31), 66 (72).

Anal. Calcd for $C_{26}H_{23}NO_2$: C, 81.86; H, 6.08; N, 3.67. Found: C, 81.87; H, 6.12; N, 3.53.

Decomposition of Lactone 3 in Refluxing Benzene. A suspension of 5.38 g (0.010 mol) of **3** in 50 ml of benzene was refluxed for 24 hr. Carbon dioxide was liberated. The yellow solution was filtered from 0.2 g of a white solid which was not further characterized. Evaporation of the filtrate gave a yellow solid which turned orange on further drying. Recrystallization of the orange solid from methanol yielded 4.31 g (88%) of yellow-green crystals of **5**: mp 202–204°; ir (Nujol) 1710, 1660, 1615, 1530, 1165, 765, 745, and 695 cm^{-1}; NMR ($CDCl_3$) δ 1.92 (1 H, d, J = 10.5 Hz), 2.41 (3 H, s), 2.7–3.5 (2 H, m), 4.48 (1 H, d, J = 2.5 Hz), 4.90 (1 H, d, J = 2.0 Hz), 4.95 (1 H, d, J = 10.5 Hz), 6.7–7.6 (18 H, m); uv ($CHCl_3$) 318 nm (ε 5530) and 368 (15,260); mass spectrum (70 eV) *m/e* (rel intensity) 493 (3), 315 (100), 258 (30), 178 (95), 118 (35).

Anal. Calcd for $C_{35}H_{27}NO_2$: C, 85.17; H, 5.51; N, 2.84. Found: C, 84.96; H, 5.55; N, 2.80.

Decomposition of Lactone 2 in Aqueous Sodium Hydroxide. Three grams (0.007 mol) of **2** was stirred with 50 ml of 5% aqueous sodium hydroxide for 4 hr. The dark red, turbid solution was allowed to stand for 18 hr, then filtered, leaving no measureable amount of residue. The red solution was concentrated to dryness, and the residue was resuspended in methylene chloride. The undissolved solid was collected and washed with additional CH_2Cl_2. The solid was sodium carbonate. Evaporation of the filtrate left an orange solid, which was taken up in hot methanol and left standing for 1 week. Orange-red crystals, 1.46 g (54%), of pyrrole **6** were collected: mp 184–185°; ir (Nujol) 1660, 1155, 755, 690 cm^{-1}; NMR ($CDCl_3$) δ 1.45 (2 H, broad s), 3.29 (3 H, s), 3.20–3.65 (4 H, m), 6.10 (2 H, m), 7.48 (10 H, s); uv (EtOH) 244 nm (ε 30,760) and 314 (11,540); mass spectrum (70 eV) *m/e* (rel intensity) 379 (29), 313 (100), 118 (36), 77 (20), 66 (94).

Anal. Calcd for $C_{26}H_{21}NO_2$: C, 82.30; H, 5.58; N, 3.69. Found: C, 82.01; H, 5.68; N, 3.65.

Decomposition of Lactone 3 in Aqueous Sodium Hydroxide. Three grams (0.006 mol) of **3** was stirred with 50 ml of 5% aqueous sodium hydroxide for 4 hr. Normal work-up gave 1.8 g of a mixture of pale yellow plates and small orange crystals. They proved to be identical except in melting point with the plates melting at 234–238° and the crystals melting at 238–241°. This represents a 65% yield of two crystalline forms of pyrrole **7**: ir (Nujol) 1655, 1525, 1260, 1145, 1095, 750, 690 cm^{-1}; NMR ($CDCl_3$) δ 3.13 (5 H, apparent s), 4.95 (2 H, broad s), 6.9–7.6 (18 H, m); uv ($CHCl_3$) 316 nm (ϵ 12,600); mass spectrum (70 eV) *m/e* (rel intensity) 491 (13), 313 (22), 178 (100).

Anal. Calcd for $C_{35}H_{25}NO_2$: C, 85.52; H, 5.13; N, 2.85. Found: C, 85.39; H, 5.20; N, 2.83 (orange crystals). Found: C, 85.61; H, 5.19; N, 2.76 (pale yellow plates).

Decomposition of Lactone 2 in Refluxing Xylene. Two grams (0.005 mol) of **2** was decomposed in 50 ml of refluxing xylene over a 2-hr period. Carbon dioxide was liberated. Evaporation of the resulting solution under reduced pressure gave a dark oil, which was taken up in hot methanol and left standing for 1 week. Dark red crystals separated, and 1.13 g (76%) of the tetracyclic diketone **9** was collected: sublimation at 185°, mp 224–227°; ir (Nujol) 1665, 1530, 1110, 1000, 975, 755, 705, 690 cm^{-1}; NMR ($CDCl_3$) δ 2.85 (4 H, s), 3.30 (3 H, s), and 7.47 (10 H, s); uv (EtOH) 238 nm (ϵ 29,000), 249 (28,700), and 308 (10,400); mass spectrum (70 eV) *m/e* (rel intensity) 315 (100), 287 (7), 259 (18), 258 (22), 157.5 (7), 118 (53).

Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 79.62; H, 5.47; N, 4.44.

Decomposition of Lactone 3 in Refluxing Xylene. Two grams (0.004 mol) of **3** was decomposed in 50 ml of refluxing xylene over a 2-hr period. Carbon dioxide was liberated. The resulting dark solution was concentrated under reduced pressure to a dark oil. The oil was dissolved in hot methanol and left standing for 1 week. An orange solid, 1.2 g, which appeared to be composed of two types of crystals—finely powdered, bright yellow crystals and larger, dark orange crystals—was deposited. All spectra indicated that the product was a mixture of pyrroline **5** and pyrrole **7**. Extraction of the product with hot cyclohexane–benzene yielded a yellow solid, mp 231–235°, with spectral characteristics matching those of pyrrole **7**.

Decomposition of Pyrroline 4 in Refluxing Xylene. Two grams (0.005 mol) of pyrroline **4** was added to 50 ml of xylene, and the mixture was refluxed for 2 hr. The resulting dark green solution was concentrated to one-third of the original volume under reduced pressure. On standing 0.35 g (21%) of dark red-green crystals, mp 221–224°, separated. The ir spectrum was identical with that of the tetracyclic diketone **9**. Further concentration of the filtrate gave 0.70 g (35%) of pyrrole **6**.

Acknowledgment. The authors thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Minority Biomedical Support Program of the National Institutes of Health for their generous support of this research. The assistance of Drs. David Brent and Stuart Hurlbert of Burroughs-Wellcome Research Laboratories and Mr. Fred Williams of the Research Triangle Center for Mass Spectrometry in obtaining the NMR and mass spectra is gratefully acknowledged.

Registry No.—**1**, 13712-75-9; **2**, 55975-64-9; **3**, 55975-65-0; **4**, 55975-66-1; **5**, 55975-67-2; **6**, 55975-68-3; **7**, 55975-69-4; **9**, 55975-70-7; cyclopentadienequinone, 1200-89-1; anthracenequinone, 1711-46-2.

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p-Cyanophenol from *p*-Nitrobenzaldoxime by an Apparent Dehydration–Displacement, and a Suggested Modification of the Miller–Loudon Conversion of Aldehydes to Nitriles

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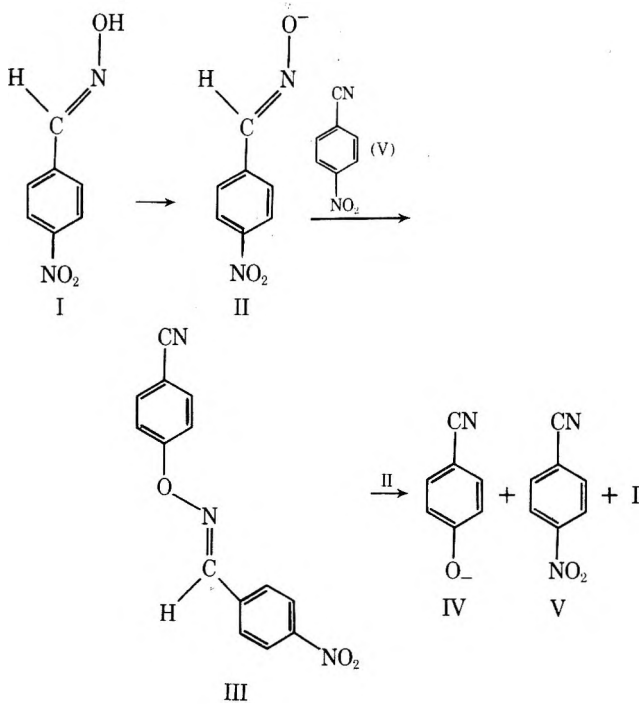
Received May 6, 1975

In Me_2SO solution a salt of *syn*-*p*-nitrobenzaldoxime generates the *p*-cyanophenoxide anion via a chain process in which *p*-nitrobenzonitrile, formed in trace amounts from the oximate anion, is attacked by the oximate with displacement of the nitro group to form *O*-(*p*-cyanophenyl)-*p*-nitrobenzaldoxime (III), which undergoes cleavage as a result of attack by a second oximate anion. The cleavage produces the cyanophenoxide anion and *p*-nitrobenzaldoxime and regenerates the *p*-nitrobenzonitrile, which, reentering the cycle, acts as a chain carrier. Addition of a small amount of *p*-nitrobenzonitrile to the mixture permits the reaction to be carried out in a short time, and the further addition of a suitable base, by converting the oxime formed in the cleavage to the reactive oximate ion, permits the high-yield transformation to the cyanophenol. The salt of *syn*-*o*-nitrobenzaldoxime behaves similarly. The cleavage of the *O*-*p*-cyanophenyl ether formed from the anion of an oxime and *p*-nitrobenzonitrile affords a simple means of converting an aldehyde to a nitrile. Thus, in the presence of a suitable base, piperonaldoxime, employed as such or prepared in situ, gives a high yield of piperonylonitrile.

The observation[1] that an oximate anion is sufficiently basic to effect the cleavage of an *O*-arylaldoxime, e.g., III, in aprotic solution, generating a phenoxide anion, e.g., IV, and a nitrile, e.g., V, leads to the prediction that in Me_2SO solution at room temperature the anion (II) of *p*-nitrobenzaldoxime would readily change to the cyanophenoxide anion IV. To initiate the process it would only be necessary for the oximate II to generate a small amount of *p*-nitrobenzonitrile V, which would react with the oximate ion II undergoing displacement of the nitro group and forming the *O*-arylaldoxime[1] III. Cleavage of III by a second oximate anion, II, acting as a base, would produce the cyanophenoxide IV, regenerating the nitronitrile V, which reentering the cycle would become a chain carrier, and also producing the free oxime I. The crucial step, the formation of



the chain-carrying nitronitrile V from the oximate ion II, sufficiently resembles the formation of nitriles from some aldoximes under the influence of aqueous base[2] that it could be expected to occur to the extent necessary to initiate the process. However, if not enough of the nitronitrile V were formed in this way to permit the rapid conversion of II to IV and I, a little of the chain carrier could be added to serve as a "catalyst". Only half of the oximate II used would be converted to the cyanophenoxide IV unless additional base were added to reconvert the free oxime I also formed to the anion II.

To test these predictions, the sodium salt of *syn*-*p*-nitrobenzaldoxime[3] (II) was stirred in Me_2SO for 1.25 hr at room temperature. From this solution a small amount (7.5%) of *p*-cyanophenol was isolated and 73% of the *p*-nitrobenzaldoxime was recovered. The mass spectrum of early fractions from the chromatography of the alkali-insoluble residue indicated the presence of traces of the nitronitrile V. When the reaction was repeated with a little (2 mol %, based on the oximate used) added nitronitrile V, the conversion to the cyanophenol was 40% and 44% of the oxime was recovered. Thus, there seems little doubt but that the reactions proceed as indicated.

It should be possible to increase the conversion of the oxime to the cyanophenol by introducing additional base into the solution to reconvert the oxime formed in the last step to the salt I. When an additional equivalent of a base, finely ground potassium hydroxide, was added to a mixture of the sodium salt of *p*-nitrobenzaldoxime (II) and a trace of the nitronitrile V, and the mixture was stirred for 5 hr at room temperature (potassium hydroxide has a limited solubility in Me_2SO and dissolves slowly at room temperature), the yield of the cyanophenol was 79%. With the free oxime and a somewhat weaker base (sodium carbonate, 2 equiv) at a higher temperature (114°) the reaction was essentially complete in 10 hr and the yield of *p*-cyanophenol was 83%. A similar reaction without added *p*-nitrobenzonitrile proceeded more slowly, but gave a good yield (80%) after 18.5 hr. With the very strong base (sodium methylsulfinylmethide, 2 equiv) none of the cyanophenol could be detected.

Similar results were obtained with the salt of *syn*-*o*-nitrobenzaldoxime,[3] although a longer reaction time was required and the yield of product, *o*-cyanophenol, was lower. Thus, when a mixture of *syn*-*o*-nitrobenzaldoxime sodium salt, a small amount of *o*-nitrobenzonitrile, and 1 equiv of finely ground potassium hydroxide was stirred at room temperature for 8 hr, the yield of *o*-cyanophenol was 66% (allowing for conversion of the nitronitrile added). In similar tests with the free oxime and 2 equiv of potassium hydroxide at room temperature and with the sodium salt alone at 100°, but in neither case with the addition of the

nitronitrile, there was very little indication (TLC) of formation of product after long periods (greater than 24 hr). Thus, the o-cyanophenol obtained in the first experiment did not arise by isomerization of the aldoximate ion to the anti form and internal displacement of the nitro group.

In the process under study, an aldoxime is in effect dehydrated to the corresponding nitrile through the cleavage of an O-aryl oxime ether (III) formed by displacement of an activated nitro group. The displacement and cleavage form an attractive[1] means of converting certain nitro compounds to phenols. The cleavage of an oxime ether similar to III is the step which permits the conversion of an aldehyde to a nitrile by the Miller–Loudon[4] process, in which the ether is formed from the aldehyde by reaction with O-2,4-dinitrophenylhydroxylamine. It would seem possible to simplify the latter process by utilizing in situ the ether formed from a salt of the oxime, perhaps also formed in situ, in the displacement reaction with a suitable nitro compound, e.g., V, thus avoiding the need for the use of the dinitrophenylhydroxylamine. The modified process might then be as convenient as the Vonwinkel–Bartel[5] method of converting aldehydes to nitriles by dehydration of the oximes, which need not be isolated, with dicyclohexylcarbodiimide in the presence of a copper catalyst. To test the modified process, piperonaldoxime was stirred in Me_2SO with a slight excess of p-nitrobenzonitrile and 2 equiv of potassium hydroxide at room temperature for 3–4 hr. The expected nitrile was obtained in 92% yield (73% after recrystallization to analytical purity). Furthermore, it is not necessary to isolate the oxime; a similar reaction in which the oxime was prepared in situ also gave a good yield of the nitrile.

Although the modified process has been tested on only one of the aldehydes used by Miller and Loudon,[4] the success with both aromatic and aliphatic oximes in the application[1] of the same reactions for the preparation of phenols and the generality of the Miller–Loudon process suggest a rather broad applicability. An obvious exception is a nitroaromatic aldehyde whose oxime (e.g., I) can participate in the reactions discussed above, leading indirectly to the replacement of the nitro group by hydroxyl as well as to the nitrile formation.

The ideal base for use in the present processes would be one strong enough to permit the desired reactions but not capable itself of displacing the nitro group from the nitronitrile V. The success with potassium hydroxide may result from its low solubility and low rate of solution in Me_2SO, with the result that as it enters the solution it is largely neutralized by the free oxime present or produced and hence does not attack the nitronitrile to a damaging extent. The use of strenuous conditions may promote the displacement of the nitro group by other anions; in the reaction employing sodium carbonate at 114° a trace of p,p′-dicyanodiphenyl ether,[6] presumably formed from the nitronitrile V and the cyanophenoxide ion IV, was isolated. Miller and Loudon[4] found ethanolic triethylamine to be a sufficiently strong base to cleave the isolated O-aryloxime, corresponding to III, in their conversion of aldoxime ethers to nitriles. This observation suggests the possibility of using triethylamine as the only base in the reaction of piperonaldoxime with p-nitrobenzonitrile. However, a trial gave none of the nitrile, and the mixture did not develop the transient deep red color characteristic of the successful runs with potassium hydroxide. The similar color in the cyanide ion reactions[1] has been attributed to the presence of Jackson–Meisenheimer complexes,[7] which, although formed reversibly and not necessarily leading to the observed products, give indication through the color formation that the anion is sufficiently basic to give an addition product with the aromatic nitro compound. In Me_2SO triethylamine evidently is not sufficiently basic to develop the necessary concentration of the oximate anion.

Experimental Section

Either a Perkin-Elmer 521 or a Beckman IR-12 spectrophotometer was used for ir spectra, which were run as KBr disks. NMR spectra were recorded on a Varian A-60A or A-56/60 spectrometer. Mass spectra were recorded by Mr. J. Wrona and associates on an Atlas CH5 spectrometer at 70 eV. Microanalyses were performed by Mr. J. Nemeth and associates. Products were identified by comparison of ir and NMR spectra unless otherwise noted. All starting materials were either commercially available reagent grade and were used as received or were prepared in the laboratory by well-known synthetic routes. Me_2SO was stored over Linde Type 4A molecular sieves for 2 weeks before use.

1. p-Cyanophenol from the Sodium Salt of syn-p-Nitrobenzaldoxime. A. With No Added Reagents. The sodium salt was prepared by adding syn-p-nitrobenzaldoxime[8] to 1 equiv of sodium ethoxide in absolute ethanol. After dilution with absolute ether the precipitated salt was collected and dried. A solution of 1.88 g (10 mmol) of the salt in 35 ml of Me_2SO was stirred at room temperature for 1.25 hr and then poured into 150 ml of ice–water containing 2 ml of concentrated hydrochloric acid. The solution was extracted with ether and the ether extract was washed with water, dried ($MgSO_4$), and evaporated. The light yellow residue was chromatographed on silica gel. Elution with hexane–benzene (1:1) produced 1.21 g (73% recovery) of p-nitrobenzaldoxime (NMR spectrum identical with that of an authentic sample). Elution with benzene produced 0.09 g (7.5% conversion) of p-cyanophenol (NMR spectrum identical with that of an authentic sample).

B. With Added p-Nitrobenzonitrile. A mixture of the sodium salt (1.88 g, 10 mmol), p-nitrobenzonitrile (0.09 g, 0.06 mmol), and 35 ml of Me_2SO was stirred at room temperature for 1.25 hr and treated as described above. From the chromatography 0.74 g (44% recovery) of the p-nitrobenzaldoxime and 0.48 g (40% conversion) of p-cyanophenol, both identified by NMR spectra identical with those of authentic samples, were obtained.

C. With Added p-Nitrobenzonitrile and Potassium Hydroxide. A mixture of the sodium salt (1.13 g, 6 mmol), p-nitrobenzonitrile (20 mg, 0.14 mmol), freshly ground potassium hydroxide (338 mg, 6 mmol), and Me_2SO (20 ml) was stirred at room temperature for 5 hr. The mixture was poured into 120 ml of ice–water and the acidified solution was extracted with ether. The ether solution was extracted with 5% aqueous sodium hydroxide and the alkaline solutions were acidified and reextracted with ether. Evaporation of the dried ($MgSO_4$) ether solution gave 566 mg (79%) of slightly impure p-cyanophenol, mp 97–102° (lit.[9] mp 112°).

2. p-Cyanophenol from syn-p-Nitrobenzaldoxime via Salt Formation in Situ. A. Use of Sodium Carbonate with Added p-Nitrobenzonitrile. Anhydrous powdered sodium carbonate (4.24 g, 40 mmol) was added to Me_2SO (25 ml) and the mixture was heated to 70°. A solution of syn-p-nitrobenzaldoxime (3.32 g, 20 mmol) and p-nitrobenzonitrile (0.15 g, 1 mmol) in Me_2SO (35 ml) was added and the resulting bright orange mixture was heated at 114° for 10.5 hr. The cooled mixture was poured into 150 ml of ice–water containing 5 ml of concentrated hydrochloric acid. Ether extraction followed by reextraction into aqueous 5% sodium hydroxide and acidification gave an oil which soon crystallized to give 1.97 g (83%) of p-cyanophenol, mp 103–107°. Recrystallization from benzene raised the melting point to 111–112° (lit.[9] mp 112°). The spectra (ir and NMR) were identical with those of an authentic sample, and the molecular weight as determined by mass spectrometry was 119 (calcd 119).

The ether solution above which had been extracted with alkali was washed with water, dried, and evaporated and the residue was chromatographed on silica gel. Benzene elution gave 0.07 g (3%) of p,p′-dicyanodiphenyl ether: mp 178–180° (lit.[6] mp 180°); ir (KBr) 2230, 1595, 1495, 1253, 1160, 1175, 880, 845 cm^{-1}; NMR ($CDCl_3$) δ 7.66 (d, 2 H), 7.08 (d, 2 H); mass spectrum m/e (rel intensity) (I) 51 (11), 75 (17), 76 (10), 102 (41), 192 (24), 220 (100).

B. Use of Sodium Carbonate without Added p-Nitrobenzonitrile. A similar reaction with no added p-nitrobenzonitrile proceeded more slowly at the same temperature as judged by the color change and the composition as followed by TLC. After a few hours a spot with retention time identical with that of p-nitrobenzonitrile was observed in the TLC. After 18.5 hr at 114° the reaction appeared complete (TLC) and the mixture was worked up as described above, giving 1.90 g (80%) of p-cyanophenol.

3. o-Cyanophenol from the Sodium Salt of *syn*-o-Nitrobenzaldoxime. A reaction mixture similar to 1c employing the sodium salt of *syn*-o-nitrobenzaldoxime[8] (1.13 g, 6 mmol), o-nitrobenzonitrile (20 mg, 0.14 mmol), freshly ground potassium hydroxide (338 mg, 6 mmol), and Me_2SO (20 ml) stirred at room temperature for 8 hr and worked up as in 1c gave 500 mg (66%) of o-cyanophenol, mp 94–95° (lit.[10] mp 98°).

4. Piperonylonitrile. A. From Isolated Piperonaldoxime. The oxime employed, prepared quantitatively in aqueous ethanol, melted at 107–110° (lit.[11] syn isomer 112°, anti isomer 146°); NMR [$(CD_3)_2SO$] δ 8.07 (s, 1, HC=N), 11.01 (s, 1, NOH). A mixture of the oxime (1 g, 6 mmol), p-nitrobenzonitrile (900 mg, 6.1 mmol), freshly ground potassium hydroxide (676 mg, 12 mmol), and 20 ml of Me_2SO was stirred at room temperature for 3–4 hr. The mixture was poured into ice water (150 ml) and the solution was acidified and extracted with ether. The ethereal extract was successively washed with cold 5% aqueous sodium hydroxide and water. After drying ($MgSO_4$) and removal of the solvent in vacuo, 807 mg (92%) of the nitrile was obtained. Recrystallization from ethanol–water gave analytically pure material (645 mg, 73%), mp 87–89° (lit.[4] mp 91–93°).

Anal. Calcd for $C_8H_5NO_2$: C, 65.31; H, 3.43; N, 9.52. Found: C, 65.16; H, 3.46; N, 9.66.

B. From Piperonaldoxime Prepared in Situ. A mixture of hydroxylamine hydrochloride (462 mg, 6.5 mmol), sodium methoxide (350 mg, 6.5 mmol), and 20 ml of Me_2SO was stirred at room temperature for 15 min. Piperonal (1 g, 6.5 mmol) was added and the mixture was heated at 70° for 2 hr. Heating was then discontinued, p-nitrobenzonitrile (980 mg, 6.5 mmol) and freshly ground potassium hydroxide (758 mg, 13 mmol) were added, and the mixture was stirred at room temperature for 3–4 hr. Work-up as in part A and recrystallization from ethanol–water afforded 742 mg (78%) of piperonylonitrile, mp 87–89[10] (lit.[4] mp 92–93°).

Acknowledgment. The authors are grateful to the National Science Foundation (GP 34198X) for the support of this work.

Registry No.—I sodium salt, 56086-86-3; V, 619-72-7; p-cyanophenol, 767-00-0; potassium hydroxide, 1310-58-3; sodium carbonate, 497-19-8; *p,p'*-dicyanodiphenyl ether, 6508-04-9; o-cyanophenol, 611-20-1; *syn*-o-nitrobenzaldoxime sodium salt, 56086-87-4; o-nitrobenzonitrile, 612-24-8; piperonylonitrile, 4421-09-4; *syn*-piperonaldoxime, 20747-41-5; *anti*-piperonaldoxime, 20747-42-6.

References and Notes

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(2) For references see K. Friedrich and K. Wallenfels in Z. Rappaport, Ed., "The Chemistry of the Cyano Group", Interscience, New York, N.Y., 1970, p 93.
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Photoreaction of Benzofurazan and Dimethyl Acetylenedicarboxylate. Synthesis of Isomeric Isoxazoles. Carbon-13 Nuclear Magnetic Resonance Spectra of Isoxazoles and Oxazoles[1]

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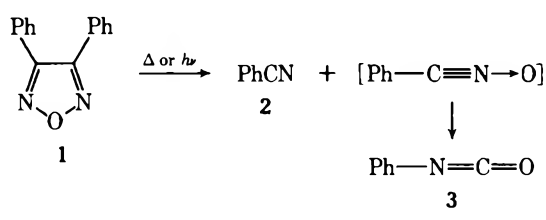
Received April 26, 1974

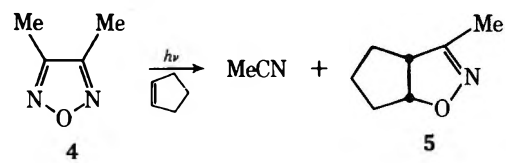
When benzofurazan is irradiated by ultraviolet light (3000 Å), a reactive nitrile oxide intermediate is produced. In order to trap this intermediate, benzofurazan has been irradiated in dimethyl acetylenedicarboxylate (DAD). The nitrile oxide reacts with DAD to produce various geometrical isomers of dimethyl 3-(4-cyanobuta-1,3-dienyl)isoxazole-4,5-dicarboxylate (8). The isoxazoles have been characterized by their ^{13}C NMR spectra. All the isomers have been degraded to the same dimethyl 3-carboxaldehydeisoxazole-4,5-dicarboxylate (9) by ozonolysis. Cis,cis, trans,cis, and trans,trans isomers of 8 have been identified.

The thermal splitting of diphenylfurazan (1) to give benzonitrile (2) and phenyl isocyanate (3) has been known since 1888.[3,4] Ultraviolet irradiation of a 5% ethereal solution of 1 produces the same two compounds.[5]



1 2 3

In order to prove the presence of the highly reactive nitrile oxide intermediate, dimethylfurazan (4) was irradiated in the presence of excess cyclopentene to yield 3-methyl-4,5-trimethylene-2-isoxazoline (5).[5] Irradiation of 1 in cyclopentene produced only 2 and 3 in yields similar to those obtained in the absence of cyclopentene. It has been suggested that this failure to trap the benzonitrile oxide by 1,3-dipolar addition is due to a rearrangement of the intermediate to the isocyanate which is faster than the ground-state 1,3-dipolar addition to cyclopentene.[5] Photolysis of 1 in benzene has yielded diphenylfuroxan, 3,5-diphenyl-1,2,4-oxadiazole, and 3.[6]



4 5

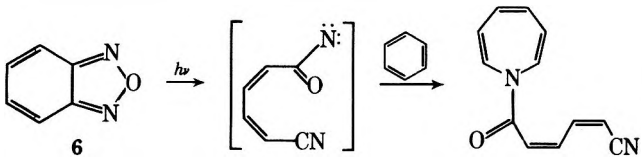
It has been shown recently that the irradiation of benzo-, naphthalo-, and phenanthrofurazan derivatives in the presence of triethyl phosphite affords 1,4-dinitrile derivatives in high yields.[7] An azepide 7 has been isolated from the reaction mixture after irradiation of benzofurazan in ben-

Table I
^{13}C Chemical Shift Data[a,d]

Assignments[b]	8a	[J(CH), Hz]	8b[c]	8c	10	11	12	13	14
CH_3O	53.1	(148.5)	53.4	53.4	53.4				
	53.8	(148.5)	53.9	53.7	53.6				
CN	114.7		114.4	113.9					114.8
CH(6)	120.9	(167.7)	125.3	124.6					
CH(7)	132.1	(163.2)	132.6	134.1					
CH(8)	145.3	(170.6)	147.6	148.6					142.8
CH(9)	103.6	(179.4)	102.5	104.0					106.2
ring C(2)							164.1	160.4	
C(3)	157.1		157.1	157.0	156.9	160.0			
C(4)	115.8		116.0	117.5	116.5	102.7	142.1	137.1	
C(5)	158.2		158.8	158.6	159.9	169.4	151.5	145.7	
C=O	160.7		161.3	161.1	161.7				
	161.7		161.8	162.1	162.3				

[a] Chemical shifts in parts per million relative to Me_4Si. [b] Suggested assignments, some may be interchanged. [c] Resonance peaks due to contamination by 8c omitted. [d] Other resonance peaks: 10 phenyl, 127.5, 128.5, 129.4 and 131.2 ppm; 11 methyl, 11.2 and 11.9 ppm; 12 methyl, 14.3 ppm; 12 benzo, 110.6, 119.8, 124.4 and 124.8 ppm; 13 phenyl, multiple peaks between 126.2 and 132.9 ppm.

zene.[8] Irradiation of 1 or 6 in methanol yields the corresponding N-substituted carbamate.[5,8]

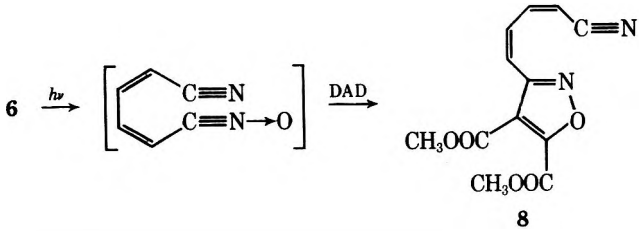


6 7

The work reported here was undertaken in order to determine the possibility of trapping the highly reactive nitrile oxide intermediate using the powerful dipolarophile dimethyl acetylenedicarboxylate. The 1,3-cycloaddition of acetylenes to nitrile oxides is well known[9] and is used here in the preparation of hitherto unknown isomeric isoxazoles.

Results

The photochemical reaction of benzofurazan (6) and DAD yields a mixture of isomeric isoxazoles 8. Chromatographic separation on a silica gel column yields three fractions of crystalline materials (8a, 8b, and 8c). The compounds 8a and 8c are pure isomers as shown by ir and NMR spectroscopy, but the intermediate product 8b could not be totally freed of contamination by 8c. TLC and column chromatography and fractional recrystallization have been employed in attempts to purify 8b but TLC of the purest fraction exhibited two distinguishable spots.

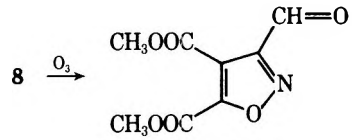


8

All the isoxazoles are white, crystalline compounds, insoluble in water but soluble in most organic solvents. Their solubility decreases in the order of their elution from the column, and their melting points increase in the same order.

The isoxazoles decolorize potassium permanganate with ease but are almost completely resistant to a solution of bromine in carbon tetrachloride. Hydrolysis in boiling 2 *N* HCl or in hot aqueous KOH affords a resinous product which could not be identified. No –C≡N stretching vibration is present in the infrared spectrum of this product.

Oxidation of the isomers with potassium permanganate,[10] osmate and periodate,[11] and permanganate and periodate[12] in all cases yields a yellow-red oil after work-up. This oil exhibits no –C≡N stretching vibration in the infrared, and its NMR spectrum includes a weak aldehydic proton resonance. The low intensity of this peak, and the presence of other peaks in the spectrum, indicated the oil to be a mixture of several compounds. Treatment with 2,4-dinitrophenylhydrazine produced a derivative with a broad melting point. Ozonolysis of the isoxazoles gives a much cleaner reaction, producing the aldehyde 9 in good yield.



9

Discussion

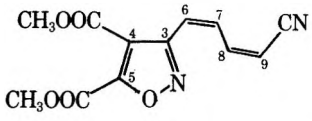
The essential structure of the isomeric photoproducts is clearly shown to be the isoxazole 8 by uv, ir, and NMR spectroscopy and mass spectrometry. The sensitivity of the compounds to permanganate oxidation, and the lack of reaction with Br_2–CCl_4 indicate the 1,4-disubstituted diene structure.[13] Although isoxazoles are known to rearrange readily under the influence of ultraviolet radiation to the corresponding oxazoles via an azirine intermediate,[14] the compounds described here are characterized as isoxazoles by ^{13}C NMR spectroscopy. The various structures of the individual isomers are deduced from their ^1H NMR spectra.

The electronic spectra of the photoproducts exhibit two bands: at ca. 205 nm due to the isoxazole ring,[15] and at ca. 273 nm due to the butadiene moiety.

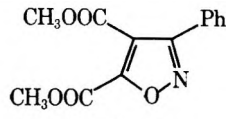
The mass spectra of the isomeric products are very similar, as expected, and confirm the molecular weight of 262. Initial fragmentations involve loss from or of the isoxazole side chains (–CN, $-OCH_3$, $-CO_2CH_3$) and in many cases are supported by metastable peaks. The molecular ion peak is absent in the spectrum of the isoxazole aldehyde. Instead, the spectrum exhibits a relatively weak M + 1 peak at *m/e* 214 (15%) due to the protonation of the isoxazole in the mass spectrometer. The ion at *m/e* 126 (100%) is assigned to a methyl 2-carboxaldehyde–azirinium-3-carboxylate ion.[16]

The resonance peaks in the ^{13}C NMR spectra of the three isomeric isoxazoles 8a, 8b, and 8c are listed in Table I

with data for related compounds. In general, an isoxazole ring is expected to exhibit two low-field peaks due to C_3 and C_5 with a *higher* field resonance due to C_4; an oxazole ring is expected to exhibit two low field peaks due to C_4 and C_5 with a *lower* resonance due to C_2. These predictions are borne out by the data in Table I.



8a



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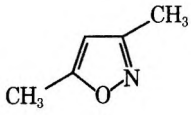

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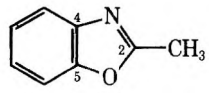

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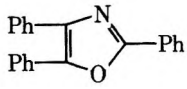

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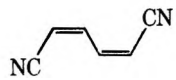


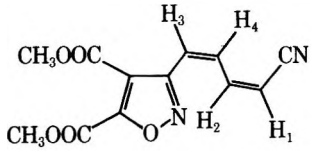
14

The ^{13}C resonances of the butadiene moiety are assigned by comparison with **14** and by examination of the $J(CH)$ coupling observed in the **8a** spectrum obtained in the absence of wide-band proton decoupling. Owing to the approximate symmetry of the 1,4-disubstituted cis,cis isomer **8a**, the coupling generates the same long-range $J(CH)$ splitting pattern for both C_6 and C_9, and for both C_7 and C_8.

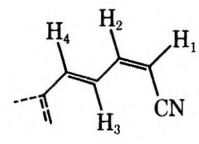
Although a cis,cis structure is expected to be the initial product obtained in the photolysis of **6**, a trans,trans structure should be the most stable configuration for the 1,4-disubstituted butadiene.[17]

Analyses of the **8a** proton spectra at 100 and 251 MHz, with limited iteration (LAOCN3), yield the best, but not unique, fit: H_1, 5.76; H_2, 7.89; H_3, 7.07; H_4, 6.92 (δ ppm) and J_{12} = 10.98; J_{23} = 11.64; J_{24} = −0.28; J_{34} = 11.60; J_{13} and $J_{14} \simeq 0$ Hz. The high-field resonance of H_1 is due to its position within the shielding cone of the anisotropic cyanide group[13] and the low-field resonance of H_2 is attributed to its position adjacent to the isoxazole nitrogen within the deshielding region of the heteroaromatic ring. Double resonance experiments confirm the observed coupling. The parameters above provide valuable information concerning the configuration of the isomer **8a**: thus, protons H_1 and H_2, and protons H_3 and H_4 are cis,[13,17,18] the conformation is s-trans, and the isomer is assigned a cis,cis structure.

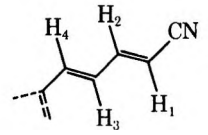
The isomer **8c** exhibits a complex second-order spectrum due to a coincidence of the H_2 and H_3 resonance frequencies. However, since J_{12} and $J_{34} \simeq 14.6$ Hz (i.e., both H_1 and H_2, and H_3 and H_4 are trans), and proton H_2 is removed from the vicinity of the isoxazole ring (indicated by the upfield shift in its resonant frequency), this isomer is assigned the trans,trans configuration.



cis,cis isomer **8a**



trans,cis isomer **8b**



trans,trans isomer **8c**

The isomer **8b** is assigned a trans,cis configuration since $J_{12} \simeq 11.5$ Hz and again proton H_2 resonates at the higher field.

Experimental Section

General. A Rayonet Srinivisan-Griffin photochemical reactor (No. RPR-100) was used for the reaction of benzofurazan and DAD. Ozonolysis was performed using a Welsbach Laboratory ozonator (T-408). Benzofurazan was prepared by reduction[19a] of benzofurazan oxide.[19b] Dimethyl acetylenedicarboxylate (DAD) was obtained from Fluka AG, Switzerland, and was rapidly distilled prior to use. Compounds **10**,[20] **11**,[21] **12**,[21] **13**,[21] and **14**[22] were prepared as previously described. Petroleum ether mentioned below was a 60–80° fraction. ^1H NMR spectra at 60 and 100 MHz were taken on Varian A-60 and HA-100 spectrometers in $CDCl_3$ solution. ^{13}C NMR spectra at 63.1 MHz and ^1H NMR spectra at 251 MHz were obtained in Professor F. A. L. Anet's laboratory at UCLA by one of us (I.Y.). Ir spectra were determined for KBr disks with a Beckman IR-20 spectrophotometer. Uv spectra were obtained in 95% ethanol solution with a Unicam SP-800 spectrometer. Mass spectra (70 eV) were obtained on an AEI MS12 spectrometer at the University of Surrey, England. Elemental analyses were performed by the University of Surrey Microanalytical unit.

Photochemical Reaction of Benzofurazan and DAD. Benzofurazan (12 g, 0.1 mol) was dissolved in DAD (14.2 g, 0.1 mol) and this solution was placed in the annular cavity between two concentric glass tubes (inner tube, Pyrex, 42 mm o.d.; outer tube, quartz, 46 mm i.d.). The solution was irradiated using lamps with principal emission at 3000 Å, when the color changed slowly from yellow to red. After 30 hr, some bright yellow crystals appeared between the tubes. By removing and reimmersing the inner tube these crystals were moved to the bottom, thus exposing more solution to the light. After 120 hr, the photoreaction was stopped and the reaction mixture was transferred to a 500-ml flask, washing the tubes with 100 ml of ethyl acetate. The mixture was dissolved in 200 ml of ethyl acetate by warming on a steam bath. Silica gel (30 g) was added and the solvent was evaporated. Dry silica gel and the residue were placed over a column of silica gel (400 g) and elution first made with petroleum ether. The first yellowish oil (2.5 g) obtained solidified after a few hours and was identified as benzofurazan. The second oily compound (3.3 g) with the characteristic smell of DAD was identified as unreacted ester (ir). Elution was continued gradually increasing the polarity of the eluent by using 75:25 and 50:50 compositions of petroleum ether and benzene. With this solvent mixture a bright yellow oil was obtained. This solidified after a few hours (4.9 g, mp 77–80°, 18.7%). Recrystallization from petroleum ether yielded white needle crystals (4.4 g, mp 82–83°). This compound is referred to as **8a**: mass spectrum *m/e* (rel intensity) 262 (70), 236 (20), 231 (18), 203 (67), 172 (19), 171 (100), 144 (18), 116 (17), 103 (26), 78 (59), 77 (26), 59 (80); ir 2200 (C≡N), 1725 and 1750 (C=O), 810, 960, 1460, and 1620 cm^{-1} (isoxazole ring[23]); uv 205 nm (log ϵ 3.93) (isoxazole ring[15]), 272 (4.29) (diene). Anal. Calcd for $C_{12}H_{10}N_2O_5$: C, 54.96; H, 3.84; N, 10.68. Found: C, 55.16; H, 3.58; N, 10.76.

Elution with pure benzene yielded a white solid compound)7.2 g, mp 101–110°, 27%). Recrystallization from benzene–petroleum ether yielded fine white needles (6.0 g, mp varies between 104 and 114°). This fraction is referred to as **8b**: ir 2200 (C≡N), 1735 and 1750 cm^{-1} (C=O); uv 205 nm (log ϵ 3.93), 273 (4.54); NMR δ 4.00, 4.06 (carboxylic CH_3); 5.60 (H_1); 6.90–7.50 ppm (H_2, H_3 and H_4).

Elution with mixtures of benzene and chloroform (75:25 and 50:50) yielded a white solid compound (3.8 g, mp 145–150°, 14.5%). Recrystallization of this compound from benzene–petroleum ether produced hard, white crystals (3.1 g, mp 156–157°). This compound is referred to as **8c**: ir 2200 (C≡N), 1732 and 1755 cm^{-1} (well resolved, C=O); uv 205 nm (log ϵ 3.93), 274 (4.52); NMR δ 3.94, 4.03 (carboxylic CH_3); 5.66 (H_1); 6.90–7.50 ppm (H_2, H_3, and H_4). Anal. Calcd as above. Found: C, 55.16; H, 3.63; N, 10.87.

The end fraction, eluted by chloroform, was an unidentified dark red oil (5.1 g) which failed to solidify even after several weeks.

Ozonolysis of the Isoxazoles. Ozone–oxygen was bubbled through a solution of the isomer **8a** (1.31 g, 5 mmol) in methylene chloride (200 ml) at −10°. The ozonolysis was continued until a deep blue color developed in the reaction solution, indicating an

excess of dissolved ozone. The reaction was assumed to be complete and oxygen was passed through the mixture for 5 min to remove excess ozone. The solution became colorless. Methanol (25 ml) was then added and the mixture was left to stand at room temperature for 1 hr. Work-up involved the addition of 50 ml of water followed by solvent removal to give a yellow oil (750 mg, 70%).[24] This yellow oil exhibited no C≡N stretching band in the ir, and the NMR spectrum exhibited an intense aldehydic proton resonance. The NMR spectrum indicated the presence of some impurities which were removed by distillation of the oil at 150° (2 mm) in a molecular still. The distillate solidified to give a white compound (550 mg, mp 74–76°, 52%, 2,4-DNP derivative mp 232–234°). Ozonolysis of the isomers **8b** and **8c** gave the same aldehyde in comparable yields: mass spectrum *m/e* (rel intensity) 214 (15), 182 (66), 138 (15), 127 (65), 126 (100), 124 (42), 94 (83), 92 (97), 81 (55), 80 (34); ir 2800 (CH aldehyde), 1707 cm^{-1} (C=O aldehyde); uv 205 nm (log ϵ 3.60), 215 (3.55, broad), 267 (3.20, broad); NMR δ 3.98, 4.04 (carboxylic CH_3); 10.65 ppm (CHO). Anal. Calcd for $C_8H_7NO_6$: C, 45.08; H, 3.31; N, 6.57. Found: C, 45.18; H, 3.26; N, 6.45.

Acknowledgments. We wish to thank Dr. G. A. Webb and the University of Surrey, England, for 100-MHz ^1H NMR spectra, mass spectra, and computing facilities. We greatly appreciate the use of Professor F. A. L. Anet's ^{13}C and ^1H NMR equipment at UCLA and we should like to acknowledge the assistance of Dr. F. H. Köhler at Technischen Universität München in taking some ^{13}C NMR spectra.

Registry No.—**6**, 273-09-6; **8a**, 56086-88-5; **8b**, 56086-89-6; **8c**, 56086-90-9; **9**, 56086-91-0; **9** 2,4-DNPH, 56086-92-1; **10**, 7710-44-3; **11**, 300-87-8; **12**, 95-21-6; **13**, 573-34-2; **14**, 1557-59-1; DAD, 762-42-5.

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Photochemical Synthesis of 6,7-Dihydro-5*H*-dibenz[*c,e*]azepine and 5,6,7,8-Tetrahydrodibenz[*c,e*]azocine Derivatives[1]

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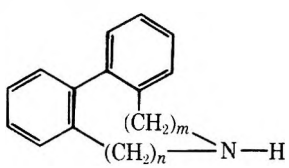
Received March 18, 1975

Photolysis of several substituted 2-iododibenzylamine hydrochlorides in aqueous solution provided convenient syntheses of the corresponding 6,7-dihydro-5*H*-dibenz[*c,e*]azepines in useful yields. Thus, irradiation of amines **2**, **3**, **4**, and **5** gave dibenzazepines **1a**, **10**, **11**, and **12** in 57, 44, 32, and 27% yield, respectively. However, irradiation of **6** yielded only biphenyl **14** together with a small amount of dibenzoxepine **15**. The formation of **14** and **15** was rationalized as originating from a photoassisted hydrolysis of the desired product **13**. Likewise, photolysis of three *N*-(2-halogenobenzyl)-β-phenethylamine hydrochlorides provided convenient syntheses of the corresponding 5,6,7,8-tetrahydrodibenz[*c,e*]azocines. Thus, irradiation of amines **7** and **8** gave dibenzazocines **1b** and **16** in 33% yield, while irradiation of **9** yielded the corresponding cyclic product in 22% yield. ^1H NMR examination of the dibenzazocines confirmed that they existed in a skewed biphenyl conformation, and that inversion of the system by rotation through the planar biphenyl was hindered.

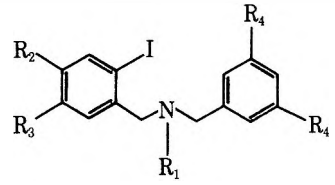
The physiological activities manifested by certain compounds containing either the bridged biphenyl system **1a**,[3–5] **1b**,[4] or **1c**[5,6] continue to stimulate interest in the development of general synthetic routes to these ring systems. The reported synthesis of substituted biphenyls by the photolysis of aryl iodides in benzene[8] prompted us to investigate a photochemical route to the bridged biphenyl systems **1a** and **1b**. During the course of our investigation an extension of the original reaction was employed for effecting intramolecular arylations leading to phenanthrenes,[9] and later to the synthesis of aporphines.[10]



1a, $n = m = 1$
b, $n = 1; m = 2$
c, $n = m = 2$

The results of our investigation demonstrate that photochemically induced intramolecular arylation may be employed not only in the formation of six-membered rings but also for constructing some seven- and eight-membered cycles. In this paper, we summarize the synthesis of several 6,7-dihydro-5*H*-dibenz[*c,e*]azepine (**1a**) derivatives and provide further details on the synthesis of the 5,6,7,8-tetrahydrodibenz[*c,e*]azocine (**1b**) ring system.

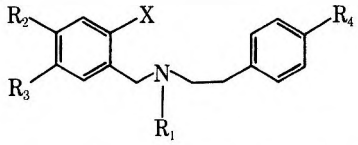
Table I
Substituted 2-Iododibenzylamines



Compd	Method	R_1	R_2	R_3	R_4	Yield, %[a]	HCl mp, °C
2	1	H	H	H	H	95	153–155
3	1	Me	H	H	H	88	190.5–192.5
4	2	H	H	NO_2	H	62	216–218
5	2	H	H	NO_2	OMe	52	253–255
6	2	H	H	H	OMe	94	180–182

[a] For the steps depicted in eq 1 or 2.

Table II
***N*-(2-Halogenobenzyl)-β-phenethylamines**



Compd	X	R_1	R_2	R_3	R_4	Yield, %	HCl mp, °C
7	I	H	H	H	H	82	145
8	I	Me	H	H	H	89	168–170
9	Br	H	OCH_2O		OH	77	226–228

Results and Discussion

Aryl Halides. The preparation of the substituted 2-iododibenzylamines used in this study was readily accomplished by one of two alternate methods: (1) nucleophilic displacement on a 2-iodobenzyl bromide by a substituted benzylamine (eq 1), or (2) condensation of a substituted 2-

$$ArCH_2Br \xrightarrow{Ar'CH_2NHR} ArCH_2NRCH_2Ar' + HBr \quad (1)$$

iodobenzaldehyde with a substituted benzylamine and subsequent reduction of the resultant Schiff base with borohydride (eq 2). The choice between method 1 and method 2

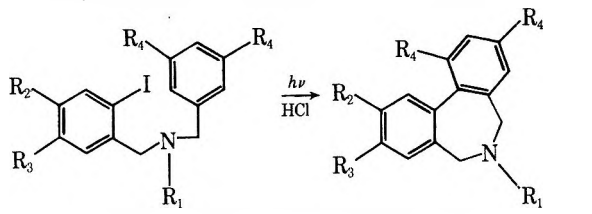
$$ArCHO \xrightarrow{Ar'CH_2NH_2} ArCH{=}NCH_2Ar' \xrightarrow{BH_4^-} ArCH_2NHCH_2Ar' \quad (2)$$

was generally dictated by the available starting materials. The structures of the 2-iododibenzylamines employed in this study are summarized in Table I.

The *N*-(2-iodobenzyl)-β-phenethylamines used in this study were also prepared by the displacement method. The aryl bromide was synthesized by the second method.[11] The *N*-(2-halogeno)-β-phenethylamines prepared are summarized in Table II.

Photolysis Conditions. The photolysis of 2-iododibenzylamine (**2**) was studied in some detail in order to establish the optimum reaction conditions. Irradiation of **2** in hexane solution with light of wavelength >280 nm from a medium-pressure mercury lamp afforded dibenzylamine as the only identifiable product.[12] From this result it appeared that water, a very poor hydrogen atom donor, would be a better choice of solvent.[13] Accordingly, irradiation of a dilute aqueous solution of **2**, as the hydrochloride, gave, after 196 hr, dibenzazepine **1a** in 57% yield together with 13% of the starting material.[1a] Characterization of **1a** was established by comparison with an authentic sample.[14]

Table III
Photolysis of Substituted 2-Iododibenzylamines



Compd	Irradiation time, hr	Starting material, %	Dibenzazepine, %	Other products, %
2	196	13	**1a**, 57	
3	96	10[a]	**10**, 44	Chloro compd, 5[a] Dehalogenated compd, <1
4	192	8	**11**, 32	
5	480	26	**12**, 27	
6	192	0	**13**, 0	**14**, 22; **15**, <5

[a] GC yield.

We found that optimum yields of **1a** were obtained when the longer wavelength regions of the ultraviolet spectrum were used to effect photolysis. The synthesis of **1a** using light of wavelengths <280 nm gave a low recovery of basic material, suggesting that photolytic cleavage of the benzylic carbon–nitrogen bond occurred on irradiation at shorter wavelengths.

As a result of the above observations, the standard photolysis procedure used for the aryl iodides was the irradiation of the amine hydrochlorides in water under a nitrogen atmosphere and with a mercury lamp fitted with a Pyrex filter. As noted below, a variation in the procedure was possible with aryl bromide **9**. The progress of the photolysis reactions was monitored by either gas chromatography (GC) or thin layer chromatography (TLC).

Photolysis of Substituted 2-Iododibenzylamines. Having established the apparently optimum conditions for the photochemical synthesis of the 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine ring system, we turned our attention to the effect of various substituents on the reaction. The subsequent photolysis experiments are summarized in Table III.

A logical first variation was the use of tertiary amine **3** instead of the secondary amine.[15] Accordingly, we found that irradiation of **3** afforded a 44% yield of 6-methyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine (**10**). In addition, the reaction mixture contained starting material (10%), *N*-methyl-2-chlorodibenzylamine (5%),[16] and a trace of *N*-methyldibenzylamine (<1%).

Identification of **10** was facilitated by the agreement of the melting point of its hydrobromide salt with the reported value.[3a] The mass spectral fragmentation pattern of this compound was also of diagnostic value. It showed strong M^+ and M − 1 peaks together with minor ions resulting from cleavage of the heteroatom bridge. This fragmentation behavior was also characteristic of the mass spectra of the other dibenzazepines prepared during this study. Final confirmation of the structure of **10** was obtained by its independent synthesis from **1a** by reductive methylation.

Photolysis of the aryl-substituted amines **4** and **5** afforded, respectively, 3-nitro-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine (**11**) and 1,3-dimethoxy-9-nitro-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine (**12**). Although the yields of **11** and **12** were considerably lower than that of **1a**, the photolysis pro-

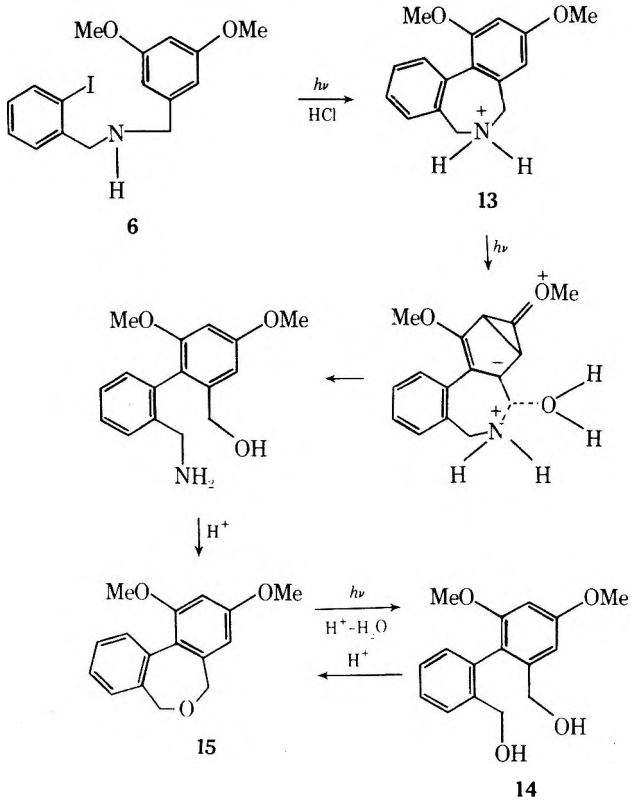
cedure nevertheless was superior to alternative methods of synthesis. The slow rate of the latter reaction may have been due to the intense absorptions of 12 in the long-wavelength ultraviolet region, thus decreasing the energy available to effect homolysis of the carbon–iodine bond.

In addition to the mass spectral evidence, characterization of compound 11 was provided by its uv spectrum, which showed a strong maximum at 300 nm (log ϵ 4.13), consistent with the presence of the 4-nitrobiphenyl chromophore.

The ^{1}H NMR spectrum of 12 was especially useful in assigning its structure. The occurrence of a clearly defined ABX pattern at low field was indicative of the substitution pattern on the nitro-substituted aromatic ring and the appearance of two nonequivalent methoxyl resonances at δ 3.83 and 3.80 was in full accord with the dibenzazepine structure. A variable-temperature ^{1}H NMR study resulted in a sharpening of the benzylic methylenes[17] from a broad diffuse multiplet at 25° to two singlets at 100°. This result implied that dibenzazepine 12 existed in a preferred skewed biphenyl conformation in which the benzylic hydrogens were diastereotopic and that conformational interchange to the equivalent skewed form was slow at 25°.[18]

A limitation of the photolysis reaction for the general synthesis of aryl-substituted dibenzazepines was demonstrated in the case of 3′,5′-dimethoxy-2-iododibenzylamine (6). Irradiation of 6 yielded 2,2′-bis(hydroxymethyl)-4,6-dimethoxybiphenyl (14) as the major product together with a very small amount of 1,3-dimethoxy-5,7-dihydrodibenz[c,*e*]oxepine (15). The molecular formulae of 14 and 15 were established by high-resolution mass spectrometry, and the fragmentation pattern of 14 below the M − 18 peak was essentially identical with that of 15. The ^{1}H NMR and ir spectra of 14 and 15 were likewise confirmatory of the structures. Treatment of 14 with *p*-toluenesulfonic acid in refluxing benzene effected its conversion to 15, thereby establishing the relationship between the two compounds.

Scheme I
Photolysis of 3′,5′-Dimethoxy-2-iodobenzylamine (6)



In previous studies Zimmerman and Sandel[20] had shown that electron-donating groups have the ability to stabilize a negative charge at a meta position in a benzene ring in the first photoexcited state. Thus, the formation of 14 and 15 may be rationalized as having occurred through a photoassisted hydrolysis of the desired dibenzazepine 13 (cf. Scheme I) with charge stabilization of the transition state provided by the first excited state of the *m*-dimethoxy aryl system. Additional driving force for hydrolytic cleavage was undoubtedly provided by the relief of strain attendant upon opening of the seven-membered ring. However, it appeared that strain relief alone was not sufficient to promote the hydrolytic cleavage, since the other dibenzazepines were stable to the photolysis conditions. Furthermore, the presence of the nitro group in 11 appeared to counteract the facilitating effect on the hydrolysis, since no neutral cleavage product was detected in this reaction.

In summary, photolysis of several substituted 2-iododibenzylamine hydrochlorides in aqueous solution provided convenient syntheses of the corresponding dibenzazepines in synthetically useful yields. The chief limitations of the method were the long reaction times required and the possibility of competing hydrolysis reactions in the presence of aryl oxygen substituents meta to the bridging carbons.

Photolysis of *N*-(2-Iodobenzyl)-β-phenethylamines. We previously reported that irradiation of 7 for 113 hr afforded a 25% yield of 5,6,7,8-tetrahydrodibenz[c,*e*]azocine (1b) together with *N*-benzyl-β-phenethylamine (10%).[1a] However, further examination of the reaction mixture indicated the presence of other unidentified bases. In subsequent experiments, the structures of these bases were elucidated by spectral examination and confirmed by unambiguous syntheses. Thus, the products obtained from the irradiation of 7 for 222 hr are shown in Scheme II and the yield data for the experiment are summarized in Table IV. These data were obtained by GC examination of the reaction mixture.

A similar mixture resulted from the irradiation of the tertiary amine 8 for 144 hr (Scheme II and Table IV). In

Scheme II
Photolysis of *N*-(2-Iodobenzyl)-β-phenethylamine (7) and Its *N*-Methyl Derivative (8)

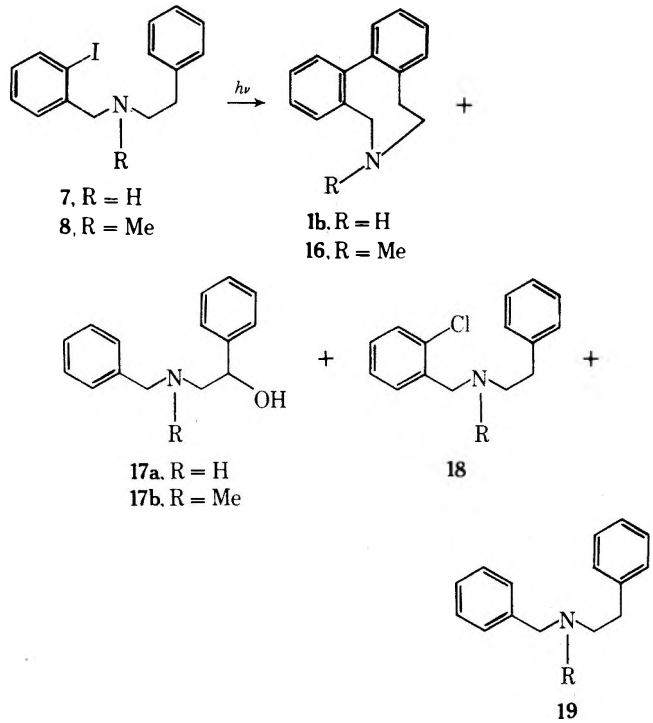


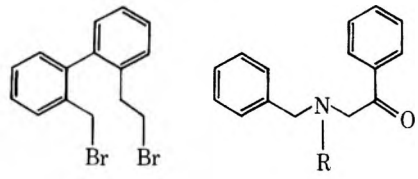
Table IV
Yield Data for the Photolysis of 7 and 8

Component	Yield, % a (R = H)	b (R = Me)
7 or 8	15 (7)	28 (8)
Dibenzazocine	33 (1b)	33[a] (16)
17	15	12[a]
18	8	5
19	13.5	6

[a] Isolated yield.

this case, the 6-methyl-5,6,7,8-tetrahydrodibenz[c,e]azocine (**16**) and the ethanolamine derivative **17b** were isolated from the reaction mixture. The remainder of the yield data for the experiment was derived from GC analysis.

The structure of dibenzazocine **1b** was verified by an unambiguous synthesis from dibromide **20**.[1a] Compound **20**



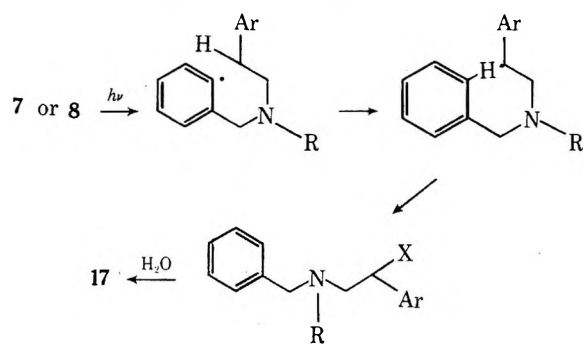
20 **21**

was prepared in seven steps from 2,2′-diphenic acid using procedures reported by Ahmed and Hall.[21] Careful methylation of **1b** with methyl iodide gave **16**.

The ethanolamine derivatives **17a** and **17b** were prepared independently by reaction of α-bromoacetophenone with the appropriate benzylamine followed by borohydride reduction of the intermediate ketones **21**. The chlorinated and dehalogenated photolysis products were likewise prepared by standard procedures.

The photolysis of **7** and **8** presumably involved the initial formation of an aryl radical by the homolysis of the carbon–iodine bond.[8] The isolation of **17** provided some evidence that this pathway was indeed followed. The most logical mechanism for the formation of **17** is depicted in Scheme III and involves the formation of a benzyl radical from the initial aryl radical via hydrogen transfer. An alternative, the production of **17** from dehalogenated compound **19**, seems unlikely in the absence of any ethanolamine byproducts corresponding to **1b** or **16**.

Scheme III
Radical Mechanism for the Formation of Ethanolamine Derivative 17



X = halogen

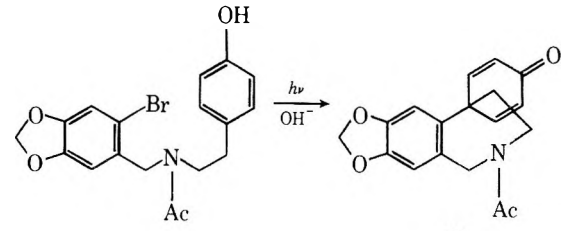
The synthesis of **1b** and **16** demonstrated that the photolysis procedure used to prepare some dibenzazepine derivatives could also be applied to the synthesis of some simple dibenzazocines. Once again, the long reaction times were a drawback to the method.

Table V
Chemical Shifts and Geminal Coupling Constants for the Dibenzazocine $ArCH_2N$ Protons

Compd	δ values, ppm	J_{gem}, Hz
1b	3.10, 3.83	15.0
16	3.14, 3.49	13.5
23	3.02, 5.22	14.0
24	3.07, 5.25	14.0

Photolysis of *N*-(2-Bromobenzyl)-β-phenethylamines. During the course of our investigation Omura and Matsuura[22] reported that the irradiation of *p*-bromophenol in a basic medium gave, among other products, 2,4′-dihydroxybiphenyl and 4,4′-dihydroxybiphenyl. At the same time, Kametani and coworkers[23] summarized the synthesis of several aporphines and morphinandienones by irradiation of the appropriate phenolic bromoisoquinolines under similar conditions. In a later paper, this same group reported the photochemical synthesis of the crinine ring system in 5% yield by irradiation of 4′-hydroxy-*N*-(2-bromopiperonyl)-β-phenethylamine (**9**). No other photoproducts were reported.

In our hands attempts to reproduce this result were unsuccessful. However, irradiation of the *N*-acetyl derivative of **9** in an alkaline solution did afford a 2% yield of the dienone **22** as the only isolable product.



22

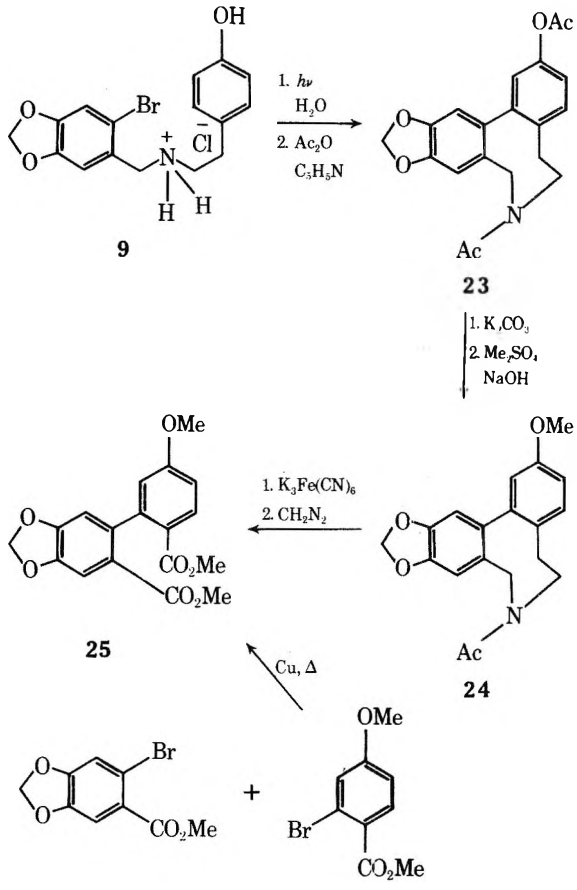
In contrast to these results, we found that irradiation of the hydrochloride of **9** in water for 10 hr followed by acetylation of the total product gave a 22% yield of 6,11-diacetoxy-2,3-methylenedioxy-5,6,7,8-tetrahydrodibenz[c,e]azocine (**23**) together with starting material *O,N*-diacetate (57%, Scheme IV).[24] Moreover, use of a Corex filter shortened the reaction time to 2 hr without decreasing the product yield. In both cases, the reaction times were substantially shorter than those encountered in the aryl iodide photolysis and the desired product was formed in a synthetically useful yield.

The structure of **23** was confirmed by the stepwise degradation outlined in Scheme IV. Previous experience in our laboratory[25] suggested that intermediate **24** could be further degraded using excess potassium hexacyanoferrate(III) in a strongly basic medium. The two-step procedure afforded the 2,2′-diphenic ester **25** in low yield. The structure of **25** was subsequently verified by an Ullmann synthesis.

The synthesis of **23** suggested that photolysis of other *N*-(2-bromobenzyl)-β-phenethylamines might be the preferred method for preparing various substituted 5,6,7,8-tetrahydrodibenz[c,e]azocines. The generality of this reaction is presently under investigation.

^{1}H NMR Data on the Dibenzazocines. ^{1}H NMR examination of the dibenzazocines prepared in this study showed that the bridge protons of each compound exhibited geminal coupling. In particular, the $ArCH_2N$ protons in this series appeared in the spectra as easily recognized doublets which are summarized in Table V. In view of the large chemical shift difference between the two diastereotopic protons of the $ArCH_2N$ group in compounds **23** and

Scheme IV
Formation and Stepwise Degradation of 6,11-Diacetoxy-2,3-methylenedioxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (23)



24, the assignment was verified by both double resonance and homonuclear INDOR decoupling experiments. The nonequivalence of the bridge protons indicated that the eight-membered ring existed predominantly in one conformation at room temperature, and that inversion of the system by partial rotation of the skewed biphenyl was hindered.

The magnitude of the chemical shift difference (ca. 2.2 ppm) between the diastereotopic hydrogens of the $ArCH_2N$ group in **23** and **24** is a consequence of the geometry of the preferred conformation. Examination of models indicates that such a result is best accounted for if these compounds adopt a distorted half-tub conformation similar to that suggested by Mislow and coworkers[1c] for the analogous carbocyclic system. It is in this conformation that one of the hydrogens of the benzylic aminomethyl group experiences deshielding from the more proximate aromatic ring and the amide carbonyl[26] while its diasteotopic partner is placed in a position to experience shielding from the more distant aromatic ring. As a consequence of the skewed biphenyl conformation, the methylenedioxy protons of **23** and **24** were also expected to be in slightly different environments with respect to the bridge atoms. In accordance with our expectations, we found that these protons appeared as two narrow doublets with a geminal coupling of 1.2 Hz.[27,28]

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt apparatus. ^1H NMR spectra were recorded on the following spectrometers: Varian A-60, Bruker HF-X 90, and Jeol MH-100. Chemical shifts are reported in parts per million downfield from Me_4Si as an internal standard. Ir spectra were obtained on a Perkin-Elmer 137 or 621 spectrometer and uv spectra were run on a Beckman DB-G spectrometer. Mass spectra were run on the AEI MS-902 mass spectrometer at the Research Triangle Institute, Research Triangle Park, N.C. Gas chromatographic analyses were carried out on a F & M Model 402 instrument equipped with a flame ionization detector. Elemental analyses were performed by Janssen Pharmaceutica, Beerse, Belgium, Galbraith Laboratories, Inc., Knoxville, Tenn., and M-H-W Laboratories, Garden City, Mich.

2-Iodo-5-nitrobenzaldehyde. 2-Acetamidobenzaldehyde[29] was nitrated and hydrolyzed to 2-amino-5-nitrobenzaldehyde by the procedure of Cohn and Springer.[30] This product (33.2 g, 0.2 mol) was added to 20% H_2SO_4 (400 ml) cooled below 10°. The mixture was cooled and maintained at 0° while $NaNO_2$ (13.8 g, 0.2 mol) in water (200 ml) was added slowly with vigorous stirring. Thirty minutes after the addition was complete the mixture was filtered rapidly into an iced flask and the filtrate was added to a solution of KI (200 g) in water (250 ml). The resulting mixture was heated on a steam bath for 30 min, cooled in ice, and filtered. The residue was dissolved in $CHCl_3$ and the solution was washed successively with water, aqueous Na_2CO_3, aqueous $Na_2S_2O_3$, and water, and then dried ($MgSO_4$). Evaporation of the solvent left a solid residue which yielded 28.0 g (51.3%) of yellow needles after chromatography on alumina with C_6H_6 and recrystallization from EtOH. An analytical sample, recrystallized from C_6H_6–hexane as yellow flakes, had mp 111–112°; ir (Nujol) 1685 cm^{-1}; ^1H NMR (Me_2CO-d_6) δ 8.33 (dd, 1, J = 2.5, 9 Hz), 8.54 (dd, 1, J = 0.75, 9 Hz), 8.66 (dd, 1, J = 0.75, 2.5 Hz), 10.26 (s, 1). Anal. Calcd for $C_7H_4INO_3$: C, 30.35; H, 1.46; N, 5.05. Found: C, 30.11; H, 1.35; N, 5.07.

3,5-Dimethoxybenzylamine. To a stirred refluxing suspension of $LiAlH_4$ (3.5 g, 0.09 mol) in dry THF (75 ml) was added dropwise a solution of 3,5-dimethoxybenzonitrile (10.0 g, 0.06 mol) in THF (50 ml). One hour after addition was complete, the reaction mixture was cooled and a solution of water (5 ml) in THF (25 ml) was added slowly. The mixture was filtered and the residue was washed with Et_2O. The combined filtrate and wash were evaporated and the residual oil was dissolved in MeOH (50 ml) and treated with concentrated HCl (6 ml). Addition of Et_2O precipitated 10.5 g (84.3%) of the hydrochloride, mp 205–207°. (Although 3,5-dimethoxybenzylamine had been previously reported,[31] its hydrochloride salt had not been reported.)

Substituted 2-Iododibenzylamines. A representative procedure for each different method of synthesis is provided.

2-Iododibenzylamine (2). 2-Iodobenzyl bromide[32] (2.0 g, 6.7 mmol) in DME (25 ml) was added to a threefold quantity of benzylamine in DME (10 ml) and the resulting mixture was stirred for 2.5 hr at room temperature. Afterwards, the solvent was evaporated and the residue was washed with aqueous Na_2CO_3 and with water. The residual yellow oil was then dissolved in Et_2O and the hydrochloride generated with anhydrous HCl gas. Two recrystallizations from EtOH–Et_2O afforded 2.3 g (95%) of white microneedles, mp 153–155°. The free base vacuum distilled as a pale yellow oil: bp 154–156° (0.4 mm); ^1H NMR ($CDCl_3$) δ 1.48 (broad s, 1), 3.67 (s, 2), 3.70 (s, 2), 6.65–7.53 (m, 8), 7.70 (dd, 1, J = 7.0, 1.2 Hz). Anal. Calcd for $C_{14}H_{15}ClIN$: C, 46.73; H, 4.17; N, 3.89. Found: C, 47.04; H, 4.21; N, 4.04.

***N*-Methyl-2-iododibenzylamine (3).** The tertiary amine was prepared and isolated by the same method described for **2**. Anal. Calcd for $C_{15}H_{17}ClIN$: C, 48.21; H, 4.59; N, 3.75. Found: C, 48.38; H, 4.66; N, 3.80.

2-Iodo-5-nitrodibenzylamine (4). A solution of 2-iodo-5-nitrobenzaldehyde (1.0 g, 3.6 mmol) and benzylamine (0.4 g, 3.7 mmol) in MeOH (75 ml) was stirred at room temperature for 4 hr. The solvent was then removed, the solid residue (1.31 g) was dissolved in warm MeOH (100 ml), and KBH_4 (500 mg) was added to the still warm solution (about 40°). The solution was allowed to cool to room temperature and, after 1 hr, additional KBH_4 (500 mg) was added. After stirring overnight, the solvent was removed in vacuo and the residue was treated with water (25 ml) and extracted with Et_2O. Addition of concentrated HCl to the Et_2O gave 935 mg (62.3%) of the amine hydrochloride as pale yellow flakes: mp 216–218° dec; ^1H NMR ($CDCl_3$, amine) δ 1.91 (s, 1), 3.90 (s, 2), and 3.91 (s, 2, overlapping), 7.40 (s, 5), 7.82 (dd, 1, J = 2.5, 8.2 Hz), 8.08 (d, 1, J = 8.2 Hz), 8.38 (d, 1, J = 2.5 Hz). Anal. Calcd for $C_{14}H_{14}ClIN_2O_2$: C, 41.55; H, 3.49; N, 6.92. Found: C, 41.22; H, 3.37; N, 6.88.

3′,5′-Dimethoxy-2-iodo-5-nitrodibenzylamine (5). The alcohol insoluble Schiff base derived from 2-iodo-5-nitrobenzaldehyde and 3,5-dimethoxybenzylamine was reduced in DME using $Zn(BH_4)_2$.[33] The product was isolated as the hydrochloride salt, mp 245–245° dec. Anal. Calcd for $C_{16}H_{18}ClIN_2O_4$: C, 41.35; H, 3.91; N, 6.03. Found: C, 41.11; H, 3.91; N, 6.04.

3',5'-Dimethoxy-2-iododibenzylamine (6). The synthesis and isolation of **6** was carried out by the same method described for **4**. The hydrochloride salt crystallized from MeOH–Et_2O, mp 176–178°. Anal. Calcd for $C_{16}H_{19}ClINO_2$: C, 45.79; H, 4.57; N, 3.34. Found: C, 46.02; H, 4.71; N, 3.47.

***N*-(2-Iodobenzyl)-β-phenethylamine (7).** A mixture of 2-iodobenzyl bromide[32] (5.0 g, 17 mmol) and β-phenethylamine (3.5 ml) in DME (30 ml) was stirred at room temperature for 45 min. The mixture was then poured into dilute Na_2CO_3 (250 ml) and the resulting suspension was extracted with several portions of Et_2O. The combined Et_2O extracts were washed with water, dried (Na_2SO_4), and evaporated. The residual oil was dissolved in ethanolic HCl and crystallized by addition of Et_2O and cooling. The hydrochloride was recrystallized from Me_2CO as white plates: 5.14 g (81.9%); mp 145°; ^1H NMR (CCl_4, amine) δ 1.90 (s, 1), 2.70 (s, 4), 3.73 (s, 2), 6.67–7.57 (m, 8), 7.72 (d, 1, J = 8.0 Hz). Anal. Calcd for $C_{15}H_{17}ClIN$: C, 48.21; H, 4.59; N, 3.75. Found: C, 48.44; H, 4.75; N, 3.77.

***N*-Methyl-*N*-(2-iodobenzyl)-β-phenethylamine (8).** The synthesis and isolation of **8** was analogous to that described for **7**. The hydrochloride salt was crystallized from Me_2CO, mp 168–170°. Anal. Calcd for $C_{16}H_{19}ClIN$: C, 49.56; H, 4.95; N, 3.61. Found: C, 49.85; H, 4.89; N, 3.74.

4'-Hydroxy-*N*-(2-bromopiperonyl)-β-phenethylamine (9). A mixture of 2-bromopiperonal[34] (2.29 g, 0.01 mol), tyramine hydrochloride (1.735 g, 0.01 mol), and anhydrous K_2CO_3 (4.14 g, 0.03 mol) in MeOH (450 ml) was refluxed for 2.5 hr and then cooled to 0°. In one batch KBH_4 (3.24 g, 0.06 mol) was added and the resulting mixture was stirred for 2.5 hr at room temperature. Solid CO_2 was then added in small portions until pH 8. The MeOH was removed, the residue was partitioned between H_2O (60 ml) and $CHCl_3$ (100 ml), and the aqueous phase was extracted with additional $CHCl_3$ (three times). After drying (Na_2SO_4), the combined $CHCl_3$ extracts were evaporated and the residual solid was dissolved in hot methanolic HCl. Concentration and cooling gave 2.99 g (77.3%) of the hydrochloride, mp 227–228.5° dec. An analytical sample recrystallized from MeOH gave plates, mp 226–228° dec (lit.[11] mp 234–236°). Anal. Calcd for $C_{16}H_{17}BrClNO_3$: C, 49.70; H, 4.43; N, 3.62. Found: C, 49.52; H, 4.44; N, 3.45.

The amine was regenerated with K_2CO_3 and crystallized as white needles, mp 139–141°, from C_6H_6–hexane. Anal. Calcd for $C_{16}H_{16}BrNO_3$: C, 54.87; H, 4.60; N, 4.00. Found: C, 54.63; H, 4.47; N, 4.02.

The *O,N*-diacetate of **9** was prepared by acetylation in C_5H_5N–Ac_2O (2:1). Recrystallization from C_6H_6–hexane afforded needles: mp 133–133.5°; ir ($CHCl_3$) 1754, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 and 2.08 (two s, 3 total, NAc), 2.27 (s, 3, OAc), 2.77–2.98 and 3.30–3.69 (m, 2 each, $ArCH_2CH_2N$), 4.38 and 4.73 (two s, 2 total, $ArCH_2N$), 5.97 (s, 2), 6.63–7.33 (m, 6). Anal. Calcd for $C_{20}H_{20}BrNO_5$: C, 55.31; H, 4.64; N, 3.33. Found: C, 55.26, H, 4.43; N, 3.11.

Photolysis Apparatus. The apparatus used in the photolysis experiments contained an outer glass vessel in which the solution to be irradiated was placed. Fitting inside this vessel was a water-cooled quartz well containing a type L 450-W medium-pressure mercury vapor lamp manufactured by Englehard Hanovia, Inc. When in use the Pyrex or Corex filter sleeve was inserted around the lamp within the quartz well. Inlet and outlet ports on the outer vessel provided a means of purging the solution continuously with nitrogen.

GC analysis of the photolysis reactions was done using a glass column (8 ft × 0.1 in. i.d.) packed with 4% SE-30 on Aeropak 30. TLC analyses were carried out on microscope slides coated with a 4:1 mixture of silica gel H and silica gel HF_{254} (Brinkmann).

Photochemical Synthesis of 6,7-Dihydro-5*H*-dibenz[*c,e*]azepines. A. Irradiation of 2. Using the standard conditions discussed in the text, a solution of **2** (1.24 g, 3.8 mmol) in 2% HCl (425 ml) was irradiated for 196 hr. The yellow solution was washed with Et_2O (2 × 75 ml), made basic with aqueous Na_2CO_3, and reextracted with Et_2O (3 × 100 ml). Evaporation of the second Et_2O extract gave a yellow oil. When a solution of the oil in fresh Et_2O was treated with anhydrous HCl gas, an off-white solid precipitated. Two recrystallizations from EtOH–Et_2O gave 108 mg of white needles identified as 6,7-dihydro-5*H*-dibenz[c,*e*]azepine (**1a**) hydrochloride by ir comparison with an authentic sample.[14] The mother liquors were combined, basified, and extracted with Et_2O. The residual oil from evaporation of the Et_2O was subsequently chromatographed on alumina. Elution with C_6H_6 yielded 165 mg (13%) of slightly impure **2** while further elution with C_6H_6–$CHCl_3$ (3:1) and $CHCl_3$ gave 177 and 159 mg, respectively, of **1a**. The total yield of the product, as the amine, was thus 428 mg (57%). The amine formed white needles from C_6H_6–hexane: mp 50°; ir (film) 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.08 (s, 1), 3.53 (s, 4), 7.08–7.50 (m, 8). The hydrochloride formed white needles from EtOH–Et_2O: mp 292° dec (lit.[3a] mp 288° dec); uv (95% EtOH) 247 nm (log ε 4.18). Anal. Calcd for $C_{14}H_{14}NCl$: C, 72.55; H, 6.10; N, 6.05. Found: C, 72.73; H, 6.18; N, 6.21.

B. Irradiation of 3. The irradiation of **3** (1.01 g, 3.0 mmol) was carried out by the same procedure described for **2**. On alumina chromatography, elution with C_6H_6 removed all of the product mixture components except the major one. The yields of the minor components reported in the text were estimated from the GC and column chromatography data. Further elution of the column with a C_6H_6–$CHCl_3$ gradient yielded 276 mg (44%) of **10** as a yellow oil: ^1H NMR (CCl_4) δ 2.42 (s, 3), 3.32 (s, 4, bridge methylene), 7.17–7.50 (m, 8); mass spectrum *m/e* (rel intensity) 209 (M^+, 65.6), 208 (M − 1, 100). The hydrobromide salt formed nodules from EtOH–Et_2O, mp 225–227° (lit.[3a] mp 223–225°). The hydroperchlorate salt precipitated from an aqueous solution of the hydrobromide on addition of 35% $HClO_4$, and gave white prisms, mp 193–195°, from EtOH–Et_2O. Anal. Calcd for $C_{15}H_{16}ClNO_4$: C, 58.16; H, 5.22; N, 4.52. Found: C, 57.91; H, 5.35; N, 4.53.

Methylation of compound **1a** using modified Clarke–Eschweiler conditions[35] afforded a product whose spectral and chromatographic properties were identical with those of the sample obtained from the photolysis reaction.

C. Irradiation of 4. The hydrochloride salt (1.21 g, 3.0 mmol) of **4** was irradiated in water (435 ml) and the resulting cyclic product **11** was purified as the hydrochloride salt: mp 320–321° dec; uv (95% EtOH) 300 nm (log ε 4.13); ir (Nujol) 1335 cm^{-1}; ^1H NMR (CCl_4, amine) δ 2.13 (s, 1), 3.60 (s, 2), and 3.66 (s, 2, overlapping, bridge methylene), 7.33–7.83 (m, 5), 8.17–8.33 (overlapping s, 2); mass spectrum *m/e* (rel intensity) 240 (M^+, 89.5), 239 (M − 1, 100), 193 (47.5), 165 (73.5). Anal. Calcd for $C_{14}H_{13}ClN_2O_2$: C, 60.76; H, 4.74; N, 10.12. Found: C, 60.96; H, 4.79; N, 9.89.

D. Irradiation of 5. The experiment was carried out in the same manner described above for **4** using the hydrochloride salt (1.39 g, 3.0 mmol) of **5**. The oily product, **12**, was converted to the hydrochloride, mp 281–282° dec, after recrystallization from EtOH as yellow needles: uv (95% EtOH) 348 nm (log ε 4.00), 236 (4.08); ^1H NMR (CCl_4, amine) δ 2.08 (s, 1), 3.00–3.80 (m, 4, bridge methylene), 3.80 (s, 3), 3.83 (s, 3), 6.48 (overlapping d, 2), 7.67 (d, 1, J = 9 Hz), 8.03–8.23 (overlapping d, 2); mass spectrum *m/e* (rel intensity) 300 (M^+, 100), 299 (M − 1, 53.2), 271 (73.5), 269 (78.2). Anal. Calcd for $C_{16}H_{17}ClN_2O_4$: C, 57.05; H, 5.10; N, 8.32. Found: C, 56.95; H, 5.09; N, 8.10.

E. Irradiation of 6. An aqueous solution of the hydrochloride salt (900 mg, 2.1 mmol) of **6** was irradiated under the usual conditions for 192 hr. Following an acid–base extraction, the major product was shown by GC to be in the nonbasic fraction. Subsequent chromatography of this fraction on alumina gave 130 mg (22.4%) of diol **14** as a brown oil which was shown to be essentially pure by GC and ^1H NMR. A portion of the oil was sublimed at 150° (0.2 mm) to get a waxy solid which recrystallized as white prisms, mp 72.5–74.5°, from C_6H_6–hexane: uv (95% EtOH) 282 nm (log ε 3.52); ir (Nujol) 3500–3100 cm^{-1} (hydrogen-bonded hydroxyl); ^1H NMR (CCl_4) δ 3.51 (s, 3), 3.67 (s, 3), 3.90–4.20 (m, 6, methylene and hydroxyl), 6.33 (d, 1, J = 2 Hz), 6.55 (d, 1, J = 2 Hz), 6.70–7.40 (m, 4); mass spectrum *m/e* (rel intensity) 274 (M^+, 92.5), 256 (M − 18, 100), 44 (62.9). Anal. Calcd for $C_{16}H_{18}O_4$: 274.1205. Found: 274.1208.

A small amount of a second component was noted by GC in the mother liquors from the crystallization of **14**. This component, dibenzoxepine **15**, was isolated from a separate reaction in low yield (<5%) as a solid which recrystallized as white prisms from C_6H_6–hexane: mp 137–138.5°; uv (95% EtOH) 261 nm (log ε 4.14), 287 (3.95), 293 (3.92); ^1H NMR (CCl_4) δ 4.80 (s, 3), 4.83 (s, 3), 4.00–4.40 (m, 4, bridge methylene), 6.54 (s, 2), 7.20–7.70 (m, 4); mass spectrum *m/e* (rel intensity) 256 (M^+, 100). Anal. Calcd for $C_{16}H_{16}O_3$: 256.1099. Found: 256.1124.

A solution of the diol **14** (39.4 mg) in C_6H_6 (10 ml) containing a catalytic amount of *p*-toluenesulfonic acid was refluxed overnight in an apparatus fitted with a Dean-Stark trap. Preparative chromatography of the resulting residue on a silica gel plate afforded a white solid (17.2 mg), mp 137–138°, which proved identical in its chromatographic and spectral properties with compound **15** obtained from the photolysis experiment.

5,6,7,8-Tetrahydrodibenz[*c,e*]azocine (1b). A. From Irradia-

tion of 7. A solution of **7** (3.37 g, 10 mmol) in 2% HCl (435 ml) was irradiated for 222 hr. Afterwards, the reaction mixture was subjected to an acid–base extraction and the basic fraction was passed through a short alumina clean-up column to get 2.14 g of a mixture of bases (cf. Scheme II). The components of the mixture were identified by comparison of the GC retention times with those of authentic samples prepared by unambiguous methods (vide infra). In addition, small samples of **17a** and **18a** were isolated by preparative GC and were found to have spectral properties identical with those of the reference compounds.

The basic mixture obtained from a 113-hr photolysis of **7** was chromatographed on alumina to get **19a** (10%), a mixture of the other as then unidentified bases, and **1b** (25%).[1a] The cyclic product was purified as the hydrochloride salt, which crystallized from EtOH as needles: mp 321–323° dec; uv (95% EtOH) 231 nm (log ε 4.15), 276 (2.89). The free base was regenerated with aqueous Na_2CO_3 and crystallized from hexane as prisms: mp 119–120°; ^1H NMR (CCl_4) δ 2.10–3.20 (m, 5, $ArCH_2CH_2NH$), 3.10 and 3.83 (d, 1 each, J = 15.0 Hz, $ArCH_2N$), 6.95–7.38 (m, 8). Anal. Calcd for $C_{15}H_{15}N$: C, 86.07; H, 7.24; N, 6.69. Found: C, 85.77; H, 7.28; N, 6.64.

B. From Dibromide 20.[21] Overnight treatment of a C_6H_6 solution of **20** with excess benzylamine at 50° afforded, in low yield, 6-benzyl-5,6,7,8-tetrahydrodibenz[c,e]azocine: ^1H NMR (CCl_4) δ 2.55 (s, 2), 2.30–4.00 (m, 6, bridge methylene), 6.90–7.50 (m, 13). The product was isolated by acid–base extraction and preparative chromatography on a silica gel plate. The hydroperchlorate salt crystallized from EtOH–Et_2O as white prisms, mp 227–229°. Anal. Calcd for $C_{22}H_{22}ClNO_4$: C, 66.07; H, 5.56; N, 3.50. Found: C, 65.83; H, 5.64; N, 3.40.

Catalytic debenzylation was effected over 10% Pd/C at atmospheric pressure and in the presence of a few drops of concentrated HCl. Hydrogen uptake was 98% complete after 45 min. The catalyst was removed by filtration and the solvent was evaporated to get a white, solid residue. Recrystallization from EtOH–Et_2O gave an 86% yield of amine hydrochloride that was identical with the photochemically produced material.

2-Benzylamino-1-phenylethanol (17a). α-Bromoacetophenone (500 mg, 2.7 mmol) and benzylamine (600 mg, 5.6 mmol) were condensed in DME to get ketone **21a** (R = H). A solution of the product in Et_2O was treated with HCl gas and the resulting amorphous solid, 130 mg, was dissolved in MeOH. The solution was cooled in ice and treated with KBH_4 (70 mg), added in small portions over 45 min. Following addition, the mixture was kept cold for 90 min and then allowed to stand overnight at room temperature. Water was added and the mixture was extracted with Et_2O. Evaporation of the Et_2O gave **17a** as a pale yellow oil which solidified on standing. The product sublimed readily over a steam bath at 2 mm to yield white crystals: mp 100–102°; ir (Nujol) 3250 cm^{-1}; ^1H NMR (CCl_4, amine) δ 2.50–3.00 (m, 4), 3.71 (s, 2), 4.60 (broad s, 1), 7.20 (broad s, 10); mass spectrum m/e (rel intensity) 227 (M^+, 8), 120 (100), 91 (84.5). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.25; H, 7.55; N, 6.16. Found: C, 79.40; H, 7.42; N, 6.09.

***N*-(2-Chlorobenzyl)-β-phenethylamine (18a).** The amine was produced in 88.9% yield by the in situ $NaBH_4$ reduction of the Schiff base formed from β-phenethylamine (1.0 g) and excess 2-chlorobenzaldehyde in EtOH. The hydroperchlorate salt formed white needles, mp 198–200°, from EtOH. Anal. Calcd for $C_{15}H_{17}Cl_2NO_4$: C, 52.03; H, 4.96; N, 4.05. Found: C, 52.33; H, 4.94; N, 4.12.

6-Methyl-5,6,7,8-tetrahydrodibenz[c,e]azocine (16). A. From Irradiation of 8. The photolysis experiment was carried out in the same manner as described for the irradiation of **7**. The requisite reference compounds were prepared using the methods described for the corresponding secondary amines. Following the GC analysis, the basic mixture was chromatographed on alumina to get, in pure form, **17b** (12%) and **16** (33%): ^1H NMR (CCl_4) δ 2.00–2.90 (m, 4, $ArCH_2CH_2N$), 2.33 (s, 3, NMe), 3.14 and 3.49 (d, 1 each, J = 13.5 Hz, $ArCH_2N$), 7.00–7.30 (m, 8); mass spectrum m/e (rel intensity) 223 (M^+, 93), 222 (M − 1, 52), 208 (54), 180 (66), 179 (100), 178 (68), 155 (64). The hydroperchlorate salt crystallized from EtOH as white rods, mp 185–186°. Anal. Calcd for $C_{16}H_{18}ClNO_4$: C, 59.35; H, 5.61; N, 4.32. Found: C, 59.34; H, 5.62; N, 4.33.

B. From Dibenzazocine 1b. Treatment of **1b** with MeI in Et_2O gave a crystalline precipitate which was dissolved in dilute Na_2CO_3 and extracted with Et_2O. The Et_2O extract was dried ($MgSO_4$) and evaporated. The residual oil was treated with ethanolic HCl and some unreacted **1b** was recovered by crystallization of the hydrochloride salt. The mother liquor residue was then dissolved in dilute hydrochloric acid and treated with 35% $HClO_4$ to get the hydroperchlorate salt of **16** that was identical with the above photochemically produced material.

6,11-Diacetoxy-2,3-methylenedioxy-5,6,7,8-tetrahydrodibenz[c,e]azocine (23). The hydrochloride salt (400 mg, 1.034 mmol) of **9** was dissolved in water (700 ml) and the solution was divided into two batches. Each was irradiated for 2 hr under the usual conditions except that the Corex filter was used. Afterwards, the mixtures were adjusted to pH 2 with 6 *N* HCl and extracted once with Et_2O (175 ml). The Et_2O extracts were discarded. The mixtures were then adjusted to pH 7–8 with 10% NaOH and extracted with $CHCl_3$ (2 × 200 ml). The combined $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated to get 182.0 mg of basic residue. Acetylation of this residue in C_5H_5N–Ac_2O (2:1 by volume) overnight afforded 243.0 mg of an *O,N*-diacetate mixture.

Preparative chromatography of the mixture on a silica gel plate gave 68.7 mg (15%) of the starting material *O,N*-diacetate and 75.7 mg (21%) of **23** as a white foam. Bulb-to-bulb distillation of the foam gave a clear, pale yellow glass: bp 140° (0.003 mm); uv (MeOH) 222 nm (log ε 4.28), 259 (3.84), 290 (3.67); ir ($CHCl_3$) 1755, 1628, 1499 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (s, 3, NAc), 2.30 (s, 3, OAc), 2.34–5.00 (m, 4, $ArCH_2CH_2N$), 3.02 and 5.22 (d, 1 each, J = 14.0 Hz, $ArCH_2N$), 5.95 (two narrow d, 2, J = 1.2 Hz, OCH_2O), 6.73 and 7.37 (s, 1 each), 6.99–7.33 (m, 3); mass spectrum m/e (rel intensity) 353 (M^+, 100). Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.94; H, 5.17; N, 3.76.

6-Acetyl-11-methoxy-2,3-methylenedioxy-5,6,7,8-tetrahydrodibenz[c,e]azocine (24). Compound **23** (27.3 mg, 0.077 mmol) and K_2CO_3 (10.7 mg, 0.077 mmol) were stirred at room temperature in MeOH for 25 min. The reaction was quenched by addition of small pieces of Dry Ice (to pH 7–8). Preparative chromatography then gave 18.1 mg (75%) of the intermediate phenol as a white solid. Recrystallization from MeOH yielded needles: mp 275–277°; ir (KBr) 1608, 1500 cm^{-1}. Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.25; H, 5.19; N, 4.40.

A solution of the phenol (28.6 mg, 0.092 mmol) in refluxing 95% EtOH (4 ml) was treated, under nitrogen, with 10% NaOH and Me_2SO_4, both added dropwise, after the procedure of Uyas and Shah.[36] When the reaction was complete by TLC, the mixture was cooled, adjusted to pH 7, diluted with water, and extracted with $CHCl_3$ (three times). Evaporation of the dried (Na_2SO_4) extracts gave 32.4 mg (108%) of **24** as a solid. Recrystallization from C_6H_6 afforded a solid: mp 187.5–188.5°; ir ($CHCl_3$) 1625, 1604, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12 (s, 3, NAc), 2.30–4.43 (m, 4, $ArCH_2CH_2N$), 3.82 (s, 3, OMe), 3.07 and 5.25 (d, 1 each, J = 14.0 Hz, $ArCH_2N$), 5.98 (two narrow d, 2, J = 1.2 Hz, OCH_2O), 6.76 and 7.43 (s, 1 each, 1-H and 4-H), 6.80 (d, 1, J = 2.7 Hz, 12-H), 6.90 (dd, 1, J = 2.7, 8.0 Hz, 10-H), 7.11 (d, 1, J = 8.0 Hz, 9-H); mass spectrum m/e (rel intensity) 325 (M^+, 100). Anal. Calcd for $C_{19}H_{19}NO_4$: 325.1314. Found: 325.1313.

2,2′-Dicarbomethoxy-4,5-methylenedioxy-5′-methoxybiphenyl (25). A. From the Degradation of 24. A mixture of **24** (53 mg, 0.163 mmol), KOH (4.4 g), and $K_3Fe(CN)_6$ (25 g) in water (100 ml) was heated on a steam bath with occasional swirling for 71 hr. Additional KOH (4.4 g) and $K_3Fe(CN)_6$ (25 g) were added every 24 hr. Afterwards, the mixture was cooled and filtered, and the separated yellow solid was washed with cold water. The combined filtrate and washings were acidified with 50% H_2SO_4 and reheated on a steam bath for 24 hr. Upon cooling a very dark blue solid precipitated. Both the solid and the dark blue aqueous phase were continuously extracted with $CHCl_3$ for 38 hr. The combined $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated to get 370.4 mg of yellow oil.

A solution of the oil and CH_2N_2 in CH_2Cl_2 was stored in a freezer for 18 hr. Afterwards, the solvent and excess CH_2N_2 were evaporated and the resulting residue was subjected to three preparative chromatographs to get 6.2 mg (11%) of **25** as a solid. Although the material still contained some traces of impurity by TLC and GC, the R_f, retention time, and spectral properties were identical with those of the unambiguously prepared sample. Anal. Calcd for $C_{18}H_{16}O_7$: 344.0896. Found: 344.0900.

B. From the Ullmann Synthesis. A mixture of methyl 2-bromopiperonylate[37] (375 mg, 1.45 mmol), methyl 2-bromo-4-methoxybenzoate[38] (375 mg, 1.53 mmol), and copper powder (200 mg, 3.15 mmol) was heated under nitrogen in a Woods metal bath at 225° for 4 hr. After cooling the mixture was dissolved in $CHCl_3$, filtered, and twice subjected to preparative chromatography to get 313.8

mg of yellow oil. GC analysis showed this to be a mixture of three components. Subsequent purification by preparative GC using a 10 ft × 0.25 in. 20% SE-30 column at 250–260° then gave 29.3 mg (6%) of **25** as a yellow-white solid. Sublimation at 125° (0.9 mm) yielded an analytically pure white solid: ir ($CHCl_3$) 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.59 (s, 3), 3.65 (s, 3), 3.84 (s, 3), 6.08 (s, 2), 6.67 and 7.54 (s, 1 each), 6.70 (d, 1, J = 2–3 Hz), 6.94 (dd, 1, J = 2–3, 9.0 Hz), 8.05 (d, 1, J = 9.0 Hz). Anal. Calcd for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68. Found: C, 62.77; H, 4.75.

Irradiation of *N*-Acetyl-4′-hydroxy-*N*-(2-bromopiperonyl)-β-phenethylamine in Alkaline Solution. A solution of the *N*-acetyl derivative of **9** (200 mg, 0.509 mmol) and NaOH (200 mg) in deionized H_2O–EtOH (3:2, 425 ml) was irradiated for 5 hr under standard conditions. Afterwards the reaction mixture was concentrated by in vacuo removal of the EtOH, and the aqueous phase was treated with an excess of solid NH_4Cl and extracted with $CHCl_3$ (twice). Evaporation of the dried (Na_2SO_4) $CHCl_3$ extracts yielded 149.8 mg of brown residue. Purification by preparative TLC (5% Me_2CO in $CHCl_3$, three developments) afforded eight components. Comparative TLC on the major component, weighing 74.5 mg, established that it was unreacted starting material (37.2% recovery).

Examination of the remaining components by ir revealed one, weighing 15.3 mg, which had the dienone bands expected for **22**. Further purification via preparative TLC (20% Me_2CO in $CHCl_3$) yielded 5.8 mg of **22** as a white residue. This material appeared pure by TLC but was impure by high-pressure liquid chromatography. Final purification of **22** was accomplished on two 2 ft × 0.125 in. stainless steel alumina (40 μm) columns with a $CHCl_3$–hexane (1:1) solvent system to give 2.2 mg of **22** as a white residue: uv (MeOH) 216 nm (log ε 4.28), 227.5 (4.20), 285 (3.51), 320 (313); ir ($CHCl_3$) 1663 (CO), 1635 (amide), 1627 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) 2.06 δ (s, 3, NAc), 4.51 (s, 2, $ArCH_2N$), 5.89 (s, 2, OCH_2O), 6.22 (d, 2, J = 10.0 Hz, αα′), 6.51 and 6.58 (s, 1 each, Ar), 6.68 (d, 2, J = 10.0 Hz, ββ′). Anal. Calcd for $C_{18}H_{17}NO_4$: 311.1158. Found: 311.1151.

Registry No.—**1a,** 6672-69-1; **1a** HCl, 32372-86-4; **1b,** 6196-54-9; **1b** HCl, 6196-36-7; **2,** 56008-40-3; **2** HCl, 56008-41-4; **3** HCl, 56087-02-6; **4** HCl, 56008-42-5; **5** HCl, 56008-43-6; **6** HCl, 56008-44-7; **7** HCl, 56008-45-8; 8 HCl, 56008-46-9; **9,** 34315-37-2; **9** HCl, 38715-00-3; **9** *N*-acetate, 56008-47-0; **9** diacetate, 56008-48-1; **10,** 35232-96-3; **10** $HClO_4$, 56008-49-3; **11** HCl, 56008-50-5; **12** HCl, 56008-51-6; **14,** 56008-52-7; **15,** 56008-53-8; **16,** 6188-86-9; **16** $HClO_4$, 56008-54-9; **17a,** 27159-30-4; **18a** $HClO_4$, 56008-55-0; **20,** 21851-83-2; **21a,** 50606-93-4; **22,** 56008-56-1; **23,** 56008-57-2; **24,** 56008-58-3; **25,** 56008-59-4; 2-iodo-5-nitrobenzaldehyde, 56008-60-7; 2-amino-5-nitrobenzaldehyde, 56008-61-8; 3,5-dimethoxybenzylamine, 56008-62-9; 3,5-dimethoxybenzonitrile, 19179-31-8; 2-iodobenzyl bromide, 40400-13-3; benzylamine, 100-46-9; β-phenethylamine, 64-04-0; 2-bromopiperonal, 56008-63-0; tyramine hydrochloride, 60-19-5; 6-benzyl-5,6,7,8-tetrahydrodibenz[*c,e*]azocine, 6188-49-4; 6-benzyl-5,6,7,8-tetrahydrodibenz[*c,e*]azocinehydroperchlorate, 56008-64-1; 2-chlorobenzaldehyde, 89-98-5; 6-acetyl-11-hydroxy-2:3-methylenedioxy-5,6,7,8-tetrahydrodibenz-[*c,e*]azocine, 56008-65-2; 2-bromopiperonylate, 56008-66-3; 2-bromo-4-methoxybenzoate, 17100-65-1.

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(2) (a) NASA Trainee, 1964–1967; (b) Charles R. Hauser Fellow, 1972–1973.

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(12) Presumably, the dibenzylamine was formed by hydrogen atom abstraction from the solvent by the aryl radical produced by the homolysis of the carbon–iodine bond.[8]

(13) In their preliminary communication Kupchan and Kanojia[10a] also reported that amines were best irradiated as the hydrochlorides in water rather than as the free bases.

(14) We are indebted to Dr. W. E. Scott, Hoffmann-La Roche, Nutley, N.J., for providing an authentic sample of **1a** for comparison.

(15) Kupchan and Kanojia[10a] showed that secondary and tertiary amines could both be used in the synthesis of the aporphine system.

(16) The formation of this compound through halogen interchange with the solvent was suggested by a brief study of the effect of concentrated hydrochloric acid on the photolysis reaction. Thus, irradiation of 2-iododibenzylamine hydrochloride in water gave no halogen exchange. Repetition of the photolysis in 2% hydrochloric acid afforded a small amount of 2-chlorodibenzylamine (GC identification). However, when the solvent was concentrated hydrochloric acid, very little cyclization could be detected and the major products were 2-chlorodibenzylamine and dibenzylamine.

(17) Comparable effects on the benzylic methylene signals were observed in the ^1H NMR spectra of the benzazepines **1a, 10,** and **11.**

(18) This result was in accord with the observations of Mislow and coworkers[19] on the conformational behavior of biphenyls incorporating a seven-membered ring.

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(26) In the ^1H NMR spectrum of 6-hydroxy-2,3-methylenedioxy-5,6,7,8-tetrahydrodibenz[*c,e*]azocine, the $ArCH_2N$ protons appeared at δ 3.00 and 3.78 ppm with J_{gem} of 14.0 Hz.

(27) The magnitude of the coupling constant is consistent with other reported values. See S. M. Jackson and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, Oxford, 1969, p 277.

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Photochemistry of β-Iodoacrylamides

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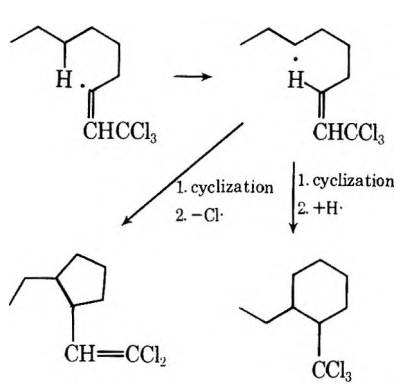
Received February 13, 1975

The irradiation of *N*-alkyl-β-iodoacrylamides at 253.7 nm affords the dealkylated acrylamides. In the case of amides derived from acyclic amines such as *N,N*-dibutyl-*cis*-β-iodoacrylamide (**3**) two fragments are found, the dealkylated amide, *N*-butylacrylamide (**4**), and a carbonyl compound, butanal. The β-iodoacrylamides of cyclic amines yield ring-cleaved ketoacrylamides which may be recyclized under anhydrous acidic conditions to yield novel acrylyl enamides; thus *N*-(*trans*-β-iodoacrylyl)-2,6-dimethylpiperidine (**5**) is photolytically cleaved to form 6-acrylamidoheptan-2-one (**6**), which may be recyclized with *p*-toluenesulfonic acid to *N*-acrylyl-2,6-dimethyl-Δ^2-piperideine (**8**). The unsymmetrical amine (±)-sedridine (**13**) forms a much more complex mixture of products upon irradiation of the *cis*-β-iodoacrylamide derivative in methanol. Cleavage of the more highly substituted carbon–nitrogen ring bond leads to formation of 8-acrylamido-2-octen-4-one (**16**) and 8-acrylamido-2-methoxyoctan-4-one (**15**). In sharp contrast, oxidation of the less highly substituted carbon–nitrogen ring bond does not lead to ring cleavage, but instead affords the unusually stable acrylenamide **17**. These reactions are thought to proceed through vinyl radicals which readily abstract hydrogen atoms situated α to the amide nitrogen atom. The resulting α amido radicals proceed to labile intermediates which are subsequently hydrolyzed to the products. This overall process provides a novel means of selectively degrading secondary amines as well as ready access to unusual enamide derivatives.

In view of the extensive examination of aryl halide photochemistry,[1] it is surprising that very little is known about the related photochemistry of vinyl halides. It does appear that the primary photochemical reaction of vinyl iodides is the homolytic cleavage of the carbon–iodine bond to form vinyl radicals,[2] and that once formed these vinyl radicals are powerful hydrogen abstracting species.[2,3] Of particular interest are several reported examples in which thermally generated vinyl radicals have been observed to undergo intramolecular hydrogen abstraction reactions (Scheme I) followed by ring formation in limited yields.[3b,4]

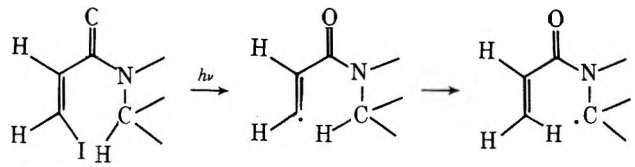
Scheme I



One might expect vinyl radicals to be particularly well suited for hydrogen abstraction reactions by virtue of the sp^2 hybridization of the unpaired electron. In this configuration the unpaired electron would be more electrophilic than either an sp^3 or p hybridized species, and the abstraction of a hydrogen atom from either an sp^3 methylene or methinyl group should be an exothermic process by about 10–15 kcal/mol.[5] Therefore, it would seem that in appropriately designed molecules intramolecular vinyl radical hydrogen abstraction might become the dominant mode of reaction.

The acrylamido vinyl radical (**1**) illustrated in Scheme II would seem to provide such a system. Therefore, we have investigated the photochemistry of β-iodoacrylamides in order to determine the ultimate fate of the vinyl radicals in this system, and to explore the synthetic possibilities of this method of remote functionalization which at least in a general sense is very reminiscent of the synthetically most useful Hofmann–Löffler–Fretag[6] and Barton reactions.[7]

Scheme II

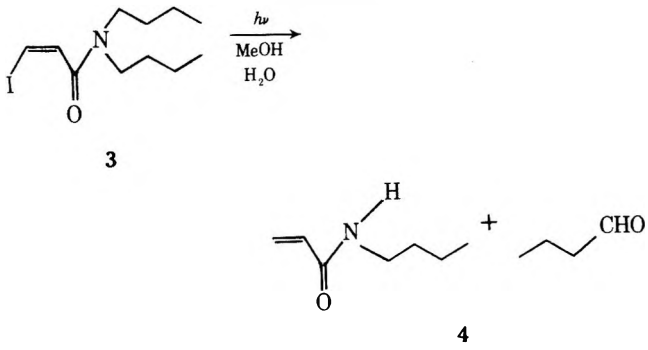


Results and Discussion

In the following examples the starting β-iodoacrylamides were formed from the appropriate amine and either *cis*- or *trans*-β-iodoacrylyl chloride. These acrylyl chlorides were prepared by treatment of propiolic acid with 47% hydrogen iodide[8] followed by generation of the acid chloride with oxalyl chloride. The cis isomer is the exclusive product obtained when the acid chloride is prepared at room temperature. However, the cis isomer is isomerized to the trans isomer when exposed to traces of iodine. When *cis*-β-iodoacrylyl chloride is heated, iodine is released and isomerization occurs to the extent that after heating for 27 hr at 80° the trans:cis ratio is 92:8. This isomerization provides a facile preparation of the *trans*-β-iodoacrylyl chloride. Since the photochemistry of the acrylamides does not seem to be influenced by the stereochemistry of the β-iodoacrylamide moiety (vide infra), the decision as to which acid chloride isomer to use in the synthesis of a particular amide was based entirely upon the ease of preparation and characterization of that amide.

The simplest system studied was *N,N*-dibutyl-*cis*-β-iodoacrylamide (**3**). Irradiation of this material at 253.7 nm in methanol solution led to a surprisingly clean reaction in which the only products were *N*-butylacrylamide (**4**), 65% yield, and butanal, which was isolated as its 2,4-DNP derivative, 62% yield (Scheme III). The structures of these products are in accord with what might be expected from the general mechanistic considerations outlined in Scheme II. The vinyl iodide moiety has been reduced while at the same time the amine moiety has been oxidized. In this particular example the exact nature of the oxidized amine moiety could not be determined as any intermediates are apparently very labile with respect to hydrolysis to the ob-

Scheme III

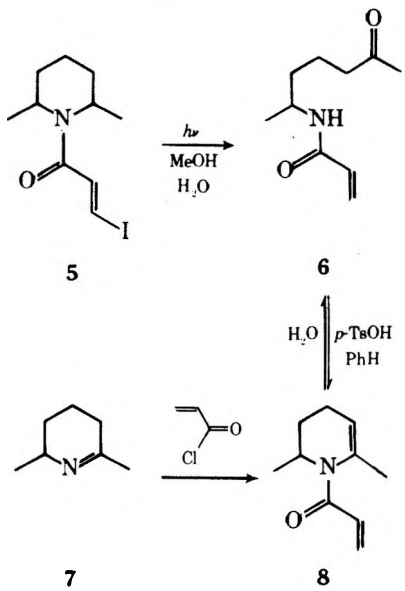


served products. The source of the water involved in this and subsequent hydrolyses may be the solvent, as no special precautions were taken to dry the methanol. Alternatively, it was observed that thin layer chromatographic analyses of these crude reaction mixtures were frequently complicated by the presence of significant amounts of iodine. Upon removal of the iodine by extraction with aqueous thiosulfate, one could obtain thin layer chromatograms that exhibited well-defined hydrolysis product spots. Therefore, it may be that the hydrolysis also is occurring during the aqueous extraction steps frequently employed in the isolation of the products.

N-(*trans*-β-Iodoacrylyl)-2,6-dimethylpiperidine (**5**) was examined rather than the *cis*-β-iodoacryl isomer, since the cis isomer could only be prepared in low yields. The difficulty in forming the cis isomer can probably be attributed to the steric congestion between the cis iodo group and the two ring methyl groups. When **5** was irradiated with 253.7-nm light, isomerization of the trans to the cis isomer could be observed during the early stages of the reaction. Upon completion of the reaction a single product **6** was obtained in 77% yield.

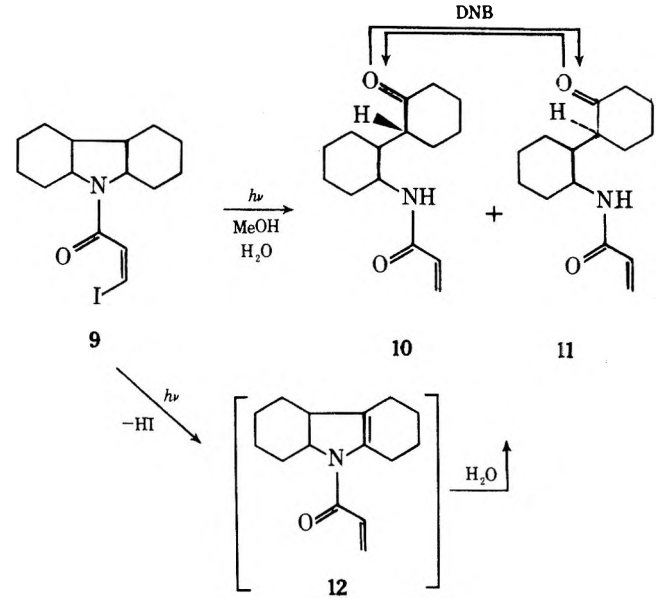
The structure of **6** was confirmed both spectroscopically: [O=CNH- ν_{max} (KBr) 3235, 1655 (s), and 1625 cm^{-1} (s); O=CCH$_3$ ν_{max} (KBr) 1705 cm^{-1}; δ ($CDCl_3$) singlet 2.13 ppm (3 H); CH_2=CHC=O δ ($CDCl_3$) doublet of doublets (J = 4 and 8 Hz) 5.64 ppm (1 H), doublet (J = 8 Hz) 6.18 (1 H), doublet (J = 4 Hz) 6.21 (1 H)] and by comparison with material prepared by an alternate route (Scheme IV). Acylation[9] of Δ^1-piperideine (**7**)[10] with acrylyl chloride afforded the enamide **8** [>NC(CH$_3$)=CH- δ ($CDCl_3$) singlet 2.02 ppm (3 H), broad 4.97 (1 H); CH_2=CHC=O δ ($CDCl_3$) doublet of doublets (J = 4 and 8 Hz) 5.56 ppm (1 H), complex 6.0–6.5 (2 H)] which was extremely sensitive to moisture and hydrolyzed to **6** upon standing overnight in solution exposed to the atmosphere. The reverse reaction from **6** to **8** could be readily effected by simply heating **6** in benzene solution containing *p*-toluenesulfonic acid. The possibility that **8** might be an intermediate in the photochemical formation of **6** was considered. However, here again, perhaps owing to the presence of iodine and the extreme sensitivity of **8** to moisture, **8** could not be observed in the crude photolysis mixture.

Scheme IV



The photolysis of *N*-(*cis*-β-iodoacrylyl)decahydrocarbazole (**9**) was complicated by the formation of epimeric products **10** (26% yield) and **11** (12% yield) (Scheme V).

Scheme V

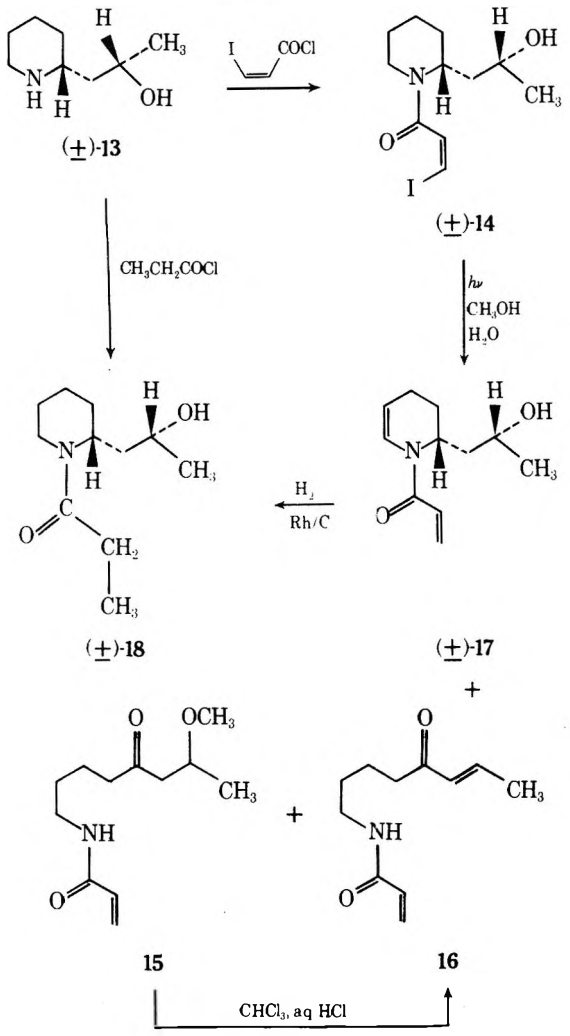


The stereochemistry of these substances is uncertain, but their epimeric relationship to each other was established by their interconversion upon treatment with the base 1,5-diazabicyclo[3.4.0]nonene-5 (DBN). Here again the possibility exists that these epimers arise from the hydrolysis of the enamide **12**. However, it is also possible that epimerization occurs following the generation of the ketones **10** and **11**. Whatever the case may be, it is clear that epimeric products should be anticipated in this reaction when the carbon atom β to the amide nitrogen in the starting material is an asymmetric center.

The unsymmetrically substituted amine (±)-sedridine (**13**) was prepared by a modification of known procedures (see Experimental Section),[11] and its *cis*-β-iodoacrylamide **14** photolyzed.[12] A complex reaction mixture resulted (Scheme VI) which after extensive chromatography afforded the ring-cleaved ketones **15** (21%) and **16** (5%) and the enamide **17** (25%).[13]

The structures of the ketones **15** and **16** were assigned on the basis of spectroscopic data [for **15** -CH_2C(=O)CH_2-$CH(OCH_3)CH_3$ ν_{max} (neat) 1705 cm^{-1}, δ ($CDCl_3$) doublet (J = 6 Hz) 1.17 ppm (3 H), complex 2.33–2.77 (4 H), singlet 3.33 (3 H), and triplet of quartets (J = 6 and 6 Hz) 3.82 (1 H); CH_2=CHC(=O)NH- ν_{max} (neat) 3260, 1655 (s), and 1625 cm^{-1} (s), δ ($CDCl_3$) doublet of doublets (J = 6 and 6 Hz) 5.60 ppm (1 H), two doublets (J = 6 and 6 Hz) both at 6.27 (1 H each); for **16** -CH_2C(=O)CH=$CHCH_3$ ν_{max} (KBr) 1690 cm^{-1}, δ ($CDCl_3$) doublet of doublets (J = 6 and 2 Hz) 1.90 ppm (3 H), broad triplet 2.60 (2 H), doublet of

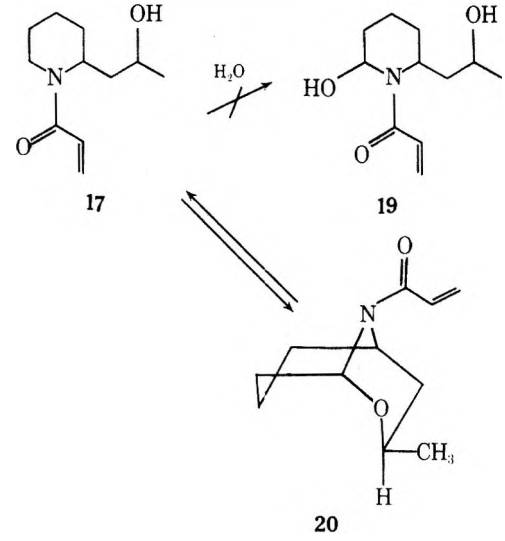
Scheme VI



quartets (J = 6 and 16 Hz) 6.85 (1 H); CH_2=CHC(=O)NH- ν_{max} (KBr) 3230, 1650 (s), and 1625 (s) cm^{-1}, δ ($CDCl_3$) doublet of doublets (J = 8 and 4 Hz) 5.57 ppm (1 H), complex 5.90–6.50 (4 H) includes the α proton of the α,β-unsaturated ketone moiety, m/e 195 (M^+)] as well as the conversion of **15** to **16** upon treatment with aqueous acid (Scheme VI). The assignment of structure to the enamide **17** presented a greater problem, since this material was inert to acidic hydrolysis conditions that would normally be expected to cleave an enamide linkage. The presence of an enamide system in **17** was most conspicuous in the ultraviolet absorption spectrum, λ_{max} (EtOH) 278 nm (ε 1340). The unrearranged carbon skeleton of **17** was demonstrated by catalytic hydrogenation to form a single amide **18** which could also be prepared by treatment of (±)-sedridine (**13**) with propionyl chloride. Furthermore, the observation of only the sedridine-derived amide **18** upon catalytic hydrogenation strongly suggested that the formation of the enamide system had not altered the asymmetric ring carbon atom present in the starting material. The structure **17** was also in accord with the rather complex NMR spectrum, which displayed signals at δ 4.6 ppm broad singlet (-OH), 5.2–4.6 multiplet (-NCH- and -CH=CHN<), 5.83 doublet of doublets (J = 9.0 and 4.0 Hz, >NCOCH=CH_2), 7.3–6.2 multiplet (>NCOCH=CH_2 and -CH=CHN<).

A possible explanation for the failure of enamide **17** to undergo hydrolytic ring cleavage is provided in Scheme VII. The usual hydrolysis of enamide systems requires the addition of water to the enamide carbon–carbon double

Scheme VII

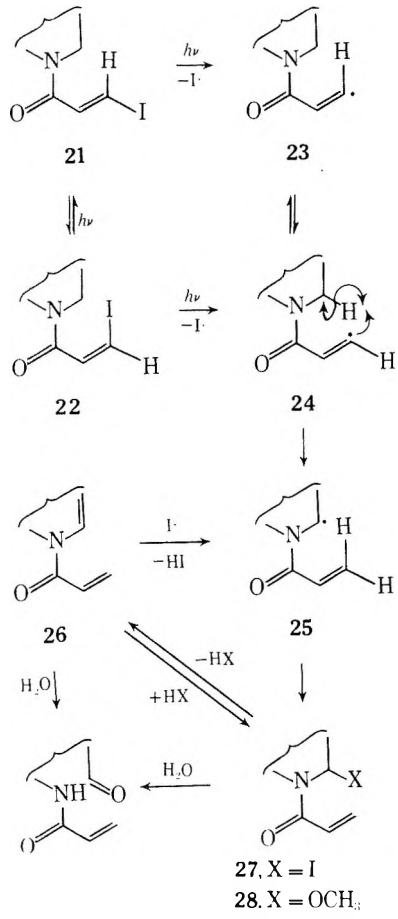


bond (**19**). This type of addition of an external nucleophile might be blocked in **17** by the more facile internal addition of the alcohol moiety to afford **20**. In support of this hypothesis it has been possible in large-scale reactions to isolate small quantities of an unstable oil which upon standing is rapidly transformed into **17**. While it was very difficult to obtain this substance free of contamination by **17**, it was possible to obtain simple spectroscopic data which were in accord with the proposed structure **20**. The infrared spectrum of the unstable material did not display significant absorption in the 3500-cm^{-1} region. In the NMR spectrum the signals associated with the vinyl protons remained unchanged relative to those in the spectrum of **17**. A new one-proton signal appears at δ 5.6 ppm which might be assigned to the -OCHNCO- proton of **20**, and two signals appear as a complex pattern between δ 5.1 and 4.2 ppm which might be attributed to the >CCHNCO- and the >CHO- protons of **20**. Finally, the signals assigned to the -OH and the -CH=CHNCO- protons in the spectrum of **17** are absent in the spectrum of the unstable substance.

From these data, it must be concluded that the photodegradation of unsymmetrical amines by this method results in the oxidation of either methinyl or methylene groups α to the nitrogen atom. It is of interest to compare the relative reactivities of the methinyl and the methylene hydrogens in **14** with the relative reactivities of the same type of hydrogens in intermolecular vinyl radical hydrogen abstraction reactions. Since abstraction of the methinyl ring hydrogen atom in **14** ultimately gives rise to ring-cleavage products **15** and **16**, and abstraction of a methylene ring hydrogen atom gives rise to the enamide **17**, the relative reactivities of methinyl vs. methylene hydrogens observed here would be (**15** + **16**:**17**/2) 2.1:1. This value compares very well with the relative reactivities determined from intermolecular vinyl radical hydrogen abstractions, 2.2:1.[3a]

On the basis of the examples described above it would seem possible to draw the following conclusions regarding the mechanism of this novel remote functionalization of β-iodoacrylamides. In each of these cases the primary photochemical event is certainly the homolytic cleavage of the carbon–iodine bond (Scheme VIII). In order for the resulting vinyl radical to abstract one of the hydrogen atoms α to the amide nitrogen atom, the radical must assume a cis stereochemistry with respect to the amide carbonyl (**24**). As indicated previously, this reaction does not seem to be influenced by the geometry of the iodine atom in the starting material. Both the trans (**21**) and the cis (**22**) isomers ex-

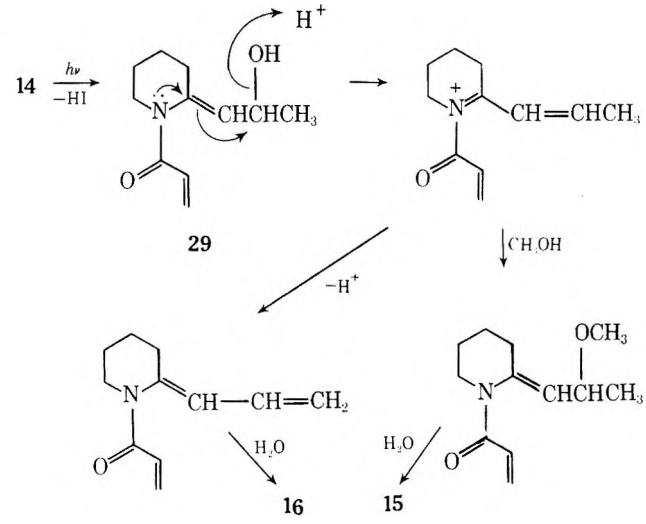
Scheme VIII



hibit the same photochemistry. This is at least in part due to the rapid equilibration of these isomers during the early stages of the irradiation. Cis–trans interconversion was easily observed by thin layer chromatography in each case, and in the case of **5** both cis and trans isomers have been recovered from partially photolyzed reaction mixtures. Furthermore, if the trans β-iodoamide **21** undergoes photolytic cleavage to the vinyl radical with the improper geometry (**23**), α hydrogen abstraction could still take place through a rapid prior inversion to the vinyl radical of the appropriate geometry (**24**).[14]

The course of the reaction following the formation of the α amido radical **25** is not entirely clear. There is considerable evidence that an enamide intermediate (**26**) is involved. Such an intermediate would normally not be isolable under the irradiation conditions where moist methanol was used as a solvent. Under these conditions the enamide **8** was rapidly hydrolyzed to the keto amide **6**. However, the unusual enamide **17** could be isolated owing to its stability toward hydrolysis. Further indirect evidence for an enamide intermediate was observed with amide **9**, which was substituted at the carbon atom β to the nitrogen. Epimerization at the β carbon accompanied dealkylation of **9** as would be expected if the dealkylation occurred through the hydrolysis of the enamide **12**. Also the ring-cleaved products **15** and **16** afforded by the sedridine amide **14** indicated the intermediacy of enamide **29** (Scheme IX). In neither **15** nor **16** was the hydroxyl group retained. This hydroxyl group would be expected to be labilized by the formation of enamide **29**, and should undergo a facile exchange with methanol in the presence of HI. The dehydration of **29** might account for the formation of **16**, although **16** might also arise following ring cleavage to **15** through the loss of methanol.

Scheme IX



It is interesting that in no instance were the 1,3-acyl migration products,[15] which are characteristic of enamide photochemistry, observed. This may be due to the rapid reactions of the enamides with the hydroxylic solvents, methanol and water. Indeed, reactions conducted in hydrocarbon solvents led to polymeric mixtures from which no discrete products could be isolated. As implied in Scheme IX, methanol might very well react with protonated enamides to mask the enamide as an α amido ether **28** (Scheme VIII). Alternatively, an α amido iodide **27** might intervene and undergo exchange with methanol to form **28**. Any of these rather complex sequences of events outlined in Scheme VIII would serve to reduce the enamide concentration to the point where the enamide was effectively masked against further photochemical reaction, but not against the intramolecular processes mentioned in Scheme IX.

In conclusion it appears that the mechanism of this reaction is fairly well defined up to the point where the α amido radical **25** is formed. From **25** a variety of alternative pathways are possible. However, most of these pathways lead to products which would be sensitive to hydrolysis, and upon hydrolysis would converge to a greatly simplified set of products. Therefore, while further investigation of the chemistry of species related to **25** may lead to the development of other useful reactions such as cyclizations analogous to those illustrated in Scheme I, the present work has clearly outlined the scope of the hydrolytic pathway.

Summary

A new photochemical degradation of secondary amines has been developed which provides entry to unusual acrylamide derivatives and acrylylenamides. Good yields of a single acrylamide may be realized from the β-iodoacrylamides of symmetrically substituted amines, although there is a tendency for alkyl groups β to the amide nitrogen to suffer epimerization during the course of the reaction. Amides of unsymmetrically substituted amines give rise to mixtures of products which are derived from the oxidation of either of the *N*-alkyl groups. This unusual process represents the first deliberate application of sp_2 hybridized vinyl radicals in intramolecular hydrogen abstraction reactions and gives some indication of the promise of vinyl iodide photochemistry.

Experimental Section

Melting points and boiling points are uncorrected; melting points were determined on a Mettler FP-2 hot-stage apparatus with a polarizing microscope. Nuclear magnetic resonance spectra

were recorded with a Varian Associates A-60 or T-60 spectrometer. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 337 or 700 spectrophotometer. Ultraviolet spectra were determined on a Carey Model 14 spectrophotometer. Mass spectra were recorded on a Hitachi RMU 7 spectrometer at 70 eV. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Thick layer chromatography was performed with Brinkmann silica gel $PF_{254+366}$ and column chromatography with Brinkmann silica gel (less than 0.08 mm). All organic extracts were dried over anhydrous magnesium sulfate and all solvents were removed with a rotary evaporator under reduced pressure unless noted otherwise.

Synthesis of *cis*- and *trans*-β-Iodoacrylyl Chloride. Oxalyl chloride (29.0 ml, 0.340 mol) was added dropwise with stirring at room temperature to 24.94 g (0.126 mol) of *cis*-β-iodoacrylic acid, mp 65.1–67.0° (lit.[8] mp 65°). After stirring for 12 hr at room temperature, the reaction mixture was distilled to yield 22.4 g (82%) of *cis*-β-iodoacrylyl chloride: bp 36° (0.08 mm); NMR (neat) δ 7.48 (d, 1 H, J = 8.0 Hz), 8.01 ppm (d, 1 H, J = 8.0 Hz). NMR signals associated with the trans isomer were not detected. Caution must be exercised not to allow the distillation bath temperature go above about 40–50°. At temperatures higher than this iodine is formed and cis–trans isomerization takes place. Isomerization will also take place at room temperature during the course of the reaction if the *cis*-β-iodoacrylic acid is not thoroughly recrystallized so as to remove all traces of iodine.

Pure *cis*-β-iodoacrylyl chloride was stirred for 27 hr at 80°. Analysis of the reaction mixture by NMR indicated that the trans isomer now predominated (trans:cis 92:8). The *trans*-β-iodoacrylyl chloride had NMR (neat) δ 7.05 (d, 1 H, J = 15.0 Hz), 8.38 ppm (d, 1 H, J = 15 Hz). This material was used in subsequent reactions without further purification. An analytical sample that was free of the cis isomer as judged by NMR was obtained by Kugelrohr distillation, bp 40–50° (3 mm). Anal. Calcd for C_3H_2ClIO: C, 16.28; H, 0.94, Cl, 16.46; I, 58.91. Found: C, 16.46; H, 0.93; Cl, 16.45; I, 58.70.

Synthesis of *N,N*-Dibutyl-*cis*-β-iodoacrylamide (3). To a solution of 1.7 ml (10.1 mmol) of dibutylamine and 1.3 ml (9.83 mmol) of collidine in 100 ml of benzene was added dropwise with stirring at room temperature 2.16 g (9.98 mmol) of *cis*-β-iodoacrylyl chloride in 10 ml of benzene. After 2 hr the collidinium hydrochloride was removed by filtration, and the benzene filtrate was evaporated to dryness to afford a dark oil which was purified by column chromatography on silica gel. The major impurity was the trans isomer (349.5 mg, 11.3%). The cis isomer **3** was obtained as an oil which following a Kugelrohr distillation afforded 2.45 g (79.5%) of **3** as a colorless liquid: bp 90–98° (0.05 mm); ir (neat) 1640 cm^{-1}; NMR ($CDCl_3$) δ 0.53–1.90 (complex, 14 H), 3.21 and 3.38 (two overlapping triplets, 4 H, J = 10 and 7 Hz), 6.78 (d, 1 H, J = 8.0 Hz), 7.13 (d, 1 H, J = 8.0 Hz).

Anal. Calcd for $C_{11}H_{20}NOI$: C, 42.73; H, 6.52; N, 4.53; I, 41.04. Found: C, 42.71; H, 6.70; N, 4.74; I. 41.25.

Irradiation of *N,N*-Dibutyl-*cis*-β-iodoacrylamide (3). A solution of 182.1 mg (0.589 mmol) of **3** in 5 ml of methanol in a Vycor tube was irradiated with 253.7-nm light (Rayonet photochemical reactor) under an atmosphere of nitrogen for 22 hr. The crude reaction mixture was treated with 10 ml of 2,4-DNP solution (246.7 mg of 2,4-DNP, 13 drops of concentrated hydrochloric acid diluted to 25 ml with methanol) and warmed on a steam bath. Removal of the solvent and recrystallization from methanol yielded two crops of the 2,4-DNP derivative of butanal. Treatment of the mother liquors with sodium thiosulfate to remove the iodine followed by preparative thick layer chromatography of the mother liquor residue afforded a third crop of the 2,4-DNP derivative of butanal for a combined yield of 91.6 mg (62%). This material was identical as judged by thin layer chromatography and NMR with an authentic sample prepared from butanal and 2,4-DNP solution.

Isolation of the major band from the thick layer chromatography of the aforementioned mother liquors afforded an oil which following a Kugelrohr distillation [92–98° (0.005 mm)] provided a pure sample of *N*-butylacrylamide (**4**): 49.0 mg (65%); ir (neat) 3250, 3050, 2945, 2905 (sh), 2850, 1650, and 1625 cm^{-1}; NMR ($CDCl_3$) δ 0.57–1.83 (m, 7 H), 3.23 and 3.38 (two overlapping triplets, 2 H, J = 6 and 7 Hz), 5.55 (d of d, 1 H, J = 7.0 and 5.0 Hz), 6.36 (d, 1 H, J = 5 Hz), 6.39 (d, 1 H, J = 7 Hz), 7.60 ppm (broad, 1 H). This material was identical as judged by thin layer chromatography, ir, and NMR with an authentic sample prepared from acrylyl chloride and *N*-butylamine purified by conventional distillation, bp 84.0–85.5° (0.1 mm) [lit.[16] bp 88–92° (0.01 mm)].

Synthesis of *N*-(*trans*-β-Iodoacrylyl-2,6-dimethylpiperidine (5). A solution of 2,6-dimethylpiperidine (4.6 ml, 33.13 mmol) in 25 ml of benzene was added dropwise over 20 min to an ice-cold solution of 1.25 g (5.78 mmol) of *trans*-β-iodoacrylyl chloride in 100 ml of benzene. The reaction mixture was stirred for 1 hr at room temperature, the piperidinium salt was removed by filtration, and the filtrate was evaporated to dryness to afford a dark brown oil that was purified by column chromatography on silica gel eluting with chloroform. The major fraction was a light brown oil which crystallized upon standing (1.32 g, 78%). Recrystallization from methylene chloride–ligroin gave the amide **5** (1.11 g, 66%) as a colorless solid: mp 69.0–69.4°; ir (KBr) 1620 and 1565 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (d, 6 H, J = 7.0 Hz), 1.63 (m, 6 H), 4.42 (m, 2 H), 7.18 (d, 1 H, J = 14.0 Hz), 7.57 ppm (d, 1 H, J = 14.0 Hz); λ_{max} (95% EtOH) 249 nm (ε 11,500); m/e 293 (M^+).

Anal. Calcd for $C_{10}H_{16}NOI$: C, 40.97; H, 5.50; N, 4.78; I, 43.29. Found: C, 40.99; H, 5.53; N, 4.83; I, 43.17.

Photolysis of *N*-(*trans*-β-Iodoacrylyl)-2,6-dimethylpiperidine (5). A solution of 749.1 mg (2.56 mmol) of **5** in 40 ml of methanol in a Vycor tube was irradiated with 253.7-nm light (Rayonet photochemical reactor) for 15 hr. Evaporation of the solvent followed by column chromatography of the residue on silica gel eluting with chloroform provided a light brown oil which crystallized upon standing. Recrystallization from ether afforded the ring-cleaved keto amide **6** (359.1 mg, 77%) as a colorless solid: mp 38.0–39.1°; ir (KBr) 3235, 3030, 2910, 1705, 1655, 1625, and 1545 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (d, 3 H, J = 7.0 Hz), 1.53 (m, 4 H), 2.13 (s, 3 H), 2.43 (m, 2 H), 4.03 (m, 1 H), 5.64 (d of d, 1 H, J = 4.0 and 8.0 Hz), 5.76 (broad, 1 H), 6.18 (d, 1 H, J = 8 Hz), 6.21 ppm (d, 1 H, J = 4 Hz); λ_{max} (95% EtOH) 225 nm (ε 5040); m/e 183 (M^+).

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.42; H, 9.36; N, 7.62.

Synthesis of *N*-(1-Methyl-5-oxohexyl)acrylamide (6). Acrylyl chloride[9] (660 mg, 7.29 mmol) was added dropwise with stirring to an ice-cold solution of 610 mg (5.5 mmol) of 2,6-dimethyl-Δ^1-piperideine (**7**)[10] and 727.9 mg (7.19 mmol) of triethylamine in 25 ml of benzene. After stirring at room temperature for 40 min, the salt was removed by filtration and the filtrate was evaporated to dryness to afford a dark brown oil. Purification by column chromatography on silica gel yielded the enamide **8** as an unstable, light brown oil: NMR ($CDCl_3$) δ 1.15 (d, 3 H, J = 7.0 Hz), 1.40–2.40 (complex, 4 H), 2.02 (s, 3 H), 4.43 (m, 1 H), 4.97 (m, 1 H), 5.56 (d of d, 1 H, J = 4.0 and 8.0 Hz), 6.0–6.5 ppm (complex, 2 H). Upon standing exposed to the atmosphere overnight or treatment with hydrochloric acid in moist ether for 3 hr, **8** was completely hydrolyzed to the ring-cleaved amide **6** (0.370 g, 37% based on **7**): mp 39.7–40.9°, undepressed mixture melting point with the photoproduct of **5** and identical ir, NMR, and TLC behavior.

The reverse reaction from **6** to **8** may be realized by refluxing **6** in benzene solution containing a trace of *p*-toluenesuflonic acid.

Synthesis of *N*-(*cis*-β-Iodoacrylyl)dodecahydrocarbazole (9). To a solution of 1.94 g (10.9 mmol) of dodecahydrocarbazole and 1.5 ml (11.3 mmol) collidine in 100 ml of benzene was added dropwise with stirring at room temperature 2.49 g (11.5 mmol) of *cis*-β-iodoacrylyl chloride. After stirring for 2.5 hr the collidinium hydrochloride was removed by filtration and the filtrate was evaporated to dryness to afford a dark brown oil that was purified by column chromatography on silica gel eluting with chloroform. The major fraction was an oil which crystallized upon standing and yielded the pure amide **9** upon recrystallization from methylene chloride–ligroin: 3.23 g, 83%; mp 102.8–103.0°; ir (KBr) 1645 and 1595 cm^{-1}; NMR ($CDCl_3$) δ 0.60–2.63 (complex, 17 H), 2.63–3.40 (complex, 2 H), 3.40–4.43 (complex, 7 H), 7.03 ppm (AB, 2 H, J = 8.0 Hz); λ_{max} (95% EtOH) 222 nm (ε 7570); m/e 359 (M^+).

Anal. Calcd for $C_{25}H_{22}NOI$: C, 50.15; H, 6.17; N, 3.90; I, 35.32. Found: C, 50.16; H, 6.09; N, 3.89; I, 35.38.

Photolysis of *N*-(*cis*-β-Iodoacrylyl)dodecahydrocarbazole (9). A solution of 1.09 g (3.04 mmol) of **9** in 40 ml of methanol in a Vycor tube was irradiated under a nitrogen atmosphere with 253.7-nm light (Rayonet photochemical reactor) for 55 hr. Evaporation of the solvent afforded an oil composed of two very similar components (TLC). These components were separated by multiple elutions on thick layer chromatography plates. The faster moving band afforded an oil which crystallized upon standing (196.9 mg, 27% based on recovered starting material). Recrystallization from ether provided colorless crystals of the ring-cleaved amide **10**: mp 99.2–100.3°; ir (KBr) 3255, 1710, 1660, and 1625 cm^{-1}; NMR ($CDCl_3$) δ 0.53–2.77 (complex, 18 H), 3.53 (m, 1 H), 5.55 (two overlapping d of d, 1 H, J = 4.0 and 9.0 Hz), 6.08 (d, 1 H, J = 9.0 Hz), 6.15 (d, 1 H, J = 4.0 Hz), 6.30 ppm (broad, 1 H); λ_{max} (95% EtOH) 229 nm (ε 5520); m/e 249 (M^+).

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.27; H, 9.22; N, 5.64.

The slower moving band afforded a solid (87.5 mg, 12% based on recovered starting material) which following recrystallization from methylene chloride–ligroin afforded colorless crystals of the epimeric ring-cleaved amide **11**: mp 116.8–118.1°; ir (KBr) 3235, 1705, 1650, and 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.57–2.70 (complex, 18 H), 3.70 (m, 1 H), 5.62 (two overlapping d of d, 1 H, J = 4.0 and 8.0 Hz), 5.60 (broad, 1 H), 6.17 (d, 1 H, J = 9.0 Hz), 6.21 ppm (d, 1 H, J = 4.0 Hz); λ_{max} (95% EtOH) 228 nm (ϵ 5260); m/e 249 (M^+).

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.30; H, 9.24; N, 5.61.

Treatment of either **10** or **11** with 1,5-diazabicyclo[3.4.0]nonene-5 (DBN) in benzene at room temperature afforded an equilibrium mixture of **10** and **11** in which **11** was the major component.

Modified Synthesis of (±)-Sedridine (13) and (±)-Allosedridine.[11] A solution of 10.56 (77.1 mmol) of 1-(2-pyridyl)propan-2-ol[11a] and 3.80 g of 5% rhodium on carbon in 25 ml of absolute ethanol was shaken in a hydrogen atmosphere (50 psi) at 40–50° for 28 hr. Removal of the catalyst by filtration and evaporation of the solvent afforded an oil which crystallized upon standing (9.11 g, 84%). This mixture of the diasteromers, (±)-sedridine and (±)-allosedridine, was used in the next step without further purification.

To a stirred solution of the aforementioned diastereomer mixture (365.8 mg, 2.55 mmol) and collidine (340 μl, 2.57 mmol) in 20 ml of chloroform was added dropwise at room temperature 370 μl (2.60 mmol) of benzyl chloroformate in 10 ml of chloroform. After 24 hr the reaction mixture was extracted with 10% hydrochloric acid. The organic layer was dried and evaporated to dryness to yield an oil that was easily separated into two components by column chromatography on 50 g of silica gel eluting with chloroform. The less polar material (298.1 mg, 45%) was recrystallized from ether to yield the carbobenzoxy derivative of (±)-sedridine as colorless crystals: mp 32.6–34.4°; ir 3420 and 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.18 (d, 3 H, J = 6.0 Hz), 1.00–1.88 (complex, 8 H), 1.88–4.77 (complex, 5 H), 5.17 (s, 2 H), 7.33 ppm (s, 5 H). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.41; H, 8.38; N, 4.98. The more polar material (174.5 mg, 25%), the carbobenzoxy derivative of (±)-allosedridine, was isolated as an oil: ir (neat) 3410 and 1685 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (d, 3 H, J = 8.0 Hz), 1.27–2.23 (complex, 8 H), 2.43–3.33 (complex, 2 H), 3.47–4.67 (complex, 3 H), 5.12 (s, 2 H), 7.33 ppm (s, 5 H).

A solution of the crystalline carbobenzoxy derivative (2.3859 g, 8.60 mmol) and 900 mg of 10% palladium on carbon in 25 ml of absolute ethanol was stirred under 1 atm of hydrogen at room temperature for 15 hr. Following removal of the catalyst by filtration and evaporation of the filtrate to dryness, the residue was recrystallized from ether to give (±)-sedridine (**13**) (1.07 g, 87%) as a colorless solid, mp 73.0–75.0° (lit.[11b,c] mp 75.0°). In a similar fashion the oily carbobenzoxy derivative was converted to (±)-allosedridine (81%), which following recrystallization from ether had mp 69.7–70.3° (lit.[11b,c] mp 70–71°).

Synthesis of *N*-(*cis*-β-Iodoacrylyl)sedridine (14). To an ice-cold solution of 438.3 mg (3.06 mmol) of sedridine (**13**) and 400 μl (3.02 mmol) of collidine in 50 ml of benzene was added dropwise with stirring 660 mg (3.05 mmol) of *cis*-β-iodoacrylyl chloride in 10 ml of benzene. The mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was extracted with 10% hydrochloric acid, and the organic layer was dried and evaporated to dryness to afford a light brown oil that was purified by column chromatography on silica gel. Recrystallization from ether of the material from the most polar band afforded the amide **14** (673.4 mg, 69%) as colorless crystals: mp 51.1–52.0°; ir (KBr) 3390, 1600, and 1590 cm^{-1}; NMR ($CDCl_3$) δ 1.18 (d, 3 H, J = 6.0 Hz), 1.38–2.42 (complex, 8 H), 2.75–3.38 (m, 1 H), 3.42–4.00 (complex, 2 H), 4.00–4.55 (m, 1 H), 6.85 (d, 1 H, J = 9.0 Hz), 7.20 ppm (d, 1 H, J = 9.0 Hz).

Anal. Calcd for $C_{11}H_{18}NO_2I$: C, 40.88; H, 5.61; N, 4.33; I, 39.27. Found: C, 40.79; H, 5.51; N, 4.29; I, 39.11.

Photolysis of *N*-(*cis*-β-Iodoacrylyl)sedridine (14). A solution of 2.625 g (8.12 mmol) of **14** in 400 ml of methanol in a quartz flask was irradiated under a nitrogen atmosphere with 253.7-nm light (Rayonet photochemical reactor) for 26.5 hr. The solvent was removed under reduced pressure, and the residual oil was redissolved in chloroform and extracted with aqueous sodium thiosulfate. The organic layer was dried and evaporated to dryness. The residue was purified initially by column chromatography on silica gel eluting with carbon tetrachloride–chloroform. The fractions from the column chromatography were further purified by thick layer chromatography where necessary. The following materials were obtained in order of their elution from the column.

A. Bicyclic Amide 20. This material was separated from the following material, **17**, by extensive thick layer chromatography and was isolated as a light yellow oil (57.4 mg, 4%). Upon standing for several days it was converted to **17**. Nevertheless, it was possible to obtain limited spectroscopic data with a sample contaminated with only a minor amount of **17**: ir (neat) 1650 and 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (d, 3 H, J = 6.0 Hz), 1.43–2.43 (complex, 8 H), 4.17–5.17 (complex, 2 H), 5.58 (m, 1 H), 5.72 (d of d, 1 H, J = 4.0 and 9.0 Hz), 6.41 (d, 1 H, J = 4.0 Hz), 6.55 ppm (d, 1 H, J = 9.0 Hz).

B. Enamide 17. Recrystallization from ether afforded enamide **17** (341 mg, 21%, including the additional material obtained from the conversion of **20**, 25%) as colorless crystals: mp 64.7–65.0°; ir (KBr) 3375, 1640, and 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.17 (d, 3 H, J = 6.0 Hz), 1.00–2.43 (m, 6 H), 3.23–3.87 (m, 1 H), 4.23–5.40 (complex, 3 H), 5.83 (d of d, 1 H, J = 4.0 and 9.0 Hz), 6.50 (d, 1 H, J = 4.0 Hz), 6.63 (d, 1 H, J = 9.0 Hz), 6.66 ppm (br d, 1 H, J = 8.0 Hz); λ_{max} (95% EtOH) 278 nm (ϵ 7340); m/e 195 (M^+).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.51, H, 8.52; N, 7.19.

C. The Acetylene. An acetylenic compound[13] was obtained as a yellow oil (307.6 mg, 19%) contaminated with small amounts of the starting material which could not be removed even after extensive thick layer chromatography: ir (neat) 3370, 2080, and 1600 cm^{-1} (broad); NMR ($CDCl_3$) δ 1.23 (d, 3 H, J = 6.0 Hz), 1.07–2.43 (complex, 8 H), 3.00–4.12 (complex, 3 H), 3.37 (s, 1 H), 4.05–4.60 (complex, 1 H), 4.60–5.20 ppm ((complex, 1 H).

D. α,β-Unsaturated Ketone 16. Recrystallization from ether afforded the ketone **16** (36.0 mg, 5%) as colorless needles: mp 86.2–86.3°; ir (KBr) 3230, 3050, 2910, 1690, 1650, 1625, and 1560 cm^{-1}; NMR ($CDCl_3$) δ 1.33–1.77 (complex, 4 H), 1.90 (d of d, 3 H, J = 6.0 and 2.0 Hz), 2.27–2.89 (m, 2 H), 3.03–3.53 (m, 2 H), 5.57 (d of d, 1 H, J = 8.0 and 4.0 Hz), 5.90–6.50 (complex, 4 H), 6.85 (d of q, 1 H, J = 6.0 and 16.0 Hz); m/e 195 (M^+).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.63: H, 8.72; N, 7.08.

E. Methoxy Ketone 15. Recrystallization of **15** in an ice bath using ether with a trace of methylene chloride to eliminate clouding of the solution before crystallization began provided **15** (411.6 mg, 22%) as a colorless powder: mp 26.8–27.4°; ir (neat) 3260, 1705, 1655, 1625, and 1545 cm^{-1}; NMR ($CDCl_3$) δ 1.17 (d, 3 H, J = 6.0 Hz), 1.40–1.90 (m, 4 H), 2.33–2.77 (m, 4 H), 3.03–3.50 (m, 2 H), 3.33 (s, 3 H), 3.82 (t of q, 1 H, J = 6.0 and 6.0 Hz), 5.60 (d of d, 1 H, J = 6.0 and 6.0 Hz), 6.27 (two d, 2 H, J = 6.0 Hz), 6.90–7.40 ppm (broad, 1 H).

Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.45; H, 9.45; N, 6.24.

The methoxy ketone **15** is converted to the α,β-unsaturated ketone **16** in nearly quantitative yield upon dissolving in a moist chlorform solution of hydrochloric acid and refluxing for 65 hr.

Synthesis of *N*-Propionyl Sedridine (18). To a solution of 177.5 mg (1.24 mmol) of (±)-sedridine (**13**) and 180 μl (1.29 mmol) of triethylamine in 10 ml of benzene was added dropwise with stirring at room temperature 110 μl (1.27 mmol) of propionyl chloride in 10 ml of benzene. The reaction mixture was extracted with 10% aqueous hydrochloric acid after 1.5 hr. The organic layer was dried and evaporated to dryness to provide a light yellow oil which was purified by a Kugelrohr distillation. The fraction collected between 129 and 135° (0.25 mm), 196.6 mg (80%), was the pure amide **18**: ir ($CHCl_3$) 3370 and 1605 cm^{-1}; NMR ($CDCl_3$) δ 1.14 (t, 3 H, J = 8.0 Hz), 1.18 (d, 3 H, J = 5.0 Hz), 1.40–2.20 (complex, 8 H), 2.49 (q, 2 H, J = 6.0 Hz), 2.66–4.50 (complex, 4 H), 4.70–5.10 ppm (complex, 1 H).

Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.11; H, 10.98; N, 7.14.

The enamide **17** (8.7 mg, 0.045 mmol) and 98.5 mg of 5% rhodium on carbon in 5 ml of absolute ethanol were stirred under one atmosphere of hydrogen for 12.5 hr. The catalyst was removed by filtration and the filtrate was evaporated to dryness to afford a light yellow oil in quantitative yield. The oil was homogeneous by TLC and was identical with **18** prepared by the aforementioned procedure as judged by TLC, ir, and NMR comparison.

Acknowledgment. We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health (GM-17267) for their generous support of this work.

Registry No.—**3**, 55711-80-3; **4**, 2565-18-6; **5**, 55711-81-4; **6**, 55711-82-5; **7**, 823-20-1; **8**, 55711-83-6; **9**, 55711-84-7; **10**, 55711-85-8; **13**, 41447-10-3; **13** carbobenzoxy derivative 55711-86-9; **14**, 55711-87-0; **15**, 55711-88-1; **16**, 55711-89-2; **17**, 55711-90-5; **18**, 55711-91-6; **20**, 55711-92-7; *cis*-β-iodoacrylyl chloride, 55711-93-8; *trans*-β-iodoacrylyl chloride, 55711-94-9; oxalyl chloride, 79-37-8; *cis*-β-iodoacrylic acid, 6214-35-3; dibutylamine, 111-92-2; 2,6-dimethylpiperidine, 504-03-0; acrylyl chloride, 814-68-6; dodecahydrocarbazole, 6326-88-1; 1,5-diazabicyclo[3.4.0]nonene-5, 3001-72-7; (±)-allosedridine, 26623-96-1; (±)-allosedridine carbobenzoxy derivative, 55711-95-0; 1-(2-pyridyl)-propan-2-ol 5307-19-7; benzyl chloroformate, 501-53-1; propionyl chloride, 79-03-8.

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Optically Active Amines. XX.[1,2] Application of the Salicylidenimino Chirality Rule to Cyclic Terpene Amines[3]

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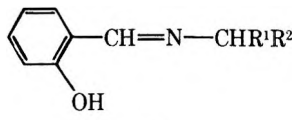
Received May 9, 1975

The signs of the Cotton effects near 255 and 315 nm observed in the circular dichroism spectra of the *N*-salicylidene derivatives of a group of cyclic terpene amines (menthane, thujane, and fenchane ring systems) correlate with the absolute configurations of the amines. The Cotton effects are generated by the coupled oscillator mechanism, and their signs are determined by the chirality (right-handed screw for positive chirality) of the vicinal carbon–carbon bonds and the attachment bond of the salicylidenimino chromophore.

Application of the salicylidenimino chirality rule to the establishment of the absolute configuration of *N*-salicylidene (Schiff base) derivatives (**1**) of chiral α- and β-arylalk-



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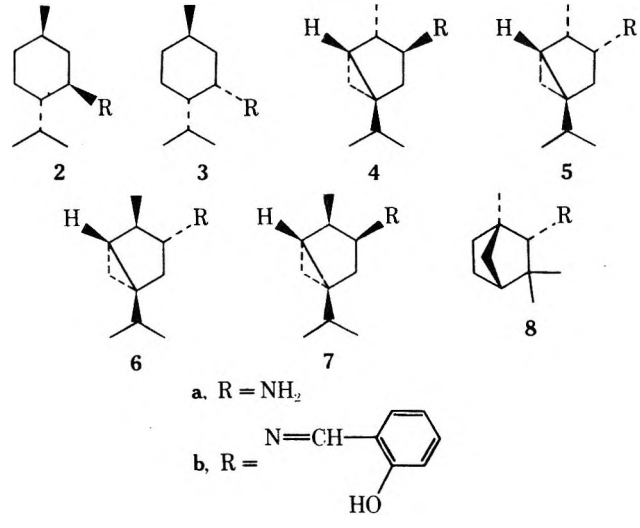
ylamines has been extensively documented.[1,6] The rule correlates the absolute configuration of these derivatives with their optical rotatory dispersion[7] (ORD) and circular dichroism[6] (CD) spectra. The magnitudes of the rotational strengths for the observed Cotton effects near 255 and 315 nm and the general features of the spectra indicate that the dominant mechanism operative in generation of the Cotton effects is electric transition moment dipole–dipole coupling of the aryl group with the salicylidenimino chromophore.[6] Positive chirality (right-handed screw) results in positive Cotton effects at 255 and 315 nm.

For the *N*-salicylidene derivatives of chiral alkylamines corresponding but less intense Cotton effects are observed.[8–11] As an extension of this work, we now report the CD spectra of the *N*-salicylidene derivatives of a group of cyclic terpene amines (**2a–8a**) (Chart I and Table I). In these spectra the signs of the observed Cotton effects near 255 and 315 nm, considered to be generated by the coupled oscillator mechanism,[15] correlate with the absolute configuration of the amine moiety.

Chart I



Results and Discussion

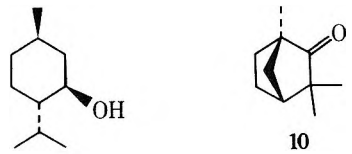
Configuration and Preferred Conformation. The absolute configurations of the *N*-salicylidene derivatives **2b–8b** follow from those of the respective amines. Both

Table I
Terpene Amines

Compd[a]	Present name	Previous name	$[\alpha]^{25}D$ of free base [or salt] used, deg
2a[b]	(−)-Menthylamine		−37 (*c* 2.0, $CHCl_3$)
3a[b]	(+)-Neomenthylamine		+15.5 (neat)
4a[c,d]	(+)-Thujylamine	(+)-Isothujylamine[b]	+114 (*c* 2.4, 95% C_2H_5OH)
5a[c,d]	(+)-Neothujylamine	(+)-Neoisothujylamine[b]	+53 (*c* 2.5, 95% C_2H_5OH)
6a[d]	(−)-Isothujylamine	(−)-Neothujylamine[b]	[+61 (*c* 1.0, H_2O)][e]
7a[d]	(−)-Neoisothujylamine	(−)-Thujylamine[b]	[−10 (*c* 1.0, H_2O)][f]
8a[g]	(−)-*endo*-Fenchylamine	(−)-α-Fenchylamine[g]	−25.3 (neat)

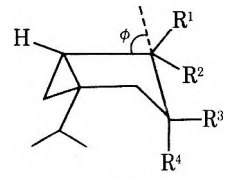
[a] References for sources of amines and further characterizations are footnotes. [b] Reference 12. [c] Reference 13. [d] H. L. Dickison and A.W. Ingersoll, *J. Am. Chem. Soc.*, 61, 2477 (1939). [e] (+)-Mandelate. [f] *p*-Toluenesulfonate. [g] Reference 14.

menthylamines (**2a** and **3a**) were prepared from (−)-menthone,[12] an oxidation product of (−)-menthol[16] (**9**), the relative configurations of the amines following from their preparation[17] and interconversion.[12] The absolute configurations of the thujylamines (**4a** and **5a**) and isothujylamines (**6a** and **7a**) were also established earlier,[12,13] and their present names (Table I) now conform to the new rational nomenclature for the monoterpenes first suggested in connection with names for the isomeric menthols and carvomenthols[18] and later applied to the thujones and thujanols.[19] The absolute configuration of (−)-*endo*-fenchylamine (**8a**) follows from its preparation[20] from (+)-fenchone[16] (**10**) and the establishment of the amino group as endo.[21]



9 **10**

In the preferred conformation of the *N*-salicylidene derivatives of the menthylamines, the cyclohexane ring is a chair and the salicylidenimino moiety takes an equatorial (**2b**) or an axial (**3b**) position. For the thujylamines (**4b** and **5b**) and the isothujylamines (**6b** and **7b**), the ring of the amine moiety is preferably in a boat-like conformation[13,22] (**11**). For the alcohols corresponding to **4a** and **7a** (**11**, R^1 and R^2 = H or CH_3; R^3 = OH; R^4 = H) the "flap angle"[22] (ϕ) has been found by ^1H NMR to be 20–30°. In the fenchylamine derivative (**8b**), the ring bearing the amino substituent is in rigid boat conformation with the salicylidenimino group axial.



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Electronic Absorption and Circular Dichroism. The electronic (isotropic) adsorption (EA) and CD spectra of the *N*-salicylidene derivatives are summarized in Tables II and III. The EA spectra (Figure 1) are similar to those of other *N*-salicylidene derivatives.[1,6-11] In hexane, the spectra exhibit three broad absorption bands centered at about 315, 255, and 215 nm, designated as bands I, II, and III, respectively, and assigned to transitions of the intramolecularly hydrogen bonded salicylidenimino chromophore[6] (**12**). In polar solvents such as methanol and dioxane a broad band at 400 nm and a shoulder near 280 nm become evident in addition to a slight decrease in the intensity of the other three bands. The appearance of the 400- and 280-nm absorption bands has been attributed to the presence of a quinoid tautomer (**13**) in polar solvents.[23,24]

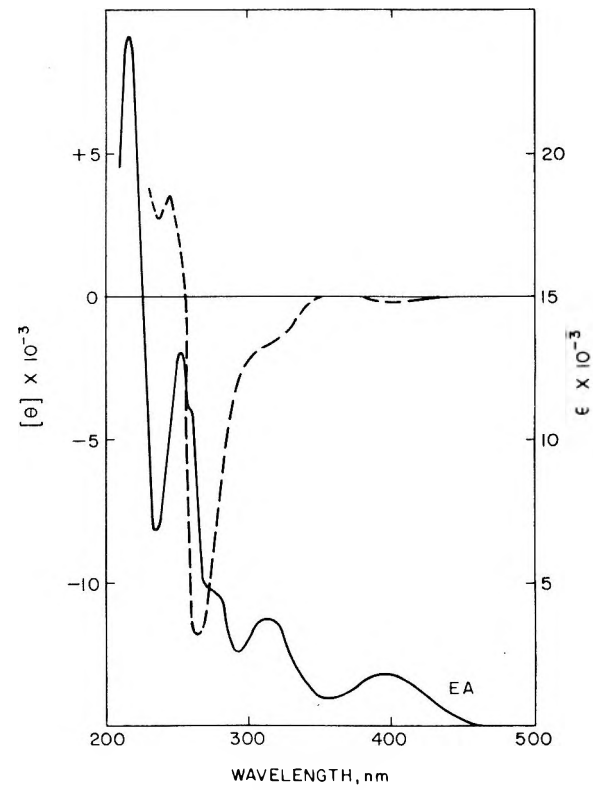
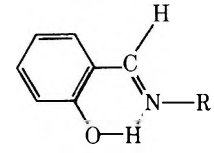


Figure 1. The EA and CD spectra of *N*-salicylidenementhylamine (**2b**) in methanol.



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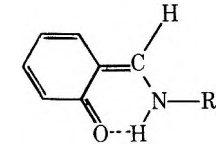

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The corresponding CD spectra are in general also similar to those of other *N*-salicylidene derivatives.[1,6-11] When a single CD maximum is associated with band I and with band II, these maxima are of the same sign. For **2b** and **5b**, which show S-shaped (double-humped[25]) CD curves associated with band II (Figure 1), the sign of the longer wavelength maximum is the same as that of the maximum associated with band I.

In the absence of exciton splitting, S-shaped CD curves associated with a single electronic transition have been interpreted in terms of conformational equilibria, the opposite signed maximum being due to a different conformer, or a solution equilibrium involving different solvated

Table II
Spectral Data for *N*-Salicylidene Derivatives of the Menthylamines and *endo*-Fenchylamine

Compd (solvent)	Band assignment	EA max, λ, nm (ε[b])	CD,[a] λ, nm ([θ][c])
2b (hexane)	I	319 (5,400)	316 (–2,500)[d]
	II	261 (14,000)[d]	264 (–19,000) (max)
		255 (16,000)	245 (+1,200) (max)
			238 (+700) (min)
			233 (+2,300)
	III	217 (31,000)	
2b (MeOH)	Quinoid	401 (1,800)	400 (–150) (max)
	I	315 (3,700)	315 (–1,400)[d]
	Quinoid	276 (4,700)[d]	
	II	260 (11,000)[d]	267 (–12,000) (max)
		255 (13,000)	245 (+3,500) (max)
			237 (+2,700) (min)
			231 (+3,700)
	III	216 (24,000)	
3b (hexane)	I	319 (5,100)	315 (+680)[d]
	II	261 (14,000)[d]	264 (+9,700) (max)
		255 (15,000)	
			238 (+1,000) (min)
			233 (+3,100)
	III	217 (29,000)	
3b (MeOH)	Quinoid	399 (2,400)	396 (+860) (max)
	I	315 (3,100)	314 (+710)[d]
	Quinoid	276 (5,900)[d]	
	II	259 (11,000)[d]	264 (+6,500) (max)
		254 (12,000)	
			243 (+780) (min)
			230 (+4,100)
	III	217 (24,000)	
8b (hexane)	I	320 (5,400)	318 (+3,000) (max)
	II	264 (13,000)[d]	263 (+4,800) (max)
		258 (16,000)	
			242 (±0)
			233 (+5,200)
	III	223 (23,000)[d]	
		217 (25,000)	
8b (MeOH)	Quinoid	401 (2,100)	400 (+730) (max)
	I	315 (3,900)	316 (+2,700) (max)
	Quinoid	277 (5,600)[d]	
	II	256 (13,000)	259 (+7,100) (max)
			240 (+3,700) (min)
			235 (+4,200)
	III	215 (23,000)	

[a] Last entry for each spectrum is cut-off. [b] Molar absorptivity. [c] Molecular ellipticity. [d] Shoulder.

Table III
Spectral Data for *N*-Salicylidene Derivatives of the Thujylamines and Isothujylamines

Compd (solvent)	Band assignment	EA λ, nm (ε[b])	CD,[a] λ, nm ([θ][c])
4b (hexane)	I	318 (5,300)	314 (+430)[d]
	II	262 (14,000)[d]	262 (+3,900) (max)
		254 (15,000)	
			238 (±0)
			230 (+2,100)
	III	216 (28,000)	
4b (MeOH)	Quinoid	400 (1,400)	398 (+400) (max)
	I	315 (4,100)	313 (+1,700) (max)
	Quinoid	278 (3,700)[d]	280 (+2,800)[d]
	II	260 (12,000)[d]	264 (+4,800) (max)
		254 (14,000)	
			238 (+1,700) (min)
			230 (+3,400)
	III	214 (25,000)	
5b (hexane)	I	320 (4,900)	315 (–1,700) (max)
	II	262 (13,000)[d]	272 (–5,800) (max)
		256 (14,000)	254 (+7,700) (max)
			238 (+2,700) (min)
			230 (+8,500)
	III	216 (28,000)	
5b (MeOH)	Quinoid	399 (1,400)	398 (–170) (max)
	I	314 (3,700)	315 (–630)[d]
	Quinoid	276 (4,000)[d]	
	II	259 (12,000)[d]	273 (–2,300) (max)
		254 (13,000)	254 (+8,800) (max)
			238 (+5,000) (min)
			230 (+9,000)
	III	215 (24,000)	
6b (hexane)	I	318 (4,800)	~315 (+) (max)[e]
	II	261 (12,000)[d]	
		256 (13,000)	
			230 (±0)
	III	216 (23,000)	
6b (MeOH)	Quinoid	399 (1,200)	~400 (+) (max)[e]
	I	316 (4,100)	~315 (+) (max)[e]
	Quinoid	280 (3,500)[d]	
	II	255 (14,000)	
			230 (±0)
	III	215 (26,000)	
7b (hexane)	I	319 (4,900)	315 (–1,200) (max)
	II	261 (12,000)[d]	255 (–3,600) (max)
		256 (13,000)	
			230 (±0)
	III	216 (24,000)	
7b (MeOH)	Quinoid	400 (2,100)	398 (–240)[d]
	I	315 (3,800)	314 (–2,000) (max)
	Quinoid	278 (9,100)[d]	
	II	255 (16,000)	254 (–6,500) (max)
			230 (±0)
	III	216 (26,000)	

[a] Last entry for each spectrum is cut-off. [b] Molar absorptivity. [c] Molecular ellipticity. [d] Shoulder. [e] The anisotropy factor ($\Delta\epsilon/\epsilon$) for this band was such that the CD measurement was not quantitatively significant.

species.[26] However, the S-shaped CD curves for band II in **2b** and **5b** are interpreted in terms of vibronic coupling which also predicts alternate signed CD bands for a single electronic transition.[27,28] The S-shaped feature in band II may be the manifestation of the combined effect of an allowed progression of a totally symmetric vibrational mode and a forbidden progression of a possibly nontotally symmetric mode whose differential dichroic absorption maximum occurs at a shorter wavelength and borrows its intensity chiefly from the nearby intense band III.[27] In the EA spectra, the fine structure of band II, a shoulder near 260 nm with the absorption maximum near 255 nm, is evidence for the presence of these two vibrational progressions. An S-shaped CD curve for band II appears only when the two progressions have opposite signs and their rotational strengths are of approximately equal intensity.

The absence of S-shaped CD curves for band I indicates the relative unimportance of forbidden character in band I due to the absence of an intense band from which to borrow intensity.

In the absence of exciton splitting no S-shaped CD curve associated with band II was observed[1,6,7] for the *N*-salicylidene derivatives of aryl-substituted amines.

The sign of the CD maximum for band I and that of the CD maximum for band II (or that of the longer wavelength

Table IV
N-Salicylidene Derivatives of Terpene Amines

Compd	Mp [bp], °C	$[\alpha]^{25}D$, deg (solvent)[a]
2b[b]	56–58	−119 ($CHCl_3$)
3b[c]	94–96	+33 ($CHCl_3$)
4b[d]	[176 (4.5 mm)]	+91 (CH_3OH)
5b[e]	85–86	+8 (CH_3OH)
6b[f]	62–63	−17 (heptane)
7b[f,g]	65–66[h]	−5 (hexane)
8b[i]	95–96	+74 (CH_3OH)

[a] 1.0–2.0 g/100 ml. [b] Lit.[17] mp 57–58°; $[\alpha]D$ −119.2° ($CHCl_3$). [c] Lit.[17] mp 99–100°, $[\alpha]^{15}D$ + 30.0° ($CHCl_3$). [d] Oil, $n^{25}D$ 1.5444. Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01. Found: C, 79.28; H, 9.18. [e] Anal. Found: C, 79.67; H, 8.82. [f] Sublimed at 60° (0.005 mm). [g] Anal. Found: C, 79.80; H, 8.72. [h] Kofler hot stage. [i] Lit.[14] mp 95.5°; $[\alpha]D$ +73.5° (c 4, CH_3OH).

portion of band II) are the same since the electronic transition moments of bands I and II, although not coinciding exactly with each other, are both almost parallel to the chromophore attachment bond.[6] There are, however, a few reported[10,11] CD spectra of N-salicylidene derivatives for which the signs of band I and band II are not the same. This is probably a consequence of the slightly different orientation of the respective transition moments.

Menthylamines (Table II). In the preferred conformation of **2b** and **3b**, the cyclohexane ring is symmetrically disposed with respect to the attachment bond of the salicylidenimino group. Further, if the effect due to the polarizability of carbon–hydrogen bonds is assumed to be negligible,[29] only the attached methyl and isopropyl groups will be effective in inducing differential dichroic absorption in the chromophore. The methyl group attachment bond to the cyclohexane ring and the methyl group attachment bonds in the isopropyl substitutent are all separated from the chromophore by a substantial distance. Thus their contribution to the CD will be small compared to that of the isopropyl group attachment bond. Consequently, it appears that the sign of the CD maximum associated with bands I and II (or the longer wavelength portion of band II) is largely determined by the orientation of the isopropyl group attachment bond with respect to the chromophore attachment bond, since the purely electronic transition moments of bands I and II of the chromophore are approximately parallel to its attachment bond,[6] and the chirality rule developed for the N-salicylidene derivatives of β-arylalkylamines[6] will be applicable.

The sign of the CD maxima for bands I and II (or the longer wavelength portion of band II) is determined by the chirality (right-handed screw for positive chirality) of the vicinal carbon–carbon bond and the attachment bond of the chromophore. For **2b** in its preferred conformation, this chirality between the salicylidenimino and the isopropyl group attachment bonds is negative and thus negative allowed vibrational progressions for bands I and II are predicted. The latter allowed progression coupled with a positive nontotally symmetric vibrational progression results in a strong negative CD maximum near 265 nm and a moderately positive maximum centered at 245 nm. For **3b**, the chirality between the salicylidenimino and the isopropyl group attachment bonds is positive. Positive allowed progressions are predicted for bands I and II. Band II augmented by a positive forbidden progression results in a single positive maximum at 264 nm.

Thujyl and Isothujylamines (Table III). For these derivatives the bicyclic carbon skeleton is also symmetrically disposed with respect to the salicylidenimino group attachment bond, and the sign of the CD associated with allowed vibrational progressions of bands I and II is largely determined by the chirality of the attachment bonds of the vicinal methyl group and the chromophore. For **4b** in a boat-like conformation, this chirality is positive and positive CD maxima near 315 and 264 nm are observed. For **7b** in a boat-like conformation, this chirality is negative in agreement with the observed negative CD maxima for bands I and II.

For **5b**, an S-shaped CD curve appears for band II, indicating that the two vibrational progressions for this band have opposite signs. However, the signs for band I and the longer wavelength portion of band II are both negative in agreement with the negative chirality of the attachment bonds of the vicinal methyl group and the chromophore for **5b** in a boat-like conformation. The large magnitude of the shorter wavelength portion of band II is related to the high rotational strength associated with band III as indicated by the molecular ellipticity shown by **5b** at 230 nm (cut-off). That the sign of the forbidden vibrational progression for **2b–5b** and **8b** agrees with the sign of band III lends support to the conclusion that the rotational strength of this progression is borrowed mainly from band III.

In the preferred, boat-like conformation of **6b**, the attachment bonds of the vicinal methyl group and the chromophore are almost antiparallel to each other (**11**, R^1 = CH_3; R^4 = chromophore). As a result, the coupled oscillator contribution of the vicinal carbon–carbon bond to the differential dichroic absorption will be small, and the contribution due to other carbon–carbon bonds must be taken into account. This analysis is in agreement with the observation that the rotational strengths for bands I and II are very small.

Fenchylamine (Table II). The interpretation of the CD spectrum of **8b** is complicated by the fact that the bicyclic carbon skeleton of **8b** is not symmetrically disposed with respect to the salicylidenimino group attachment bond. However, if only the nearest neighboring carbon–carbon bonds are considered, more bonds have positive chirality with respect to the chromophore attachment bond. Thus positive allowed vibrational progressions for bands I and II are predicted, and the observed CD maxima are positive.

Experimental Section

Melting points were taken in open capillary tubes unless otherwise noted, and are corrected. The boiling point is also corrected. Optical rotations at the sodium D line were measured using a visual polarimeter and a 1-dm sample tube. Isotropic electronic absorption (EA) spectra were obtained with a Cary Model 14 spectrophotometer with the normal variable slit and matched 1-cm cells. Circular dichroism (CD) spectra were measured with a Cary Model 60 spectropolarimeter with a CD Model 6001 accessory at 25–28° using a 1-cm cell. The slit was programmed for a spectral band width of 1.5 nm. The sample concentrations were 2.4×10^{-3} to 2.64×10^{-2} g/100 ml, and cut-off was indicated when the dynode voltage reached 400 V. Elemental analyses were done by Galibraith Laboratories, Inc., Knoxville, Tenn.

N-Salicylidene Derivatives. The derivatives were formed and purified as outlined previously.[30] In cases where they did not crystallize (**4b**, **6b**, and **7b**), the methanol was evaporated and the residue was distilled (**4b**) or sublimed (**6b** and **7b**). Details are given in Table IV.

Registry No.—**2b**, 56087-03-7; **3b**, 56087-04-8; **4b**, 56087-05-9; **5b**, 56087-06-0; **6b**, 56087-07-1; **7b**, 56087-08-2; **8b**, 56087-09-3.

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(4) (a) Vanderbilt University; (b) Tennessee State University.
(5) National Defense Education Act Fellow, 1961–1964.
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Synthesis of Condensed Heterocyclic Systems. VI.[1a] Some Ring Closure Reactions Involving 1-Hydrazinophthalazine

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Received February 20, 1975

The acylation of 1-hydrazinophthalazine (1, hydralazine) with mono-, di-, tri-, and tetracarboxylic acids and acid derivatives gave 3-substituted *s*-triazolo[3,4-*a*]phthalazines; use of *p*-nitrophenol esters of carboxylic acids facilitates the dehydrative cyclization reaction and enlarges the scope of this type of reaction considerably. Though the annelation of five-membered rings to the phthalazine ring proceeds with exceptional ease, fusion of a six-membered ring to this system proceeds with difficulties only. Annelation of larger rings met with failure.

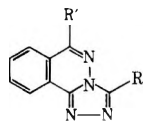
As the result of work by our group[2–5] and others[6–8] on the determination and clarification of the structure of human metabolites of 1, a common hypotensive agent, we were prompted to investigate in detail the reaction between 1 and a variety of acylating agents. Originally,[7] it had been proposed that 1 undergoes enzymatic acetylation to give 1-(2-acetylhydrazino)phthalazine (**2**, R = CH_3; R′ = H). However, it has subsequently been shown independently by two groups[3,8] that enzymatic acetylation instead leads to 3-methyl-*s*-triazolo[3,4-*a*]phthalazine (**3**, R = CH_3; R′ = H). It has also been found that attempts to synthesize **2** under a variety of conditions[3] failed and always yielded the cyclized product **3**. This seems to be unique for the phthalazine system. In other cases, e.g., the acylation of 1-aminomethylisoquinoline[9] and corresponding benzoisoquinoline and benzoquinoline compounds,[10] the expected amides were obtained as stable and isolable compounds. These amides underwent dehydrative cyclization only upon catalysis by strong mineral or Lewis acids. It was, therefore, decided to investigate the acylation of 1 with a variety of acids and acid derivatives to determine whether ring closure to 3-substituted *s*-triazolo[3,4-*a*]phthalazines is in all cases the product in this type of reaction or if it is only typical for the acetylation reaction. Consequently, the acylation of 1 was studied using a variety of mono-, functional mono-, and dicarboxylic acids and derivatives as well as a tri- and a tetracarboxylic acid ester. In addition, attempts were made to fuse six-, seven-, and eight-membered rings to the phthalazine system.

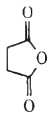
In agreement with earlier investigators[11] we also found that the acid chloride–$POCl_3$ method for achieving dehydrative cyclization to yield the *s*-triazolo system is not a general one and often not suitable at all owing to instability of the acid chlorides. We found that *p*-nitrophenol esters of such acids are excellent materials for the projected reaction, undergoing amide formation and ring closure under very mild conditions. Use of these esters extends the scope of this cyclization reaction considerably.

s-Triazolo[3,4-*a*]phthalazines from Monocarboxylic Acid Derivatives. In every case, the reaction of monocarboxylic acids or acid derivatives with widely varying R groups (Table I) led to the formation of 3-substituted *s*-triazolo[3,4-*a*]phthalazines (**3**, R′ = H) (Scheme I). The scope of this reaction is shown by the substituents in **3** shown in Table I. A unique acylation agent, trichloroacetonitrile, was also used to prepare 3-trichloromethyl-*s*-triazolo[3,4-*a*]phthalazine although in poorer yield than with the acid. This reaction involving the nitrile is analogous to the formation of **3** (R = NH_2; R′ = H) from cyanogen bromide.[11]

In agreement with previous work,[11] the acylation of 1,4-dihydrazinophthalazine (1, R = R′ = $NHNH_2$) does not yield by a double ring closure reaction the bis-*s*-triazolo[3,4-*a*:4,3-c]phthalazine system (**4**, R = CF_3), but a mixture of

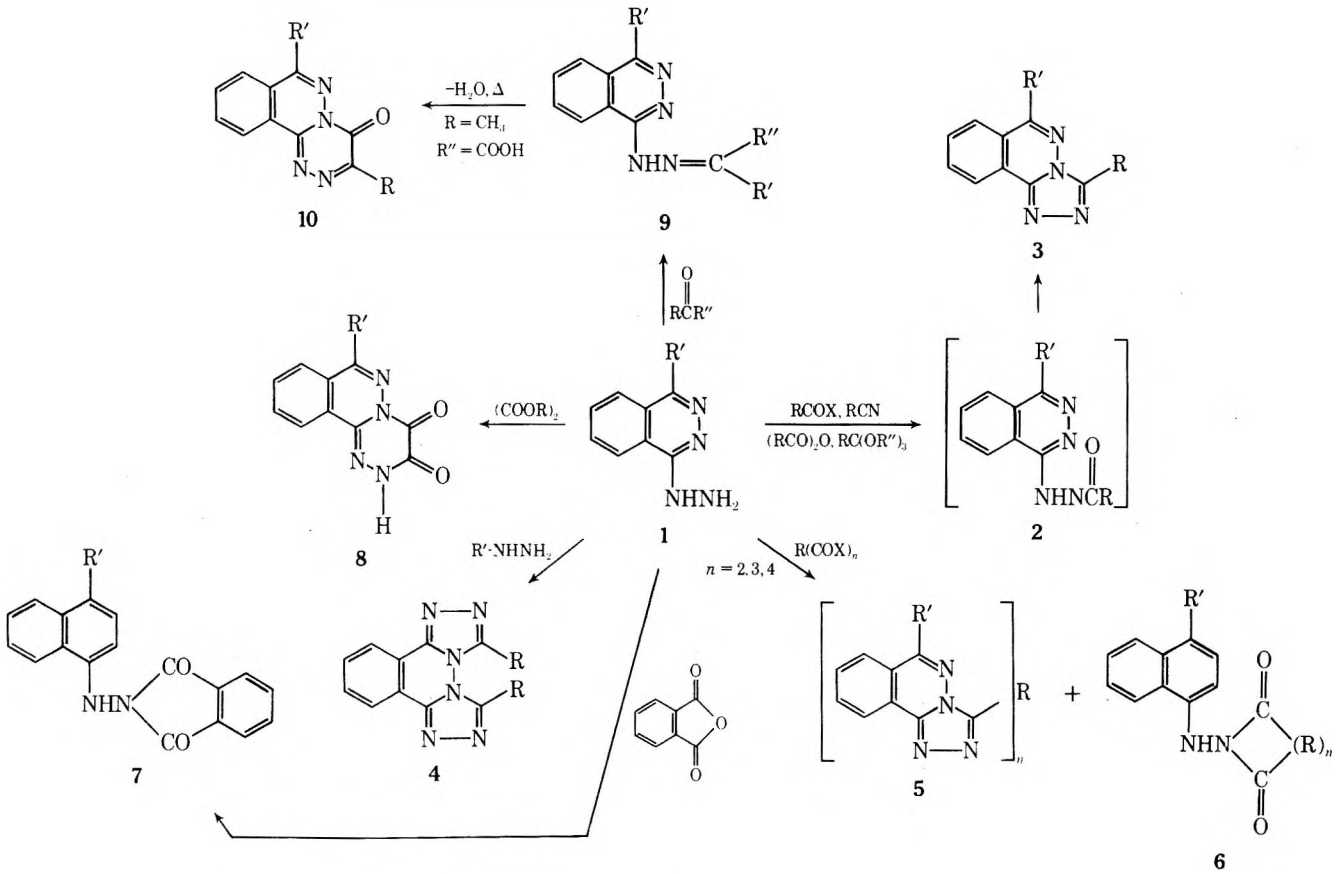
Table I
Reactions of Hydralazine with Various Acids and Acid Derivatives[a]



Acid derivative	Registry no.	R	R′	Molecular formula	Mp, °C	Yield, %	Method of prepn[g]
$Cl_3CC{\equiv}N$	545-06-2	CCl_3	H	$C_{10}H_5Cl_3N_4$	252–253	61[b]	A-1
Cl_3CCOOH	76-03-9	CCl_3	H	$C_{10}H_5Cl_3N_4$	252–253	82[b]	B-1
CF_3COCCF_3 (O O)	407-25-0	CF_3	H	$C_{10}H_5F_3N_4$	309–310	80[b]	C
$HSCH_2COOH$	68-11-1	CH_2SH	H	$C_{10}H_8N_4S$	170–171 dec	53[f]	A-2
PhCHOHCOOH	611-72-3	CHOHPh	H	$C_{16}H_{12}N_4O$	208–209	72[b]	B-2
	108-30-5	$(CH_2)_2COOH$	H	$C_{12}H_{10}N_4O_2$	302–304 dec	81[c]	B-3
$(CH_3)_3COCl$	3282-30-2	$C(CH_3)_3$	H	$C_{13}H_{14}N_4$	192–193	22[d]	D
$CF_3CCOCCF_3$ (O O)	96-63-9	CF_3	$N_2H_2COCF_3$	$C_{12}H_6F_6N_6O$	309.5–310.5	43[d]	A-1
		CF_3	N_2H_3	$C_{10}H_7F_3N_6$	324 dec	23[e]	

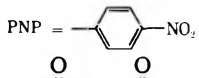
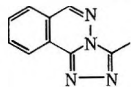
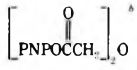
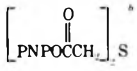
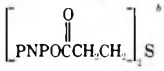
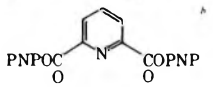
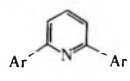
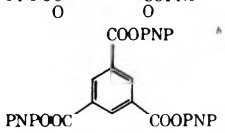
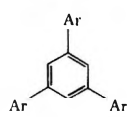
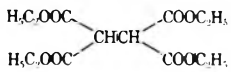
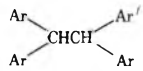
[a] Satisfactory analytical data (±0.4% in C, H, N) for all compounds in Tables I–III were submitted for review: Ed. [b] Recrystalized from ethanol. [c] From dimethylformamide. [d] From ethanol–water. [e] From methanol–water. [f] Vacuum sublimation at 140° (0.1 mm). [g] A-1, refluxed in acid derivative for 24 hr; A-2, refluxed in acid for 90 min; B-1, melt solution at 100° for 1 hr; B-2, melt solution at 130° for 1 hr; B-3, melt solution at 160–180° for 1 hr; C, stirred with anhydride at 5° for 2 hr; D, stirred with acid chloride in THF in presence of sodium acetate.

Scheme I
Some Compounds Derived from 1-Hydrazinophthalazine



3-trifluoromethyl-*s*-triazolo[3,4-*a*]phthalazin-6-yltrifluoroacetic acid hydrazide (**3**, R = CF_3; R′ = $NHNHCOCF_3$) and 3-trifluoromethyl-6-hydrazino-*s*-triazolo[3,4-*a*]phthalazine (**3**, R = CF_3; R′ = $NHNH_2$), the latter compound presumably arising from basic hydrolysis during work-up. Evidently, the steric repulsion between two trifluoromethyl groups at C_3 and C_6 in **4** prohibits annelation of a second *s*-triazolo ring; thus steric hindrance rather than electronic effects seemed to have prevented the ring formation in this case. However, use of the bulky pivaloyl chloride as acylat-

Table II
Reaction of Hydralazine with Esters and Activated Esters

Acid derivative	Registry no.	Product	Molecular formula	Mp, °C	Yield, %	Method of prepn[a]
PNP =  Ar = 						
PNPOC(CH$_2$)$_n$COPNP						
n = 1[b]	141-82-2	ArCH$_2$Ar	C$_{19}$H$_{12}$N$_8$	337–338	82[c]	A
n = 2[b]	110-15-6	Ar(CH$_2$)$_2$Ar	C$_{20}$H$_{14}$N$_8$	330–331	95[c]	A
n = 3[b]	110-94-1	Ar(CH$_2$)$_3$Ar	C$_{21}$H$_{16}$N$_8$	272–273	97[c]	A
n = 4[b]	124-04-9	Ar(CH$_2$)$_4$Ar	C$_{22}$H$_{18}$N$_8$	261–262	94[c]	A
n = 5[b]	111-16-0	Ar(CH$_2$)$_5$Ar	C$_{23}$H$_{20}$N$_8$	215–216	80[c]	A
	56173-23-0	ArCH$_2$OCH$_2$Ar[e]	C$_{20}$H$_{14}$N$_8$O·$^1/_4$H$_2$O	312–313	83[c]	A
	56173-24-1	ArCH$_2$SCH$_2$Ar	C$_{20}$H$_{14}$N$_8$S	283–284 dec	72[c]	A
	56173-25-2	ArCH$_2$CH$_2$SCH$_2$CH$_2$Ar	C$_{22}$H$_{18}$N$_8$S	241–243	72[c]	A
	56173-26-3		C$_{23}$H$_{13}$N$_9$	342–343 dec	76[c]	A
	56173-27-4		C$_{33}$H$_{18}$N$_{12}$	341–343 dec	96[c]	A
	632-56-4		C$_{38}$H$_{22}$N$_{16}$·2H$_2$O	≥200 dec	28[d]	B

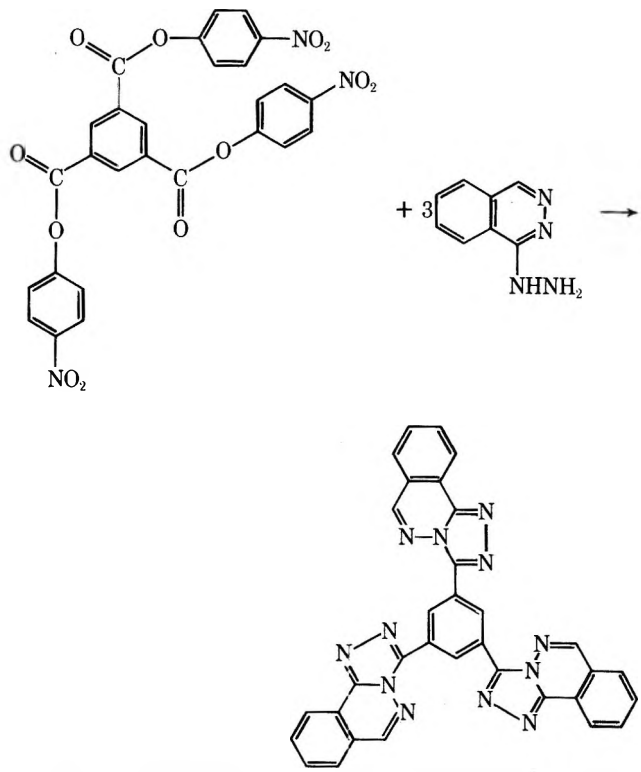
[a] Prepared from acid chloride and *p*-nitrophenol. [b] Prepared from acid and *p*-nitrophenyltrifluoroacetate in pyridine. [c] Recrystalized from dimethylformamide. [d] From dimethylformamide-water. [e] Anal. Calcd for C$_{20}$H$_{14}$N$_8$O·¼H$_2$O: C, 61.91; H, 3.77; N, 29.62. Found: C, 61.92; H, 3.64; N, 29. [f] Anal. Calcd for C$_{38}$H$_{22}$N$_{16}$·2H$_2$O: C, 6178; H, 3.55; N, 30.34. Found: C, 61.97; H, 3.53; N, 29. [g] A, dimethylformamide solvent at 30° for 24 hr; B, dimethylformamide solvent at reflux for 24 hr.

ing agent gave only 3-*tert*-butyl-*s*-triazolo[3,4-*a*]phthalazine (**3**, R = Me$_3$C; R′ = H), indicating that mono ring closure is not prone to steric hindrance.

***s*-Triazolo[3,4-*a*]phthalazines from Di-, Tri-, and Tetracarboxylic Acid Derivatives.** A series of α,ω-bis(3-*s*-triazolo[3,4-*a*]phthalazinyl)alkanes [**5**, R = (CH$_2$)$_{1-5}$, n = 2] was prepared from *p*-nitrophenyl esters of malonic, succinic, glutamic, adipic, and pimelic acid, respectively, by treating 1 equiv of the ester with 2 equiv of **1** at 30° in dimethylformamide as solvent. Similarly, from *p*-nitrophenyl diglycolate, *p*-nitrophenyl thiodiglycolate, *p*-nitrophenyl thiodipropionate, and *p*-nitrophenyl dipicolinate were obtained 1,1′-bis(3-*s*-triazolo[3,4-*a*]phthalazinyl)dimethyl ether (**5**, R = –CH$_2$OCH$_2$–, n = 2), 1,1′-bis(3-*s*-triazolo[3,4-*a*]phthalazinyl)dimethyl sulfide (**5**, R = –CH$_2$SCH$_2$–, n = 2), 2,2′-bis(3-*s*-triazolo[3,4-*a*]phthalazinyl)diethyl sulfide (**5**, R = –CH$_2$CH$_2$SCH$_2$CH$_2$–, n = 2), and 2,6-bis(3-*s*-triazolo[3,4-*a*]phthalazinyl)pyridine [**5**, R = 2,6-C$_5$H$_3$N$_2$, n = 2].

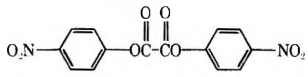
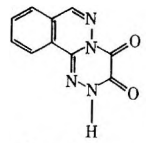
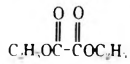
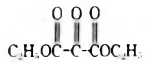
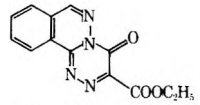
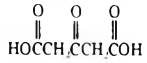
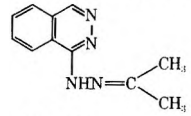
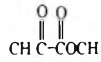
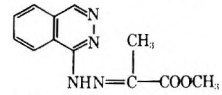
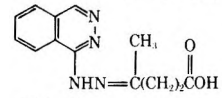
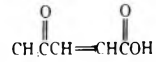
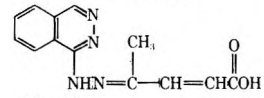
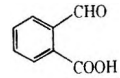
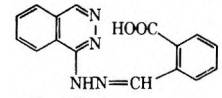
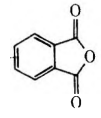
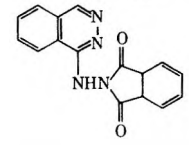
Finally, reaction of **1** with a tricarboxylic acid ester, *p*-nitrophenyl trimesitylate, in a similar fashion gave 1,3,5-tri(3-*s*-triazolo[3,4-*a*]phthalazinyl)benzene [**5**, R = 1,3,5-C$_6$H$_3$, n = 3] and with a tetracarboxylic acid ester, tetraethyl 1,1′,2,2′-ethanetetracarboxylate, in refluxing dimethylformide gave 1,1,2,2-tetra(3-*s*-triazolo[3,4-*a*]phthalazinyl)ethane dihydrate (R = >CHCH<, n = 4) (Table II).

The reactions involving the *p*-nitrophenyl esters of di- and tricarboxylic acids in ring closure reaction with **1** are rather remarkable. To our knowledge there is in the field of heterocyclic synthesis no other reaction known in which in a very high yield (up to 96%, see Table II) three cyclizations with formation of heterocyclic rings occur simultaneously, e.g.



The possibility that the reaction of the bis esters with **1** might give rise to cyclic imides of type **6** was also considered. 1-Phthalazinyl-2-phthalimidohydrazine **7** was, therefore, prepared by refluxing **1** with phthalic anhydride in dimethylformamide. Comparison of the spectral properties of **7** with those of all of the isolated products showed that no

Table III
Reaction of Hydralazine Designed to Give Fused Six- and Seven-Membered Ring Systems

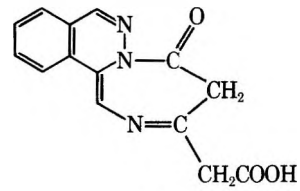
Acid derivative (aldehyde)	Registry no.	Product	Molecular formula	Mp, °C	Yield, %	Method of prepn[g]
	5070-15-5		$C_{10}H_6N_4O_2$	355[d]	91[a]	A
	95-92-1			355[d]	90[a]	B
	609-09-6		$C_{13}H_{10}N_4O_3$	233–234[d]	87[d]	C
	542-05-2		$C_{11}H_{12}N_4$	116–117[f]	98[e]	D
	600-22-6		$C_{12}H_{12}N_4O_2$	185–186	82[c]	D
	123-76-2		$C_{13}H_{14}N_4O_2$	194–195	84[c]	D
	4743-82-2		$C_{13}H_{12}N_4O_2$	202–203	81[d]	D
	119-67-5		$C_{16}H_{12}N_4O_2$	198	90[d]	D
	85-44-9		$C_{16}H_{10}N_4O_2$	297–298	40[a]	E

[a] Recrystalized from dimethylformamide. [b] From ethanol. [c] From ethyl acetate. [d] From 1-butanol. [e] Sublimed at 80° (0.1 mm). [f] Lit.[12] mp 114°. [g] A, solvent, dimethylformamide at 30° for 24 hr; B, ester at reflux for 1 hr; C, ethanol at 25° for 18 hr; D, methanol at 25° for 30 min; E, dimethylformamide at reflux for 30 min.

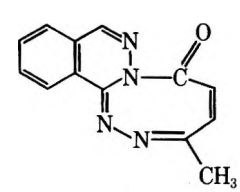
cyclic imides were formed in these reactions, not even when **1** was treated with large excesses of bis esters. The only product isolated beside the *s*-triazolo[3,4-*a*]phthalazines was an oxidation product of **1**, namely 1,2-di(phthalazinyl)hydrazine.

The *as*-Triazino[3,4-*a*]phthalazine System. Recently[11] it was reported that the reaction of an excess of oxalic acid with **1** at 160° gave a 50% yield of *s*-triazolo[3,4-*a*]phthalazine (**3**, R = R′ = H), presumably arising from the decarboxylation of the originally formed *s*-triazolo[3,4-*a*]phthalazine-3-carboxylic acid (**3**, R = COOH; R′ = H). However, when we refluxed a solution of **1** in ethyl oxalate, the product isolated in 90% yield was not the expected ethyl *s*-triazolo[3,4-*a*]phthalazine-3-carboxylate (**3**, R = $COOC_2H_5$; R′ = H) but 2-*H*-*as*-triazino[3,4-*a*]phthalazine-3,4-dione (**8**), mp 355°, as evidenced by the analytical (Table III) and spectral data.

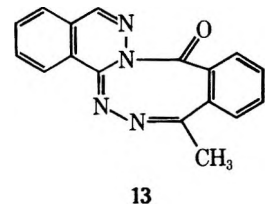
In 1954 Druey and Ringier[12] reported that the hydralazine hydrazone of pyruvic acid (**9**, R = CH_3; R[11] = COOH), when heated to its melting point or upon refluxing with acetic acid, undergoes cyclodehydration to give 3-methyl-*as*-triazino[3,4-*a*]phthalazine-4-one (**10**, R = CH_3), a system in which a six-membered ring has been fused to phthalazine. Formation of this system seems to be a general reaction because if **1** equv of **1** was treated with diethyl oxomalonate an 87% yield of 3-carbethoxy-*as*-triazino[3,4-*a*]phthalazin-4-one (**10**, R = $COOC_2H_5$) was obtained. However, when an attempt was made to prepare and cyclize the **1** hydralazone of β-ketoglutaric acid (**9**, R = R″ = CH_2COOH) analogously to a seven-membered fused ring system, **11**, the product isolated was found to be the **1** hydrazone of acetone, presumably arising from the spontaneous decarboxylation of the initially formed hydrazone. Attempts to cyclize the hydrazone of β-acetylacrylic acid (**9**, R = CH_3; R″ = CH=CHCOOH) to **12** by heating it to the melting point, refluxing in acetic acid, refluxing in trifluoroacetic anhydride, and uv irradiation of an ethanolic solution gave, other than starting material, an oil with a characteristic odor of β-acrylic acid. Similar attempts to cyclize the hydrazones of phthaladehydic acid (**9**, R = CH_3; R″ = O-C_6H_4COOH) to give **13** and levulinic acid (**9**, R = CH_3; R″ = CH_2CH_2COOH) to give **14** also failed.



11



12



13

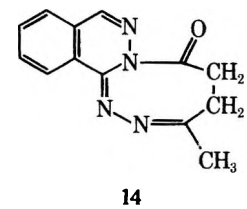


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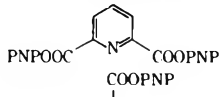
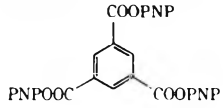
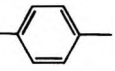
Table IV
p-Nitrophenyl Esters

Ester[a]	Molecular formula	Mp, °C	Yield, %
$[PNPOOCCH_2]_2O$	$C_{16}H_{12}N_2O_9$	116–167	82
$[PNPOOCCH_2]_2S$	$C_{16}H_{12}N_2O_8S$	114.5–115.5	83
$[PNPOOCCH_2CH_2]_2S$	$C_{18}H_{16}N_2O_8S$	106.5–107.5	92
	$C_{19}H_{11}N_3O_8$	233–234	73
	$C_{27}H_{15}N_3O_{12}$	287–290	70

[a] PNP = O_2N– 

The exceptional ease of formation of the *s*-triazolo[3,4-*a*]phthalazine ring system in comparison to the imidazo[5,1-*a*]isoquinoline which needs strong acid catalysis to occur could be explained by a markedly higher nucleophilicity of the N atom in the 2 position of the 1-acylhydrazinophthalazines as compared to the ring nitrogen atom in acylated 1-aminomethylisoquinolines.

Experimental Section

General. All melting points were determined on a Fisher-Jones apparatus and are uncorrected. Infrared, nuclear magnetic resonance, and ultraviolet spectra were taken on a Perkin-Elmer 700, Varian T-60 or Bruker HFX-10, and a Unicam SP-800 spectrophotometer, respectively. All C, H, N analyses were obtained by Chemalytics, Tempe, Ariz. The observed values for all new compounds in Tables I–IV agreed within 0.4% with the calculated values.

Preparation of *s*-Triazolo[3,4-*a*]phthalazines from Monocarboxylic Acid Derivatives. 3-Trichloromethyl-*s*-triazolo[3,4-*a*]phthalazine. The brief procedures given in Table I in most cases should give sufficient information to achieve the preparation of the desired *s*-triazolo[3,4-*a*]phthalazines derived of monocarboxylic acids.

General Method for the Preparation of α,ω-Bis(3-*s*-triazolo[3,4-*a*]phthalazinyl)alkanes. 3-*s*-Triazolo[3,4-*a*]phthalazinyl Substituted Aromatics and 1,1,2,2-Tetra(3-*s*-triazolo[3,4-*a*]phthalazinyl)ethane (Table II). Method A. To 40 ml of DMF was added 1.0 molar equiv of the appropriate bis(*p*-nitrophenyl) ester and 2.2 molar equiv of $1{\cdot}H_2O$. The mixture was stirred for 24 hr at 30° (additional dimethylformamide added if the resulting slurry was too thick), and the precipitate was filtered, washed with DMF and ether, and recrystallized from DMF.

Method B. Exactly as method A, except that the DMF solution was refluxed for 24 hr.

Reactions of Hydralazine Designed to Give Six- and Seven-Membered Rings Annelated to the Phthalazine Ring System (Table III). 1-*H*-as-Triazino[3,4-*a*]phthalazine-3,4-dione. A. A slurry of 6.64 g (0.02 mol) of di-*p*-nitrophenyl oxalate[13] and 7.83 g (0.044 mol) of 1 in 40 ml of DMF was stirred at 30° for 24 hr, filtered, and washed with DMF and ether to yield 3.9 g (91%), based on the ester, recrystallized from DMF: mp 335° dec; ir (KBr) 3175 (N–H), 3030 (ArH), 2925 (C–H), 1720, 1670 (C=O), 1600 cm^{-1} (C=N); NMR (Me_2SO-d_6) δ 7.7–8.4, 8.7 (m, s, ArH); uv max (MeOH) sh 252, 260, 274, 286, sh 312, 328, sh 350.

B. A solution of 3.56 g (0.02 mol) of 1 in 50 ml of ethyl oxalate was refluxed for 1 hr and cooled, and the precipitate was filtered to give 3.9 g (90%), recrystallized from DMF, identical in all respects with compound prepared according to A.

3-Carboethoxy-as-triazino[3,4-*a*]phthalazin-4-one. To a solution of 8.7 g (0.05 mol) of diethyl oxomalonate in 10 ml of ethanol was added 8.9 g (0.05 mol) of 1 in 30 ml of ethanol. The solution was stirred for 18 hr at 25° and then refluxed for 2 hr after the addition of 20 ml of ethanol. After cooling, the yellow precipitate was filtered to give 11.75 g (87%), recrystallized from ethanol: mp 233–234° dec; ir (KBr) 3050 (ArH), 2975 (C–H), 1740 (C=O, ester), 1700 cm^{-1} (C=O); uv max (MeOH) sh 288 nm (log ε 4.04), 297 (4.17), 375 (4.16).

Hydralazine Hydrazones. These compounds were prepared according to Druey et al.[12]

Phthalaldehydic acid hydralazone was prepared from 1 and phthaldehdic acid, yield 90%, mp 198° (1-butanol). Anal. Calcd for $C_{16}H_{12}N_4C_2$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.53; H, 4.22; N, 19.03.

Levulinic acid hydralazone was prepared analogously from 1 and levulinic acid, yield 84%, mp 194–195° (ethyl acetate). Anal. Calcd for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.70. Found: C, 60.41; H, 5.41; N, 21.56.

β-Acetylacrylic acid hydralazone was prepared from 1 and β-acetylacrylic acid, yield 81%, mp 202–203° (1-butanol). Anal. Calcd for $C_{12}H_{12}N_3O_2$: C, 60.93; H, 4.72; N, 21.87. Found: C, 61.34; H, 4.85; N, 21.66.

Attempted Cyclizations of Hydralazine Hydrazones of β-Acetylacrylic Acid, Phthalaldehydic Acid, and Levulinic Acid. The following cyclization attempts were done with these three hydrazones. (1) The compounds were refluxed in glacial acetic acid and an equivalent amount of aquous HCl; the only observed reaction was a cleavage of the hydrazone linkage. (2) The compounds were heated and kept for about 30 min at their melting temperature. Only severe degradation was observed. (3) The compounds were irradiated in alcoholic solution with a mercury lamp with or without sensitizer, and with or without a Pyrex filter; in all cases only degradation but no cyclization was observed.

***N*-(1-Aminophthalazino)phthalimide.** A slurry of 1.0 g (0.0056 mol) of 1 and 0.83 g (0.0056 mol) of phthalic acid anhydride in 10 ml of dimethylformamide was refluxed for 30 min. The solution was cooled and the yellow precipitate filtered, digested with ethanol, filtered, and washed to give 0.65 g (40%), recrystallized from DMF: mp 297–298°; ir (KBr) 3250 (N–H), 1710, 1690 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 7.8–9.0 (m, ArH).

General Method for the Preparation of *p*-Nitrophenyl Esters of Dicarboxylic Acids (Table IV). A solution of 1.0 molar equiv of the appropriate bis acid and 2.0 molar equiv of *p*-nitrophenyl trifluoroacetate in 10–30 ml of dry pyridine was stirred at 30° for 15–30 min, diluted with water to precipitate the ester, and filtered. The precipitate was slurried in ethanol, ether was added and filtered before being recrystallized from an appropriate solvent.

Acknowledgment. We gratefully acknowledge financial support of this work through Department of Health, Education and Welfare Grant 2-R01 AM12297-03 and the Geyer Fund (Department of Medicine, University of Cincinnati). We thank CIBA-GEIGY Corp. (Dr. C. A. Brownly) for a gift of 1 hydrochloride.

Registry No.—1 (R′ = H), 86-54-4; 1 (R′ = $NHNH_2$), 484-23-1; 3 (R = CCl_3, R′ = H), 56172-99-7; 3 (R = CF_3, R′ = H), 53551-55-6; 3 (R = CH_2SH, R′ = H), 56173-00-3; 3 [R = $CH(C_6H_5)OH$, R′ = H], 56173-01-4; 3 [R = $(CH_2)_2COOH$, R′ = H], 56173-02-5; 3 [R = $C(CH_3)_3$, R′ = H], 56173-03-6; 3 [R = CF_3, R′ = $N_2H_2COCF_3$), 56173-04-7; 3 (R = CF_3, R′ = N_2H_3), 56173-05-8; 5 (R = CH_2), 56173-06-9; 5 [R = $(CH_2)_2$], 56173-07-0; 5 [R = $(CH_2)_3$], 56173-08-1; 5 [R = $(CH_2)_4$], 56173-09-2; 5 [R = $(CH_2)_5$], 56173-10-5; 5 (R = CH_2OCH_2) 56173-11-6; 5 (R = CH_2SCH_2), 56173-12-7; 5 (R = $CH_2CH_2SCH_2CH_2$), 56173-13-8; 5 (R = 2,6-$C_5H_3N_2$), 56173-14-9; 5 (R = 1,3,5-C_6H_3), 56173-15-0; 5 (R = >CHCH<), 56173-16-1; 8 (R′ = H), 56173-17-2; 9 (R = R′ = CH_3), 56173-18-3; 9 (R = $COOCH_3$, R″ = CH_3), 56173-19-4; 9 [R = $(CH_2)_2CO_2H$, R″ = CH_3], 56173-20-7; 9 (R = $CH{=}CHCO_2H$, R″ = CH_3), 56173-21-8; 9 (R = C_6H_4-*o*-CO_2H, R″ = H), 7211-69-0; 10 (R = $COOC_2H_5$), 56173-22-9; diglycolic acid, 110-99-6; thiodiglycolic acid, 123-93-3; *p*-nitrophenyl trifluoroacetate, 658-78-6; thiodipropionic acid, 111-17-1; dipicolinic acid, 499-83-2; trimesic acid, 554-95-0.

Supplementary Material Available. Full NMR, ir, and uv data for all the novel triazolo compounds as well as ir data on all intermediates together with detailed experimental procedures will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St.,

N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2901.

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Basic Methanolysis of Anilides. Evidence for the Mechanism Applying to the Special Case of *N*-Methyl-4′-nitroanilides

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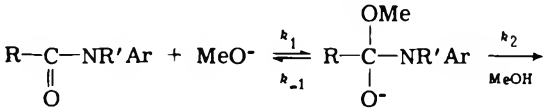
Received February 25, 1975

Evidence from activation parameters, solvent effects on rate, and solvent activity coefficients suggests that *N*-methyl-4′-nitroanilides undergo basic methanolysis by way of rate-determining methoxide addition to the amide. For other ring-substituted *N*-methyl and all NH anilides, decomposition of the tetrahedral intermediate is rate determining. Hammett data are discussed in terms of these mechanisms and an explanation of the behavior of the *N*-methyl-4′-nitroanilides is proposed.

The details of the mechanisms of basic anilide hydrolysis and alcoholysis are of current interest. To summarize (using methanolysis as the example and referring to eq 1), formation of 1 (mechanism A) or its decomposition to



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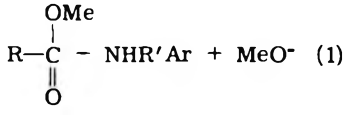
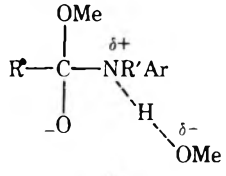


(1)

products can be rate determining. In the latter case, two extreme transition states are possible.[1] Where NR′Ar is a poor leaving group (mechanism B), protonation of the nitrogen is rate determining (transition state 2) while for better leaving groups (mechanism C) solvent-assisted C–N cleavage is rate determining (transition state 3).



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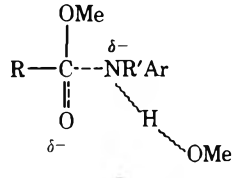

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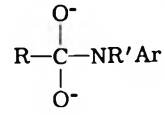
It appears that the mechanism is affected by many aspects of the structure of the anilide. For example, in acetanilides (R = Me[2] or CF_3;[1] R′ = H or Me) a gradual change from B to C occurs when the substituent on the benzene ring is changed from methoxy through to nitro. On the other hand, *N*-methylbenzanilides have been stated[3] to follow C irrespective of the nature of Ar.

Discussion of the possible occurrence of mechanism A has been limited to compounds containing the 4′-nitro substituent, the best leaving group studied to date, where decomposition of 1 to products might be so favored that A operates. It is our purpose here to summarize previous results, provide new data, and hopefully clarify the situation regarding this possibility.

Results and Discussion

pH–Rate Profiles in Basic Hydrolysis. Hydrolysis and methanolysis reactions are closely related and information about one can be related to the other with fair confidence.

Decomposition of the hydrolysis intermediate analogous to 1 can proceed via a dianionic intermediate (4). At high



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pH, this route is fast and dominates for 4′-nitro-NH-anilides, formation of 1 becomes rate determining, and k_{obsd} tends to level off.[4,5] This behavior is not observed for analogous *N*-methyl compounds[4–6] and here the pH–rate profile is linear over the entire pH range. This has been variously interpreted as consistent[6] or not[5] consistent with mechanism A operating in this pH range for the *N*-methyl compounds.

Activation Parameters. Though *N*-methyl-4′-nitroacetanilide undergoes basic methanolysis only 1.5 times faster than the NH compound at 373 K, activation parameter measurements revealed a major difference between the two.[7] The much higher activation energy but more favorable entropy for the NH compound was ascribed to a predominant ground state solvation effect, it being assumed that both compounds reacted by mechanism C.

New rate data for reactions in methanol are collected in Table I. Activation parameters for other anilides have been calculated from some of the results and these, with the literature values for the 4′-nitro compounds, are listed in Table II.

Table I
Rate Data for the Basic Methanolysis of RCONR′Ar in Methanol

Registry no.	R	R′	Ar	Temp, K	$10^3 k_{obsd}$, M^{-1} sec^{-1}
122-28-1	Me	H	3′-$NO_2C_6H_4$	373	1.75
				390	7.59
				399	18.0
2963-34-0	Me	H	3′-Cl-5′-$NO_2C_6H_3$	353	3.31
38802-18-5	Me	H	3′,5′-$(NO_2)_2C_6H_3$	334	3.45
				353	30.3
				363	67.9
21353-89-9	Me	Me	3′-$NO_2C_6H_4$	352	2.32
				374	15.5
				387	38.5
54338-36-2	Me	Me	3′,5′-$(NO_2)_2C_6H_3$	300	20.9
				309	47.4
				319	104
33672-82-1	Ph	Me	4′-$NO_2C_6H_4$	310	7.00
				321	16.3
				339	62.1
55975-43-4	Ph	Me	3′,5′-$(NO_2)_2C_6H_3$	298	24.5
				310	65.1
				333	349
55975-44-5	Ph	H	3′,5′-$(NO_2)_2C_6H_3$	373	462[a]
3393-96-2			4′-$NO_2C_6H_4$	373	260
55975-45-6			4′-$MeSO_2C_6H_4$	373	20.4
5411-13-2			4′-$COMeC_6H_4$	373	7.08
4771-08-8			3′-$NO_2C_6H_4$	373	3.93
6004-21-3			3′-ClC_6H_4	373	0.40

[a] Calculated from plot of $1/k_{exp}$ vs. $1/MeO^-$. See ref 11. $10^3 k_{exp}$ = 0.97 (0.003 M MeO^-), 1.36 (0.005 M), 1.80 (0.01 M) sec^{-1}. k_{exp} is the observed pseudo-first-order rate constant.

In the case of the 4′-nitro substituted compounds, the values obtained for benzanilides and acetanilides are very similar and it is likely that any discussion regarding acetanilides will also apply to benzanilides. It is apparent that, in the acetanilides, the values for the N-methyl-4′-nitro compound are anomalous when compared with those for other members of the series. The appreciably negative entropy for this compound is of the same order as that found[8] in ester hydrolysis (AcOEt; E_a = 14.9 kcal, $\Delta S^{\ddagger}_{298}$ = −20 cal mol^{-1} K^{-1} in 80% ethanol), where rate-determining formation of the tetrahedral intermediate occurs. A consequence of the activation energy order is that, in any Hammett treatment of data, the effective σ value for the 4′-nitro substituent in the N-methyl series will be temperature dependent. For example, the N-methylacetanilide plot in Figure 1 gives $\bar{\sigma}_{4'\text{-}NO_2}$ = 1.16 at 373 K, while analogous treatment of rate data at 318 K gives ρ = 4.3 and $\bar{\sigma}_{4'\text{-}NO_2}$ = 1.24.

Solvent Effect on Rate. Gani and Viout showed[9] that the rate of hydrolysis of N-methyl-4′-nitroacetanilide was markedly increased by the addition of Me_2SO. Using the analogy of ester hydrolysis where the same effect is observed, they concluded that the anilide hydrolyzed by mechanism A. Substituted N-methylacetanilides reacting by way of mechanism B showed a negligible solvent effect. We measured the rate of basic methanolysis of 3′-nitro-N-methyltrifluoroacetanilide in Me_2SO–MeOH, a reaction which appeared[1] to satisfy the requirements of mechanism C, and also obtained a large rate increase.[10] Thus, either both compounds reacted by the same mechanism or the effect of Me_2SO on rate could not be used to differentiate between C and A.

We have now carried out further studies on the effect of added Me_2SO on basic methanolysis of nitroacetanilides and the results are given in Table III. No results were obtained for N-methyl-3′,5′-dinitroacetanilide or for 3′-nitroacetanilide. For the former, complications due to probable methoxide addition to the aromatic ring were evident, while product instability occurred at the higher temperatures necessary for reaction of the latter compound. Extensive ionization was observed for 4′-nitroacetanilide in this solvent and the quoted rate constants have been corrected[11] to allow for this.

Table II
Activation Parameters for Basic Methanolysis of Anilides RCONR′Ar in Methanol

		R′ = Me		R′ = H	
R	Ar	E_a, kcal	$\Delta S^{\ddagger}_{298}$, cal mol^{-1} K^{-1}	E_a, kcal	$\Delta S^{\ddagger}_{298}$, cal mol^{-1} K^{-1}
Me	3′-$NO_2C_6H_4$	21.4	−12	27.8	+1
Me	4′-$NO_2C_6H_4$	14.5[a]	−23[a]	25.3[a]	+5[a]
Me	3′,5′-$(NO_2)_2C_6H_3$	15.0	−18	24.7	+2
Ph	4′-$NO_2C_6H_4$	15.7	−20	22.5[b]	−3[b]

[a] From ref 7. [b] From ref 11.

The addition of Me_2SO produces a rate increase for each compound but it is an order of magnitude less for the N-methyl-4′-nitro compound, which once again shows anomalous behavior. Thus, while a rate increase with addition of Me_2SO cannot in itself be used as evidence for a particular mechanism, the magnitude of the rate increase may be a useful mechanistic indicator. It is of interest that a solvent effect of 91 at 288 K ($k_{obsd}^{Me_2SO\text{-}MeOH}$ = 10.7; k_{obsd}^{MeOH} = 0.118 M^{-1} sec^{-1}) was obtained for reaction of N-4′-nitrophenylazetidinone (formation of the tetrahedral intermediate is rate determining)[6] and similar solvent changes in ester hydrolysis produce rate increases of ~100[12].

It is worthy of note that the NH anilide solvent effect would be smaller at higher temperatures. This is because of the much smaller activation energy for reaction of this compound in Me_2SO–MeOH (Table III) than in methanol.

Gani and Viout have recently reported[13] the effect of methanol on the hydrolysis of N-methylnitroacetanilides and have shown that the 4′-nitro and 3′-nitro compounds respond quite differently to solvent change. This is presented as favoring mechanism A for reaction of N-methyl-4′-nitroacetanilide.

Solvent Activity Coefficients. It became obvious that our original interpretation[7] of the differences in activation parameters for the NH and NMe 4′-nitroacetanilides in terms of ground-state effects was too simplified. Solvent activity coefficients,[14] determined from rate measurements and solubilities, can provide information about the effect of solvent on both ground and transition states. We have determined these for some nitroacetanilides (Table IV) for the system 80% Me_2SO–MeOH relative to methanol from

$$\log \frac{k_{DM}}{k_M} = \log {}^M\gamma^{DM}_{MeO^-} + \log {}^M\gamma^{DM}_{anilide} - \log {}^M\gamma^{DM}_{\ddagger} \quad (2)$$

eq 2. Solubility values are listed in Table IV and the required rate data are from Table III.

Large differences are apparent within the series. It is evident that the NH anilide is rather better solvated by Me_2SO relative to methanol than are the N-methyl analogs. This is reasonable if hydrogen bond donation by the anilide is important. However, major differences also occur in transition state values, though interpretation of these

Table III
Rate Data for the Basic Methanolysis of $CH_3CONR'C_6H_4NO_2$ in 80% Me_2SO–MeOH

Registry no.	R'	NO_2 position	Temp, K	$10^3 k_{obsd}$, M^{-1} sec^{-1}	$10^3 k_{obsd}^{298}$ calcd	$k_{Me_2SO-MeOH}^{298\ K}/k_{MeOH}$[a]
	Me	3'	298	27.3	27.3	2680
121-95-9	Me[b]	4'	281	79.9	380	115
			288	161		
			294	273		
			298	402		
			305	667		
104-04-1	H[c]	4'	307	139[d,e]	63.1	1070
			315	289[d,f]		
			326	694[d,g]		

[a] Calculated from Table I. [b] E_a = 15.2 kcal; $\Delta S^{\ddagger}_{298}$ = −12 cal mol^{-1} K^{-1}. [c] E_a = 16.7 kcal; $\Delta S^{\ddagger}_{298}$ = −10 cal mol^{-1} K^{-1}. [d] Calculated from plot of $1/k_{exp}$ vs. $1/MeO^-$. See ref 11. [e] $10^5 k_{exp}$ = 8.13 (0.001 *M* MeO^-), 11.4 (0.002 *M*), 16.0 (0.01 *M*) sec^{-1}. [f] $10^5 k_{exp}$ = 16.2 (0.001 *M* MeO^-), 23.3 (0.002 *M*), 30.5 (0.01 *M*) sec^{-1}. [g] $10^5 k_{exp}$ = 35.5 (0.001 *M* MeO^-), 48.0 (0.002 *M*), 63.8 (0.01 *M*).

Table IV
Solubilities and Solvent Activity Coefficients[a] for $CH_3CONR'C_6H_4NO_2$ at 298 K

		Solubility, *M*			
R'	NO_2 position	80% Me_2SO–MeOH	MeOH	Log ${}^{M}\gamma_{anilide}{}^{DM}$	Log ${}^{M}\gamma_{t}{}^{DM}$
H	4'	1.356	0.079	−1.23	−0.26
Me	4'	0.613	0.265	−0.37	+1.57
Me	3'	1.42	0.984	−0.16	+0.41

[a] Log ${}^{M}\gamma_{anilide}{}^{DM}$ = log S^M − log S^{DM}; log ${}^{M}\gamma_{MeO^-}{}^{DM}$ = 4.0 (ref 14).

must be made with caution. It may be noted from Table III that the activation parameters for reaction of both 4'-nitroanilides are quite similar, unlike the situation in methanol. The details of the effect of solvent on this reaction have not yet been fully investigated, but the mechanism applicable to the NH compound in particular may be different in Me_2SO and methanol. In such a case, solvent activity values would not give a true picture.

Nevertheless, the fact that each compound gives such different values is a useful indication of their fundamentally different behavior, and the result for *N*-methyl-4'-nitroacetanilide is probably valid. Pollack[15] has shown that k_2/k_{-1} (Me_2SO) > k_2/k_{-1} (H_2O) for hydrolysis of 4'-nitroacetanilide. Thus, if this also applies to the *N*-methyl compound and if this compound undergoes methanolysis by mechanism A in methanol, then it no doubt does so in Me_2SO–methanol also. The solvent activity coefficients are reasonable if this is so. The nearest analogy for which results are available[14] is the reaction of *p*-nitrophenylacetate with azide in DMF, with values of log (k_{DMF}/k_{MeOH}) = 1.4, log ${}^{M}\gamma_{ester}{}^{DMF}$ = −0.9, and log ${}^{M}\gamma_{t}{}^{DMF}$ = 2.6. A transition state such as **3**, where the charge is diffuse, might not be expected to be so much better solvated by methanol.

Hammett Treatment. The entire results from activation parameters, solvent effects on rate, and solvent activity coefficients are most reasonably accommodated on the basis that of all compounds studied to date, *N*-methyl-4'-nitroanilides alone react by mechanism A.

If one accepts the different mechanism for this group of compounds, it is necessary to see if an analysis of substituent effects on rate is consistent with this interpretation.

From various Hammett studies, ρ values of ~1.3[6] (mechanism A), ~0[1] (B), and ~3[1,3] (C) have been found. Thus, for acetanilides a change from B (4'-methoxy) to C (3'-nitro) results[1] in a concave upward plot while a change from C to A would result in the opposite curvature. This latter has never been observed and, for *N*-methylbenzanilides which give a linear plot,[3] the point for the 4'-nitro substituent fitted this line satisfactorily.

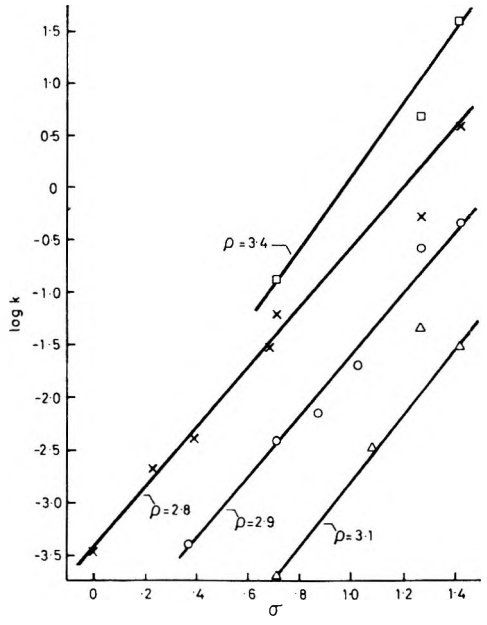


Figure 1. Hammett plots for methanolysis: □, *N*-methylacetanilides (353 K) (1 + log *k*); ×, *N*-methylbenzanilides (373 K): ○, benzanilides (373 K); △, acetanilides (373 K).

We have now measured rates of basic methanolysis in NH benzanilides and have extended measurements in three other series to compounds more reactive than the 4'-nitro substituted ones to seek evidence for downward curvature in the Hammett plots. New rate data are listed in Table I.

The appropriate Hammett plots are shown in Figure 1. The lines are drawn taking particular account of points for meta substituents and neglecting 4'-nitro values. There is clearly no sign of a decrease in slopes beyond the 3'-nitro point in any series. The ρ values are all similar (allowing for temperature differences, and a two-point line in one case) and are compatible with the operation of mechanism C. The 4'-nitro points have been placed using the standard σ^- value of 1.27.[16] It is of interest that the 4'-nitro point lies below the line in both *N*-methyl plots and above it in the NH ones. In the case of the NH acetanilides, the 4'-nitro substituted compound in fact reacts faster than does the 3',5'-dinitro one.

If mechanism A operates for *N*-methyl-4'-nitroanilides, then the fair correlation of these points may be a chance result. As mentioned above, activation energies are such that

Table V
Hammett ρ Data for the Basic Methanolysis of $Ar_1CONRAr_2$ in Methanol

Series	Ar_1	Ar_2	R	ρ_1	ρ_2	Temp, K	Ref
a	Ph	V[a]	Me		2.83	373	3, b
b	Ph	V	H		2.95	373	b
c	V	Ph	Me	1.76		373	3
d	V	4'-$NO_2C_6H_4$	Me	1.73		339	3
e	V	4'-$NO_2C_6H_4$	H	1.88		333	11

[a] V = various substituents. [b] This work.

the effective σ value for the 4'-nitro substituent is temperature dependent, if the 3'-nitro and 3',5'-dinitro points are taken as defining the correlation line. In addition, though differences are small, the opposite trend in σ values for the 4'-nitro substituent in NH and *N*-methyl series is probably real and might not be expected if the two sets reacted via very similar rate-determining transition states. The evidence to date on anilide hydrolysis[4,17] suggests that, for *N*-methyl-4'-nitro compounds, breakdown of the intermediate to products or reactants is about equally likely, i.e., $k_2/k_{-1} \sim 1$. This means that there is no one clearly rate-determining step. In this complicated situation, minimal deviation from the Hammett plot might be reasonable. In other words, the Hammett treatment is not sensitive enough in this case to pick up the mechanistic change.

The lack of curvature or change of slope in the Hammett plots in the *N*-methyl series is explicable if meta and para compounds are considered separately. This requires thinking in terms of the dual parameter Hammett equation[18] (eq 3) where the blend of resonance and inductive effects can be different for meta and para substituents.

$$\log k_2/k_2^0 = \rho_I\sigma_I + \rho_R\sigma_R \quad (3)$$

The k_2 step in mechanism C (transition state **3**, with developing charge on the nitrogen) would be powerfully aided by strong resonance-withdrawing substituents in the para position. Thus, ρ_R would be greater for a para series than for a meta one. Of the compounds measured to date in the *N*-methyl series, it may well be that only in the case of the strongest para withdrawing substituent is the stabilization sufficient to make this step so fast that formation of **1** (mechanism A) is rate determining. While 3',5'-$(NO_2)_2$ > 4'-NO_2 in total σ, the mechanism for the 3',5'-dinitro compound could still be C since ρ_R is relatively small and σ_R rather than σ_R^- would be applicable.

On the basis of mechanism A operating for *N*-methyl-4'-nitroanilides (but not the NH analogs), some of the Hammett data for benzanilide reactivity published previously[3] requires reinterpretation to be consistent with this picture.

In Table V are collected the various ρ values now available for basic benzanilide methanolysis. The first point requiring explanation is why the three ρ_1 values are very similar if series d has a different rate-determining step from the other two.

The observed second-order rate constant for conversion of reactants to products can be expressed as

$$k_{obsd} = \frac{k_1k_2}{k_{-1} + k_2} = \frac{k_1}{k_{-1}/k_2 + 1}$$

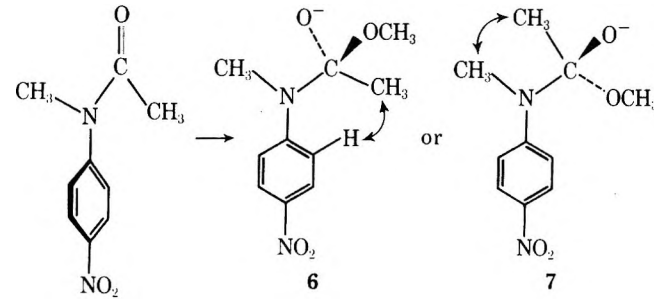
Now, it is a reasonable assumption that there will be little substituent effect from Ar_1 on the *relative* ease of loss of methoxide or amine from the tetrahedral intermediate, i.e., k_{-1}/k_2 would be effectively constant. Thus, for c and e, while the rate-determining step is breakdown of **1** to products, the effect of a substituent on k_{obsd} is essentially governed by its effect on k_1, the rate of formation of **1**. It is therefore not inconsistent that for series d, where the rate-determining step is formation of **1**, the ρ value is very similar to that for the other two series.

In the previous paper,[3] the analogy of the hydrolysis of Ar_1COOEt and CH_3COOAr_2 was used to illustrate that, for rate-determining bond formation, substituent effects in the acyl aryl ring are more pronounced and $\rho_1 > \rho_2$. This analogy is wrong since it cannot apply where substituent effects in various series are mainly on different steps. The anilide ρ_1 values all represent a substituent effect essentially only on the formation of **1**, while the ρ_2 values arise from a presumably smaller substituent effect on k_1 together with a substantial additional effect on the breakdown of **1** to products. This occurs because the partitioning ratio (k_{-1}/k_2) will be markedly affected by substituents in Ar_2. Thus $\rho_1 < \rho_2$ is compatible with the proposed mechanisms.

The Hammett ρ data are therefore not inconsistent with the following mechanistic summary: series d and the compound $PhCONMeC_6H_4NO_2$-4' react via rate-determining formation of **1**; all other benzanilides studied to date react via rate-determining decomposition of **1** to products.

The Origin of the Special Effect. The unique effect in the *N*-methyl-4'-nitroanilides must involve contributions from both the *N*-methyl (to distinguish from NH behavior) and 4'-nitro (to distinguish from 3'-nitro behavior) groups, i.e., a combination of steric and electronic effects, and we tentatively offer the following explanation.

In anilides, steric effects cause twisting of the aromatic ring out of the amide plane, especially in *N*-alkylanilides.[19] This twisting is minimized when the aromatic ring contains a para withdrawing substituent. In intermediate **1**, conjugation between the nitrogen lone pair and a 4'-nitro substituent will be more important than in the amide itself and one can envisage the aromatic ring coplanar with the nitrogen σ bonds as being the most stable configuration in the intermediate from the electronic point of view. This configuration would be retained during C–N bond cleavage. However, planarity in this part of the molecule increases steric interactions which, in the *N*-methyl case, cannot be removed by rotation about the C–N bond (**5** → **7**).



5 **6** **7**

In a *m*-nitro compound, the equivalent to **6** would not be important since there is no through conjugation to produce planarity, while in an NH compound the equivalent of **7** would not be a source of strong interaction. The *N*-methyl system can apparently gain more relief from this situation by loss of amine to give products than by loss of methoxide to revert to reactants, relative to the analogous NH compound.

It is clear from the total results available at this stage that the detailed mechanism by which an anilide can undergo basic methanolysis (and no doubt hydrolysis) is affected by many structural features in the anilide, and probably by the solvent in some cases.[31] The system is obviously finely balanced and provides a fascinating field for investi-

gating the subtle effects of structural changes on mechanism.

Experimental Section

Amines. 3,5-Dinitroaniline, mp 159° (lit.[20] mp 162–163°), and *N*-methyl-3′,5′-dinitroaniline, mp 160° (lit.[21] mp 158–159°), were prepared by literature methods. Nitration of *N*-methylaniline at <10° with concentrated sulfuric–nitric acids gave *N*-methyl-3-nitroaniline, mp 64° (lit.[20] mp 68°). Chlorosulfonation of acetanilide,[22] followed by reduction to the sulfinic acid with sodium sulfite[23] and methylation with methyl iodide,[24] gave 4′-methylsulfonylacetanilide. Hydrolysis gave 4′-methylsulfonylaniline.

3-Chloro-5-nitroaniline. A solution of sodium nitrite (4.2 g) in water (5 ml) was added dropwise, with stirring, to a suspension of 3,5-dinitroaniline (10 g) in 20% fluoroboric acid (100 ml) at 0°. The mixture was stirred for 15 min and the precipitated diazonium salt was filtered and washed with fluoroboric acid, ethanol, and ether. Cuprous chloride [prepared from cupric sulfate (25 g), sodium chloride (6.5 g), sodium metabisulfite (5 g), sodium hydroxide (3.5 g), and water (120 ml)] was dissolved in 5 *M* hydrochloric acid (50 ml). The diazonium salt in 5 *M* hydrochloric acid (20 ml) was added to this solution with stirring at 0°. Vigorous gas evolution occurred. Water (200 ml) was added, the mixture was heated at 80° for 10 min, and the 1-chloro-3,5-dinitrobenzene, mp 53° (lit.[25] mp 55°), was isolated by steam distillation. Reduction of this compound with aqueous sodium sulfide[26] gave 3-chloro-5-nitroaniline, mp 132° (lit.[27] mp 133–136°), after column chromatography (silica gel–1:1 chloroform–light petroleum).

Acetanilides. 3′-Nitro-, mp 152° (lit.[20] mp 155°); 3′,5′-dinitro-, mp 188° (lit.[28] mp 191°); *N*-methyl-3′,5′-dinitro-, mp 133–134° (EtOH) (Anal. Calcd for $C_9H_9N_3O_5$: C, 45.2; H, 3.8; N, 17.6. Found: C, 45.2; H, 3.7; N, 17.9); 3′-chloro-5′-nitro-, mp 173–174° (after chromatography on alumina–1:1 chloroform–light petroleum) (lit.[29] mp 175°); and *N*-methyl-3′-nitro-, mp 93–95° (lit.[20] mp 95°), acetanilides were prepared from the appropriate amine by standard treatment with acetic anhydride–acetic acid.

Benzanilides. The appropriate amine was treated with benzoyl chloride in acetone (A), pyridine (B), or under Schotten–Baumann conditions (C). The following benzanilides were prepared: 3′,5′-dinitro-, (A), mp 254–256° (Anal. Calcd for $C_{13}H_9N_3O_5$: C, 54.4; H, 3.1; N, 14.6. Found: C, 54.4; H, 3.35; N, 14.8); 4′-nitro-, (A), mp 200–201° (lit.[20] mp 199°); 4′-methylsulfonyl-, (A), mp 208–209° (Anal. Calcd for $C_{14}H_{13}NO_3S$: C, 61.1; H, 4.7; N, 5.1; S, 11.6. Found: C, 61.3; H, 5.1; N, 5.3; S, 11.4); *N*-methyl-3′,5′-dinitro- (B), mp 126° (lit.[21] mp 124–125°); 4′-acetyl- (C), mp 201–202° (lit.[30] mp 204–206°); 3′-chloro- (C), mp 122° (lit.[20] mp 122°); 3′-nitro- (C), mp 155–156° (lit.[20] mp 157°).

Rate Measurements. These were carried out as described previously.[3] In the few cases where ionization of the anilide was significant (noted in Tables I and III) the data were treated by a known method.[11]

Solubilities.[14] Saturated solutions were analyzed spectrophotometrically.

Acknowledgments. We are grateful to Dr. R. M. Pollack for some stimulating thoughts on this problem and to Professor A. J. Parker for helpful discussion.

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Meisenheimer Complexes. A Kinetic Analysis of the Behavior of 2,4-Dinitro-5-methoxythiophene and -selenophene in Methanol

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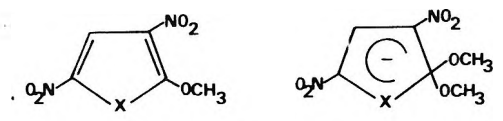
Received April 15, 1975

The kinetics of the formation and decomposition of the *gem*-dimethoxyl Meisenheimer-type complexes **2a, 2b** (X = S, Se) derived from 2,4-dinitro-5-methoxythiophene and -selenophene (**1a, 1b,** X = S, Se) has been studied in methanol. The pH–rate profiles of these reactions allowed determination of rate coefficients for attack of either methoxide ion or methanol on **1a** and **1b** as well as those for the decomposition of adducts **2a** and **2b,** whether it is in a spontaneous process or indirectly with the aid of a solvated proton. The rate of the attack of methoxide ion on **1a** and **1b** has also been measured at different temperatures in dilute potassium methoxide solutions which provides energies and entropies of activation for this reaction. The results are compared with previously reported data for the formation and decomposition of the adduct **4** derived from 2,4,6-trinitroanisole (**3**). The selenophenic complex **2b** appears to be the most stable Meisenheimer *gem*-dimethoxyl adduct yet observed in methanol.

The reaction of methoxide ion with nitro derivatives of benzene, pyridine, and pyrimidine often results in the formation of stable adducts, referred as to Meisenheimer complexes.[1] Recent rapid kinetic studies have allowed the determination of kinetic and thermodynamic parameters for the formation and decomposition of a great number of such complexes, thus leading to a better understanding of the mechanism of these processes.[2-5] The formation of similar adducts from various five-membered ring substrates such as 2,4-dinitro-5-methoxythiophene and -selenophene (**1a, 1b,** X = S, Se) has also been reported.[6,7] In this case, the thermodynamic stability of the corresponding complexes **2a, 2b** (X = S, Se) is so high that they are partially formed



1a X = S **2a**

1b X = Se **2b**

in pure methanol and only an order of magnitude could be obtained for the parameters of the reactions. We now report a comprehensive kinetic analysis of the behavior of **1a, 1b** in pure methanol.

Results

The reaction of methoxide ion with 2,4-dinitro-5-methoxythiophene (**1a**) and -selenophene (**1b**) in methanol results in the immediate formation of the red-colored adducts **2a** and **2b** which show an absorption band at 530 nm (ϵ_{2a} 22,800 M^{-1} cm^{-1}; ϵ_{2b} 21,000 M^{-1} cm^{-1}). At this wavelength the parent molecules have zero or negligible absorption. Both adducts, which were identified by NMR spectroscopy,[6,7] are completely formed in a solution with methoxide ion concentration as low as 5×10^{-4} M. Therefore, it was necessary to use buffer solutions to carry out a comprehensive study of their formation and decomposition. The buffer solutions were prepared from various carboxylic acids and phenols AH and, in general, were made up so as to give a total ionic strength of 0.01 M from the buffer species A^- alone without any added neutral salt. This low ionic strength μ was chosen because, as previously shown by electrochemical measurements in methanol,[8] the mean activity coefficient $\gamma\pm$ can then be calculated by using a simplified Debye–Hückel type equation ($\log \gamma\pm = -Bz^2\sqrt{\mu}$), thus allowing the hydrogen ion concentration $[H^+]$ of the solutions to be deduced from the measured activity (H^+) of the solvated proton. The pH values were determined as previously described[8] and are relative to the standard state in methanol. Using the same buffer at different ionization ratios $[A^-]/[AH]$, we were able to cover a range from pH 5.48, which is the value for the dichloracetate–dichloracetic acid buffer ($[A^-]/[AH] = 1/3$), to 13.70, which is that for the *p*-chlorophenoxide–*p*-chlorophenol buffer ($[A^-]/[AH] = 3$) and close to the pH value of a potassium methoxide solution 5×10^{-4} M at the same ionic strength 0.01 M (NaBr added).

Plotting the variations at 530 nm of the optical density obtained at equilibrium as a function of pH, we observed that the adducts **2a** and **2b** are half formed at pH 11.16 and 9.86, respectively. Taking into account the relatively high value of the Debye–Hückel coefficient B in methanol (B = 1.80),[8] these $pH_{1/2}$ values are identical with the pK_a values for the formation of adducts (eq 1) at $\mu = 0.01$ M and are related to the thermodynamic pK_a values at zero ionic strength by eq 2.

$$1 + CH_3OH \rightleftarrows 2 + H^+ \quad K_a = \frac{(2)(H^+)}{(1)} \tag{1}$$

$$pK_a = pH_{1/2} - \log \frac{\gamma_2}{\gamma_1} \tag{2}$$

Assuming $\gamma_1 \backsimeq 1$, which is here a quite reasonable assumption, these latter were therefore determined by a Debye–Hückel extrapolation from similar $pH_{1/2}$ measurements at $\mu = 2.5 \times 10^{-3}$, 5×10^{-3}, and 2×10^{-2} M. The following values were so obtained.

$$pK_a^{2a} = 11.36 \pm 0.03 \quad pK_a^{2b} = 10.07 \pm 0.03$$

Indeed, in the case of the thiophenic adduct **2a,** the value is not very different from that roughly estimated by Illuminati et al.[6b]

Using the stopped-flow method as well as conventional methods, we were able to follow spectrophotometrically the kinetics of formation and/or the decomposition of adducts **2a, 2b.** For adduct formation measurements were made by mixing solutions of the substrates with appropriate buffers or with dilute potassium methoxide solutions. Experimental data for adduct decomposition were similarly obtained by mixing solution of adducts in very dilute potassium methoxide solutions (5×10^{-4} M) with the more acidic buffer solutions. The appearance or fading of color was in all cases a first-order process. The logarithm of the observed first-order rate constant k_{obsd} for the combined for-

Table I
Buffer Influence on the Kinetics of Formation and Decomposition of 2a, 2b[a]

Total buffer concn [A⁻] + [AH]	4-Cyanophenoxide buffer [A⁻]/[AH] = 1 pH = 11.72 k_{obsd}, sec^{-1}		Dichloracetate buffer [A⁻]/[AH] = 1 pH = 5.96 k_{obsd}, sec^{-1}	
	2a	2b	2a	2b
5×10^{-3}	$3.59 \pm 0.10 \times 10^{-4}$	$9.05 \pm 0.25 \times 10^{-4}$	$1.71 \pm 0.06 \times 10^{-2}$	$5.05 \pm 0.15 \times 10^{-3}$
10^{-2}	$3.55 \pm 0.10 \times 10^{-4}$	$9.35 \pm 0.25 \times 10^{-4}$	$1.61 \pm 0.06 \times 10^{-2}$	$4.80 \pm 0.15 \times 10^{-3}$
1.5×10^{-2}	$3.57 \pm 0.10 \times 10^{-4}$	$9.25 \pm 0.25 \times 10^{-4}$	$1.70 \pm 0.06 \times 10^{-2}$	$5.26 \pm 0.15 \times 10^{-3}$
2×10^{-2}	$3.42 \pm 0.10 \times 10^{-4}$	$9.40 \pm 0.25 \times 10^{-4}$	$1.64 \pm 0.06 \times 10^{-2}$	$5.00 \pm 0.15 \times 10^{-3}$

[a] 20°; $\mu = 0.01$ *M*.

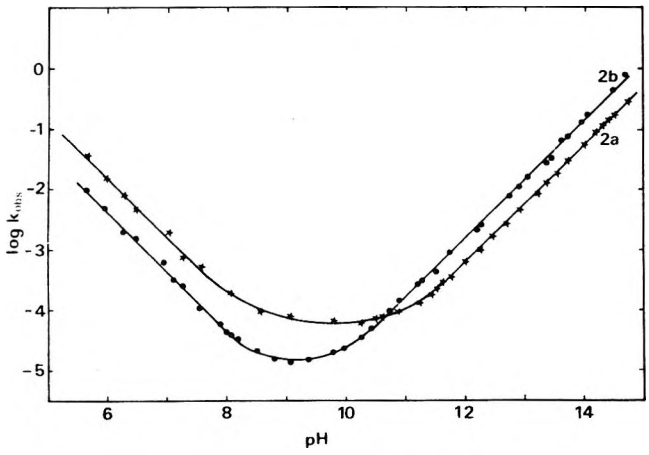


Figure 1. The pH dependence of k_{obsd} (sec^{-1}) for the formation and decomposition of adducts **2a, 2b** in methanol: 20°, $\mu = 0.01$ *M*.

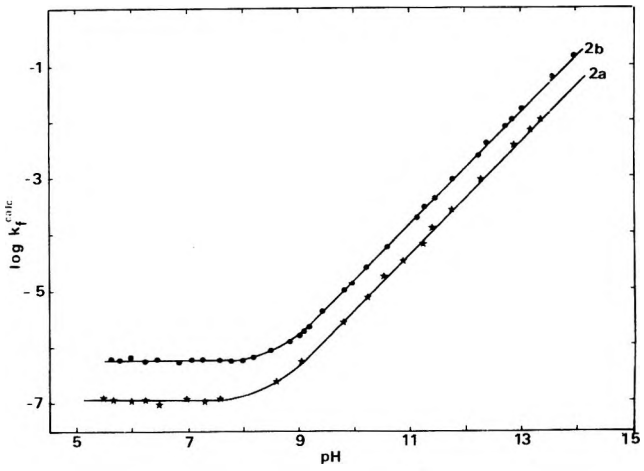


Figure 2a. The pH dependence of k_f (sec^{-1}) for the formation of adducts **2a, 2b** in methanol: 20°, $\mu = 0.01$ *M*.

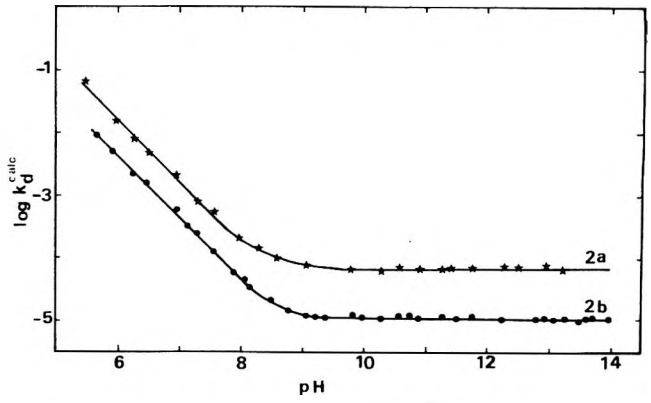


Figure 2b. The pH dependence of k_d (sec^{-1}) for the decomposition of adducts **2a, 2b** in methanol: 20°, $\mu = 0.01$ *M*.

mation and decomposition of complexes **2a, 2b** are plotted in Figure 1 as a function of pH. The data in Table I show that variation of buffer concentration at constant pH does not significantly affect the value of k_{obsd} within experimental error, indicating the absence of catalysis by buffer, at least at the low concentrations used. In addition, smooth pH–rate profiles are obtained despite the fact that buffers of varying chemical types were used, which clearly indicates, as expected in methanol, that buffer species (particularly phenoxide anions) do not react with the substrates.[9]

The observed rate constant k_{obsd} reflects the rate of approach to equilibrium between the substrates 1 and the corresponding adducts 2 and is the sum of the pseudo-first-order rate constants k_f and k_d, respectively, for the formation and decomposition of 2.

$$k_{obsd} = k_f + k_d \tag{3}$$

At equilibrium

$$k_f[1] = k_d[2] \tag{4}$$

so that k_f and k_d are related to the equilibrium constant K_a by the relation 5 and consequently with the experimental $pH_{1/2}$ value corresponding to the half-formation of adducts 2.

$$\frac{k_f}{k_d} = \frac{K_a\gamma_1}{(H^+)\gamma_2} = \frac{(H^+)_{1/2}}{(H^+)} \tag{5}$$

Combining eq 3 and 5 leads to

$$k_d = \frac{k_{obsd}}{1 + (H^+)_{1/2}/(H^+)} \tag{6}$$

$$k_f = \frac{k_{obsd}}{1 + (H^+)/(H^+)_{1/2}} \tag{7}$$

Some typical values of k_f and k_d calculated from eq 6 and 7 are given in Table II for the selenophenic adduct. Complete data are graphically represented in Figure 2, showing the pH dependence of k_f and k_d.

The observed pH–rate profiles are consistent with equations of the form

$$k_f = k_1^{CH_3OH} + k_2[CH_3O^-] = k_1^{CH_3OH} + \frac{k_2K_s}{(H^+)\gamma\pm} \tag{8}$$

(K_s = autoprotolysis constant of methanol, $10^{-16.86}$ at 20° [8])

$$k_d = k_{-1}[H^+] + k_{-2} = \frac{k_{-1}(H^+)}{\gamma\pm} + k_{-2} \tag{9}$$

$$k_{obsd} = \frac{k_{-1}(H^+)}{\gamma\pm} + k_{-2} + k_1^{CH_3OH} + \frac{k_2K_s}{(H^+)\gamma\pm} \tag{10}$$

and then with the following general scheme where the adducts 2 may be formed by attack of either methoxide ion (second-order rate constant k_2) or methanol (first-order rate constant $k_1^{CH_3OH}$) on the parent ethers 1, and may de-

Table II
Experimental and Calculated Pseudo-First-Order Rate Constants k_{obsd}, k_f, k_d for the Formation and/or Decomposition of the Selenophenic Adduct 2b in Methanol[k]

pH	$k_{obsd} \times 10^4$, sec^{-1}	$k_f \times 10^4$, sec^{-1}	$k_d \times 10^4$, sec^{-1}	pH	$k_{obsd} \times 10^4$, sec^{-1}	$k_f \times 10^4$, sec^{-1}	$k_d \times 10^4$, sec^{-1}
5.66[a]	93	5.86×10^{-3}	93	10.88[f]	1.36	1.24	0.110
5.96[a]	50	6.20×10^{-3}	50	11.24[f]	2.73	2.60	0.109
6.26[a]	19	4.80×10^{-3}	19	11.48[f]	4.4	4.29	0.103
6.44[a]	15.6	5.91×10^{-3}	15.6	12.18[g]	19.3	19.2	0.092
7.09[b]	3.20	5.45×10^{-3}	3.20	12.26[h]	26.4	26.3	0.105
7.27[b]	2.56	6.50×10^{-3}	2.56	12.75[h]	75.3	75.2	0.097
7.57[b]	1.12	5.75×10^{-3}	1.12	12.89[i]	108	108	0.100
7.87[b]	0.56	5.7×10^{-3}	0.56	13.04[h]	147	147	0.097
8.05[b]	0.42	6.5×10^{-3}	0.42	13.46[j]	317	317	0.080
8.48[c]	0.22	9×10^{-3}	0.21	13.58[j]	605	605	0.110
8.78[c]	0.16	1.21×10^{-2}	0.145	13.70[j]	740	740	0.107
9.04[d]	0.13	1.68×10^{-2}	0.11	13.98[j]	1400	1400	0.106
9.34[d]	0.14	3.22×10^{-2}	0.107	14.08[j]	1780	1780	0.107
9.95[e]	0.23	0.13	0.104	14.46[j]	4500	4500	0.112
10.25[e]	0.345	0.245	0.100	14.68[j]	7700	7700	0.115

[a] Buffers used were a, dichloracetate; b, salicylate; c, *m*-chlorobenzoate; d, benzoate; e, 2,4,6-trichlorophenoxide; f, 2,6-dichlorophenoxide; g, 4-cyanophenoxide; h, 2-bromophenoxide; i, 4-chlorophenoxide. [j] Potassium methoxide solutions 6×10^{-4}–10^{-2} *M*. [k] 20°, μ = 0.01 *M*.

compose either in a spontaneous process (first-order rate constant k_{-2}) or indirectly with the aid of H^+ (second-order rate constant k_{-1}).

$$1 + CH_3OH \underset{k_{-1}}{\overset{k_1^{CH_3OH}}{\rightleftharpoons}} 2 + H^+$$

$$1 + CH_3O^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} 2$$

At high pH, eq 8 and 9 simplify to eq 8a and 9a

$$k_f \simeq k_2[CH_3O^-] = \frac{k_2 K_s}{(H^+)\gamma\pm} \quad (8a)$$

$$k_d \simeq k_{-2} \quad (9a)$$

thus leading to a straight line of slope +1 and a plateau, respectively, in Figures 2a and 2b and allowing an easy determination of values of k_2 and k_{-2}. At low pH, eq 8 and 9 reduce similarly to eq 8b and 9b.

$$k_f \simeq k_1^{CH_3OH} \quad (8b)$$

$$k_d \simeq k_{-1}[H^+] = \frac{k_{-1}(H^+)}{\gamma\pm} \quad (9b)$$

Another plateau and straight line of slope −1 from which one can obtain values for $k_1^{CH_3OH}$ and k_{-1} is shown in Figures 2a and 2b. Table III summarizes the various rate coefficients so obtained.

Considering these values, the observed first-order rate constant k_{obsd} is expected to be identical with k_d and k_f at low and high pH, respectively, which is in agreement with the experimental observation. In the intermediate pH range, values of the terms $k_2K_s/(H^+)\gamma\pm$ and/or $k_{-1}(H^+)/\gamma\pm$ cannot be neglected relative to the sum $k_{-2} + k_1^{CH_3OH}$ so that no plateau appears in the experimental pH–rate profile.

We studied also the formation of adducts at different temperatures in dilute solutions of potassium methoxide 5×10^{-4}–10^{-2} *M*. The ionic strength was maintained constant at 0.01 *M* by adding NaBr as necessary. In this case, only the reaction

$$1 + CH_3O^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} 2$$

occurs and the expression for the observed first-order rate constant k_{obsd} reduces to

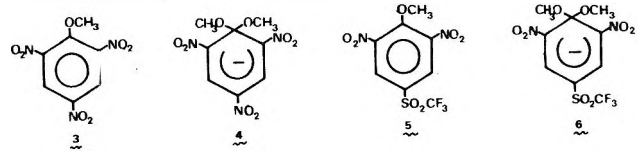
Table III
Specific Rate Constants for the Formation and Decomposition of Complexes 2a, 2b in Methanol[d]

		2a	2b	4
k_2, M^{-1} sec^{-1}	10°	15.8[a]		
	20°	28.2,[a] 26.3[b]	71,[a] 69[b]	11.8[c]
	30°	55[a]	148[a]	
	40°	104[a]	295[a]	
k_{-2}, sec^{-1}	20°	7.8×10^{-5} [b]	1.04×10^{-5} [b]	6.05×10^{-4} [c]
$k_1^{CH_3OH}$, sec^{-1}	20°	10^{-7} [b]	5.75×10^{-7} [b]	
k_{-1}, M^{-1} sec^{-1}	20°	1.05×10^4 [b]	2.65×10^3 [b]	$\sim 4.5 \times 10^3$

[a] From measurements in potassium methoxide solutions. [b] From measurements in buffer solutions. [c] Calculated from data of ref 2b. [d] μ = 0.01 *M*.

$$k_{obsd} = k_{-2} + k_2[CH_3O^-] \quad (11)$$

Plots of k_{obsd} against the methoxide ion concentration gave good straight lines whose slopes are k_2 and intercepts k_{-2}. As could be expected from the data previously obtained in the buffer solutions, the intercepts were negligible in all cases and did not allow the estimation of k_{-2}. Therefore, only k_2 values are given in Table III. As can be seen, the value obtained for k_2 at 20° agrees nicely with that determined at the same temperature from the pH–rate profile of Figure 2, thus justifying calculation of the mean activity coefficient $\gamma\pm$ by means of the simplified Debye–Hückel equation.[8] Activation parameters calculated from Arrhenius plots of log k_2 vs. $1/T$ are given in Table IV with analogous data reported for the 1,1-dimethoxy adduct 4 derived from 2,4,6-trinitroanisole (3).[2b]



3 4 5 6

Discussion

The rate of methoxide ion attack on carbon carrying the methoxy group of 2,4-dinitro-5-methoxyselenophene (1b) is about 2.5-fold faster than that on the similar carbon of

Table IV
Kinetic and Activation Parameters for the Formation of Complexes 2a, 2b in Methanol at 25°[c]

	2a	2b	4
k_2, M^{-1} sec^{-1}	40.7, 36[a]	102	17.3[b]
$\Delta H_2^{\ddagger}$, kcal mol^{-1}	9.9 ± 0.6	12.2 ± 0.6	12.9 ± 1[b]
$\Delta S_2^{\ddagger}$, eu	−17.8 ± 2.3	−8.4 ± 2.3	−9.4 ± 3.4[b]
$\Delta G_2^{\ddagger}$, kcal mol^{-1}	15.2 ± 1.3	14.7 ± 1.3	15.7 ± 2[b]

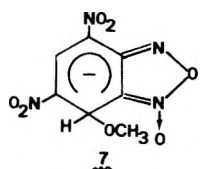
[a] Reference 6b. [b] Reference 2b. [c] μ = 0.01 M.

2,4-dinitro-5-methoxythiophene (**1a**). Although the contribution of the corresponding reaction to the formation of adducts appears to be experimentally negligible, the rate constant for attack of methanol on **1b** is found to be fivefold greater than that for attack on **1a**. These results agree well with the general features reported by Spinelli, Dell'Erba, and coworkers[10,11] for a similar nucleophilic attack of thiophenoxide and selenophenoxide anions and thus confirm the higher reactivity of selenophenic substrates toward nucleophilic reagents.

Considering especially the formation of adducts from methoxide ion attack on **1a, 1b,** inspection of Table IV is indeed very instructive. As can be seen, the enthalpy of activation for the formation of **2a** is 2.3 kcal mol^{-1} lower than that for the formation of **2b**. Consequently, this latter is kinetically favored only because the corresponding entropy of activation is significantly less negative (by about 10 cal deg^{-1} mol^{-1}) than that associated with the thiophenic complex formation, suggesting that the transition state for the formation of **2b** is less solvated than that for **2a**.

In addition to its slower formation, **2a** decomposes more rapidly than **2b,** whether spontaneously or via the aid of H^+. Consequently, the selenophenic adduct appears to be thermodynamically 20-fold more stable than the thiophenic analog. This situation is, indeed, similar to one we have recently encountered by comparing the stabilities of monomethoxyl complexes resulting from the reaction of methoxide ion with 2,4-dinitrothiophene and selenophene.[21]

In Meisenheimer complex chemistry, 2,4,6-trinitroanisole (**3**) has been used very often as a reference for comparison of reactions involving the formation and decomposition of *gem*-dimethoxy Meisenheimer-type adducts.[1,2b,3b,4] As shown in Table III, the trinitro complex **4** is thermodynamically much less stable than the adducts **2a** and **2b** ($pK_a^{2a} - pK_a^4 = -1.23$; $pK_a^{2b} - pK_a^4 = -2.53$), the stability difference arising essentially from its significantly faster rate of spontaneous decomposition: $k_{-2}^4/k_{-2}^{2a} = 7.7$; $k_{-2}^4/k_{-2}^{2b} = 58$. In contrast, the stability of **2a, 2b** is close to that of the 1,1-dimethoxy complex **6** formed from 4-trifluoromethylsulfonyl-2,6-dinitroanisole (**5**):[12] $pK_a^{2a} - pK_a^6 = +0.48$; $pK_a^{2b} - pK_a^6 = -0.82$. Evidently, **2b, 6,** and **2a** are, in this order, the most stable *gem*-dimethoxy complexes which have been observed to form in methanol. It must be noted, however, that another Meisenheimer complex, namely the monomethoxy adduct **7** formed from 4,6-



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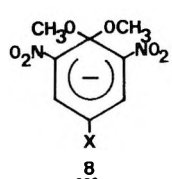
dinitrobenzofuroxan, which is currently under investigation in this laboratory, is even more stable than **2a** and **2b**: $pK_a^7 = 6.46$.[13]

Because of their high stability, demonstrated by the pK_a values which are not too far from the pH value of pure methanol, formation of **2a** and **2b** from the parent molecules **1a** and **1b** can be observed in the absence of any added methoxide. Dissolving 10^{-3} M substrates **1** in methanol results in the slow development of an absorption at 530 nm which is rather weak in the case of X = S but more intense in the case of X = Se. In addition, adding an equimolar amount of potassium methoxide and eliminating the solvent allows the adducts **2a** and **2b** to be isolated as crystalline potassium salts which are very explosive, especially **2b.** Good elemental analyses have been obtained for these solids, which also have NMR spectra identical with those previously recorded by studying the reactions in situ.[5,6]

The factors governing the stability of 1,1-*gem*-dimethoxy complexes formed from 2,4,6-trinitroanisole as well as various substituted 4-X-2,6-dinitroanisoles have been extensively discussed.[1,2b,3b,14] According to recent suggestions the release of steric strain which exists around the carbon bearing the methoxy group[15,2b] would play a major role in contributing to the stability of 1,1 complexes, together with the stabilizing influence of the two methoxy groups on their tetrahedral carbon and the capacity of the electron-withdrawing substituents to delocalize their negative charge. In considering the adducts **2a** and **2b,** a comparison with a benzene analog such as **4** is interesting. Whereas the influence of alkoxy substitution at the sp^3 carbon as well as delocalization of the negative charge by the electron-withdrawing substituents can similarly account for the stability of **2a** and **2b,** their formation involves less release of steric strain around the methoxy group of parent molecules **1a** and **1b.** Also, whereas the C_2–C_1–C_6 angle in the anisoles is almost 120°, crystallographic studies[17,18] have shown that the S–C_2–C_3 and Se–C_2–C_3 angles of the thiophene and selenophene derivatives are equal to 111°50′ and 110°40′, respectively, values which are close to that for a tetrahedral carbon. Consequently, as previously noted by Illuminati et al.,[6b] the formation of **2a, 2b** involves less bond strain than that of **4.** In addition to these steric and geometrical differences, it should also be noted that the measured pK_a values are dependent not only on the stability of the formed adducts but also on that of the starting materials; and with respect to this latter point, one may reasonably expect the ground-state energy level of 2,4-dinitro-5-methoxythiophene and -selenophene to be higher than that of 2,4,6-trinitroanisole. Consequently, it is clear that any attempt to appreciate the contribution of each of these individual factors to the increased stability of **2a, 2b** relative to that of **4** would be unrealistic.

In the case of substituted 4-X-2,6-dinitroanisoles, the appearance of 1,1 complexes **8** is often preceded by the



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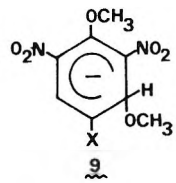

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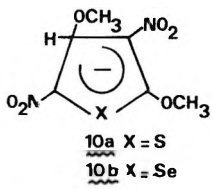

10a X = S
10b X = Se

faster formation of thermodynamically less stable 1,3 complexes **9,** the lifetime of which is strongly increased in Me_2SO.[2b,3b,4,14] Analogous to these results, it might be expected that methoxide ion attack would also occur initially on the unsubstituted 3 carbon of **1a, 1b,** leading to complexes **10a, 10b.** Despite careful NMR and kinetic investigations, we were not able to identify such complexes in methanol–Me_2SO mixtures regardless of the Me_2SO and base concentration. Indeed, the fact that complexes **10a,**

10b are not formed prior to **2a, 2b** is not really surprising, since it is known that the β position of thiophenic and selenophenic derivatives is less sensitive to nucleophilic attack than the α position.[19] Furthermore, recent kinetic studies have shown that the rate of methoxide ion attack on the 5-unsubstituted carbon of 2,4-dinitrothiophene and -selenophene is somewhat slower than that on the analogous 5 carbon bearing the methoxy group of **1a, 1b.**[20,21] This behavior, which contrasts strongly with that observed in benzenic and pyridinic series,[1,3,4] will be discussed in a forthcoming paper.

Experimental Section

Materials. 2,4-Dinitro-5-methoxythiophene was prepared by nitration of 2-methoxy-5-nitrothiophene according to the method described by Illuminati et al.,[6b] mp 140°. 2,4-Dinitro-5-methoxyselenophene was prepared by dissolving 3 g of 2-bromo-3,5-dinitroselenophene in 30 ml of methanol. To this stirred solution was added dropwise at −40° 15 ml of methanolic potassium methoxide (1 *M*). The mixture was allowed to stand for 30 min at −20° and then poured into 200 ml of hydrochloric acid (2 *N*) and extracted with ether. The ether phase was washed with water, dried, and evaporated. The dinitro compound was recrystallized from chloroform, mp 119°. Anal. Calcd for $C_5H_4N_2O_5Se$: C, 23.90; H, 1.59; N, 11.16. Found: C, 23.70; H, 1.70; N, 11.21.

Potassium 2,2-dimethoxy-3,5-dinitrothia- and -selenacyclopentenates (**2a, 2b**) were prepared by addition of nearly 1 equiv of 1 *M* methanolic potassium methoxide to a solution of the parent molecules **1a, 1b** (100 mg) in a minimum amount of methanol. The reaction mixture turned immediately reddish purple and was allowed to stand at room temperature for 15 min. Then the solvent was removed under vacuum and the residues, collected as purple solids, were washed with anhydrous ether and dried under vacuum to constant weight in order to eliminate any associated solvent.

Anal. Calcd for $C_6H_7N_2KO_6S$: C, 26.26; H, 2.57; N, 10.25; S, 11.68. Found: C, 26.20; H, 2.72; N, 10.18; S, 11.41. Calcd for $C_6H_7N_2KO_6Se$: C, 22.43; H, 2.19; N, 8.72. Found: C, 22.84; H, 2.09; N, 8.64.

Methanol and methanolic potassium methoxide solutions were prepared as previously described.[8a] The various buffers used for the rate measurements were purified according to classical methods.

Rate and pH Measurements. Stopped-flow determinations were performed on a Durrum stopped-flow spectrophotometer, the cell compartment of which was maintained to ±0.5°. Other kinetic measurements were made using a Beckman spectrophotometer. All kinetic runs were carried out under pseudo-first-order conditions with a substrate concentration of about 3×10^{-5} *M*. Rate constants are accurate to ±3%.

The pH of buffer solutions and dilute potassium methoxide solutions has been measured according to a method previously reported by using an hydrogen electrode.[8] The pH values so obtained are relative to the standard state in methanol.

Registry No.—**1a,** 27357-00-2; **1b,** 36658-93-2; **2a,** 55955-40-3; **2b,** 55955-41-4; 2-bromo-3,5-dinitroselenophene, 17580-53-9; potassium methoxide, 865-33-8.

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(9) In order to check more carefully the possibility that phenoxide ions may attack **1a, 1b** to yield a complex, some experiments have been carried out at a higher ionic strength ($\mu = 5 \times 10^{-2}$ *M*) with two different buffer systems, namely the *p*-cyanophenoxide–*p*-cyanophenol buffer ($[A^-]/[AH] = 1/2$, pH 11.20) and the 2,6-dichlorophenoxide–2,6-dichlorophenol buffer ($[A^-]/[AH] = 1.75$, pH 11.20). Increasing the concentration of the basic species from 10^{-2} to 5×10^{-2} and adding NaBr as necessary still does not significantly affect k_{obsd} within experimental error. It is thus clear that phenoxide ions do not attack **1a, 1b** and that no appreciable buffer catalysis of the formation of **2a, 2b** occurs under our experimental conditions. Another evidence is, indeed, the fairly good agreement observed between the k_2 values determined separately from measurements in buffer solutions and dilute potassium methoxide solutions.

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Some Selenium Derivatives of Imidazo[1,2-*a*]pyridines

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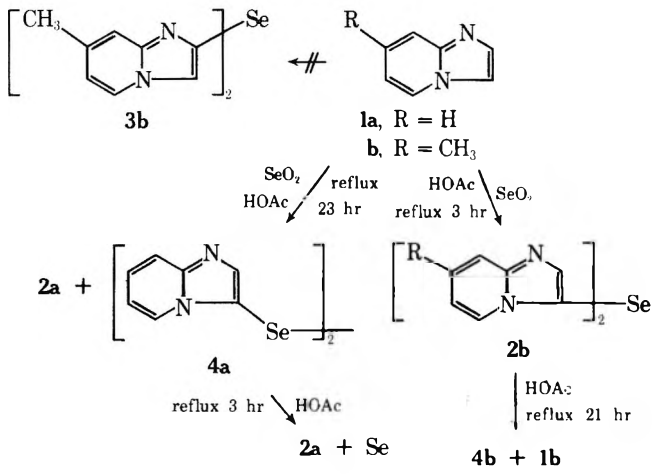
Received May 28, 1975

The reaction of imidazo[1,2-*a*]pyridine (**1a**) and its 7-methyl derivative (**1b**) with selenium dioxide affords 3,3′-di(imidazo[1,2-*a*]pyridyl) selenides (**2a,b**). Prolonged reaction time also yield the 3,3′-di(imidazo[1,2-*a*]pyridine) diselenide (**4a**) along with **2a**. The diselenide **4a** can be converted to the monoselenide **2a** by heating in glacial acetic acid, while the monoselenide **2b** affords a mixture of the diselenide **4b** and 7-methylimidazo[1,2-*a*]pyridine (**1b**) under similar reaction conditions. The monoselenide **2b** when treated with bromine yields, ultimately, 3-bromo-7-methylimidazo[1,2-*a*]pyridine (**5**). When 3-bromo-7-methylimidazo[1,2-*a*]pyridine (**5**) is treated with selenium dioxide in acetic acid, monoselenide **2b**, diselenide **4b**, 5-(2-amino-4-methylpyridyl)-3-(7-methylimidazo[1,2-*a*]pyridyl) selenide (**6**), and the parent compound **1b** are obtained. The ^{1}H NMR spectra of the various compounds, as well as possible reaction paths to account for their formation, are described.

As part of a research project requiring the preparation of imidazo[1,2-*a*]pyridine carboxaldehydes, we had occasion to attempt a selenium dioxide oxidation of 7-methylimidazo[1,2-*a*]pyridine (**1b**). Surprisingly, no carboxaldehyde derivative was obtained. Instead, a compound of molecular composition $C_{16}H_{14}N_4Se$ was isolated in 90% yield. The ^{1}H NMR spectrum of this compound (see Table I) indicates that neither the methyl group nor any of the six-membered ring protons of 7-methylimidazo[1,2-*a*]pyridine (**1b**) were affected by the reaction. The presence of a singlet at δ 7.87 ppm indicates that substitution by a selenium atom has occurred at either C-2 or C-3 of the ring system. Therefore, we can conclude that the product has either structure **2b** or **3b** (see Scheme I).

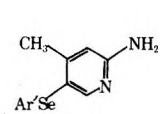
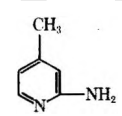
An examination of Dreiding molecular models shows that if the compound had structure **3b**, assuming free rotation about the two carbon–selenium bonds, one would expect the chemical shifts of the six-membered ring protons in this compound to be very similar to those in 7-methylimidazo[1,2-*a*]pyridine (**1b**). On the other hand, if the compound had structure **2b**, the models indicate a potential ring–ring interaction which would produce a significant shift in the resonance position of H-2 and H-5. An examination of Table I shows that the latter instance prevails. Specifically, H-5 is more deshielded by 0.39 ppm in the selenium-containing compound **2b** than it is in the starting material (**1b**). A similar shift (0.38 ppm) is apparent for H-2. Thus, we are dealing with the 3-substituted derivative **2b**.

Scheme I



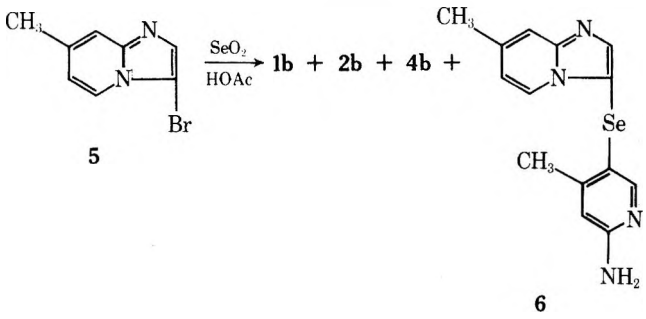
The parent imidazo[1,2-*a*]pyridine (**1a**) when treated with selenium dioxide affords the analogous monoselenide **2a** as well as a compound of molecular formula $C_{14}H_{10}N_4Se_2$ (**4a**). The ^{1}H NMR spectrum of this material differs from that of the monoselenide **2a** by increased shielding of H-2, H-5, and H-6 while maintaining the same splitting pattern. When this diselenide is heated in acetic acid, it is converted to the monoselenide. Consequently, the two compounds are structurally related to each other in terms of their sites of substitution. An analysis of the ^{1}H

Table I
Chemical Shifts[a] of Some Imidazo[1,2-*a*]pyridines[c]

	ArH[b]	ArBr	ArSeAr	$(ArSe)_2$	Ar′H[b]	Ar′Br	Ar′SeAr′[b]	$(Ar'Se)_2$		
	1a		**2a**	**4a**	**1b**	**5**	**2b**	**4b**	**6**	
H_2	7.58	7.62	7.96	7.76	7.49	7.52	7.87	7.70	7.83	
H_3	7.63				7.55					
H_5	8.05	7.90	8.51	7.84	7.99	7.96	8.38	7.67	8.27	
H_6	6.78	6.75	6.93	6.64	6.61	6.72	6.75	6.48	6.72	
H_7	7.16	7.10	7.24	7.24						
H_8	7.62	7.57	7.60	7.68	7.37	7.34	7.38	7.40	7.42	
CH_3					2.38	2.39	2.39	2.40	2.40 & 2.42	2.23
H_3'									6.34	6.34
H_6'									8.06	7.99
NH_2									~4.55	~4.40
H_5'										6.50

[a] In δ (parts per million), dilute solutions in $CDCl_3$. [b] Extrapolated to infinite dilution. [c] Typical values of coupling constants: $J_{2,3}$ = 0–1; $J_{2,8}$ = 0; $J_{3,8}$ = <1; $J_{5,6}$ = 6.6–7; $J_{5,7}$ = 1–1.5; $J_{5,8}$ = 0–1.5; $J_{6,7}$ = 6.6–7; $J_{6,8}$ = 1–1.5; $J_{7,8}$ = 9 Hz.

Scheme II



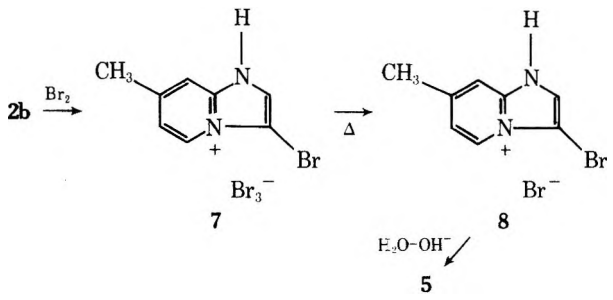
NMR spectrum of the diselenide **4a**[1] further confirms the substitution position of the hterocyclic rings, since an inspection of Dreiding models reveals that, assuming free rotation about the selenium–selenium bond, there will be ring–ring interactions affecting H-2, H-5, and H-6. A comparison of the chemical shifts of H-2 (δ 7.58 ppm), H-5 (δ 8.05 ppm), and H-6 (δ 6.78 ppm) of imidazo[1,2-*a*]pyridine with the corresponding protons in the diselenide, H-2 (δ 7.76 ppm), H-5 (δ 7.84 ppm), H-6 (δ 6.64 ppm), confirms this prediction.

When the monoselenide **2b** is refluxed in acetic acid in the presence or absence of selenium, it is converted to the diselenide **4b,** as well as the parent compound (**1b**). In the absence of selenium, larger amounts of the parent compound **1b** are formed.

The formation of these 3-substituted compounds prompted us to examine the behavior of an imidazo[1,2-*a*]pyridine blocked at that position. When 3-bromo-7-methylimidazo[1,2-*a*]pyridine (**5**) is refluxed in acetic acid in the presence of selenium dioxide, four compounds are isolated, namely, 7-methylimidazo[1,2-*a*]pyridine (**1b**), the monoselenide **2b,** the diselenide **4b,** and a compound, $C_{14}H_{14}N_4Se$ (**6**).

The ^1H NMR spectrum of compound **6** showed the same pattern as observed in the monoselenide **2b.** In addition to these absorptions, two sharp one-proton singlets (δ 6.34 and 8.06 ppm) and a broad two-proton band (δ 4.55 ppm) are observed. The methyl proton absorption of this compound integrates for six protons. Based upon these data we suggest structure **6** (see Scheme II). A comparison of the ^1H NMR spectrum of 2-amino-4-methylpyridine [H-3 (δ 6.34 ppm), H-6 (δ 7.99 ppm)] with the "extra" singlet protons in compound **6** confirms the structural assignment.

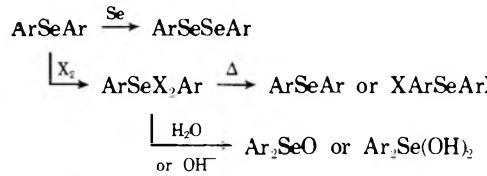
Since the bromine in compound **5** is readily displaced by selenium, it became of interest to examine the reactivity of the selenide **2b** toward bromine. When compound **2b** was treated with bromine in chloroform, a yellow precipitate formed instantaneously. This compound, $C_8H_8N_2Br_4$ (**7**), obtained in quantitative yield, when heated in wet benzene, formed a colorless material, $C_8H_8N_2Br_2$ (**8**). The ^1H NMR spectra of compounds **7** and **8** in Me_2SO-d_6 are identical. Treatment of compound **8** with cold dilute base afforded 3-bromo-7-methylimidazo[1,2-*a*]pyridine (**5**). These various transformations can be depicted as follows.



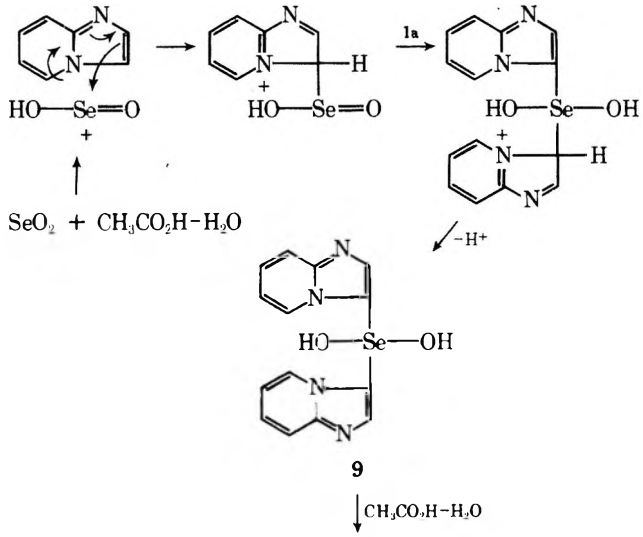
Discussion

The use of selenium dioxide in oxidations of olefins and "active" methyl and methylene groups is well known.[2,3] Some other uses of selenium dioxide in organic chemistry involve the formation of di-*p*-alkoxyphenyl selenides from aryl alkyl ethers[4] and analogous selenides from phenolic compounds.[5] Similar reactivity has been observed for selenium oxychloride, which leads to hydroxy[6] and alkoxy[6b] aryl selenides as well as another class of selenides, the *p*-dialkylaminophenyl derivatives.[7] Some unusual reactions of heterocyclic compounds with selenium dioxide are the formation of selenides from pyrazolones[8] and indoles.[9]

The chemistry of diaryl selenides, as applicable to our work, can be summarized by the following general reactions.[10,11]

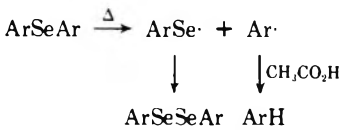


The formation of the diaryl selenides (**2a,b**) can be envisioned to occur by the following sequence of reactions.



The species $HO^+Se{=}O$ and $(HO)_3Se^+$ have been proposed[12] as the active moieties involved in the oxidation reactions of selenium dioxide in the presence of water. We are invoking the same species in the electrophilic substitutions of the imidazo[1,2-*a*]pyridines. A diarylhydroxy selenium intermediate, such as **9**, has been previously postulated, and its conversion to a diaryl selenide, in the presence of aqueous acetic acid and selenium, has been established.[4a]

The conversion of the monoselenides, ArSeAr, to a mixture of the diselenides, ArSeSeAr, and the starting compound, ArH, can be depicted by the following sequence.



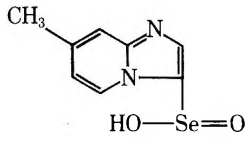
It is of interest to note that in this instance, contrary to other reports,[13] selenium is not required. The disproportionation of the diselenides **4a,b** to the monoselenides **2a,b** and selenium finds precedent in the literature.[14]

The formation of the monoselenide **2b** from 3-bromo-7-methylimidazo[1,2-*a*]pyridine (**5**) could possibly be a nu-

cleophilic or free-radical displaceme reaction at C-3. However, attempts at causing a nucleophilic displacement of bromine by methoxide (see Experimental Section), piperidine, or morpholine[15] were unsuccessful, and no evidence for the formation of free radicals in selenium dioxide oxidations has ever been obtained.[12] We therefore propose an electrophilic displacement reaction analogous to that described for the formation of the selenides **2a** and **2b**. Apparently, no precedence for this type of displacement reaction is available in the literature.

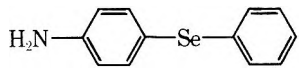
The concurrent formation of the diselenide **4b** and the parent compound (**5**) can then be rationalized as arising from the monoselenide **2b** as delineated in the previous paragraph.

The generation of the small amount of compound **6** may occur via the intermediacy of **10** and attack by 2-amino-4-



10

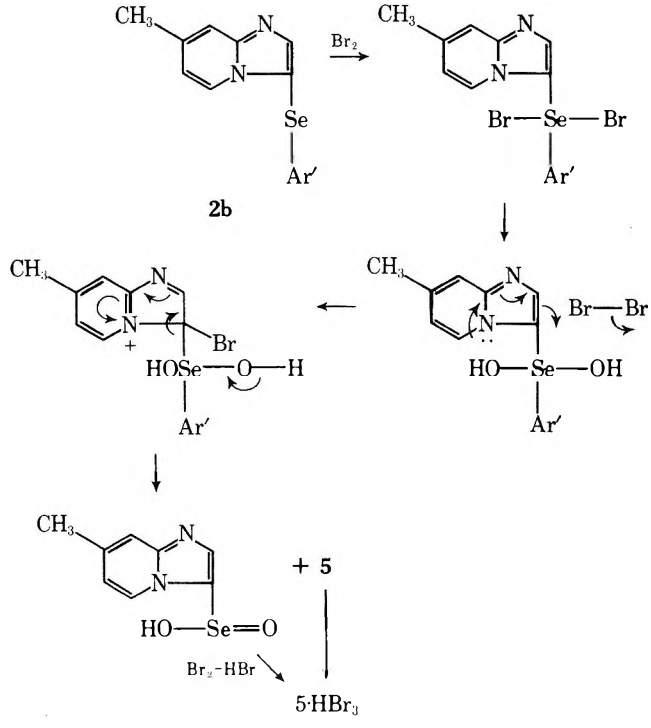
methylpyridine, generated by oxidative hydrolysis of compound **5**, on this species. In support of this path, the reaction of aniline with phenylseleninic acid to give **11** can be cited.[16]



11

The facile formation of 3-bromo-7-methylimidazo[1,2-*a*]pyridine (**5**) from the reaction of the monoselenide **2b** with bromine appears to be novel[17] in that the reported reaction of bromine with diaryl selenides invariably affords $(Ar)_2SeBr_2$.[10,11] These compounds are transformed to BrArSeAr, BrArSeArBr, and ArSeAr derivatives at high temperatures. In the presence of water, or more easily in aqueous base, the dibromodiaryl selenides (Ar_2SeBr_2) are hydrolyzed to hydrated selenoxides, $Ar_2Se(OH)_2$.

Based upon the latter observation, we can depict the formation of the 3-bromo compound **5** by the following sequence of reactions.



It is of interest also to note that only π-excessive heterocyclic rings appear to be subject to electrophilic substitution by selenium dioxide. Thus, pyrazoles, indoles (vide infra), and, now, imidazo[1,2-*a*]pyridines have been shown to form similar diaryl selenides,[18] while pyridines[2] do not.

The reactivity of polyazaindenes and analogous π-excessive heterocyclic systems toward selenium dioxide, and the general synthetic utility of the displacement reaction with bromine and other potential electrophilic agents, are under active investigation.

Experimental Section[19]

Preparation of Compound 2b. To a solution of 2.92 g (26.5 mmol) of SeO_2[20] dissolved in 40 ml of ethanol was added 3.5 g (26.5 mmol) of 7-methylimidazo[1,2-*a*]pyridine (**1b**)[21a] and the solution was refluxed overnight. Since no Se had precipitated, the ethanol was displaced with 15 ml of glacial acetic acid containing 0.5 ml of water and the solution was refluxed for an additional 3 hr. The deep red solution became orange on cooling, and contained no precipitated Se. The solution was evaporated to dryness under reduced pressure, treated with ice-water and aqueous 10% NaOH until no further oil separated (pH ca. 6), and left to stand overnight, after which time the oil had solidified. The solid was collected, rinsed with H_2O, and dried [mp 230–232°, 3.6 g (90%)]. The filtrate yielded 0.53 g of starting material. The reaction product, dissolved in ethanol, was treated with charcoal and the filtrate was concentrated to ca. 10 ml, and water was then added to the hot solution to the saturation point. A further crystallization gave an analytical sample as glistening, colorless needles, mp 234–235.5°. Anal. Calcd for $C_{16}H_{14}N_4Se$: C, 56.31; H, 4.13; N, 16.42. Found: C, 55.98; H, 4.18; N, 16.17. Mass spectrum mol wt 342, 340, 339, 338, with typical distribution for Se isotopes 80, 78, 77, 76.[22]

Preparation of Compounds 2a and 4a. A solution of 2.4 g (22 mmol) of SeO_2 in 15 ml of glacial acetic acid, 1.5 ml of H_2O, and 2.4 g (20 mmol) of imidazo[1,2-*a*]pyridine[21b] was refluxed overnight and the solvents were removed under reduced pressure. The residue was treated with ice and aqueous 10% NaOH to pH 7. The orange solid was collected and rinsed with H_2O, absolute ethanol, and ether to give 2.55 g of a two-component mixture (TLC, alumina, 50% $CHCl_3$–C_6H_6). The mixture was twice treated with 10 ml of hot ethanol, cooled, and filtered to give 1.73 g (55%) of a colorless solid, compound **2a**, mp 268–270° dec. Two crystallizations from ethanol gave an analytical sample, mp 282–282.5° dec. Anal. Calcd for $C_{14}H_{10}N_4Se$: C, 53.68; H, 3.22; N, 17.89. Found: C, 53.86; H, 3.21; N, 17.79. Mass spectrum mol wt 314, 312, 311, 310.

The material in the organic wash liquids and mother liquors was percolated through 120 g of grade 3 neutral alumina in $CHCl_3$. Early fractions were two-component (mono- and diselenide) mixtures followed by 0.83 g (21%) of a single component which was dissolved in 200 ml of ethyl acetate. The solution was filtered and the filtrate was concentrated to 50 ml to give 0.54 g of a solid, compound **4a**, mp 191–192° dec. Recrystallization from 5 ml of ethanol afforded an analytical sample as a shiny orange solid, mp 192–193°. Anal. Calcd for $C_{14}H_{10}N_4Se_2$: C, 42.87; H, 2.57; N, 14.29. Found: C, 42.85; H, 2.63; N, 14.12. The ir spectra of the two materials were very similar and differed primarily in the intensities of the bands.

When a similar reaction mixture was allowed to stand at room temperature for 67 hr, no reaction occurred.

Reaction of 4a with Glacial Acetic Acid. When a solution of 150 mg of diselenide **4a** in 2 ml of glacial acetic acid was heated in an oil bath at 110° for 3 hr, Se deposited. The mixture was evaporated to dryness under reduced pressure. Water was added to the residue and the mixture was again evaporated to dryness. Extraction of the residue with $CHCl_3$ left a small amount of black Se (ca. 10 mg). The $CHCl_3$ extracts were concentrated to ca. 3 ml and the precipitated solid was filtered and rinsed with $CHCl_3$ and absolute ethanol. The nearly colorless solid (50 mg) was identified as the monoselenide **2a** by its melting point (265–270°) and ^1H NMR spectrum. The filtrate was evaporated to dryness, the residue was heated with 3 ml of absolute ethanol and cooled, and the precipitated solid was filtered to give 40 mg of starting material (**4a**), mp 194° dec. TLC of the filtrate (alumina, 25% $CHCl_3$–75% C_6H_6) indicated the presence of primarily starting material (**4a**), some monoselenide **2a**, and a trace of imidazo[1,2-*a*]pyridine (**1a**).

Reaction of Compound 2b with Selenium. A mixture of 0.34 g (1 mmol) of compound **2b**, 0.20 g (2.5 mmol) of black Se powder, and 20 ml of glacial acetic acid was refluxed for 23 hr. The Se was

removed by filtration, and the solvent was removed from the filtrate under reduced pressure. The residue was treated with ice–water and aqueous 10% NaOH to pH 8 and then extracted four times with $CHCl_3$ (30 ml total). The combined extracts were dried over anhydrous Na_2SO_4 and filtered and the filtrate was concentrated to a small volume and percolated through 40 g of grade 3 neutral alumina with $CHCl_3$. The early fractions contained 0.15 g (57%) of 7-methylimidazo[1,2-a]pyridine (**1b**), identified by TLC and ir spectral comparisons with an authentic sample. Later fractions contained a 1:1 mixture of compounds **2b** and **4b** (0.13 g, 34%) as shown by ^1H NMR spectral comparison with authentic samples.

Treatment of Compound 2b with Acetic Acid. A solution of 0.32 g (0.9 mmol) of the monoselenide **2b** in 15 ml of glacial acetic acid was refluxed for 24 hr. The solution rapidly turned yellow, then orange, and black Se precipitated. The Se was filtered (39 mg, 50%), and the filtrate was evaporated to dryness under reduced pressure. Water and aqueous 10% NaOH were added to the residue to pH 10. The mixture was extracted five times with $CHCl_3$ (40 ml total). The combined extracts were dried over anhydrous Na_2SO_4 and filtered, and the filtrate was concentrated to a small volume and percolated through 35 g of grade 3 neutral alumina with $CHCl_3$. The first fraction yielded 30 mg of a foul-smelling semisolid which had the same R_f (TLC on alumina, 50% C_6H_6–$CHCl_3$) as 7-methylimidazo[1,2-a]pyridine (**1b**). The next fractions contained 190 mg (80%) of **1b** contaminated with some of compound **2b**. This mixture was separated by sublimation in vacuo and its components were identified by ir and TLC comparisons with authentic samples of compounds **1b** and **2b**. The final fractions contained 40 mg (ca. 12%) of a 3:1 mixture of compounds **2b** and **4b** as shown by ^1H NMR comparison with authentic samples.

Reaction of 3-Bromo-7-methylimidazo[1,2-a]pyridine with Selenium Dioxide. A solution of 0.73 g (6.6 mmol) of SeO_2, 1.40 g (6.3 mmol) of 3-bromo-7-methylimidazo[1,2-a]pyridine[21a] (**5**), and 40 ml of ethanol was refluxed overnight. TLC (alumina, C_6H_6) indicated the presence of primarily starting material. The ethanol was therefore displaced with 15 ml of acetic acid and 0.5 ml of H_2O and the solution was refluxed for 23 hr, when it was deep red and black Se had precipitated. The latter was removed by filtration (0.25 g), and the filtrate was evaporated to dryness. The residue was treated with 15 ml of H_2O. A very fine, deep red powder (30 mg, Se) was removed by filtration. The filtrate was treated with aqueous 10% NaOH to pH 9 and extracted three times with $CHCl_3$ (30 ml total). The combined extracts were dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed. The residue was percolated through 120 g of grade 3 neutral alumina with 50% C_6H_6–$CHCl_3$. Starting material (80 mg) was eluted first, followed by 50 mg (6%) of 7-methylimidazo[1,2-a]pyridine identified by comparison with an authentic sample (TLC and ir spectra). Further elution gave 0.51 g (4) of compound **2b** identified by comparison with an authentic sample (TLC and ir spectra). After three treatments with charcoal in ethanol and addition of H_2O to the filtered hot ethanolic solution to the point of saturation, colorless needles (0.31 g), mp 234–235°, were obtained. Elution with $CHCl_3$ gave 0.14 g (11%) of yellow-orange compound **4b** which was twice crystallized from ethyl acetate to give fine, orange needles, mp 197° dec. Anal. Calcd for $C_{16}H_{14}N_4Se_2$: C, 45.73; H, 3.36; N, 13.33. Found: C, 45.46; H, 3.32; N, 13.07. Mass spectrum, a weak set of peaks near *m/e* 420 (M^+), and an intense set at 211, 209, 208, 207 (corresponding to $M^+/2$) with typical Se isotope distribution intensities.

Elution with 50% absolute ethanol–$CHCl_3$ gave 80 mg (8%) of a deep red oil which solidified on standing for several days. After treatment with charcoal in $CHCl_3$, addition of C_6H_6, and removal of a very small amount of flocculent precipitate, the filtrate was evaporated to dryness and the residue was twice crystallized from <1 ml of $CHCl_3$. A very pale yellow solid (**6**), mp 196–196.5°, was obtained. Anal. Calcd for $C_{14}H_{14}N_4Se$: C, 53.00; H, 4.45; N, 17.66. Found: C, 571; H, 4.45; N, 10. Ir (Nujol) indicates the presence of NH_2, 3400, 3220, and 3160 cm^{-1}, and contains all the absorption bands of the mono- and diselenides (**2b** and **4b**). Mass spectrum mol wt 318, 316, 315, 314 with typical Se isotope distribution.

Reaction of Compound 2b with Bromine. A solution of 100 mg (0.3 mmol) of the monoselenide **2b** in 5 ml of $CHCl_3$ was treated with a solution of 10 drops of Br_2 in 1 ml of $CHCl_3$. A yellow solid, which precipitated at once, was collected, rinsed with $CHCl_3$, and dried at room temperature in vacuo for 3 hr to give 0.28 g of solid **7** (mp 130–135° dec); green flame with Cu wire; ^1H NMR spectrum (Me_2SO-d_6) identical with that of 3-bromo-7-methylimidazo[1,2-a]pyridine hydrobromide (**8**); ir (Nujol), however, does not contain the bands typical of the latter. Anal. Calcd for $C_8H_8N_2Br_4$: C, 21.27; H. 1.78; N, 6.20. Found: C, 20.90, H, 1.75; N, 6.16. On attempted crystallization from C_6H_6 the yellow solid changed to a colorless material which was very soluble in H_2O and ethanol. It was twice crystallized by dissolution in hot ethanol and adding twice the volume of ethyl acetate; the solid (mp 220°, softens ca. 210°) had an ir spectrum identical with that of compound **8**.

A small amount of the above solid (**8**) was dissolved in 1 ml of H_2O, and 2 drops of aqueous 10% NaOH were added (pH 10) whereupon an oil separated. The oil was extracted with 3 × 0.5 ml of $CHCl_3$; the combined extracts were dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated to dryness to give 3-bromo-7-methylimidazo[1,2-a]pyridine (**5**), mp 72–76° (lit.[21a] 79.6–80.3°), as established by ir spectral comparison with an authentic sample.

3-Bromo-7-methylimidazo[1,2-a]pyridine Hydrobromide (8). A solution of ca. 100 mg of 3-bromo-7-methylimidazo[1,2-a]pyridine (**5**) in 48% HBr and ca. 5 ml of C_6H_6 was evaporated to dryness on a hot plate and under a stream of N_2. When the residue was treated with 2 ml of C_6H_6 and a few drops of absolute ethanol, colorless needles separated. These were twice crystallized from ca. 0.4 ml of absolute ethanol (mp 219–220°, softens ca. 210°). Anal. Calcd for $C_8H_8N_2Br_2$: C, 32.91; H, 2.76; N, 9.59. Found: C, 32.77; H, 2.78; N, 9.67.

Attempted Reaction of 3-Bromo-7-methylimidazo[1,2-a]pyridine with Sodium Methoxide. Na (0.33 g, 14 mmol) was added to 25 ml of dry methanol to afford 0.56 *M* $NaOCH_3$; 3-bromo-7-methylimidazol[1,2-a]pyridine (**5**, 0.42 g, 2 mmol) was then added and the solution was refluxed for 20 hr. TLC (alumina, 50% C_6H_6–$CHCl_3$) indicated the presence of only starting material. The solvent was removed in vacuo and the residue was treated with H_2O and extracted with four portions of $CHCl_3$. The combined extracts were dried over anhydrous Na_2SO_4 and filtered, and the filtrate was evaporated to dryness. The residue was distilled (100°, 0.02 Torr) to give 0.37 g (88%) of solid whose ir spectrum was identical with that of the starting material.

Registry No.—**1a**, 274-76-0; **1b**, 874-39-5; **2a**, 56051-28-6; **2b**, 56051-29-7; **4a**, 56051-30-0; **4b**, 56051-31-1; **5**, 56051-32-2; **6**, 56051-33-3; **7**, 56051-35-5; **8**, 56051-36-6; SeO_2, 7446-08-4; acetic acid, 64-19-7; selenium, 7782-49-2; bromine, 7726-95-6; sodium methoxide, 124-41-4.

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Perkin-Elmer R-20B NMR spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M instrument equipped with a solid sample injector. The ionizing voltage employed was 70 eV. Elemental analyses were determined by the Analytical Services Laboratory of the University of Alabama Chemistry Department. Melting points are uncorrected.

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Nucleosides of 4-Substituted Imidazoles

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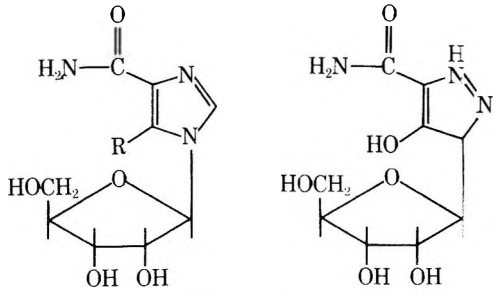
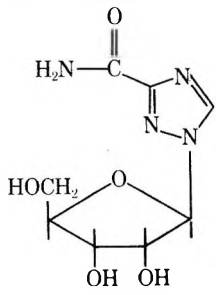
Received May 9, 1975

The synthesis of 1-(β-D-ribofuranosyl)imidazole nucleoside analogs via the deamination of the corresponding 5-aminoimidazole nucleosides is described. 5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylic acid, on treatment with acid anhydrides, was ring closed to 5-substituted nucleoside analogs of imidazo[4,5-*d*][1,3]oxazin-7-one. The intermolecular dimerization of methyl 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboximidate, to provide 2-[5-amino-1-(β-D-ribofuranosyl)imidazole-4-yl]adenosine, is also described.

The nucleoside antibiotic bredinin isolated from the culture filtrate of *Eupenicillium brefeldianum* has recently been reported as an immunosuppressive agent.[1] This antibiotic has been shown to possess structure **1** which is essentially an isomer of pyrazomycin[2] (**2**). The synthetic triazole nucleoside, ribavirin (**3**), which has close resemblance to **1** and **2**, has been reported from these laboratories to exhibit broad spectrum antiviral activity.[3] These data suggest that



bredinin (**1**, R = OH) pyrazomycin (**2**)
AICA riboside (**4**, R = NH_2)



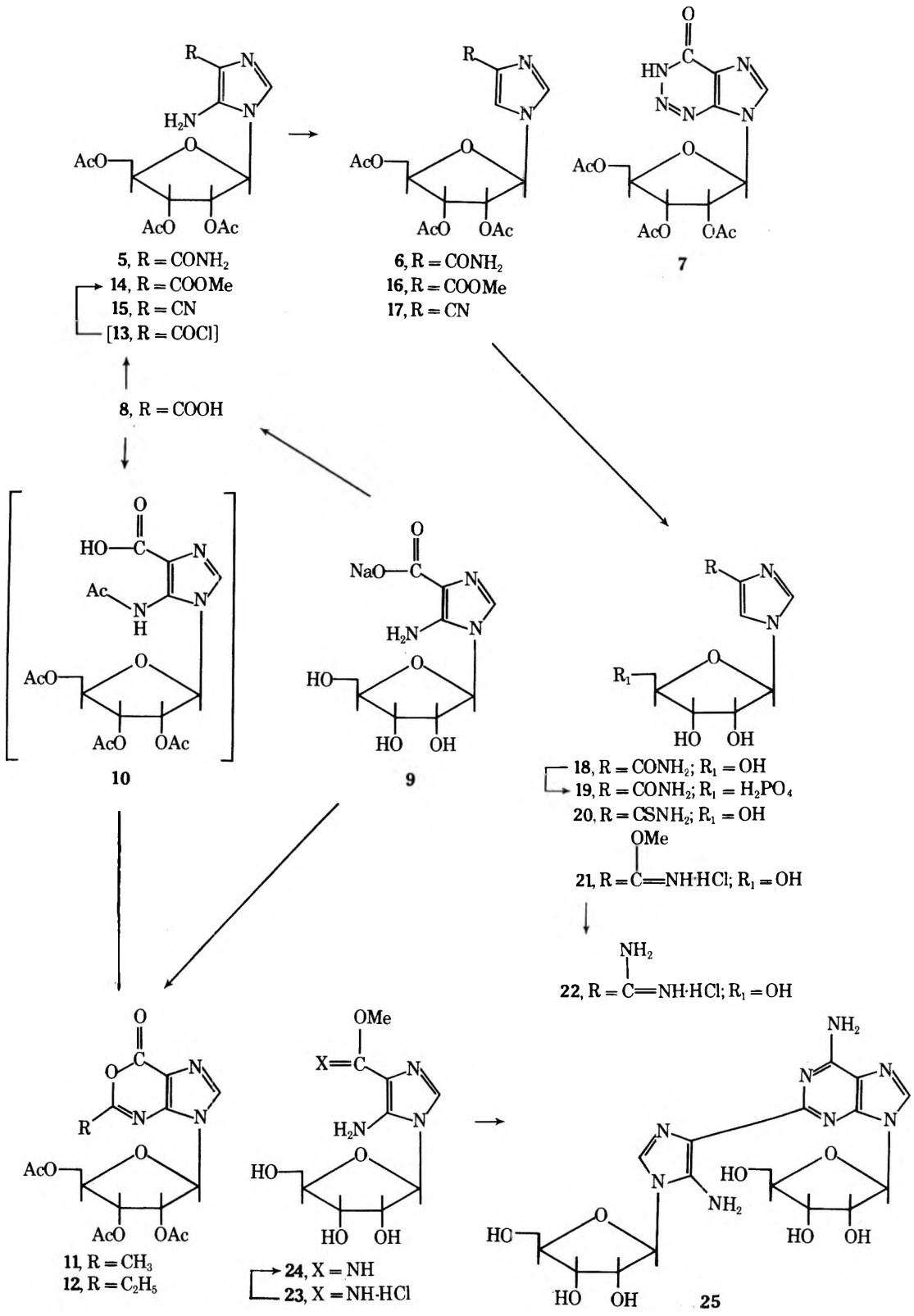
ribavirin (**3**)

nucleoside derivatives of five-membered heterocycles are of potential chemotherapeutic importance. The naturally occurring 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide 5′-phosphate (AICAR), a central intermediate in de novo purine biosynthetic pathway,[4] bears close resemblance to these derivatives; therefore, chemical modification of this molecule was considered from a biological standpoint. The commercial availability[5] of the corresponding nucleoside, 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (AICA riboside, **4**) has led us to study this approach in detail.[6-8]

In the present paper we describe the synthesis of some novel 4-substituted imidazole nucleosides related to ribavirin via diazotization of AICA riboside. In the past, this modification has proven rather difficult and attempts at altering the 5 position of **4** via diazotization under strongly acidic conditions have resulted in facile ring closure to give 2-azainosine.[9] This reaction was well utilized, however, in preparing 2-substituted 5-amino-1-(β-D-ribofuranosyl)-imidazole-4-carboxamide derivatives.[7] Further attempts were made to reductively deaminate the 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide[10] (**5**) using hypophosphorous acid and sodium nitrite. Although some deaminated product, 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**6**), was indeed formed, extensive cyclization occurred to give 7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-4-one (**7**) as the major product. The formation of **7** was not unexpected, since the synthesis of this compound has previously been reported from this laboratory.[9] In order to circumvent this ring closure, modification of the 4-carboxamide function of AICA riboside into a nonreactive group like the methyl carboxylate was investigated. The precursor, 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylic acid (**8**), was obtained via the treatment of sodium 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxylate (**9**) with pyridine and acetic anhydride at a low temperature (10 ± 5°).[6] Repeated experiments revealed that the control of temperature in this reaction was extremely important. At a high temperature (>30°) the 5-amino function of **9** was acetylated generating the corresponding tetraacetyl derivative (**10**) in situ, which immediately cyclized to furnish 5-methyl-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*][1,3]oxazin-7-one (**11**). In an experiment when **8** was heated at 100° in pyridine in the presence of acetic anhydride compound **11** was formed in almost theoretical yield within 1 hr. In a similar experiment when acetic anhydride was replaced by propionic anhydride the corresponding 5-ethyl-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*][1,3]oxazin-7-one (**12**) was obtained in quantitative yield. These novel nucleosides could provide potential intermediates for the synthesis of 1,2-disubstituted purine nucleosides if treated with the requisite amine.

The synthesis of the desired compound **14** was accomplished via treatment of **8** with dimethylformamide, thionyl chloride, and pyridine at −20° to generate the acid chloride **13** in situ, which was treated with methanol to yield

Scheme I



compound **14**. The usefulness of 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (**15**) for deamination studies was obvious owing to the presence of a nitrile group at the 4 position and it was synthesized as described in a patent.[10]

The subsequent reductive deamination of **14** and **15** was able to be carried out successfully via diazotization using hypophosphorous acid and sodium nitrite. These reactions were achieved at a low temperature (≤20°) to avoid excessive cleavage of the glycosidic bond. Methyl 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylate (**16**) and 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (**17**) were isolated by silicic acid column chromatography as a syrup and a crystalline product, respectively, in 60–65% yields. Treatment of **16** with methanol and ammonium hydroxide readily provided 1-(β-D-ribofuranosyl)imidazole-4-carboxamide (**18**). Compound **18** was also obtained when **17** was treated with hydrogen peroxide in the presence of concentrated ammonium hydroxide. Nucleoside **18** is the first example of the synthesis of 2-deazariba-

virin. The synthesis of 1-(β-D-ribofuranosyl)imidazole-4-carboxamide 5′-phosphate (**19**) was also of interest and was achieved in 63% yield by selective 5′-phosphorylation of **18** in the presence of triethyl phosphate and phosphorus oxychloride.

The synthesis of 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (**17**) provided the possibility of further modifications at the 4 position of 1-β-D-ribofuranosylimidazole. The treatment of **17** with potassium hydrosulfide and hydrogen sulfide in methanol at 80–90° gave 1-(β-D-ribofuranosyl)imidazole-4-thiocarboxamide (**20**) as a crystalline compound in 75% yield. When **17** was treated with dry hydrogen chloride in methanol at 0°, it was deacetylated in situ and provided the interesting methyl 1-(β-D-ribofuranosyl)imidazole-4-carboximidate hydrochloride (**21**). The latter compound was further converted into 1-(β-D-ribofuranosyl)imidazole-4-carboxamidine hydrochloride (**22**) when treated with methanolic ammonia at 100°.

Although the synthesis of 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamidine has been previously reported,[11] we wanted to develop an alternate synthesis starting from 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (**15**). When **15** was treated with dry hydrogen chloride in methanol at 0° methyl 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboximidate hydrochloride (**23**) was obtained. The basic methyl 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboximidate (**24**) could be liberated in the crystalline form when an aqueous ethanolic solution of **23** was gradually adjusted with triethylamine to pH 7. We observed an unusual, although not entirely unexpected, intermolecular cyclization[12] when **24** was treated with liquid ammonia at 100° and 2-[5-amino-1-(β-D-ribofuranosyl)imidazole-4-yl]adenosine (**25**) was obtained as a crystalline compound in 25% yield. The structure of compound **25** was assigned on the basis of uv, NMR, and elemental analysis. The desired 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamidine was not isolated in this experiment.

Experimental Section

All the deamination reactions were performed at a temperature of −23 ± 3° to avoid hydrolysis of the glycosyl bond. The physical properties were determined with the following instruments: melting points, Thomas-Hoover apparatus (uncorrected); ^{1}H NMR, Hitachi Perkin-Elmer R-20A spectrometer (DSS); uv spectra, Cary 15 uv spectrophotometer (pH 1 and pH 11). Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and M-H-W Laboratories, Garden City, Mich. Silica gel (Woelm, 0.063–0.2 mm) was used for column chromatography. Solvent systems (A) ethyl acetate–chloroform–acetone (5:3:2 v/v) and (B) ethyl acetate–1-propanol–water (4:1:2 v/v, top layer) were used respectively to check the homogeneity of the blocked and deblocked nucleosides on thin layer chromatography. Presence of exchangeable protons was confirmed by NMR spectroscopy in absolute Me_2SO-d_6 by exchange with D_2O followed by reintegration.

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (6). 5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-imidazole-4-carboxamide (**5**, 1.152 g, 3.00 mmol) was dissolved in 50% H_3PO_2 (20 ml) at −20° with vigorous stirring. To this was added dropwise a solution of $NaNO_2$ (227 mg, 3.3 mmol) in water (2 ml). The reaction mixture turned deep purple. After 2 hr of stirring the reaction mixture was adjusted to pH 6 by careful addition of ammonium hydroxide. It was extracted with ethyl acetate (4 × 100 ml). The combined extracts were dried ($MgSO_4$) and evaporated to dryness in vacuo. The residue (1.01 g) was applied to a dry column of silica gel (2 × 40 cm). It was eluted with EtOAc–CH_2Cl_2–MeOH (350:125:25 v/v) and 20-ml fractions were collected. Fraction 2 contained 190 mg of compound **7** (found identical, in every respect, with an authentic sample[9]).

Fractions 4, 5, and 6 were evaporated in vacuo to give crude compound **6** (280 mg). This was purified by rechromatography through a silica gel column (1 × 20 cm, packed in $CHCl_3$) and elution with $CHCl_3$–EtOAc (60:40 v/v). Upon evaporation, fractions 3–10 (20 ml each) gave 120 mg of pure compound **6** in the form of a thick syrup: NMR ($CDCl_3$–D_2O) δ 5.85 (d, 1, J = 4.5 Hz, C_1′H) and 7.69 and 7.87 ppm [s (pair), 2, C_2H and C_5H].

Anal. Calcd for $C_{15}H_{19}N_3O_8$: C, 48.78; H, 5.19; N, 11.38. Found: C, 48.55; H, 5.28; N, 11.10.

5-Methyl-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*][1,3]oxazin-7-one (11). Method A. 5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylic acid[6] (8, 385 mg, 1 mmol) was gently refluxed in pyridine (5.3 ml) and acetic anhydride (2.7 ml) for 2 hr. The reaction mixture was concentrated to dryness in vacuo. The residue was dissolved in ethyl acetate (20 ml) and washed with water. The ethyl acetate portion was dried ($MgSO_4$) and evaporated in vacuo. The residue thus obtained was crystallized from benzene–petroleum ether to give 360 mg (90%) of **11** in the form of fine needles: mp 115°; NMR (Me_2SO-d_6) δ 2.51 (s, 3, CH_3), 6.19 (d, 1, J = 5 Hz, C_1′H), and 8.39 ppm (s, 1, C_2H).

Anal. Calcd for $C_{17}H_{19}N_3O_9$: C, 49.88; H, 4.68; N, 10.27. Found: C, 49.87; H, 4.61; N, 10.04.

Method B. Compound **11** was also obtained when sodium 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxylate[6] (**9**) was treated as reported in method A. The yield in this case was 30% and the product characterized as for method A.

5-Ethyl-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*][1,3]oxazin-7-one (12). In this experiment 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylic acid was treated with propionic anhydride in pyridine. The reaction and isolation was performed in the same manner as for **11** in method A. The product **12** was crystallized from carbon tetrachloride: mp 136°; NMR (Me_2SO-d_6) δ 1.29 (s, 3, J = 7.5 Hz, CH_3 of 5-ethyl), 2.81 (d, 2, J = 7.5 Hz, CH_2 of 5-ethyl), 6.21 (d, 1, J = 4 Hz, C_1′H), and 8.35 ppm (s, 1, C_2H).

Anal. Calcd for $C_{18}H_{21}N_3O_9$: C, 51.06; H, 5.00; N, 9.93. Found: C, 51.28; H, 5.23; N, 9.74.

Methyl 5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-imidazole-4-carboxylate (14). Under nitrogen atmosphere and anhydrous conditions, 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylic acid (8, 770 mg, 2 mmol) and pyridine (158 mg, 0.161 ml, 2 mmol) were dissolved in dry DMF (8 ml). This mixture was cooled to −20°. A precooled (−10°) solution of DMF–$SOCl_2$ (0.144 ml of $SOCl_2$ in DMF to make the total volume 0.3 ml) was added to the mixture. The reaction mixture was stirred at −20 ± 3°) for 2 hr. After this period methanol (10 ml) was added dropwise to the reaction solution and after complete addition (10 min) the reaction was allowed to come to room temperature. After 8 hr of additional stirring, the solvents were evaporated in vacuo. The residue thus obtained was dissolved in CH_2Cl_2 and washed with water and the organic phase was dried ($MgSO_4$). Compound **14** crystallized when the syrup, obtained after evaporating the solvent in vacuo, was treated with benzene (15 ml). The product was recrystallized from chloroform–ether or 2-propanol to yield 335 mg (42%): mp 145°; NMR (Me_2SO-d_6) δ 3.71 (s, 3, $COOCH_3$), 5.97 (d, 1, J = 6 Hz, C_1′H), 6.25 [s (br), 2, NH_2], and 7.47 ppm (s, 1, C_2H).

Anal. Calcd for $C_{16}H_{21}N_3O_9$: C, 48.12; H, 5.30; N, 10.52. Found: C, 47.99; H, 5.36; N, 10.73.

Methyl 1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylate (16). Compound **14** (799 mg, 2 mmol) was added to a precooled (−20°) stirred solution of hypophosphorous acid (48–50%, 20 ml) containing a few drops of hydrochloric acid. To the above clear solution was added slowly (8 min) a solution of $NaNO_2$ (345 mg, 5.00 mmol) in water (3 ml). The stirring was continued for 3 hr at −20°. The reaction solution was adjusted to pH 6 by careful addition of a saturated solution of sodium bicarbonate. The final reaction mixture was extracted with ethyl acetate (4 × 40 ml) and the organic layer in turn was washed thoroughly with water (2 × 50 ml). The ethyl acetate portion was dried ($MgSO_4$) and the crude residue was chromatographed through a silica gel column (2 × 35 cm, packed in $CHCl_3$). The first $CHCl_3$ eluate (250 ml) was rejected. The column was again eluted with $CHCl_3$–EtOAC (75:25 v/v) and fractions (25 ml) were collected. Fractions 3–10, on evaporation, gave 450 mg (60%) of pure compound **16** as a syrup: NMR (Me_2SO-d_6) δ 3.8 (s, 1, $COOCH_3$), 6.13 (d, 1, J = 5 Hz, C_1′H), and 8.09 and 8.22 ppm [s (pair), 2, C_2H and C_5H].

Anal. Calcd for $C_{16}H_{20}N_2O_9$: C, 50.00; H, 5.25; N, 7.29. Found: C, 49.93; H, 5.48; N, 7.08.

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (17). A solution of 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-

ribofuranosyl)imidazole-4-carbonitrile[10] (3.7 g, 10.00 mmol) in methanol (20 ml) was added to a precooled (−20 to −25°) solution of hypophosphorous acid (48–50%, 100 ml) containing a few drops of concentrated hydrochloric acid. To this was added a solution of sodium nitrite 3.5 g in water (8 ml). The reductive deamination and the isolation of product **17** was performed exactly the same way as described for the synthesis of **16.** The syrup thus obtained by column chromatography was crystallized from methanol to give the pure product **17:** yield 2.3 g (65%); mp 122–123°; λ_{max} (pH 1) 218 nm (ϵ 13,330); λ_{max} (pH 11) 226 nm (ϵ 7694); ν_{max} (KBr) 2234 cm^{-1} (C≡N); NMR ($CDCl_3$ δ 5.85 (d, 1, J = 4 Hz, C_1·H) and 7.75 and 7.81 ppm [s (pair), 2, C_2H and C_5H].

Anal. Calcd for $C_{15}H_{17}N_3O_7$: C, 51.28; H, 4.88; N, 11.96. Found: C, 51.30; H, 4.76; N, 11.98.

1-(β-D-Ribofuranosyl)imidazole-4-carboxamide (18). Method A (from 6 or 16). The blocked compounds **6** and **16** (1 mmol) were respectively treated with a solution of methanol–NH_4OH (10 ml, 1:1 v/v) for 5 hr at room temperature (in case of **16** the reaction went to completion only after 5 days owing to slow reactivity of methyl ester). The solvent was removed in vacuo and the residue was dried in vacuo (0.1 mm) at 40° for 5–7 hr. The residue could then easily be crystallized from methanol. The product **18** obtained from **6** was identical in all respects with the one obtained from **16:** yield 70–75%; mp 156–157°; λ_{max} (pH 1) 213 nm (ϵ 12,900); λ_{max} (pH 11) 235 nm (ϵ 10,200); NMR (Me_2SO-d_6–D_2O) δ 5.65 (d, 1, J = 5.0 Hz, C_1·H) and 7.92 and 7.99 [s (pair), 2, C_2H and C_5H].

Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.39; N, 17.28. Found: C, 44.24; H, 5.25; N, 17.13.

Method B (from 17). Compound **17** (350 mg, 1 mmol) was suspended in 10 ml of ammonium hydroxide. The suspension was cooled to 0° in ice and a 30% solution of hydrogen peroxide (0.5 ml) was added. The suspension was stirred overnight to give a clear solution. The solvent was evaporated and the residue was triturated with acetone. The supernatant was decanted and the resultant residue was crystallized from water, yield 180 mg (74%). The product was found to be identical with that isolated by method A.

1-(β-D-Ribofuranosyl)imidazole-4-carboxamide 5′-Phosphate (19). To a stirred suspension of 1-(β-D-ribofuranosyl)imidazole-4-carboxamide (**18**, 1.216 g, 5 mmol) in triethyl phosphate (20 ml) was added $POCl_3$ (1.6 g) at −5 to 5°. After complete addition (5 min) the reaction mixture was stirred for 5 hr at 0°. This was poured into ice–water (15 ml) and the mixture was diluted with H_2O (50 ml). The solution was adjusted to pH 1.5 by adding 2 *N* NaOH, applied to a Dowex X1 (formate) column (2 × 15 cm), and eluted with water (1000 ml), and the eluate was discarded. The column was subsequently eluted with 0.5 *N* formic acid and 20-ml fractions collected. Fractions 5–11 were evaporated to dryness in vacuo. The residue was triturated well with acetone (3 × 15 ml) and the supernatant was discarded. The residue thus obtained was crystallized from water to yield 1.0 g (33%): mp 197°; NMR (Me_2SO-d_6–D_2O) δ 5.7 (d, 1, J = 5 Hz, C_1·H) and 7.92 and 8.08 ppm [s (pair), 2, C_2H and C_5H].

Anal. Calcd for $C_9H_{14}N_3O_8P$: C, 33.45; H, 4.37; N, 13.00. Found: C, 33.40; H, 4.41; N, 13.02.

1-(β-D-Ribofuranosyl)imidazole-4-thiocarboxamide (20). Compound **17** (500 mg, 1.42 mmol) and KOH (200 mg) in methanol (10 ml) were saturated with H_2S at 0° and heated in a bomb at 100° for 4 hr. After removal of the solvent the residue was taken into water (2 ml) and adjusted to pH 5 by adding dilute HCl. The mixture was cooled in ice for 10–15 min and the separated solid collected by filtration. The crude product was recrystallized from water to give 280 mg of white needles (75%): mp 185°; λ_{max} (pH 1) 246 nm (ϵ 9603) and 298.5 (9982); λ_{max} (pH 11) 256 (12,585) and 301.5 (11,372); NMR (Me_2SO-fd_6–D_2O) δ 5.64 (d, 1, J = 5 Hz) and 8.0 and 8.07 ppm [s (pair), 2, C_2H and C_5H].

Anal. Calcd for $C_9H_{13}N_3O_4S$: C, 41.69; H, 5.05; N, 16.21; S, 12.37. Found: C, 41.58; H, 4.96; N, 16.05; S, 12.51.

Methyl 1-(β-D-Ribofuranosyl)imidazole-4-carboximidate Hydrochloride (21). A solution of **17** (1.9 g, 5.00 mmol) in methanol (30 ml) was saturated with dry hydrogen chloride at 0°. The reaction mixture was allowed to stand overnight at −10°. The separated product was filtered, washed with dry ether, and dried in vacuo to yield 1.4 g (50%) of the hydrochloride **21** as a white solid. The product was recrystallized from acetone–water, mp 155–158° dec.

Anal. Calcd for $C_{10}H_{15}N_3O_5HCl$: C, 40.89; H, 5.49; N, 14.31. Found: C, 40.75; H, 5.30; N, 14.21.

1-(β-D-Ribofuranosyl)imidazole-4-carboxamidine Hydrochloride (22). Compound **21** (1.45 g, 5 mmol) after drying in vacuo over P_2O_5 for 24 hr at room temperature was treated with liquid ammonia (10 ml) in a bomb at 80°. The ammonia was evaporated and the residue was treated with absolute ethanol. The ethanol was evaporated in vacuo and the residue was crystallized from ethanol to give **22** in the form of white crystals: yield 850 mg (60%); mp 166–167° (213° dec); λ_{max} (pH 1) 243 nm (ϵ 10,800); λ_{max} (pH 11) 242 (10,450); NMR (Me_2SO-d_6) δ 5.76 (d, 1, J = 4.5 Hz, C_1·H), 8.3 and 8.61 [s (pair), 2, C_2H and C_5H], and 8.7–9.5 ppm (m, 4, HN=CNH_2·HCl).

Anal. Calcd for $C_9H_{14}N_4O_4$·HCl: C, 38.79; H, 5.42; N, 20.10. Found: C, 38.50; H, 5.60; N, 19.89.

Methyl 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboximidate Hydrochloride (23). 5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (**15**, 3.6 g, 10 mmol) was dissolved in methanol (25 ml). This solution was saturated with dry HCl at 0° and allowed to stand at the same temperature for 24 hr. The separated white solid was filtered, washed with acetone, and dried in vacuo (P_2O_5) to give 2.7 g (90%) of the product **23** which was recrystallized from acetone–water: mp 113° dec; NMR (Me_2SO-d_6–D_2O) δ 4.18 (s, 3, CH_3 of carboximidate), 5.62 (d, 1, J = 6.5 Hz, C_1·H), and 7.67 ppm (s, 1, C_2H).

Anal. Calcd for $C_{10}H_{16}N_4O_5$·HCl: C, 38.91; H, 5.55; N, 18.15. Found: C, 38.79; H, 5.42; N, 17.89.

Methyl 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboximidate (24). An ice-cold aqueous methanolic solution of **23** was adjusted to pH 7 by adding triethylamine. The solution was stirred well and the liberated white solid was filtered and recrystallized from water to give **24** in the form of white crystals: mp 181° dec; λ_{max} (pH 1) 293 nm (ϵ 20,700); λ_{max} (pH 11) 260 (14,300); NMR (Me_2SO-d_6–D_2O) δ 3.81 (s, 3, CH_3 of carboximidate), 5.52 (d, 1, J = 6.5 Hz, C_1·H), and 7.47 ppm (s, 1, C_2H).

Anal. Calcd for $C_{10}H_{16}N_4O_5$: C, 44.11; H, 5.92; N, 20.58. Found: C, 44.13; H, 6.02; N, 20.44.

2-[5-Amino-1-(β-D-ribofuranosyl)imidazole-4-yl]adenosine (25). Methyl 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboximidate (**24**, 272 mg, 1 mmol) was treated with liquid ammonia at 100° for 16 hr. After evaporation of ammonia the residue was crystallized from hot water to give 55 mg (20%) of compound **25:** mp 221° (dec; λ_{max} (pH 1) 257 nm (ϵ 14,400) and 312 (19,200); λ_{max} (pH 11) 252 (15,400) and 310 (20,200); NMR (Me_2SO-d_6–D_2O) δ 5.6 [s (br), 1, C_1·H of imidazole riboside], 5.98 [s (br), 1, C_1·H of adenosine], 7.42 [s (br), 1, C_2H], and 8.25 ppm [s (br), 1, C_8H].

Anal. Calcd for $C_{18}H_{24}N_8O_8$: C, 45.00; H, 5.04; N, 23.33. Found: C, 44.70; H, 5.05; N, 23.37.

Acknowledgments. We wish to thank Drs. L. N. Simon and M. G. Stout for occasional discussions and Dr. R. B. Meyer, Jr., for helpful suggestions.

Registry No.—**5,** 23274-21-7; **6,** 56086-74-9; **8,** 53459-69-1; **9,** 53459-67-9; **11,** 56086-75-0; **12,** 56086-76-1; **14,** 56086-77-2; **15,** 23192-63-4; **16,** 56086-78-3; **17,** 56086-79-4; **18,** 5624-04-4; **19,** 56086-80-7; **20,** 56086-81-8; **21,** 56172-95-3; **22,** 56086-82-9; **23,** 56086-83-0; **24,** 56086-84-1; **25,** 56086-85-2; acetic anhydride, 108-24-7; propionic anhydride, 123-62-6; triethyl phosphate, 78-40-0.

References and Notes

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Electrochemistry of Natural Products. V. Intramolecular Coupling of Phenolic Alkaloid Precursors[1]

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Received August 9, 1974

Intramolecular coupling of some diphenols by electrochemical oxidation is reported. Specifically, 1-(4-hydroxyphenylethyl)- and 1-(4-hydroxy-3-methoxyphenylethyl)-7-hydroxy-6-methoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinolines have been coupled to the corresponding dienones in yields of 20–40% and *N*-acyl-*N*-norreticulines have been coupled to *N*-acyl-*N*-norpallidines in yields of about 18%. Attempts to couple *N*-benzylphenylethylamines to alkaloids of the Amaryllidaceae type were not successful.

The important role played by phenol coupling in alkaloid biosynthesis has been thoroughly documented and reviewed.[3] In general, attempts to carry out phenol coupling reactions in vitro have been only partially successful, mainly owing to low yields caused by overoxidation. In an attempt to develop a more specific oxidizing system, we have been exploring controlled potential, electrochemical oxidation. Intermolecular coupling reactions have been carried out in good yields (50–95%) and our work has recently been summarized.[4] In this paper, we would like to report our more limited success with intramolecular coupling of diphenols. Such electrochemical reactions do not appear to have been previously reported. Although diphenols have not been coupled electrochemiccally before, their methyl ethers have been coupled recently[5] with considerable success. Yields have been high, and the reactions have been remarkably clean. Although these reactions have the greater potential as useful synthetic methods, the coupling of diphenols is more relevant to biosynthesis and biomimetic synthesis of natural products.

The 1-Phenylethyltetrahydroisoquinolines. The compounds oxidized were **7** and **8**, which were prepared (Scheme I) by the method generalized by Harmon and his coworkers.[6] The actual reactions used, however, are substantially different from those previously recorded[7-9] in that the side chain double bond is left in place until the final debenzylation step (**6** to **7** and **8**). Using this sequence, the intermediates were easier to crystallize and work with.

The oxidations of the hydrochlorides of **7** and **8** were carried out on a graphite felt anode in water using tetraethylammonium perchlorate as an electrolyte. The potentials were controlled at 0.7 V for **7** and at 0.8 V for **8** [as measured against a standard calomel electrode (SCE)]. The dienone **9** was obtained from **7** in 23% yield as compared with 19% using $FeCl_3$ as an oxidizing agent.[8] The two dienones, **10** and **11** (differing in the stereochemistry at the spiro ring system) were obtained in a combined yield of 36% as compared to 9% using $K_3Fe(CN)_6$[9] and 31% using $FeCl_3$.[10] The isomers, **10** and **11**, were separated as previously described,[9] but, unfortunately, there was no preponderance of one isomer. One of the isomers is the alkaloid kreysiginone.[10]

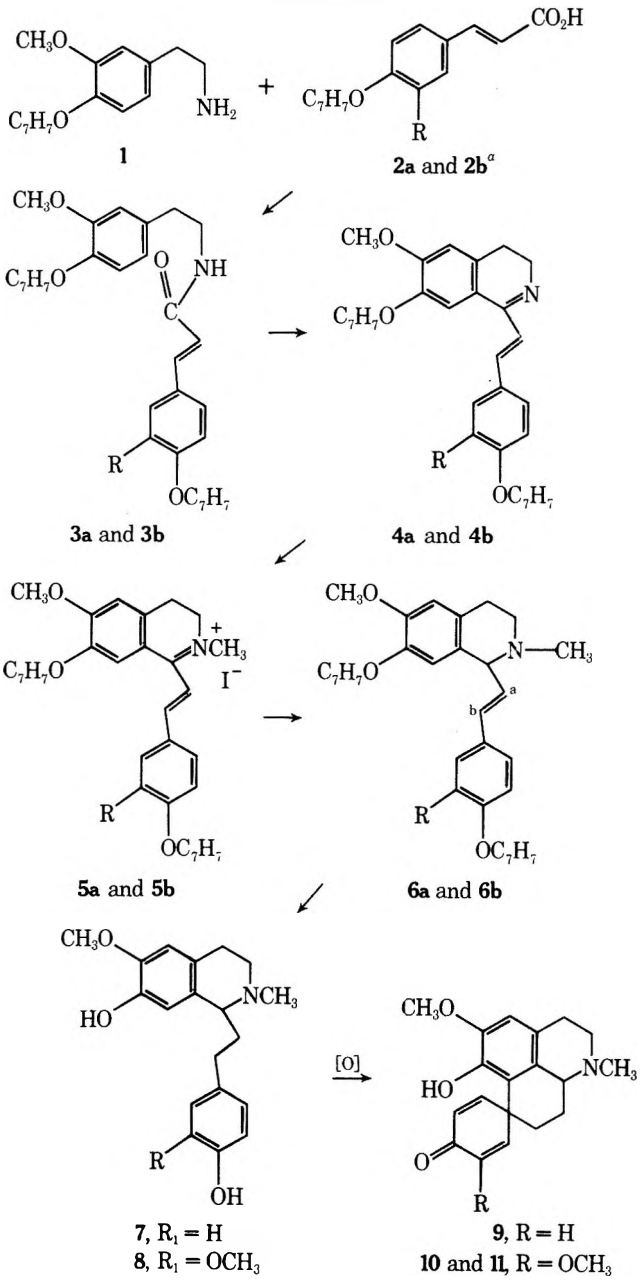
The Acyl Reticuline Derivatives. The oxidative ring closure of reticuline (**12**, Scheme II) to a dienone skeleton, **16**, and thence to morphine has been one of the major goals in alkaloid synthesis for many years. Although **16** was obtained once in very low yield,[11] the more usual product has been the isomeric dienone, **17**, albeit also in low yields (0–4%). The work has been well summarized.[3c]

Attempts to oxidize reticuline (**12**) and its nor derivative, **13**, electrochemically have yielded no isolable products and the starting material was destroyed either by extensive overoxidation or by some sort of fragmentation process.[12] Thus, the *N*-carbethoxy (**14**) and the *N*-carbobenzyloxy (**15**) derivatives of norreticuline were chosen for oxidation studies. Compound **14** was prepared from reticuline dibenzyl ether[13] and **15** was prepared from reticuline itself[14] by acylation. Compounds **12** and **13** were prepared by a general Bischler–Napieralski synthesis.[14]

Experimental conditions for the oxidation of **14** were explored extensively. The optimum conditions were found to be oxidation on a graphite felt anode in 50% aqueous *tert*-butyl alcohol with 4 molar equiv of potassium *tert*-butoxide and an equivalent amount of palladium chloride.[5d,15] The current was controlled at 0.2 V vs. SCE, and the oxidations were performed under nitrogen at 20° for a time equivalent to a two-electron oxidation. Under these conditions, the dienone **18** was obtained in a yield of 15.5%, corrected to 18% by recovery of starting material. Yields were lower in aqueous acetonitrile with tetraethylammonium perchlorate as electrolyte, at higher or lower temperatures, at higher or lower potentials, and in the absence of palladium chloride. Compound **18** was methylated to **20** with diazomethane, but all attempts to remove the carbethoxy group by hydrolysis or reduction failed to yield isolable products.

Although **18** and **20** were not crystalline, they gave satisfactory analyses and had spectroscopic properties corresponding to the structures. Both **18** and **20** had strong molecular ion peaks at *m/e* 385 and 399, respectively, with strong peaks corresponding to loss of ethyl, carbethoxy, and CH_2NCO_2Et. The uv spectra showed maxima at 283 and 236 nm in agreement with a cross-conjugated α-methoxycyclohexadienone structure[16] and lacked a strong peak at 300 nm expected from any aporphine system.[3e] The ir spectra show three bands at 1665, 1635, and 1615 cm^{-1}

Scheme I

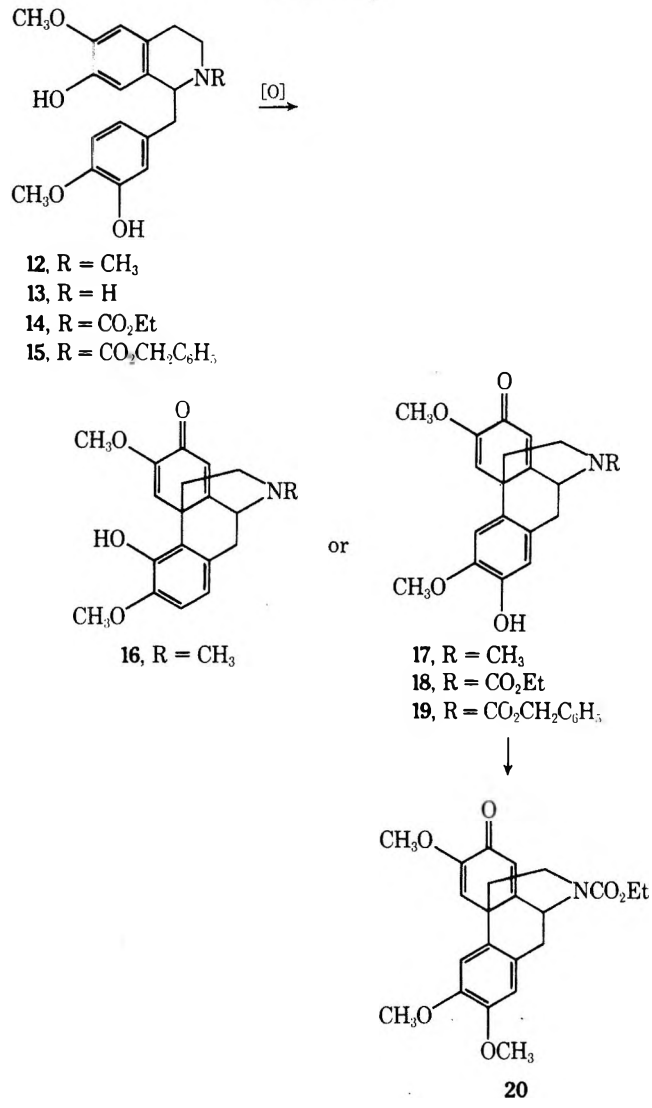


[a] In the a series R = H; in the b series, R = OCH_3.

thought[17] to be characteristic of the methoxydienone system as well as the expected amide carbonyl and hydroxyl absorptions. The NMR spectra showed the expected number of methyl groups for both compounds and four singlets in the region δ 6.3–6.9 corresponding to the aromatic protons and the olefinic protons.[18] Structures such as **16** would be expected to show an AB pattern in this region.

When it appeared that the carbethoxy group of **18** could not be easily removed, attention was shifted to the carbobenzyloxy derivative, **15**, in anticipation that the blocking group could be removed by hydrogenation. Compound **15** was oxidized under the same conditions as described for **14** except that palladium chloride was not used and the potential was kept at a minimum to yield 20 mA of current (0.0–0.024 V vs. SCE). The yield of dienone, **19**, was 10%, corrected to 11% for recovered starting material. The mass spectrum of **19** had a weak molecular ion peak at *m/e* 447 and strong peaks at *m/e* 356 and 312 corresponding to loss of the benzyl group and the carbobenzyloxy group. The uv

Scheme II



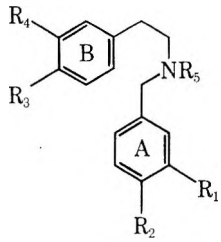
and ir spectra of **19** were quite similar to those of **18** and **20**. The NMR spectra showed the expected methyl and benzyl peaks and three singlet peaks in the aromatic olefinic region δ 6.3–6.8. However, one of these corresponded to two protons.

The Amaryllidaceae Alkaloid Precursors. A number of alkaloids appear to be formed in nature from the coupling of diphenolic benzylphenylethylamines.[3a] Intramolecular coupling reactions in this series have been carried out successfully by Schwartz and his coworkers using such oxidizing agents as vanadium oxychloride[19] and thallium salts,[20] by Franck and Lubs using ferric chloride,[21] and by Kametani and his coworkers using various oxidizing agents.[3c] Methyl ethers of this series have been coupled electrochemically by Kotani, Takeuchi, and Tobinaga.[5f] The electrochemistry of catechol amines such as dopamine and its derivatives has been studied extensively by Adams and his coworkers.[22]

Several compounds, **21–25** (Scheme III), were chosen for study. They fall in two general groups. Compounds **21** and **22** contained two adjacent phenol groups in ring B. It was reasoned that the diphenol should be easily oxidized to an ortho quinone which could add either the nitrogen of the amine or the other phenolic ring (ring A) as postulated by one of the several theories of phenol coupling.[1,3a] Compound **22**, with the methylenedioxy group was prepared to avoid any difficulties caused by the ring A phenol in **21**.

The syntheses of these new compounds are given in the Experimental Section. Unfortunately, electrochemical oxidation of **21** and **22** under various conditions produced extensive electrode coating, extensive polymerization, and no isolable products.

Scheme III



	R_1	R_2	R_3	R_4	R_5
21.	H	OH	OH	OH	H·HCl
22.	$-OCH_2O-$		OH	OH	H·HCl
23.	OCH_3	OH	OH	H	H·HCl
24.	OCH_3	OH	OH	H	$COCF_3$
25.	H	OH	OH	OCH_3	H·HCl
26.	H	OH	OH	OCH_3	$COCF_3$
27.	OCH_3	OH	OH	OCH_3	H·HCl
28.	OCH_3	OH	OH	OCH_3	$COCF_3$
29.	$-OCH_2O-$		OH	H	H·HCl
30.	$-OCH_2O-$		OH	H	$COCF_3$

The second set of compounds, **23–28,** contained only one phenol group in each ring. Preliminary oxidation studies of the known compound **23**[23] indicated extensive decomposition, probably due to fragmentation.[12] To avoid this problem, the nitrogen of the remaining three compounds, **24–26,** was blocked with the trifluoroacetyl group so successfully used by Schwartz.[19] Compound **23** and its *N*-trifluoroacetyl derivative **24** are known[25] and the syntheses of compounds **25–28** are detailed in the Experimental Section.

Electrochemical oxidation of the three amides **24, 26,** and **28** failed to yield any intramolecularly coupled products, either by isolation or, in the case of **24,** by comparison of the reaction mixtures with known compounds[26] by TLC. The oxidations were carried out on graphite felt anodes in 10% aqueous acetonitrile using KCl or tetraethylammonium perchlorate (0.1 *N*) as electrolyte. The pH was kept at about 9 by periodic additions of ammonium hydroxide. When the current fell off rapidly, it was assumed to be due to electrode coating, and a new anode was introduced.

The products isolated in each case were mixtures of dimers. The mixtures, analyzed as such, gave correct analytical data for carbon, hydrogen, and nitrogen. When the mixtures were methylated, the resulting mixed ethers could be resolved. These, in turn analyzed correctly and showed mass spectral data corresponding to carbon–carbon linked dimers. Although coupling is presumed to have been ortho and para to the phenol groups, none of the products were crystalline, and structural assignments are tenuous.[2]

Compound **30** was not oxidized appreciably under the conditions used: 0.4 V at pH 9 and 0.75 V at pH 7.

Discussion and Summary

Several generalizations arise from this work. First, it appears that electrochemical oxidation of phenols is much better for intermolecular coupling reactions than for intramolecular coupling, although in the phenethylisoquinoline series and the benzylisoquinoline series, it is as good as or better than chemical oxidation. This is in sharp contrast to the intramolecular coupling of aromatic ethers[5] where electrochemical methods have given superb results. The necessity for acylation in the benzylisoquinoline series and the improved yields over Franck's work[18,27] (18% as opposed to 4% for the coupling reaction) would seem to be in agreement with two of Franck's postulates: that a surface assists the reaction (he used silica) and that the electron pair from the nitrogen interferes with the reaction.

Finally, it should be recognized that these results are the best obtainable on the *presently available electrode surfaces.* A portion of our research program is directed toward the development of new and modified surfaces,[28] and it is anticipated that these compounds will be used as model substances for their exploration.

Experimental Section[29]

The Cinnamides, 3. A mixture of **1**[30] (22 g, 0.086 mol) and **2a**[31] (20 g, 0.08 mol) was heated under N_2 at 180–190° for 3 hr. The mixture was cooled, dissolved in $CHCl_3$, washed (10% HCl followed by 10% NaOH and water), dried (K_2CO_3), and evaporated to a brown powder which crystallized from MeOH–ether to give 29 g (69%) of **3a,** mp 187–189°.

Anal. Calcd for $C_{32}H_{31}NO_4$: C, 77.86; H, 6.33; N, 2.84. Found: C, 77.67; H, 6.21; N, 3.09.

In a similar manner, **3b** was prepared in 85% yield and melted at 166–167°.

Anal. Calcd for $C_{33}H_{33}NO_5$: C, 75.69; H, 6.35; N, 2.68. Found: C, 75.31; H, 6.27; N, 2.92.

The 3,4-Dihydroisoquinolines, 4. A mixture of **3a** (11.0 g), phosphorus oxychloride (25 ml), and dry benzene (250 ml) was heated under reflux for 2.5 hr and poured into 1 l. of hexane. The brownish powder which precipitated was collected by filtration, washed with ether, and crystallized from EtOH to give 10.5 g (93%) of the hydrochloride of **4a** as yellow prisms, mp 105–107°.

Anal. Calcd for $C_{32}H_{29}NO_3$·HCl: C, 75.04; H, 5.88; N, 2.73. Found: C, 75.57; H, 5.65; N, 2.59.

The hydrochloride of **4a** was suspended in benzene and basified with NH_4OH. The benzene layer was dried (K_2CO_3) and evaporated to a syrup which was crystallized from ether–hexane to afford the free base, mp 135–136°. The base was used in the next step without extensive purification.

In an analogous manner, the hydrochloride of **4b** was obtained in 81% yield and melted at 164–166°.

Anal. Calcd for $C_{33}H_{31}NO_4$·HCl: C, 73.12; H, 5.95; N, 2.58. Found: C, 72.74; H, 6.21; N, 2.43.

The free base **4b** melted at 116–117°.

The Methiodides, 5. The dihydroisoquinoline **4a** (8 g) dissolved in 20 ml of MeOH was treated with 15 ml of CH_3I and allowed to stand for 2 hr. The excess solvent was removed to give a reddish residue which crystallized from MeOH–ether to give 7.0 g (67%) of **5a** as yellow prisms, mp 143–144°. In the same manner **5b** was obtained from **4b** in 93% yield and melted at 117–118°. The compounds were not analyzed.

The *N*-Methyltetrahydroisoquinolines, 6. Sodium borohydride (2.8 g, 0.075 mol) was added in small portions to a stirred solution of 6.5 g (0.01 mol) of **5a** in 500 ml of MeOH. Evaporation of the solvent gave a residue which was decomposed with water and partitioned between water and benzene. The benzene was washed (H_2O), dried (K_2CO_3), and evaporated to a colorless syrup which crystallized from ether–hexane to give 4.5 g (86%) of **6a,** mp 92–93°: NMR ($CDCl_3$) δ 7.22 (d, J = 9 Hz, 2, aromatic), 6.92 (d, J = 9 Hz, 2, aromatic), 6.62 (broad s, 2, aromatic), 6.47 (d, J = 15 Hz, 1, H_a), 5.83 (two d's, J = 15 and 8.5 Hz, 1, H_b) 5.09, 5.01 (each s, each 2 H, $OCH_2C_6H_5$), 3.85 (s, 3, OCH_3), 2.42 (s, 3, NCH_3).

Anal. Calcd for $C_{33}H_{33}NO_3$: C, 80.62; H, 6.77; N, 2.85. Found: C, 80.55; H, 6.74; N, 3.13.

In an identical manner, **5b** was converted (95%) to **6b,** mp 141–142°: NMR ($CDCl_3$) δ 6.63 (2, broad s, aromatic), 6.46 (1, d, J = 15 Hz, H_a), 5.83 (1, pair of doublets, J = 15 and 8.5 Hz, H_b), 5.18, 5.02 (each 2, s, $OCH_2C_6H_5$), 3.77 (6, s, OCH_3), 2.42 (3, s, NCH_3).

Anal. Calcd for $C_{34}H_{35}NO_4$: C, 78.28; H, 6.76; N, 2.69. Found: C, 78.64; H, 6.82; N, 2.43.

The Free Phenols, 7 and 8. Compound **6a** (4 g) in 200 ml of EtOH was hydrogenated at 40–45 psi over 3 g of 5% palladium on carbon for 20 hr. The catalyst was removed by filtration, and the solution was evaporated to a colorless powder which was crystallized from ether–hexane to give 1.9 g (72%) of **7** as colorless nee-

dles, mp 161–162° (sintered at 101°) (lit.[32] mp 159–160°).

In an identical manner, **6b** was debenzylated to yield, after crystallization from chloroform–hexane, 79% of **8**, mp 100–102° (sintered at 91°).[33]

Oxidation of 7. The hydrochloride prepared from 200 mg of **7** was dissolved in 200 ml of water containing 3 g of tetraethylammonium perchlorate. The solution was oxidized in a two-compartment system[34] using a graphite felt anode (Union Carbide WDF, 10 × 10 cm) and a platinum cathode. The potential was controlled at +0.7 V vs. SCE[35] for 4 hr. The mixture was removed from the cell, and the graphite anode was shredded in a Waring blendor with MeOH. The graphite fibers were removed by filtration and washed several times with MeOH. The collected filtrates and the cell contents were concentrated to about 20 ml, basified with ammonia, and extracted three times with $CHCl_3$. The $CHCl_3$ extracts were washed (H_2O), dried ($MgSO_4$), and evaporated to a brownish residue which was separated by preparative TLC [$CHCl_3$–acetone–CH_3OH (5:4:2)]. The top zone yielded 22 mg of starting material. The second zone gave 41 mg (23% corrected for recovered starting material) of **9** as colorless prisms, mp 248–249° dec (lit.[8] mp 248–249°). Compound **9** was also prepared by ferric chloride oxidation of **7**.

Oxidation of 8. The hydrochloride prepared from 450 mg of **8** was oxidized at +0.8 V for 12 hr, and the products were isolated as described for **7**. The top zone from preparative TLC yielded 160 mg of starting material. The second zone yielded 105 mg (36%) of a mixture of two dienones **10** and **11**. The dienones were separated by fractional crystallization from benzene. Further crystallization from benzene yielded 32 mg of pure (±)-kresiginone, mp 195° dec (lit.[7] mp 190–192 and 193–195°).[9] Crystallization of the other fraction from benzene–ether gave 35 mg of the isomeric dienone, mp 206–207° (lit.[9] mp 156–158° and 202°).[10] Both dienones were identical with samples prepared by ferric chloride oxidation of **8**.[10]

***N*-Carbethoxynorreticuline (14).** 1-(3-Benzyloxy-4-methoxybenzyl)-7-benzyloxy-6-methoxy-*N*-carbethoxy-1,2,3,4-tetrahydroisoquinoline[13] (3 g) was hydrogenated at 40 psi over 1.2 g of 5% Pd on carbon in 200 ml of EtOH. The catalyst was removed by filtration, and the filtrate was concentrated to yield 2.1 g (98%) of a colorless glass: NMR ($CDCl_3$) δ 6.64 (m, 5, aromatic), 5.15 (m, 1, H-1), 3.80 (s, 6, 2 OCH_3), 2.90 (m, 4, H on C-3 and C-4), 1.08 (t, 3, CH_3).[36]

Anal. Calcd for $C_{21}H_{25}NO_6$: C, 65.12; H, 6.46; N, 3.62. Found: C, 65.37; H, 6.36; N, 3.44.

***N*-Carbobenzyloxynorreticuline (15).** *N*-Norreticuline[14] (3 g, 9.5 mmol) was dissolved in 200 ml of $CHCl_3$ and 6 ml of triethylamine. The mixture was cooled to 10–15° during the dropwise addition of 8 g (47 mmol) of carbobenzyloxychloride and allowed to stir at room temperature for 1 hr. The $CHCl_3$ was removed, and the residue was crystallized from EtOH to give 4.1 g (60%) of *N*-carbobenzyloxy-3,7-dicarbobenzyloxy-4,6-dimethoxy-1,2,3,4-tetrahydroisoquinoline, mp 92–94°. This derivative was not characterized, but was allowed to stir for 1 hr at room temperature in 30 ml of EtOH containing 1.25 g of sodium hydroxide. The solvent was evaporated, and the residual sodium salt was dissolved in water, washed ($CHCl_3$), acidified (HCl), and extracted ($CHCl_3$). The $CHCl_3$ extract was dried ($MgSO_4$) and evaporated to yield 1.6 g (62%) of crystalline **15**: mp 86–88° from EtOH; NMR ($CDCl_3$) δ 7.30 (m, 5, aromatic), 6.60 (m, 5, aromatic), 3.78 (s, 6, 2 OCH_3), 2.95 (m, 4, C-3 and C-4).

Anal. Calcd for $C_{26}H_{27}NO_6$: C, 69.44; H, 6.01; N, 3.12. Found: C, 69.27; H, 5.81; N, 2.95.

Oxidation of 14. Compound **14** (200 mg) was dissolved in 125 ml of H_2O and 125 ml of *tert*-butyl alcohol containing 2.8 g of potassium *tert*-butoxide and 0.090 g of palladium chloride.[37] The mixture was electrolyzed in a two-compartment cell like the one described for **7** and **8** at +0.2 V (vs. SCE) for 30 min. The average current was 100 mA, and the temperature was held at 20°. The felt anode was blended and extracted as described above, and the combined electrolyte and washings were acidified to pH 4 (HCl) and extracted several times ($CHCl_3$). The $CHCl_3$ extract was dried ($MgSO_4$) and evaporated to a residue which was dissolved in $CHCl_3$–MeOH (2:1) and applied to three preparative TLC layers. The layers were developed with benzene–acetone (3:1). The top zone yielded 26 mg of starting material. The second zone yielded 33 mg (18% corrected) of noncrystalline dienone **18**, which showed only one spot on TLC. The spectral properties were: NMR ($CDCl_3$) δ 6.85 (s, 1, C-5), 6.70 and 6.40 (singlets, 2, aromatic), 6.35 (s, 1, C-8), 5.18 (s, 1, phenol); mass spectrum M^+ *m/e* 385; uv max (MeOH) 283 nm (ϵ 11,200), 236 (16,100); ir (film) 1665, 1635, 1615 cm^{-1}.

Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.50; H, 5.97; N, 3.63. Found: C, 65.27; H, 5.91; N, 3.48.

The dienone was methylated with diazomethane (prepared from *N,N'*-dimethyl-N,N'-dinitrosoterephthalamide) in MeOH–dioxane (1:1) to yield **20** as a glass: NMR ($CDCl_3$) δ 6.86 (s, 1, C-5), 6.70 (s, 1, aromatic), 6.37 (m, 2, C-8 and aromatic), 3.92, 3.85, 3.80 (3 singlets, 9, OCH_3); mass spectrum M^+ *m/e* 399.

Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.19; H, 6.30; N, 3.53. Found: C, 66.30; H, 6.28; N, 3.27.

Oxidation of 15. Compound **15** (200 mg) was oxidized in the same electrolyte and cell as used for **14**, except that no palladium chloride was used. The potential was controlled at +0.2 V for 38 min, and the reaction was carried out at room temperature. The products were isolated in the same manner as described for **14** to yield 2 mg of starting material and 22 mg (11%) of **19** as a glass: NMR ($CDCl_3$) δ 7.35 (m, 5, aromatic), 6.85 (s, 1, C-8), 6.72 (s, 1, aromatic), 6.4 (s, 2, aromatic and C-5), 5.2 (s, 2, $CH_2C_6H_5$), 3.95 and 3.84 (2 singlets, 6, $2OCH_3$); uv (MeOH) 283 nm (ϵ 9400) and 236 (14,800).

Anal. Calcd for $C_{26}H_{29}NO_6$: C, 69.79; H, 5.59; N, 2.81. Found: C, 69.83; H, 5.81; N, 3.13.

Preparation of 21. 3-Hydroxybenzaldehyde (4.88 g, 0.04 mol) and homoveratrylamine (7.24 g, 0.04 mol) were dissolved in 200 ml of EtOH and hydrogenated at 25 psi over 200 mg of prereduced PtO_2. The white solid which precipitated during reduction was dissolved in more solvent, the catalyst was removed by filtration, and the filtrate was concentrated. The product precipitated to give, after collection, 5.1 g (45%) of *N*-(3-hydroxybenzyl)homoveratrylamine, mp 145–146°.

Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.08; H, 7.32; N, 4.88. Found: C, 70.80; H, 7.32; N, 4.82.

The dimethyl ether was demethylated by heating 300 mg with 6 ml of light yellow 45% HI at 80° under nitrogen until the methyl iodide was evolved.[38] The mixture was then heated to 121° until most of the HI was distilled and then evaporated to dryness under vacuum. The crystalline HI salt (95% yield) was stirred with freshly prepared but moist solid AgCl (from 10 ml of 0.5 *M* $AgNO_3$ and HCl) with a spatula until the yellow solid AgI formed. Water (10 ml) was added and the mixture was filtered. Removal of the water under vacuum followed by addition of absolute EtOH and evaporation gave an oil which eventually crystallized to give 0.190 g of **21**, mp 163–165°.

Anal. Calcd for $C_{15}H_{18}NO_3Cl$: C, 60.91; H, 6.09; N, 4.74; Cl, 12.01. Found: C, 60.91; H, 6.17; N, 4.86; Cl, 12.26.

Preparation of 22. Piperonal (1.5 g, 0.01 mol), 3,4-dihydroxy-β-phenylethylamine (1.9 g, 0.01 mol), and sodium acetate (0.82 g, 0.01 mol) were dissolved in 200 ml of EtOH and hydrogenated at 25 psi over 100 mg of prereduced PtO_2. The mixture was acidified (HCl) and filtered; the filtrate was concentrated under vacuum; and the residue was crystallized from H_2O to give 1.7 g (55%) of **22**, mp 240–242°.

Anal. Calcd for $C_{16}H_{18}NO_4Cl$: C, 59.26; H, 5.56; N, 4.32. Found: C, 59.08; H, 5.67; N, 4.51.

Preparation of 25. A mixture of 3-hydroxybenzaldehyde (4.27 g, 0.035 mol), 4-benzyloxy-3-methoxy-β-phenylethylamine (7.61 g, 0.03 mol), and 0.8 g of *p*-toluenesulfonic acid in 300 ml of benzene was heated under a Dean-Stark tube until no more H_2O came off. The solvent was removed, and the residue was taken up in 50 ml of MeOH and reduced with 3 g (0.078 mol) of sodium borohydride over 0.5 hr. The solvent was removed, and the residue was dissolved in 50 ml of H_2O, acidified (HCl), basified (NH_4OH), and extracted with $CHCl_3$. The $CHCl_3$ extract was concentrated to a residue, dissolved in MeOH, acidified (HCl), and hydrogenated at 40 psi over 5 g of 5% Pd on carbon. Filtration of the mixture and concentration of the filtrate yielded 8.1 g (80%) of **25**, mp 183–185°.

Anal. Calcd for $C_{16}H_{20}NO_3Cl$: C, 62.03; H, 6.46; N, 4.52. Found: C, 61.97; H, 6.55; N, 4.67.

Preparation of 26. A mixture of 1 g of **25**, 5 ml of dry pyridine, and 10 ml of trifluoroacetic anhydride was stirred at room temperature for 4 hr, diluted with 50 ml of EtOAc, and washed (first with 100 ml of 3 *N* HCl and then with H_2O). The organic layer was evaporated to a residue which was dissolved in 150 ml of MeOH–H_2O (10:1) and stirred for 24 hr. The solution was diluted with 200 ml of H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was dried (Na_2SO_4) and evaporated to a residue. The residue was triturated with hexane and cooled in Dry Ice–MeOH. The precipitated amide was collected and reprecipitated from MeOH–H_2O to yield a partially crystalline solid **26**, mp 51–55°.

Anal. Calcd for $C_{18}H_{18}NO_4F_3$: C, 58.53; H, 4.88; N, 3.79. Found: C, 58.80; H, 5.06; N, 4.05.

Preparation of 27 and 28. Compound **27** was prepared from benzylisovanillin[39] and 3-methoxy-4-benzyloxy-β-phenylethylamine[30] in a manner directly analogous to the preparation of **25** and **26** to yield **27** (88%), mp 186–188° (free base of **27**, mp 95–97°), and **28**, mp 77–78°.

Anal. Calcd for **27** free base, $C_{17}H_{21}NO_4$: C, 67.32; H, 6.93; N, 4.62. Found: C, 67.07; H, 6.95; N, 4.45.

Anal. Calcd for **28**, $C_{19}H_{20}NO_5F_3$: C, 57.14; H, 5.01; N, 3.51. Found: C, 56.86; H, 5.20; N, 3.64.

Preparation of 29 and 30. Compound **29** was prepared from piperonal and tyramine by the method used for **25** except that the debenzylation by hydrogenolysis was not necessary. Compound **29** was obtained in 92% yield and melted at 216–218°.

Anal. Calcd for $C_{16}H_{18}NO_3Cl$: C, 62.44; H, 5.85; N, 4.55. Found: C, 62.24; H, 5.81; N, 4.64.

In a manner analogous to the preparation of **26**, **29** was trifluoroacetylated to **30** (95%), mp 91–95°.

Anal. Calcd for $C_{18}H_{16}NO_4F_3$: C, 58.85; H, 4.36; N, 3.81. Found: C, 59.14; H, 4.48; N, 3.94.

Oxidation of 24.[25] Compound **24** (0.74 g) was oxidized in 200 ml of CH_3CN–H_2O (10:1) containing KCl (0.1 *N*) at +0.7–0.8 V (vs. SCE) in a two-compartment system on a graphite felt anode. The oxidation showed a low current, about 10 mA, and required 7.5 hr. The anode compartment was kept at a pH of about 9 by dropwise addition of NH_4OH. The anode was blended and extracted as described for **7**. The combined washings and electrolyte were evaporated to the aqueous portion and extracted ($CHCl_3$). The $CHCl_3$ extract was dried ($MgSO_4$), evaporated to dryness, and separated into three major fractions by preparative TLC [benzene–acetone (3:1)]. The top zone yielded 0.30 g of starting material. The middle zone yielded 22 mg of a material of unknown structure, but which was not intramolecularly coupled product. The most polar zone yielded 0.220 g of a mixture (by NMR) of two products.

Anal. Calcd for $C_{36}H_{34}N_2O_8F_6$: C, 58.69; H, 4.62; N, 3.74. Found: C, 58.55; H, 4.60; N, 3.76.

The mixture was methylated as described above for **18**, and the mixture was separated by preparative TLC [double development with benzene–acetone (20:1)] into two noncrystalline ethers (total overall yield of 15%). Each of these gave correct analyses and had molecular ion peaks at 792 corresponding to the addition of four methoxy groups, thus mandating a carbon–carbon dimer.

Oxidation of 26. The oxidation of **26** was carried out in the same way as **24** except that tetraethylammonium perchlorate was used as an electrolyte. The products were isolated as described for **24** to yield starting material, tars, and a mixture of at least two dimers.

Anal. Calcd for $C_{36}H_{34}N_2O_8F_6$: C, 58.69; H, 4.62; N, 3.74. Found: C, 59.39; H, 4.62; N, 3.74.

After methylation of the mixture, only one compound was isolable (overall yield 15%). It was not crystalline, but gave a correct microanalysis and showed the expected molecular ion at 792 for a tetramethylated carbon–carbon dimer.

Oxidation of 28. The oxidation of **28** was carried out exactly as described for **26**. The major zone of dimers gave the following analysis.

Anal. Calcd for $C_{38}H_{38}N_2O_{10}F_6$: C, 57.29; H, 4.77; N, 3.52. Found: C, 57.42; H, 4.70; N, 3.31.

After methylation of the mixture, only one compound was isolable (overall yield 12%). It was not crystalline, but gave a correct microanalysis and showed the expected molecular ion at 852 for a tetramethylated carbon–carbon dimer.

Registry No.—**1**, 22231-61-4; **2a**, 6272-45-3; **3a**, 56113-93-0; **3b**, 56113-94-1; **4a**, 56113-95-2; **4a** HCl, 56113-96-3; **4b**, 56113-97-4; **4b** HCl, 56113-98-5; **5a**, 56113-99-6; **5b**, 56114-00-2; **6a**, 56114-01-3; **6b**, 56114-02-4; **7**, 56114-03-5; **7** HCl, 56114-04-6; **8**, 56114-05-7; **8** HCl, 30242-74-1; **9**, 30816-29-6; **10**, 30040-57-4; **11**, 56192-84-8; **13**, 13168-51-9; **14**, 55869-76-6; **15**, 56114-06-8; **18**, 37729-28-5; **19**, 56114-07-9; **20**, 56114-08-0; **21**, 56114-09-1; **22**, 56114-10-4; **24**, 26668-50-8; **25**, 56114-11-5; **26**, 56114-12-6; **27**, 7239-28-3; **27** free base, 22231-53-4; **28**, 56114-13-7; **29**, 56114-14-8; **30**, 40135-88-4; 1-(3-benzyloxy-4-methoxybenzyl)-7-benzyloxy-6-methoxy-*N*-carbethoxy-1,2,3,4-tetrahydroisoquinoline, 56114-15-9; carbobenzyloxychloride, 501-53-1; *N*-carbobenzyloxy-3,7-dicarbobenzyloxy-4,6-dimethoxy-1,2,3,4-tetrahydroisoquinoline, 56114-16-0; diazomethane, 157-22-2; 3-hydroxybenzaldehyde, 100-83-4; homoveratrylamine, 120-20-7; *N*-(3-hydroxybenzyl)homoveratrylamine, 32372-76-2; piperonal, 120-50-7; 3,4-dihydroxy-β-phenylethylamine, 51-61-6; trifluoroacetic anhydride, 407-25-0; tyramine, 51-67-2.

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Identification of Intermediates in the Trifluoromethanesulfonic Acid Catalyzed Adamantane Rearrangement of 2,3-*endo*- and -*exo*-Tetramethylenenorbornane

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Received February 21, 1975

Eleven intermediates of unknown structure, besides 6,7-*exo*-trimethylenebicyclo[3.2.1]octane (*exo*-**7**) and homoadamantane (**8**), have been detected in the trifluoromethanesulfonic acid catalyzed adamantane rearrangement of 2,3-*endo*- and -*exo*-tetramethylenenorbornane (*endo*-**1** and *exo*-**1**) via 4-homoisotwistane (tricyclo[5.3.1.$0^{3,8}$]undecane, **9**). Eight of these unknowns were now identified as 1,2-*endo*- and -*exo*-tetramethylenenorbornane (*endo*-**2** and *exo*-**2**), 1,2-trimethylenebicyclo[2.2.2]octane (**3**), [3.3.3]propellane (**4**), 1,2-*exo*-trimethylene-*cis*-bicyclo[3.3.0]octane (**5**), 1,7-*exo*-trimethylenebicyclo[3.2.1]octane (**6**), 7-methylisotwistane (**10**), and 1-methylisotwistane (**11**). Although ^{13}C NMR spectroscopy offered enough basis of structure determination for compounds with more or less symmetricity, independent syntheses were necessary for asymmetrical compounds. Time-conversion study of *endo*-**1**, *exo*-**1**, and **9** suggested that four (unknown C_2, *endo*-**2**, *exo*-**2**, and **3**) of these 11 intermediates were formed directly from the precursors and, therefore, true intermediates to **9**. Addition of adamantane or 1-methyladamantane to the reaction of *exo*-**1** effected increase in proportions of these four intermediates, accompanied by a considerable acceleration of the isomerization rate. The stable intermediate **9** then rearranges to a mixture of unknown C_1 and D, *exo*-**2**, **3**, **4**, **5**, **6**, *exo*-**7**, **8**, **10**, and **11**, of which only **8**, **10** and **11** isomerize to methyladamantane, while the others are in equilibrium with **9**.

In the aluminum chloride catalyzed adamantane rearrangement of 2,3-*exo*-tetramethylenenorbornane (*exo*-**1**)[1,2] was isolated 4-homoisotwistane (tricyclo[5.3.1.$0^{3,8}$]undecane, **9**)[3,4] as an intermediate.[5,6] The compound was shown to be one of the most stable tricycloundecane isomers on the basis of molecular mechanics calculation.[5] Careful examination of the reaction mixture enabled us to isolate and identify two other intermediates, 6,7-*exo*-trimethylenebicyclo[3.2.1.]octane (*exo*-**7**) and homoadamantane (**8**).[7] Our recent findings on the trifluoromethanesulfonic acid catalysis of the rearrangement,[7] together with use of fast isomerizing precursors[8] such as 2,3-*endo*-tetramethylenenorbornane (*endo*-**1**),[9] 2,3-trimethylenebicyclo[2.2.2]octane,[6-8,10] and 6,7-*endo*-trimethylenebicyclo[3.2.1]octane (*endo*-**7**),[8] indicated more than 20 intermediates of unknown structure to show up during the rearrangements. In this study, partially completed isomerization reactions were quenched and the mixture of products were separated into fractions by VPC and chemical reactions. Eight among 11 unknowns thus isolated in the rearrangement of 2,3-*endo*- and -*exo*-tetramethylenenorbornane (*endo*-**1** and *exo*-**1**) were assigned structures by means of independent syntheses or ^{13}C NMR spectroscopy.

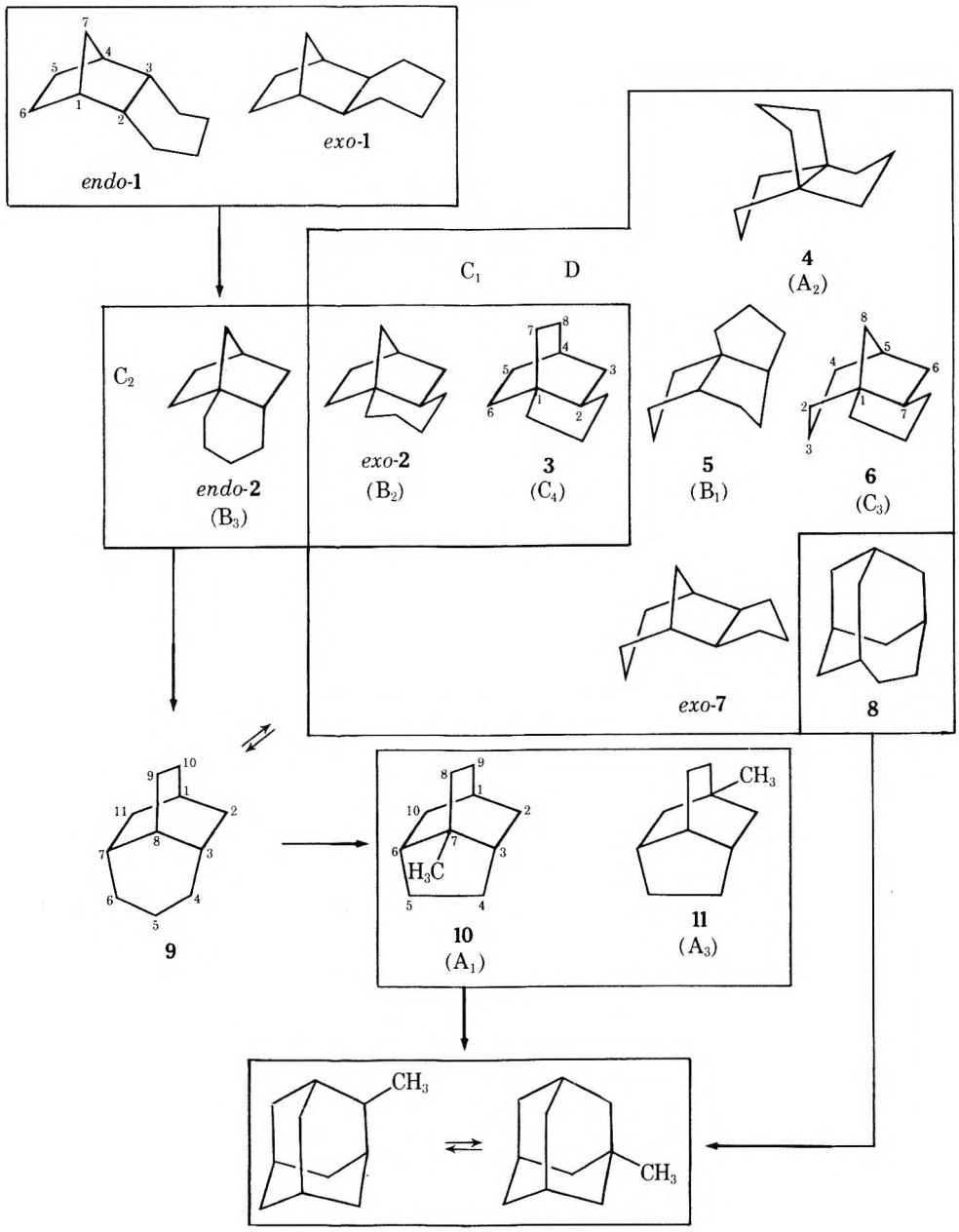
Identification of Unknown B_2, B_3, C_3, and C_4. Distribution of products in the isomerization of 2,3-*endo*- and -*exo*-tetramethylenenorbornane (*endo*-**1** and *exo*-**1**) as well as that of 4-homoisotwistane (**9**) was determined, as listed in Table I, on a Golay (capillary) column VPC–mass spectrometer with which was also taken the mass spectrum of each intermediate.[11] Fractions B and C were isolated with a preparative VPC[11] to measure total and off-resonance proton-decoupled ^{13}C NMR spectra. It was indicated that all the components of the fractions had quaternary carbon atoms. Little information will be obtainable by spectral methods about the structure of the unknowns, unless we have appropriate reference compounds. Therefore, syntheses of tricycloundecanes having quaternary carbon atoms were investigated.

1,2-Trimethylenebicyclo[2.2.2]octane (**3**)[3] is one of the two tricycloundecanes ever synthesized that are asymmetrical and contain quaternary carbon atoms.[12] The synthesis of **3**[3] was repeated to give an authentic specimen. The specimen was found to be identical with unknown C_4 on comparison of their VPC retention times and mass spectra.

1,6-Tetramethylene-2-norbornene was prepared[13] through an intramolecular Diels–Alder reaction of 1-(5-hexenyl)cyclopentadiene. Hydrogenation of the compound should give another asymmetrical tricycloundecane with a quaternary carbon atom. Although Brieger and Anderson[13] did not examine the homogeneity, nor determine the configuration, of their 1,6-tetramethylene-2-norbornene, we found a specimen synthesized according to their method to be a mixture. Separation of the olefin mixture, however, was impossible even in Golay columns, but hydrogenation over palladium on charcoal catalyst revealed the presence of two components in 2:1 ratio. We assigned the structure of 1,2-*exo*-tetramethylenenorbornane (*exo*-**2**) to the more abundant component for the following reasons. Exo compounds are usually more stable than endo isomers, as exemplified in 2,3-trimethylenenorbornane (**20**),[14] **1**,[8] and 6,7-trimethylenebicyclo[3.2.1]octane (**7**).[8] This would also be true for epimers of **2**. The reasoning may be supported by the exclusive formation of 1,6-*exo*-trimethylene-2-norbornene (**12**) in the intramolecular Diels–Alder addition of 1-(4-pentenyl)cyclopentadiene,[15] where the endo epimer would be too strained to be formed. An additional methylene group, however, should release a part of the strain in 1,6-*endo*-trimethylene-2-norbornene and make the energy difference between epimers of 1,6-tetramethylene-2-norbornene less than it would be without the additional methylene group. Thus 1,6-*endo*-tetramethylene-2-norbornene may have some degree of stability and could be formed in the reaction of 1-(5-hexenyl)cyclopentadiene. Secondly, the more abundant component of the mixture was eluted ahead of the other in several VPC columns. We have noticed exo isomers of 2,3-trimethylenenorbornane (**20**), **1**, and **7** to have shorter retention times than the corresponding endo isomers. The more abundant component of the mixture was in this way assigned the structure of *exo*-**2**. *exo*-**2** was then found to have the same VPC retention times as those of unknown B_2, and their mass spectra were also identical. Similarly, unknown B_3 was identified as *endo*-**2**.

1,7-*exo*-Trimethylenebicyclo[3.2.1]octane (**6**), another new, asymmetrical tricycloundecane containing a quaternary carbon atom, was obtained from 1,6-*exo*-trimethy-

Chart I



lene-2-norbornene (**12**)[15] through a series of reactions. Dichlorocarbene ring expansion[7,8,16] of **12** gave in 47% yield a mixture consisting of 84% 3,4-dichloro-5,6-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene (**13**) and 16% 3,4-dichloro-1,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene (**14**). The more abundant constituent of the mixture was assigned the structure **13** because of the ^{1}H NMR signal (δ 4.18) of the mixture assignable to the 4 proton showed a singlet. By sodium–liquid ammonia dechlorination[8,17] the mixture was transformed in 31% yield into a mixture of 86% 5,6-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene (**15**) and 14% 1,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene (**16**). No structural alteration was assumed during dechlorination. Both olefins were hydrogenated over palladium on charcoal catalyst to the identical product, **6**, in 96% yield (Chart II).

Total and off-resonance proton-decoupled ^{13}C NMR spectra of thus synthesized authentic **6** (Table II) contained 11 resonances that comprised one singlet, two doublets, and eight triplets. All the signals had a similar intensity, except for the singlet at lowest field, which was less intense than the others and hence assigned to the quaternary carbon atom. The spectrum, therefore, was in good agreement with the structure. Compound **6** was found identical with unknown C_3 on comparison of VPC retention time and mass spectra.

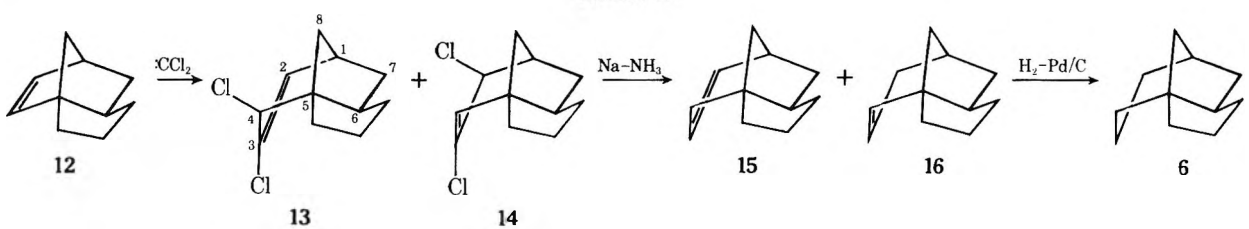
^{13}C NMR Spectra as Supporting Evidence for the Identification of Unknowns. Identification of unknown B_2, B_3, C_3, and C_4 by VPC retention time and mass spectrum as described in the preceding section is further supported by ^{13}C NMR spectroscopic evidences. Fraction C isolated from the reaction mixture of run 21 (Table I) on a preparative VPC[11] consisted only of C_3 (**6**) and C_4 (**3**) in about 3:1 ratio, as shown in Table I. The fraction exhibited 21 ^{13}C NMR signals in a total decoupled spectrum. These absorptions could be divided into two sets according to the relative intensity: each ten signals with relative intensities of 3 and 1, respectively. The last one, with an intensity of 4, should belong to both sets. One resonance at lowest field in each set had somewhat smaller intensity than other members of the set it belonged to. Eleven signals with higher intensities including one with an intensity of 4 were divided into one singlet for the lowest field signal, two doublets, and eight triplets, on off-resonance proton decoupling. The chemical shifts, relative intensities, and splittings in the

Table I
Distribution of Intermediates in the Rearrangements of Tricycloundecanes[a]

Run	Reactant	Catalyst (mol equiv)[d]	Reaction time, hr (min)	Product,[b] %[c] A_1 (10)	A_2 (4)	A_3 (11)	1-Me-Ad	B_1 (5)	B_2 (*exo*-2)	B_3 (*endo*-2)	C_1 (unknown)	C_2 (unknown)	C_3 (6)	C_4 (3)	2-Me-Ad	*exo*-7	D (unknown)	9	Homo-adamantane
1	*endo*-**1**	T (1.0)	(1)						4.0	3.5		2.1		0.7			2.1	21.8	
2			(2)						8.8	6.2		3.5		1.3			2.2	42.1	
3			(4)						15.4	8.2		4.2		1.4			5.1	59.4	
4			(17)						15.5	7.7		4.4		1.5			5.0	58.1	
5			2						14.3	6.8		4.3		1.6			5.0	57.8	
11	*exo*-**1**	T (1.0)	24						1.5	0.3		0.7		0.3		0.4	1.5	10.4	0.3
12[e]			(10)						7.8	4.1		2.0		0.7			1.0	8.3	
21	*exo*-**1**	T (3.0)	5.5	0.5		1.0	2.3	8.9	11.6		0.2		14.8	5.0	2.6	3.3	2.8	43.0	2.5
31	*exo*-**1**	A (0.15)	(14)			0.7		2.9	17.2				7.9	3.6	2.9	0.6	2.8	45.8	
32			(40)	0.6		1.9	1.5	10.6	8.1				13.9	5.2	6.3	4.0	2.6	44.3	1.0
33			(80)	1.2		2.0	3.7	13.7	4.2		0.3		13.9	4.6	7.7	5.1	3.2	37.1	2.3
34			3	2.6	1.0	5.0	28.9	9.8	0.5		1.1		4.5	1.2	23.7	5.3	0.7	14.5	0.3
41	**9**	T (2.0)	(35)					1.0					2.1	5.2	0.2	0.2	3.9	83.5	
42			2					1.6					3.7	6.3	0.7	0.9	4.6	79.0	
43			6					2.7	0.3				6.6	7.6	1.2	1.4	4.8	70.9	0.8
51	**9**	T (4.0)	1	0.1		0.3	1.6	8.2	2.1				14.7	4.9	3.2	4.1	4.5	51.8	2.3
52			100	3.1	0.7	6.2	20.3	11.6[f]	0.9		1.5		5.1	1.4	25.2	5.5	1.3	15.0	1.2

[a] 100 mg of reactant in 5 ml of methylene chloride at reflux. [b] Combined yield of the intermediates and final products (methyladamantanes) were almost quantitative. Products were analyzed on a Golay GC-MS and aligned in the order of increasing retention time. [c] That of the VPC peak area. In case the sum of figures is less than 100, the balance consists of the unreacted starting material together with a few percent by-products. [d] T, trifluoromethanesulfonic acid; A, aluminum chloride ($AlCl_3$). Figures in parentheses are molar equivalents of the catalyst to reactant. [e] A reaction in the presence of 0.2 molar equiv of 1-methyladamantane. All the 1-methyladamantane detected in product analysis was considered to be that added at the beginning, and percentage composition of the products was calculated for the rest of the compounds. [f] Considered to contain a small amount of unknown compound(s) other than those which have been detected so far, as is indicated by mass spectrum.

Chart II



12 13 14 15 16 6

Table II
^{13}C NMR Spectra of Tricycloundecanes

Compd		
Notation as unknown	Structure	^{13}C NMR signals, ppm (multiplicity, rel intensity)[a]
	endo-1	20.4 (t, 2), 20.7 (t, 2), 23.0 (t, 2), 39.3 (d, 2), 39.9 (t, 1), 41.2 (d, 2)
	exo-1	19.6 (t, 2), 23.6 (t, 2), 30.0 (t, 2), 33.1 (t, 1), 42.6 (d, 2), 43.3 (d, 2)
B_3	*endo*-2	23.2 (t, 1), 26.5 (t, 1), 26.9 (t, 1), 27.2 (t, 1), 32.2 (t, 1), 33.7 (t, 1), 35.1 (t, 1), 36.9 (d, 1), 45.0 (d, 1), 45.3 (t, 1), 46.5 (s, 0.7)
B_2	*exo*-2	24.6 (t, 1), 26.5 (t, 1), 30.6 (t, 1), 31.6 (t, 1), 34.2 (t, 1), 37.6 (d, 1), 37.7 (t, 1), 38.4 (t, 1), 39.3 (t, 1), 42.1 (d, 1), 46.3 (s, 0.6)
C_4	3[b]	21.8 (1), 24.4 (1), 26.0 (1), 29.3 (1), 29.4 (1), 31.3 (1), 32.6 (1), 36.1 (1), 44.4 (1), 48.0 (1), 50.4 (s, 0.5)
A_2	4	31.8 (t, 3), 39.4 (t, 6), 60.4 (s, 1.7),
B_1	5	26.8 (t, 2), 33.5 (t, 2), 33.6 (t, 2), 42.1 (t, 2), 52.4 (d, 2), 62.0 (s, 0.5)
C_3	6	21.3 (t, 1), 26.8 (t, 1), 31.9 (t, 1), 35.6 (t, 1), 37.2 (t, 1), 38.3 (t, 1), 38.6 (t, 1), 39.0 (d, 1), 44.4 (t, 1), 47.4 (d, 1), 52.9 (s, 0.7)
A_1	10	24.8 (t, 1), 28.4 (q, 1), 31.7 (t, 3), 40.5 (t, 2), 45.5 (d, 1), 52.8 (d, 2), 62.8 (s, 0.8)
A_3	11	24.8 (t, 1), 27.8 (q, 1), 31.7 (t, 1), 31.8 (t, 2), 40.5 (t, 2), 45.5 (d, 2), 51.4 (s, 0.7), 61.7 (d, 1)

[a] In parts per million downfield from the internal Me_4Si standard. [b] The signal was constructed from that of the mixture of 3 and 6. Fine structure of the signals of 3 was too complex to be analyzed because of a small concentration of 3 in the mixture. See text and also ref 18.

spectra of unknown C_3 thus constructed from those of the fraction C were in complete agreement with the corresponding values of authentic **6** listed in Table II. The remaining 11 resonances should be assigned to unknown C_4 (3), and reported in Table II.[18] These resonances became so complex, mainly because of low intensity, on off-resonance proton decoupling that no definite fine structure could be observed except for the singlet at lowest field.

Although authentic *endo*-**2** and *exo*-**2** were not isolated on a preparative VPC from their mixture prepared above (*exo*-**2**:*endo*-**2** 2:1), ^{13}C NMR spectra of each compound were obtainable from those of the mixture on consideration of the intensity. Eleven, stronger absorptions among 21 for the mixture were assigned to the more abundant constituent, *exo*-**2**, while the remaining ten were assigned to *endo*-**2**. The 11th resonance of *endo*-**2** coincided with one of *exo*-**2**'s resonance (26.5 ppm), as evidenced from its intensity (3). Fine structure of the off-resonance proton decoupled spectrum of the mixture was analyzable fairly easily to deduce splitting of each absorption. Spectra of *endo*-**2** and *exo*-**2** constructed in this way are listed in Table II. The fraction B isolated from the reaction mixture of run 4 (Table I) contained only unknown B_2 (*exo*-**2**) and B_3 (*endo*-**2**) in 2:1 ratio. Total proton-decoupled spectrum of the fraction B was exactly a reproduction of what was observed from the standard spectra of *exo*-**2** and *endo*-**2** taken in 2:1 intensity ratio.

Consideration of the intensity and splitting of the signals in relation to the symmetry property of the molecule is the only way of assigning ^{13}C NMR signals in polycyclic hydrocarbons,[19] unless appropriate reference compounds with definitely assigned spectra are available. Assignment of the signals of above four asymmetrical intermediate tricycloundecanes was impossible since no such reference spectrum was available at present.

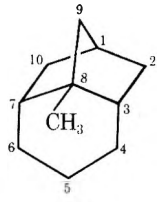
Structure of Unknown A_1, A_2, and A_3. Aluminum chloride catalyzed isomerization of *exo*-**1** (run 34) gave a mixture containing a reasonably large amount (8.6%) of fraction A. Treatment of the mixture with bromine at room temperature followed by fractional distillation of the product enabled the isolation of a mixture of unbrominated compounds. These were found on VPC analysis mainly consisted of unknown A's, B's, C's, and *exo*-**7**. 1- and 2-methyladamantane, **9**, and homoadamantane were thus almost completely removed from the isomerization product. The result is well understood in view of the high reactivity of bridgehead hydrogens of methyladamantanes,[20-22] homoadamantane,[21] and **9**[23] toward bromine. Fraction A concentrated in this procedure was then separated from the other unbrominated hydrocarbons on the preparative VPC. Isolated fraction A was again fractionated on VPC, when the former (early eluted) and the latter parts of the peak were collected spearately. The former part of the peak comprised A_1, A_2, and A_3 in 3.3:1.0:1.3 ratio, while the latter part contained them in 1.1:1.0:3.2 ratio.

Both of these specimens of fraction A exhibited 13 resonances in total proton-decoupled ^{13}C NMR specta. Fine structure of the off-resonance proton decoupled spectra was clear enough to show splitting of each resonance signal. By comparison of intensities of the signals with reference to the concentration of the constituents, it was possible to construct each spectrum of the component compound.

Unknown A_2 had by far the simplest spectrum: three signals [s (rel intensity somewhat less than 2), t (6), and t(3)]. [3.3.3]Propellane (**4**) is definitely the only tricycloundecane[24] corresponding to the spectrum, and the assignment of the signals are quite unambiguous only on the basis of their intensities and fine structures. Although some [3.3.3]propellanones were known,[25] the hydrocarbon does not seem to have been prepared or detected before. The mass spectrum of **4** was also highly characteristic, comprising three strong peaks [150 (rel intensity 40, M^+), 107 (100), and 79 (27)], and is very well consistent with the structure.

A similarity in the mass spectra of A_1 and A_3 had suggested a similar skeletal structure for them. The view was strengthened by ^{13}C NMR spectra, which showed the presence of eight kinds of carbon atoms, including a quaternary and a methyl. Actually A_1 exhibited only seven resonances (Table II). However, the relative intensity of the signal at 31.7 ppm (3) indicates that two kinds of carbon atoms would have a coincidently identical chemical shift. Two sharp singlets in ^1H NMR spectra of the specimens of fraction A also confirmed the presence of a methyl in each

compound. The singlet methyl group in turn indicates that it would be one of the substituents on the quaternary carbon atom. Two alternative structures, **10** (and **11**) or **17** (and **18**), correspond to the ^{13}C and ^{1}H NMR spectra.



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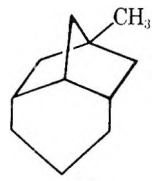


18

However, the homobrendane structure (**17** and **18**) could be excluded for the following reasons. The C-5 atom of **9** has a ^{13}C NMR resonance at exceptionally high field (15.2 ppm). This was successfully explained[6,7] with a combined effect of two axial methylene groups (C-2 and C-11) at the C-3 and C-7 and one equatorial methylene (C-9) at the C-8. Homobrendane has similar structural features, and its 5-methylene carbon atom should exhibit a resonance at as high a field as 15 ppm. No such absorption was observed for specimens of fraction A.

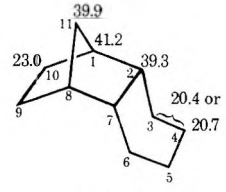
Secondly, mass spectra of A_1 and A_3 showed the base peak at *m/e* 94, indicating a loss of four carbon atoms to be the most favorable process. Fragmentation of ethano bridges (e.g., C-4 and C-5 followed by either C-2 and C-3, C-8 and C-9, or C-6 and C-10) in **10** and **11** may well account for the spectra, whereas **17** and **18** can not offer any convenient explanation.

Thirdly, result of the bromination of the isomerization mixture from *exo*-**1** may support the structure **10** and **11**. Bridgehead reactivity of bicyclononanes and -decanes was shown to be at least 10^3 times larger than that of bicyclooctanes and -heptanes.[21] Facile bromination of methyladamantanes (which may be regarded as 3,7-methanobicyclo[3.3.1]nonane), **9** (3,9-ethanobicyclo[3.3.1]nonane), and homoadamantane (3,7-methanobicyclo[3.3.2]decane), compared to that of B's, C's, and *exo*-**7** which are all bicyclooctanes and -heptanes, is in good agreement with the above reactivity. Low reactivity of A's therefore might be attributed to their bicyclic structure not larger than bicyclooctane. Structure **10** and **11** containing a bicyclo[3.2.1]octane skeleton can satisfy the requirement, but **17** and **18**, which are a bicyclo[3.3.1]nonane, cannot.

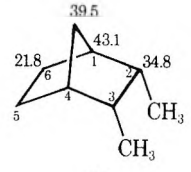
Comparison of the chemical shifts of the quaternary carbon atom and the tertiary carbon atoms giving the double intensity signals in A_1 and A_3 seems to help in determining the position (1 or 7) of the methyl group. The resonance of a carbon atom either in open chain or in ring system is always shifted to lower field by branching on that carbon atom and/or on the adjacent carbon atoms.[26] The chemical shift of the quaternary carbon atom of A_1 (62.3 ppm) is at lower field than that of A_3 (51.4 ppm). The result suggests assignment of the structure **10** to A_1, in which the quaternary (7) carbon atom should have a lower field signal under the influence of two vicinal (3 and 6) branchings. The assignment is supported by the comparison of the chemical shifts of the doublet carbon atoms at the 3 and 6 positions in both compounds (52.8 for A_1 and 45.5 ppm for A_3). Lower field absorption in A_1 would be ascribed to the effect of extra branching at the C-7 atom in **10**. Assignment of other signals of A_1 and A_3, except for the single intensity doublets, cannot be effected because of the lack of reference spectra.

Structure Determination of Unknown B_1. After fraction A had been isolated from the distilled unbrominated hydrocarbon mixture on the preparative VPC as described in the preceding section, fraction B was also collected in the same experiment. The fraction was found to contain 90% B_1 and 10% B_2 (*exo*-**2**). A total proton-decoupled ^{13}C NMR spectrum of fraction B comprised six peaks. Eleven signals of *exo*-**2**, which should appear in the spectrum, could hardly be discerned in noise signals. The lowest field signal (rel intensity less than 1) stayed singlet, while the other five (each with rel intensity 2) split into one doublet and four triplets, in off-resonance proton decoupling. The unique ^{13}C NMR spectra of unknown B_1 offered a sufficient basis for the determination of its molecular structure. 1,2-*exo*-Trimethylene-*cis*-bicyclo[3.3.0]octane (**5**), which has a molecular symmetry of C_2, is the only compound[27] corresponding to the observed spectra among all the possible tricycloundecane isomers.[24] No definite assignment of the signals, except the single-intensity singlet and the double-intensity doublet, was possible for this compound.

^{13}C NMR Spectra of 2,3-*endo*- and -*exo*-tetramethylenenorbornane (*endo*-1 and *exo*-1). ^{13}C NMR spectra of *endo*-**1** and *exo*-**1** do not seem to have been measured before. Their spectra (Table II) indicated an interesting correlation between the change in the chemical shifts and that in the configurations. Assignment of most of the signals of *endo*-**1** and *exo*-**1** was made with reference to those of 2,3-*endo*- and -*exo*-dimethylnorbornane (**19** and **20**)[28] as shown below, with the assumption that the carbon atoms in



endo-**1a**



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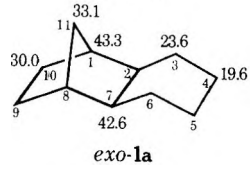
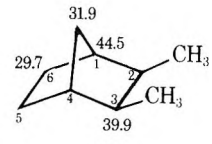


exo-**1a**



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comparable molecular environments have similar chemical shifts.

Assignment of 39.9- and 33.1-ppm signals to the C-11 atoms in *endo*-**1a** and *exo*-**1a**, respectively, will be unequivocal on the basis of the intensities (1) and fine structures (triplet) of these signals. Since the tertiary C-2 and C-3 atoms are at higher field than the bridgeheads (C-1 and C-4) in both **19** and **20**, the double-intensity doublet signals at higher field in both *endo*-**1** and *exo*-**1** (39.3 and 42.6 ppm) were assigned to the angular atoms (C-2 and C-7 in *endo*-**1a** and *exo*-**1a**), while those at lower field (41.2 and 43.3 ppm) were assigned to the bridgeheads (C-1 and C-8). Supposing that 2,3-*exo*-dimethyl and 2,3-*exo*-tetramethylene groups may exert a similar influence on the chemical shifts of C-5 and C-6 in norbornane, the 30.0-ppm double-intensity triplet of *exo*-**1** was assigned to C-9 and C-10 in *exo*-**1a**. With the same reasoning, the 23.0-ppm signal in *endo*-**1** could be assigned to C-9 and C-10 in *endo*-**1a**.

The C-4 and C-5 atoms in *endo*-**1a** and *exo*-**1a** are in the same molecular environment except that the configuration of the C-1 and C-8 atoms are opposite to each other. Under the probably small influence of C-1 and C-8 on C-4 and C-5 in either isomer because of the separation by two carbon atoms, C-4 and C-5 in *endo*-**1a** should have a similar chemical shift as that of C-4 and C-5 in *exo*-**1a**. The 19.6- and either of the 20.4- and 20.7-ppm signals were thus assigned to these atoms in *exo*-**1a** and *endo*-**1a**, respectively. Distinction between the 20.4- and 20.7-ppm signals in *endo*-**1**

seems to be impossible only on the basis of reference spectra now available.

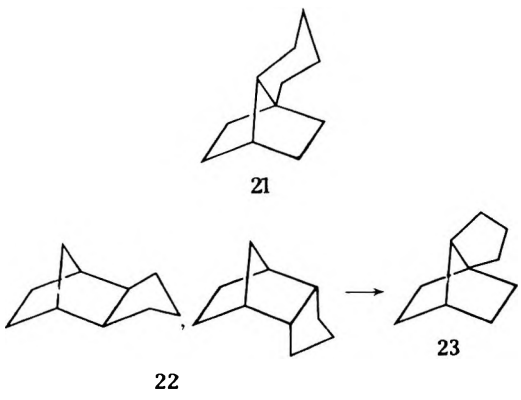
It may be interesting to note that the signal for the C-9 and C-10 atoms in *endo*-**1a** (23.0 ppm) is at fairly high field compared to that for the corresponding atoms in *exo*-**1a** (30.0 ppm). This would be ascribed to the effect of two β-axial substituents (C-2 and C-7) in *endo*-**1a**. Although the upfield shift of signals under the influence of this kind of nonbonded intereactions has been established in cyclohexanes[26] and norbornanes,[19,28] no example seems to have been recognized for tricycloundecanes. The signal for the C-11 atom in *endo*-**1a** (39.9 ppm) is at somewhat lower field than that of the corresponding atom in *exo*-**1a** (33.1 ppm). Comparison with the C-7 signal of norbornane (38.7 ppm)[26] indicates that the chemical shift of the C-11 in *endo*-**1a** is just normal, whereas that of the C-11 in *exo*-**1a** is brought upfield. Nonbonded interaction with C-3 and C-6 may also explain this upfield shift of C-11 in *exo*-**1a**.

Accelerated Isomerization of 2,3-*exo*-Tetramethylenenorbornane (*exo*-1) in the Presence of 1-Methyladamantane. It was found that the disappearance rate of *exo*-1 under trifluoromethanesulfonic acid catalysis was greatly increased in the presence of 1-methyladamantane.[29] The reaction was accelerated progressively with increase in the amount of 1-methyladamantane added, until it amounted to about 0.2 molar equiv to *exo*-1 (run 12), where disappearance of *exo*-1 was about 10^2 times faster than that in its absence. Beyond that amount of 1-methyladamantane, no appreciable increase in the effect was observed. Presence of 1-methyladamantane in the reaction also affected the product distribution. Amounts of unknown C_2, *endo*-**2**, *exo*-**2**, and **3** relative to that of **9** were appreciably increased, compared to those in the reaction without 1-methyladamantane (run 11).

Adamantane also showed the same effect but to a lesser extent. In this case product analysis was nullified because of the coincidence of the VPC retention time of adamantane with that of fraction C or D depending on the column used. Addition of 1 molar equiv of methylcyclohexane brought about entire extinction of the rearrangement of *exo*-1 in the presence of 1.5 molar equiv of the catalyst.

Discussion

A variety of tricycloundecane precursors have been shown[4-8,10] to isomerize first to the stable intermediate, 4-homoisotwistane (**9**), which then rearranges to final products, methyladamantanes. As would be evident from runs 1–5, 11, and 12 (Table I), four metastable intermediates, unknown C_2, *exo*-**2** (B_2), *endo*-**2** (B_3), and **3** (C_4), are involved in the rearrangement pathway from *endo*-1 or *exo*-1 to **9** (Chart I). It seems reasonable to assume that *exo*-**2**, *endo*-**2**, and **3** are derived from 1,7-tetramethylenenorbornane (**21**). The unstable intermediate **21** can be obtained from *endo*-1 or *exo*-1 by abstraction of 2-hydride and 1,2-alkyl shift of the 6-methylene group. Assumption of the intermediacy of **21** was made on the basis of the mechanism of the C_{10} adamantane rearrangement recently established by Schleyer,[30] in which 2,3-trimethylenenorbornane (**22**) gave unstable 1,7-trimethylenenorbornane (**23**) in the first, rate-determining step of the rearrangement. The intermediate **21** is indeed a C_{11} counterpart of **23**. An appropriate 1,2-alkyl shift in **21** would lead to either of *exo*-**2**, *endo*-**2**, and **3**.



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22 23

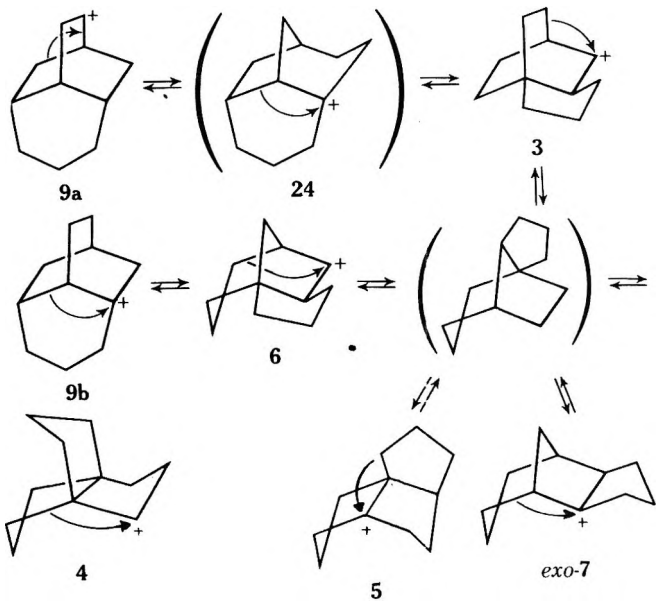
An increase in the proportion of C_2, *exo*-**2**, *endo*-**2** and **3** relative to **9** on the addition of 1-methyladamantane to the reaction of *exo*-1 may be explained in terms of hydride transfer from 1-methyladamantane. Cations of C_2, *exo*-**2**, *endo*-**2**, and **3** formed from **21** should undergo two reactions competitively: one is hydride abstraction from any surrounding hydrocarbons to become neutral molecules, and the other is further rearrangement leading to **9**. 1-Methyladamantane should donate its tertiary hydrides very easily to cations. This decreases the concentration of the intermediate cations and hence of **9** derivable from them.

Acceleration of the isomerization rate by 1-methyladamantane would be a result of an increase in the total concentraton of cationic species on addition of easily ionizable 1-methyladamantane. If abstraction of 2-hydride in *exo*-1 is rate determining, as in the C_{10} adamantane rearrangement,[30] the process should be favored in the presence of more abundant cations which are capable of hydride abstraction and, therefore, Lewis acids. Methylcyclohexane may work more as a hydride donor than as an abstractor because its cation would be relatively unstable at the temperature of refluxing methylene chloride owing to the aliphatic nature.[31]

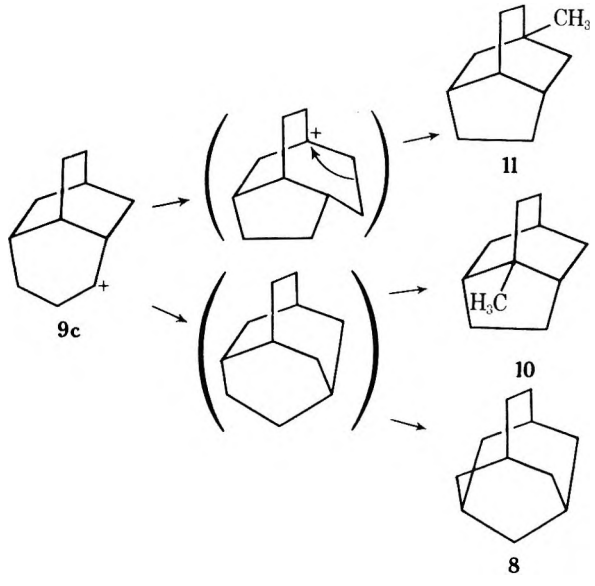
Of the four metastable intermediates derived from **21**, unknown C_2 and *endo*-**2** isomerized irreversibly to **9**, while *exo*-**2** and **3** seem to be in equilibrium with **9** since these two were formed also from **9** (runs 43–52). The fact that *endo*-**2** isomerized irreversibly to **9** whereas *exo*-**2** was in equilibrium with it may indicate a larger stability of *exo*-**2** than that of *endo*-**2**, and is in good agreement with the assignment of configuration for these isomers.

Rearrangement of **9** gives rise, in addition to *exo*-**2** and **3**, to a large number of products: unknown C_1 and D, [3.3.3]propellane (**4**, A_2), 1,2-*exo*-trimethylene-*cis*-bicyclo[3.3.0]octane (**5**, B_1), 1,7-*exo*-trimethylenebicyclo[3.2.1]octane (**6**, C_3), 6,7-exo-trimethylenebicyclo[3.2.1]octane (*exo*-**7**), homoadamantane (**8**), 7-methylisotwistane (**10**, A_1), and 1-methylisotwistane (**11**, A_3). All of these compounds except **10** and **11** seems to be in equilibrium with **9**, since rearrangement of them gave **9** as a product.[32] *exo*-**7** has been shown in a previous study[7] to be in equilibrium with **9**. The apparent equilibria between **9** and its isomerization products may be due to mutual interconversions among these compounds through 1,2-alkyl shift. An example of a mostly hypothetical isomerization sequence is cited below to show how interconversions might be realized. All the isomerizations in the scheme were so devised that they involved only assisted[33] or bridgehead ionization and 1,2-shift of those alkyl groups which were as much trans periplanar as possible to the developing(ed) vacant p orbital on the vicinal carbon atom.[34,35] This might make the scheme more than only imaginary. Intermediacy of 4-homoisotwist-3-yl cation (**9b**) would be highly probable because it should be the most stable of all the possible cations of **9** as is suggested from functionalization reactions of **9**.[23] The cation **9b** alone, however, could not explain a seemingly primary formation of **3** in the reaction of **9** (run 41). A

route from 4-homoisotwist-10-yl cation (**9a**) via 2,7-*endo*-trimethylenebicyclo[3.2.1]oct-2-yl cation (**24**) seems to be a possible alternative.



Methylisotwistanes (**10** and **11**) gave 1- and 2-methyladamantane as sole products of rearrangement.[32] A previous study[7] indicated the existence of a route via homoadamantane in the rearrangement of **9** to methyladamantanes. Accordingly, there should be at least three competitive pathways involving **8**, **10**, and **11**, respectively, from **9** to methyladamantanes. 4-Homoisotwist-4-yl cation



(**9c**) may be supposed as a common precursor to these intermediates, as shown in the scheme. Ionization of the 4-methylene group in **9** would be a process with relatively high activation energy that would account for the slow rearrangement of **9** to methyladamantanes, compared to that of **1** and other precursors to **9**.[6-8]

The result of the rearrangement of methylisotwistanes (**10** and **11**) seems to indicate that a methyl group once expelled out of a ring system can never be incorporated back again. The phenomenon was also observed in a mechanistic study of the conversion of 2-methyladamantane to the 1-methyl isomer using ^{13}C-labeled specimens[35] as well as in our study of the adamantane rearrangement of 2,4-*exo*-ethanobicyclo[3.3.1]nonane via 2-*endo*-methyl-2,3-*exo*-trimethylenenorbornane as an intermediate.[36] No return of the methyl group back into the ring would be an important clue in clarifying the rearrangement mechanism.[32]

Experimental Section

All melting and boiling points are uncorrected. Instruments for the measurement of spectra and for conventional and capillary column VPC were the same as were used in the previous work,[7,8,36] except that ^{13}C NMR spectra were measured at 25.14 MHz on a JEOL JNM PS-100 spectrometer equipped with JNM PFT-100 pulse Fourier transform. All the ir spectra were taken on neat samples. Deuteriochloroform was used as the solvent for NMR spectroscopy. Chemical shifts are reported in δ for protons and in parts per million downfield from internal Me_4Si standard for ^{13}C nuclei. Trifluoromethanesulfonic acid was a commercial product of 3M Co. Methylene chloride was dried over anhydrous calcium chloride and distilled immediately before use.

Authentic specimens of 6,7-*exo*-trimethylenebicyclo[3.2.1]octane (*exo*-**7**)[7] and 4-homoisotwistane (**9**)[10] were obtained before. 1,2-Trimethylenebicyclo[2.2.2]octane (**3**),[3] 1,6-tetramethylene-2-norbornene,[13] and 1,6-*exo*-trimethylene-2-norbornene[15] were prepared as described in the literature. Spectra of **3** synthesized:[18] ir 2930, 2860, 1460, 1450 cm^{-1} (lit.[3] ir 2942, 2868, 1461, 1454 cm^{-1}); MS *m/e* (rel intensity) 150 (40, M^+), 135 (12), 122 (17), 121 (100), 108 (10), 107 (15), 95 (12), 94 (30), 93 (24), 91 (11), 81 (25), 80 (32), 79 (36), 77 (11), 67 (28), 55 (13).

A Mixture of 1,2-*endo*- and -*exo*-Tetramethylenenorbornane (*endo*-2 and *exo*-2). A solution of 1.0 g (6.67 mmol) of 1,6-tetramethylene-2-norbornene in 30 ml of ether and 0.1 g of a palladium on charcoal catalyst (containing 5% metal) were placed in a 100-ml autoclave. After air in the vessel was replaced with hydrogen, the contents were hydrogenated with efficient stirring for 30 min at room temperature at a pressure of 5 kg/cm^2. The catalyst was filtered off from the reaction mixture, and the filtrate was fractionally distilled to give 0.9 g (89% yield) of a mixture containing 67% *exo*-**2** and 33% *endo*-**2**: bp 100–102° (36 mm); ir 2950, 2870, 1480, 1460, 1450, 1335, 1315, 1300, 1230, 1180, 1160, 1005, 910, 890, 880, 830 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 87.65; H, 12.30.

Mass spectra were taken on the Golay GC–MS instrument. *exo*-**2**: *m/e* (rel intensity) 150 (48, M^+), 135 (21), 122 (26), 121 (100), 108 (19), 93 (32), 81 (26), 79 (42), 67 (40), 41 (32). *endo*-**2**: *m/e* (rel intensity) 150 (69, M^+), 135 (75), 122 (30), 121 (100), 108 (40), 93 (50), 81 (40), 79 (66), 67 (54), 41 (57).

^{13}C NMR spectra were measured on the mixture, and the signals were allotted to each isomer according to their relative intensities (see text). Chemical shifts and multiplicities of the signals of *endo*-**2** and *exo*-**2** obtained in this way are listed in Table II.

A Mixture of 3,4-Dichloro-5,6-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene (13) and 3,4-Dichloro-1,7-exo-trimethylenebicyclo[3.2.1]oct-2-ene (14). To a mixture of 4.3 g (0.032 mol) of 1,6-*exo*-trimethylenenorborn-2-ene (**12**), 7.2 g (0.128 mol) of sodium methoxide, and 40 ml of petroleum ether was dropped with efficient stirring 20 g (0.103 mol) of ethyl trichloroacetate in a period of 3 hr, while the reaction mixture was kept below 0° by external cooling in an ice–salt bath. The reaction mixture was stirred for another 4 hr at 0°, and then allowed to warm up to ambient temperature overnight. The mixture was poured onto 100 ml of an ice–water mixture. The separated aqueous layer was extracted first with four 50-ml portions of ether and then, after being acidified with 10% hydrochloric acid, with two 50-ml portions of ether. The combined organic layer and ether extracts were washed with a saturated sodium chloride solution and dried over anhydrous sodium sulfate. Fractional distillation of the solution gave 4.1 g (47% yield) of a mixture consisting of 84% **13** and 16% **14**: bp 95–98° (0.25 mm); ir 2950, 2870, 1740, 1625, 1470, 1445, 1050, 970, 855, 740, 700 cm^{-1}; ^1H NMR δ 0.9–3.0 (complex m, 12), 4.18 (s, 1, CHCl), 6.07 (d, 1, J = 7 Hz, C=CH).

Anal. Calcd for $C_{11}H_{14}Cl_2$: C, 60.85; H, 6.50; Cl, 32.65. Found: C, 60.60; H, 6.50; Cl, 32.65.

13: MS *m/e* (rel intensity) 218 (9, M^+), 216 (13, M^+), 181 (37), 139 (29), 127 (36), 125 (100), 115 (15), 91 (25), 77 (22), 41 (30). **14**: MS *m/e* (rel intensity) 218 (18, M^+), 216 (27, M^+), 181 (25), 145 (35), 139 (29), 138 (69), 127 (39), 126 (36), 125 (100), 115 (28), 113 (68), 91 (30), 77 (47), 41 (25).

A Mixture of 5,6- and 1,7-exo-Trimethylenebicyclo[3.2.1]oct-2-ene (15 and 16). To 63 ml of liquid ammonia kept below −50° in a Dry Ice–acetone bath was added with stirring 7.8 g

(0.34 g-atom) of sodium metal in small portions in a period of 30 min, and the mixture was stirred for a further 30 min at the same temperature. A solution of 3.8 g (0.0175 mol) of the mixture of **13** and **14** prepared above in 30 ml of ether was added dropwise to the above mixture in a period of 45 min while the temperature was kept below −50°, and the reaction was stirred for another 2 hr at the same temperature. To the reaction mixture was added dropwise 30 ml of ether at room temperature while liquid ammonia was allowed to evaporate freely. Any unreacted sodium and sodium amide in the residue were decomposed by successive addition of methanol–ether mixture, methanol, and water. The aqueous layer separated was extracted with three 150-ml portions of ether. The combined organic layer and ether extracts were washed with a saturated sodium chloride solution and dried over anhydrous sodium sulfate. Fractional distillation of the ether solution gave 0.8 g (31% yield) of a mixture consisting of 86% **15** and 14% **16**, bp 56–58° (5 mm).

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 88.90; H, 11.05.

The mixture was separable on the conventional preparative VPC. **15:** ir 3010, 2920, 2850, 2800, 1625, 1435, 1370, 1255, 1000, 730, 710 cm^{-1}; ^1H NMR δ 0.9–2.61 (complex m, 14), 5.08–5.97 (complex m, 2); MS *m/e* (rel intensity) 148 (47, M^+), 120 (18), 119 (38), 106 (26), 105 (28), 94 (31), 92 (52), 91 (88), 79 (100), 77 (53), 67 (21), 66 (45), 41 (55). **16:** ir 3010, 2920, 2850, 2820, 1625, 1450, 1430, 900, 710, 690 cm^{-1}; MS *m/e* (rel intensity) 148 (48, M^+), 120 (13), 119 (33), 106 (26), 105 (30), 92 (54), 91 (70), 79 (64), 77 (29), 67 (27), 66 (100), 41 (24).

1,7-*exo*-Trimethylenebicyclo[3.2.1]octane (6). A solution of 0.3 g (2 mmol) of the mixture of **15** and **16** obtained above in 20 ml of ether was hydrogenated in a 100-ml autoclave over 0.05 g of the palladium on charcoal catalyst at room temperature at a pressure of 5 kg/cm^2. The reaction was completed in 30 min. The catalyst was filtered off, and the filtrate was evaporated to give 0.29 g (96% yield) of crude **6**, which was purified on a preparative VPC to yield a pure sample: ir 2940, 2930, 2860, 1465, 1450, 980, 870, 785, 660 cm^{-1}; ^1H NMR δ 0.7–2.5 (complex m); MS *m/e* (rel intensity) 161 (8, $M^+ + 1$), 150 (100), 135 (50), 122 (48), 121 (44), 108 (45), 107 (80), 95 (32), 94 (60), 93 (45), 81 (60), 80 (68), 79 (80), 67 (56), 55 (19), 41 (38). ^{13}C NMR signals are listed in Table II.

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found:, C, 87.70; H, 12.20.

Bromination of an Isomerization Product of 2,3-*exo*-Tetramethylenenorbornane (*exo*-1) and Isolation of a Mixture of [3.3.3]Propellane (4), 7-Methylisotwistane (10), and 1-Methylisotwistane (11). A mixture of 30 g (0.2 mol) of the reaction mixture of run 34 (Table I) and 100 ml (1.94 mol) of bromine was stirred at room temperature for 2 hr. Most of excess bromine was evaporated under diminished pressure at ambient temperature. The residue was treated repeatedly with a cold, saturated solution of sodium hydrogen sulfite until all the remaining bromine had been removed, then washed successively with a saturated solution of sodium hydrogen carbonate and water and dried over anhydrous magnesium sulfate. The mixture was distilled, and the fraction (11.2 g) boiling at 65–75° (8 mm) was collected. The fraction was again distilled through a 1-ft Vigreux column to give 2.7 g of a fraction boiling at 71–72° (11 mm). The compositon of the fraction thus obtained was unknown A_1 (**10**), 8.7; A_2 (**4**), 5.7; A_3 (**11**), 16.2; B_1 (**5**), 30.2; B_2 (*exo*-**2**), 3.1; C_3 (**6**), 14.6; C_4 (**3**), 3.6; 2-methyladamantane, 0.5; *exo*-**7**, 16.2; **9**, 0.4%. Fraction A was then isolated from the above hydrocarbon mixture on the preparative VPC, and amounted to 0.75 g.

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 87.72; H, 12.13.

The fraction A was again fractionated on the preparative VPC, when the former and the latter shoulders of the VPC peak were collected separately. The middle part of the peak was repeatedly chromatographed until enough (each 0.2 g) of the former and the latter eluted fractions were obtained. Both fractions solidified on standing at room temperature. The former eluted specimen thus obtained comprised A_1, A_2, and A_3 in 3.3:1.0:1.3 ratio, while the latter eluted fraction was in 1.1:1.0:3.2 ratio. The former eluted specimen showed two sharp singlets in a ^1H NMR spectrum. They absorbed at δ 1.08 and 1.05 whose relative intensities were 3 and 1, respectively. On the other hand, the later eluted specimen gave the same singlets with relative intensities of 1 and 3. Therefore, the δ 1.08 signal was assigned to the protons of the 7-methyl group in **10**, the δ 1.05 signal to those of 1-methyl in **11**. ^{13}C NMR spectra of **4**, **10**, and **11** were constructed from those of the two mixture specimens, as stated in the text, and are listed in Table II.

The mass spectrum of each compound was measured on the Golay GC–MS instrument. **4:** *m/e* (rel intensity) 150 (40, M^+), 135 (20), 122 (9), 121 (6), 109 (18), 108 (16), 107 (100), 94 (14), 93 (10), 91 (7), 81 (8), 80 (14), 79 (27), 67 (17), 55 (8), 53 (6), 44 (17), 41 (12), 40 (16). **10:** *m/e* (rel intensity) 150 (45, M^+), 135 (20), 122 (11), 121 (14), 108 (11), 107 (32), 95 (30), 94 (100), 93 (30), 81 (39), 80 (20), 79 (36), 78 (5), 77 (14), 68 (9), 67 (29), 55 (21), 53 (16). **11:** *m/e* (rel intensity) 150 (11, M^+), 135 (11), 122 (5), 121 (11), 108 (10), 107 (32), 95 (13), 94 (100), 93 (19), 81 (36), 80 (20), 79 (25), 77 (8), 67 (15), 55 (8), 53 (6).

Isolation of a Mixture of 1,2-*exo*-Trimethylene-*cis*-bicyclo[3.3.0]octane (5) and 1,2-exo-Tetramethylenenorbornane (*exo*-2). After fraction A was collected on the preparative VPC as described in the preceding section, fraction B was also collected in a fractionation of the unbrominated hydrocarbon mixture boiling at 71–72° (11 mm). The fraction B contained 90% B_1 (**5**) and 10% B_2 (*exo*-**2**): ir 2960, 2940, 2860, 1590, 1470, 1450, 1370, 1310, 930, 910 cm^{-1}. The absorption at 1370 cm^{-1} was considered characteristic of **5**, because the absorption was entirely absent in the ir spectrum of an authentic mixture of *exo*-**2** and *endo*-**2**.

Mass spectrum of **5** taken in the Golay GC–MS: *m/e* (rel intensity) 150 (13, M^+), 135 (13), 122 (100), 121 (37), 108 (20), 107 (82), 95 (13), 94 (22), 93 (26), 82 (9), 81 (32), 80 (38), 79 (50), 77 (14), 68 (10), 67 (29), 65 (8), 55 (12), 41 (22).

Isomerization Reactions of Tricycloundecanes. The reaction was run in the same equipment as used in the previous work.[7] A mixture of 0.1 g (0.667 mmol) of a tricycloundecane in 5 ml of methylene chloride was refluxed in the presence of an appropriate amount of the catalyst. The reactant to solvent ratio was the same in preparative runs as in analytical runs. Isolation of products for preparation purposes was made by quenching the reaction mixture with cold water followed by washing the methylene chloride layer with a saturated sodium hydrogen carbonate solution and water. The methylene chloride solution was dried over anhydrous calcium chloride.

Acknowledgment. The authors wish to express their appreciation to Dr. E. Ōsawa, Hokkaido University, for valuable discussions. They also thank Mr. I. Homma, Household Goods Research Laboratories, Kao Soap Co., for assistance in measuring and analyzing ^{13}C NMR spectra.

Registry No.—*endo*-**1**, 54676-30-1; *exo*-**1**, 54676-30-1; *endo*-**2**, 55954-91-1; *exo*-**2**, 36150-95-5; **3**, 51095-23-9; **4**, 51027-89-5; **5**, 55925-58-1; **6**, 55954-92-2; *exo*-**7**, 53495-28-6; **9**, 43000-53-9; **10**, 55925-59-2; **11**, 55925-60-5; **12**, 16489-22-8; **13**, 55925-61-6; **14**, 55925-62-7; **15**, 55925-63-8; **16**, 55925-64-9; 1,6-tetramethylene-2-norbornene, 27017-54-5; ethyl trichloroacetate, 515-84-4.

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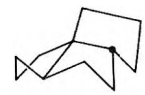

trans-**5**

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Addition of Sulfur Trioxide to Acid Halides and Esters

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Received February 26, 1975

Sulfur trioxide inserts into the carbon–halogen bond of acid fluorides and acid chlorides under mild conditions. The acyl fluorosulfates so formed are more stable thermally than the acyl chlorosulfates, but both types of product can revert to starting materials at elevated temperatures. As a class, these mixed anhydrides are strongly electrophilic, and examples of cationic polymerization and ether cleavage are presented. One example of formation of a methyl acyl sulfate from sulfur trioxide and a methyl ester is also described.

Although polyfluoroacyl fluorides were prepared earlier from sulfur trioxide and alkyl polyfluoroalkyl ethers,[1,2] the reaction of sulfur trioxide with the product acid fluorides was not reported in the literature.[3] As is shown in this paper, such reactions provide a convenient route to polyfluoroacyl fluorosulfates in quantity. Previous syntheses of fluoroacyl fluorosulfates involved mainly reactions of peroxydisulfuryl difluoride with substrates such as fluorinated anhydrides,[4] trifluoroacetyl bromide,[5] and bis(trifluoromethyl)ketene.[6]

Acyl Fluorosulfates. Preparation. Sulfur trioxide adds readily to fluoroacyl fluorides at 25–100°, with the required time and temperature dependent on the specific acid fluoride. For example, trifluoroacetyl fluoride reacted under pressure over a period of weeks with sulfur trioxide at 25° to form trifluoroacetyl fluorosulfate (**1**), whereas both α-*H*-hexafluoroisobutyroyl fluoride and perfluoromethacryloyl fluoride give **2** and **3**, respectively, in mildly exother-

$$R_FCF + SO_3 \longrightarrow R_FCOSO_2F$$

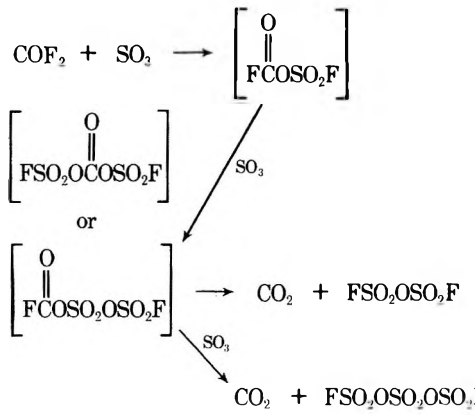
$R_F = CF_3$ (**1**)
$R_F = CH(CF_3)_2$ (**2**)
$R_F = C(CF_3)=CF_2$ (**3**)
$R_F = CHFCF_3$ (**4**)
$R_F = CF(CF_3)SO_2F$ (**5**)

mic reactions. Yields were good in all cases, and the fluoroacyl fluorosulfates have been purifiable by distillation provided the temperature is kept well below 100°. The reaction is reversible, and at elevated temperatures significant amounts of acid fluoride and sulfur trioxide are present.[7] Thus fluorosulfate **3** distilled as such at 46–48° (20 mm), but when heated at 1 atm to 125–140°, **3** distilled as a mixture of its precursors at ca 49°.

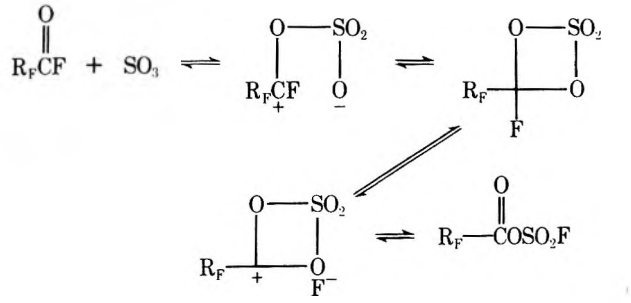
Side reactions are possible in some cases where α-H is present. Thermolysis of **2** at 120–155° (1 atm) gave 37% of bis(trifluoromethyl)ketene along with α-*H*-hexafluoroisobutyroyl fluoride. No such elimination of HF was observed when fluorosulfate **4** was pyrolyzed.

Carbonyl fluoride proved to be a special case. Reaction with sulfur trioxide occurred slowly in a glass vessel at 100° under pressure to give products apparently derived from fluorocarbonyl fluorosulfate. Major products were carbon dioxide, pyrosulfuryl fluoride, and bis(fluorosulfonyl) sulfate along with a trace of sulfuryl fluoride and small amounts of higher fluorosulfonyl compounds. The low yield of sulfuryl fluoride is an indication that fluorocarbonyl fluorosulfate is formed, but reacts readily with sulfur trioxide to form higher anhydrides which are degraded with loss of carbon dioxide to give fluorosulfonic anhydrides. The reaction should provide an attractive route to pyrosulfuryl fluoride, although one attempt to reproduce it on a molar scale at 125° in a metal bomb failed. Perhaps the equilibrium at

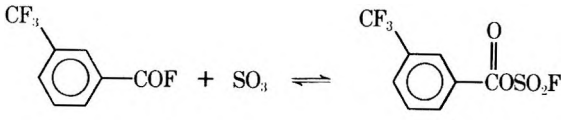
125° favors starting materials so greatly that an effective ceiling temperature near 100° was exceeded.



These reactions of sulfur trioxide with acid fluorides may proceed via preliminary coordination of sulfur trioxide to fluorine, followed by an ionization to acylium and fluorosulfate ions which recombine to product. However, the polarization of acid fluorides is such that another mechanism for these reactions should also be considered, one which involves an initial reversible cycloaddition to the carbonyl group. Assuming a conventional cycloaddition in accord with the Woodward–Hoffman rules, this addition would probably be stepwise and proceed by attack on the negatively charged carbonyl oxygen by sulfur trioxide to form a dipolar intermediate. Similar [2 + 2] cycloadducts of sulfur trioxide with fluoro olefins are well known.[8] 1–3 migration of fluoride ion from carbon to sulfur with concomitant ring-opening gives the more stable acyl fluorosulfate. With carbonyl fluoride, proposed intermediate fluorocarbonyl fluorosulfate can react further with sulfur trioxide, as observed, and elimination of carbon dioxide provides an irreversible pathway to sulfuric anhydrides.



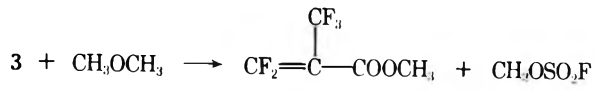
m-Trifluoromethylbenzoyl fluoride easily forms *m*-trifluoromethylbenzoyl fluorosulfate (**6**) at low temperatures. Other negatively substituted benzoyl fluorides and benzoyl fluoride itself will presumably give similar adducts. Distillation of **6** could be carried out at low temperature without appreciable sulfonation of the ring, but reversibility of the synthesis reaction hampered efforts to isolate the pure adduct.



6

Reactions. As indicated above, the acyl fluorosulfates dissociate near 100°, so that their isolation and reactions must be conducted at moderate temperatures. The products react violently with water, and those of sufficient volatility fume in air. Another indicator of reactivity is the attack of the acyl fluorosulfates on sodium chloride prisms, which necessitated the use of calcium fluoride plates for recording infrared spectra.

The acyl fluorosulfates exhibit pronounced electrophilic character. Compound **1** efficiently polymerized tetrahydrofuran to high molecular weight polymer, indicating high reactivity as a cationic initiator. Molar amounts of acyl fluorosulfate with an ether easily give the corresponding fluorinated ester. Thus, **2** reacted with diethyl ether at 0° to give a solid oxonium adduct which decomposed at 25°, leading to ethyl α-*H*-hexafluoroisobutyrate in 72% isolated yield. Similarly, **3** reacted with dimethyl ether to form methyl fluorosulfate and methyl perfluoromethacrylate (**7**). The mixture was difficult to separate by fractional distillation, but passage over sodium fluoride at 275° served to remove methyl fluorosulfate and allowed isolation of pure **7** in 79% yield. This synthesis is superior to known routes,[9] in that the ester is obtained from a simple sequence of reaction free of the saturated adduct with hydrogen fluoride.



7

Acyl trifluoromethanesulfonates are reported[10] to acylate benzene at 20°. The possibility that fluoroacyl fluorosulfates would serve as acylating agents of equal potency was tested by mixing **2** and benzene at 25°. Since no reaction was observed, the reactivity of the fluoroacyl fluorosulfates must be less than that of the acyl trifluoromethylsulfonates. This result may be a direct consequence of the greater difficulty in forming fluoroacylium cations than acylium cations. At any rate, the amount of sulfur trioxide in equilibrium with the fluoroacyl fluorosulfate at 25° must be negligible, since the known exothermic reaction of sulfur trioxide with benzene did not occur. Therefore, the fluoroacyl fluorosulfates may prove useful in acylating activated rings.

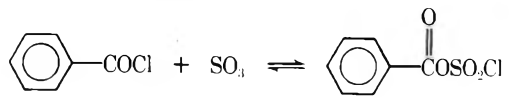
Acyl Chlorosulfates. Few descriptions of acyl chlorosulfates are found in the literature. Acetyl chlorosulfate, as an example, is said to have been obtained from acetyl chloride and chlorosulfonic acid at 25° as a thermally unstable oil.[11] The 1:1 adduct from acetyl chloride and sulfur trioxide was also assigned the chlorosulfate structure on the basis of conductometric, cryoscopic, and infrared studies of its behavior in polar media, in which solutions acylium cation and chlorosulfate anion were detected.[12] In the same study, however, chloroacetyl chloride was concluded to have formed only a complex in which sulfur trioxide was coordinated with the carbonyl oxygen; the evidence was lack of conductance in solution and a decrease in the carbonyl infrared frequency rather than an increase as observed with acetyl chloride.

In our work, reactions of two acid chlorides were examined. Heptafluorobutyroyl chloride combined with sulfur trioxide at 100° under pressure to form *n*-heptafluorobutyroyl chlorosulfate (**8**). The latter appeared to revert to starting materials near 50° at 1 atm, a temperature much lower than that required to dissociate the related fluorosulfates.

8

Benzoyl chloride combined exothermically with sulfur trioxide to form benzoyl chlorosulfate (**9**), which was distillable at very low pressure with slight decomposition. No mention of this reaction was uncovered in the literature, al-

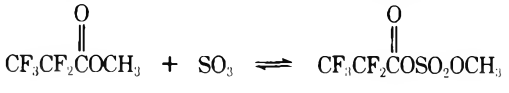
though it is well known that at higher temperatures (110–160°), benzoyl chloride and sulfur trioxide form *m*-carboxybenzenesulfonyl chloride.[13] The latter reaction and perhaps others, such as the rearrangement of acetyl chlorosulfate to sulfoacetyl chloride above 45°,[11] can now be understood to proceed by preliminary dissociation of a chlorosulfate to acid chloride and sulfur trioxide.



9

Part of the proof of structure for **9** rests on the shift of carbonyl infrared absorption to shorter wavelength than that of benzoyl chloride. This direction of shift is compatible with formation of the mixed anhydride in which a group more negative than chlorine is attached to the carbonyl, resulting in a more covalent double bond. Complex formation by association of sulfur trioxide with the carbonyl oxygen, on the other hand, would have resulted in a substantial shift of the carbonyl bond to longer wavelength.[14] The mixed anhydride structure is also supported by the facile reaction of **9** with dimethyl ether to give methyl benzoate, isolated in 60% yield. The possibility that complexed sulfur trioxide was present to form dimethyl sulfate with dimethyl ether, and dimethyl sulfate subsequently methylated benzoyl chloride to give methyl benzoate after aqueous work-up, was excluded by showing that dimethyl sulfate does not react at 25° with benzoyl chloride. Dissociation of **9** does occur readily, however, since reaction with benzene occurs exothermically to give only base-soluble products and a small amount of diphenyl sulfone. No benzophenone was detected.

Insertion into an Ester. In the only such case examined, methyl pentafluoropropionate slowly added sulfur trioxide at reflux to form methyl pentafluoropropionyl sulfate (**10**). This compound could be isolated by vacuum distillation at low temperature, but it also dissociates on heating. An attempt to interact **10** with benzene at reflux resulted in the formation of methyl pentafluoropropionate.



10

Experimental Section[15]

Trifluoroacetyl Fluorosulfate (1). Into each of two 100-ml heavy-walled polymer tubes were loaded 20 g (0.25 mol) of SO_3 and 32.5 g (0.28 mol) of trifluoroacetyl fluoride. The tubes were sealed and allowed to stand at 25° for 3 weeks, after which time single phases were present. Excess trifluoroacetyl fluoride was allowed to escape and the combined contents of both tubes were distilled to give 67.5 g (69%) of colorless product, bp 44–47° (ref 5, bp 46.5°), ^{19}F NMR +47.7 (s, 1, $-OSO_2F$) and −74.5 ppm (s, 3, CF_3).

Polymerization of Tetrahydrofuran. Into a flame-dried round-bottomed flask was injected 44.4 g (50 ml) of purified tetrahydrofuran. The contents were blanketed with dry N_2 and stirred at −25° while 0.10 ml of trifluoroacetyl fluorosulfate was injected. Stirring was continued while the mixture was allowed to warm to 25°. After 1 day the mixture was too viscous to be stirred magnetically. After 2 days, the polymerization was quenched in 250 ml of water containing 10 g of NaOH. This mixture was warmed and stirred for 1 hr, and the resulting semisolid polymer was washed with three 250-ml portions of hot water, then dried under vacuum to give 32.7 g (74%) of solid polytetrahydrofuran, η_{inh} 0.80 (0.1% solution in benzene at 25°).

***α*-*H*-Hexafluoroisobutyroyl Fluorosulfate (2).** Addition of 50 g (0.25 mol) of *α*-*H*-hexafluoroisobutyroyl fluoride to 24 g (0.30 mol) of sulfur trioxide resulted in a mildly exothermic reaction. After 2 days the mixture was distilled to afford 48.2 g (69%) of *α*-*H*-hexafluoroisobutyroyl fluorosulfate: bp 49° (50 mm); ir 3.37 (saturated CH, weak), 5.47 (C=O), 6.76 (SO_2F), and 7.2–8.5 μ (CF, SO_2); ^{1}H NMR 4.22 ppm [septet, J_{HF} = 7 Hz, $CH(CF_3)_2$]; ^{19}F NMR +46.6 (s, 1, OSO_2F), −64.6 ppm [d, 6, $CH(CF_3)_2$].

Anal. Calcd for $C_4HF_7O_4S$: C, 17.27; H, 0.36; F, 47.82. Found: C, 17.61; H, 0.69; F, 48.53.

Perfluoromethacryloyl Fluorosulfate (3). Equimolar amounts of perfluoromethacryloyl fluoride and SO_3 gave a mildly exothermic reaction to form an adduct. Attempted distillation at 125–140° and 1 atm resulted in cracking, presumably to starting materials, bp ~49°.

A 10-g sample of the distillate above, bp 49° (1 atm), was distilled under reduced pressure to give 7.5 g of perfluoromethacryloyl fluorosulfate: bp 46–48° (20 mm); ir 5.53 (C=O), 5.91 (C=C), 6.79 (SO_2F), and 7.2–8.5 μ (CF, SO_2); ^{19}F NMR +45.0 (s, 1, OSO_2F), −47.7 (m, 2, $=CF_2$), and −60.4 ppm (m, 3, CF_3).

Anal. Calcd for $C_4F_6O_4S$: C, 18.61; F, 44.17. Found: C, 18.78; F, 44.49.

Methyl Perfluoromethacrylate (7). Excess dimethyl ether was distilled into a flask topped by a −80° condenser and containing 41.7 g (0.16 mol) of perfluoromethacryloyl fluorosulfate maintained at 0°. The mixture was stirred at 0° for 1 hr and then allowed to warm to 25° while excess dimethyl ether was vented. The crude product was passed over a bed of dry NaF pellets in a hot tube at 275° (5 mm). After two passes, only traces of by-product methyl fluorosulfate remained and nearly pure methyl perfluoromethacrylate was collected in 79% (23.9 g) yield. Identity and purity were determined by comparison of the ir spectrum and GC retention time with those of an authentic sample.

***α*-*H*-Tetrafluoropropionyl Fluorosulfate (4).** A mixture of 37 g (0.25 mol) of *α*-*H*-tetrafluoropropionyl fluoride and 10 ml of sulfur trioxide was heated in a Carius tube overnight on a steam bath. Distillation gave 45.6 g (80%) of *α*-*H*-tetrafluoropropionyl fluorosulfate, bp 49° (65 mm).

Anal. Calcd for $C_3HF_5O_4S$: C, 15.80; H, 0.44; F, 41.67; S, 14.06. Found: C, 15.86; H, 0.60; F, 41.57; S, 14.07.

Pyrolysis of **4** in a platinum tube at 500° (1.6 mm) gave no indication of ketene formation.

***α*-Fluorosulfonyltetrafluoropropionyl Fluorosulfate (5).** The mixture of 46 g (0.20 mol) of *α*-fluorosulfonyl tetrafluoropropionyl fluoride and 16 g (0.20 mol) of sulfur trioxide was heated in a Carius tube overnight on a steam bath and the product distilled to afford 15.1 g (24%) of **5**: bp 71° (190 mm); ir 5.40 (C=O), 6.66, and 6.76 μ (SO_2F); ^{19}F NMR +52.1 (q, J_{FF} = 9.1 Hz, into d, J_{FF} = 4.0 Hz, 1, OSO_2F), +47.0 (s, 1, OSO_2F), −74.1 (d, J_{FF} = 9.1 Hz, into d, J_{FF} = 8.1 Hz, 3, CF_3), and −161.6 ppm (q, J_{FF} = 8.1 Hz, into d, J_{FF} = 4.0 Hz, 1, CF).

Polysulfuryl Fluorides from COF_2 and SO_3. A 100-ml heavy-walled glass tube was charged with 6.9 g (0.10 mol) of carbonyl fluoride and 16.0 g (0.20 mol) of sulfur trioxide, sealed, and heated at 100° for 5 days. Gaseous products identified by ir were carbon dioxide with traces of sulfuryl fluoride, sulfur dioxide, and silicon tetrafluoride. Distillation of liquid products gave 7.34 g (40%) of pyrosulfuryl fluoride, identified by comparison of the infrared spectrum with that of an authentic sample and by the presence of a single ^{19}F NMR peak at +48.6 ppm. A second product, trisulfuryl fluoride, $FSO_2OSO_2OSO_2F$, bp 64° (120 mm), 2.04 g (12%), was identified by ir and NMR (singlet ^{19}F NMR peak at +49.8 ppm).[16]

***m*-Trifluoromethylbenzoyl Fluorosulfate (6).** Addition of 7.5 g (0.094 mol) of SO_3 over a 10-min period to 19.2 g (0.10 mol) of *m*-trifluoromethylbenzoyl fluoride proceeded exothermically. Temperature was maintained at 30–40° by external cooling. After addition was completed, infrared analysis of the mixture showed strong bands at 5.49 (C=O) and 6.84 μ ($-OSO_2F$). Distillation at 42–47° (0.15–0.25 mm) afforded 14.2 g (~55%) of liquid. NMR analysis of a late fraction by ^{19}F NMR showed peaks at +45.3 (s, 1, $-OSO_2F$) and −64.1 ppm (s, 3, CF_3) with −COF peak present indicating ~9% starting acid fluoride as impurity; ir 3.23 (aromatic CH), 5.48 (C=O), 6.18 and 6.27 (aromatic C=C), and 6.84 μ (OSO_2F).

***n*-Heptafluorobutyroyl Chlorosulfate (8).** Reaction of heptafluorobutyroyl chloride with SO_3 at 25° did not proceed satisfactorily, as indicated by the continued presence of two phases after 3 days. The two reactants, when heated in a sealed glass tube at 100° for 2 hr, formed a homogeneous solution. After an additional 2 hr at 100°, the reaction mixture was cooled and transferred to a still. Distillation of about ⅕ of the mixture occurred readily at 33–34° with the pot at ~50°. Ir analysis of the distillate indicated it to contain a high proportion of heptafluorobutyroyl chloride (bp

39°); the corrosive, fuming nature of the distillate indicated SO_3 to be present in at least small amounts.

Ir analysis of the still pot contents showed it to contain not only heptafluorobutyroyl chloride (5.51 and 5.58 μ for C=O), but also heptafluorobutyroyl chlorosulfate (5.46 μ for C=O, 7.10 μ for OSO_2Cl).

Benzoyl Chlorosulfate (9). Benzoyl chloride (14.1 g, 0.10 mol) was stirred under dry N_2 while 8.0 g (0.10 mol) of SO_3 was added over 10 min with occasional cooling to keep the temperature at 30–40°. After the addition was completed, the mixture was allowed to stand for 1 hr, then distilled through a short Vigreux column to give 21.9 g (99%) of yellow oil, bp 37° (7.5 μ). ^1H NMR showed monosubstituted phenyl, nearly unchanged in chemical shift and in pattern from that of benzoyl chloride; ir 5.57 (C=O), 6.27 and 6.32 (aromatic C=C), and 7.07 μ (OSO_2Cl).

Methyl Pentafluoropropionyl Sulfate (10). To 27.0 g (0.15 mol) of methyl pentafluoropropionate stirred at 0° was added dropwise 12.0 g (0.15 mol) of SO_3. No exotherm was observed, so the reaction mixture was heated slowly to reflux (53°). Reflux was continued for 60 hr, at which time the pot temperature had leveled off at 73°. Distillation afforded 10.1 g (26%) of methyl pentafluoropropionyl sulfate: bp 38° (5 mm); ir 3.35 (saturated CH), 5.47 (C=O), 6.87 and 6.98 (SO_2), and broad 8 μ (CF); ^1H NMR δ 4.26 (OCH_3); ^{19}F NMR −83.3 (t, J_{FF} = 1.6 Hz, 3, CF_3) and −121.6 ppm (q, J_{FF} = 1.6 Hz, 2, CF_2).

Anal. Calcd for $C_4H_3F_5O_5S$: C, 18.61; H, 1.17; F, 36.80; S, 12.42. Found: C, 18.67; H, 1.33; F, 36.55; S, 13.04.

Acknowledgment. The expert technical assistance of Mr. William Nickerson is gratefully acknowledged, as is the interpretation of the ir spectra by Miss Naomi Schlichter.

Registry No.—1, 5762-53-8; 2, 56114-18-2; 3, 56114-19-3; 4, 40416-27-1; 5, 56114-20-6; 6, 56114-21-7; 7, 685-09-6; 8, 56114-22-8; 9, 56114-23-9; 10, 56114-24-0; trifluoroacetyl fluoride, 354-34-7; SO_3, 7446-11-9; tetrahydrofuran, 109-99-9; polytetrahydrofuran, 24979-97-3; α-*H*-hexafluoroisobutyroyl fluoride, 382-22-9; perfluoromethacryloyl fluoride, 684-36-6; dimethyl ether, 115-10-6; α-*H*-tetrafluoropropionyl fluoride, 6065-84-5; α-fluorosulfonyltetrafluoropropionyl fluoride, 754-41-6; COF_2, 353-50-4; trisulfury. fluoride, 13709-33-6; *m*-trifluoromethylbenzoyl fluoride, 328-99-4; heptafluorobutanoyl chloride, 375-16-6; benzoyl chloride, 98-88-4; methyl pentafluoropropionate, 378-75-6.

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(15) Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 21 spectrometer. The mixed anhydrides attacked NaCl and were therefore held between CaF_2 plates. Nuclear magnetic resonance spectra were recorded on Varian A-56/60 or A-60 spectrometers and were taken on ~20% carbon tetrachloride solutions. Chemical shifts are reported in parts per million from tetramethylsilane and from trichlorofluoromethane as internal standards, with downfield directions taken as positive.
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Mechanism of Hydrolysis of an Unsymmetrical Ketene *O,O*-Acetal and of Ketene *O,S*-Acetals[1a]

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Received April 3, 1975

The hydrolyses of an unsymmetrical ketene *O,O*-acetal (2,2-dichloro-1-ethoxy-1-phenoxyethylene, **1**) and of two ketene *O,S*-acetals [2,2-dichloro-1-ethoxy-1-ethylthioethylene (**2**) and 1-ethylthio-1-phenoxyethylene (**3**)] have been studied in acidic solution at 30°. The observed catalysis by hydronium ion and acetic acid, the deuterium solvent isotope effect (k_H/k_D = 3.0 with **3**), and the nonlinear dependence of rate on buffer concentration at constant pH (with **3**) are in accord with a mechanism in which proton transfer to the olefinic bond is rate determining in HCl and $HClO_4$ solutions, and at low concentrations of acetate buffer. At high buffer concentration, the rate-limiting step is suggested to be the decomposition of a carbonium ion intermediate. The variation in the nature of the products of hydrolysis of **2** (mainly ester at $HClO_4$ < 1 *M*, and mixtures of ester and thiol ester at higher acidity) is taken as evidence for a second intermediate on the reaction pathway. The products of hydrolysis of **1** and **3** are phenol and ethyl dichloroacetate or ethyl thiolacetate, respectively, and are essentially independent of acidity in the ranges examined. The pathways of breakdown of tetrahedral addition intermediates of varying structure are discussed.

A useful approach to the study of the elusive, highly reactive, tetrahedral addition intermediates which are formed in many acyl transfer reactions consists of the generation of these or closely related substances via reactions which do not lie on the reaction pathway for acyl transfer.[2] Extensive use has been made of the hydration of imidate[3] and thioimidate[4] esters to investigate the properties of the intermediates formed in the aminolysis of esters and thiol esters, and in the alcoholysis of amides. In recent publications, the results of a study[5a] of the hydrolysis of a ketene *O,S*-acetal were employed in the assignment of the rate-limiting steps in the acid-catalyzed formation[5b] and hydrolysis[5a] of thiol esters. The present paper describes experiments with additional ketene *O,S*-acetals and with an unsymmetrical ketene *O,O*-acetal, and was designed to provide further information on the factors which control the pathways of breakdown of the intermediates formed in the hydrolysis and alcoholysis of esters and thiol esters. In the course of this research, kinetic data have been obtained which suggest the occurrence of a change in rate-determin-

ing step in the hydration of the carbon–carbon double bond of ketene *O,S*-acetals.

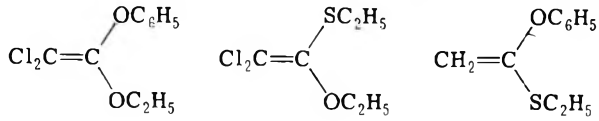
Results

Synthesis. Ketene *O,S*-acetals have been prepared by the addition of mercaptides to acetylenic ethers,[6] from ketene *O,O*-acetals,[7] by the additions of alkoxides to alkylthioacetylenes,[8] by the alkylation of thionoesters,[9] and from thiadiazoles.[10] The synthesis of **2**, by a method analogous to that used by McBee and Bolt[11] for halogenated ketene *O,O*-acetals, represents a new route, albeit of limited scope, to the preparation of certain ketene *O,S*-acetals.

$$CHCl_2CClF_2 + C_2H_5SH \longrightarrow CHCl_2CF_2SC_2H_5 \xrightarrow[C_2H_5OH]{KOH} CCl_2{=}C(OC_2H_5)SC_2H_5$$

8 2

Kinetic Studies. The rates of hydrolysis of three ketene acetals (1–3) under acidic conditions in predominantly



1 2 3

aqueous solutions were determined by spectrophotometric means (Table I).

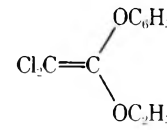
The hydrolysis of the ketene *O,O*-acetal **1** is catalyzed by acid and the rate increases linearly with acid concentration in the range of 0.08–0.8 *M* HCl. No evidence is seen for an uncatalyzed (or water-catalyzed) reaction at these acidities, although water-catalyzed reactions have been reported with reactive ketene acetals at high pH.[12-14]

The rate of hydrolysis of phenyl dichloroacetate, knowledge of which is needed to interpret the results of product analysis in the hydrolysis of **1**, was found to be essentially independent of acidity in the range of 0.83–10 *M* HCl (16.7% CH_3CN–H_2O, 30°, ionic strength equivalent to added acid) with $k_{obsd} = 1.8 \pm 0.2 \times 10^{-3}$ sec^{-1}. This observation does not necessarily mean, however, that the hydrolysis of phenyl dichloroacetate is not susceptible to acid catalysis. Under conditions of constant ionic strength, there is seen a small but definite increase of 28% in 0.96 *M* HCl over the pH-independent rate of $3.15 \pm 0.3 \times 10^{-3}$ sec^{-1} measured in the range of pH 1–5 (the latter value may be compared to that of 1.74×10^{-3} sec^{-} reported[15] for hydrolysis of phenyl dichloroacetate in H_2O, μ = 1.0, 25°). It is quite possible that a rate-decreasing effect of increasing ionic strength may mask the presence of weak acid catalysis, as was observed in the hydrolysis of, e.g., succinic[16a] and glutaric anhydrides.[16b] The detailed pH–rate profile for the hydrolysis of phenyl dichloroacetate (3.3% CH_3CN–H_2O, μ = 1.0 with added KCl, 30°, 15 pH values covering the range of pH 0–6) adheres accurately to the rate law $k_{obsd} = (8.3 \times 10^{-4}\ M^{-1}\ sec^{-1})\ [H^+] + 3.15 \times 10^{-3}$ sec^{-1}. For reasons set forth in the Discussion, the pH–rate profile for the hydrolysis of phenyl formate was also determined (1% CH_3CN–H_2O, μ = 1.0 with added LiCl, 30°, 23 pH values covering the range of pH 0–8) and was found to conform to the rate law $k_{obsd} = (3.8 \times 10^{-3}\ M^{-1}\ sec^{-1})\ [H^+] + (2.1 \times 10^3\ M^{-1}\ sec^{-1})\ [OH^-] + 4.8 \times 10^{-5}$ sec^{-1}.

The hydrolysis of the dichloroketene *O,S*-acetal **2** is subject to acid catalysis (Table I), the rate being approximately proportional to acid concentration in solutions of HCl or $HClO_4$ at < 1 *M*, and increasing much more rapidly than the stoichiometric acid concentration in more concentrated $HClO_4$ solutions. A plot of log k_{obsd} vs. the H_0 acidity function[17] is reasonably linear with a slope of 1.2, while a plot of log k_{obsd} vs. the H_c function (based on the protonation of azulenes, 1,1-diarylethylenes, and aromatic polyethers[18]) is similarly linear with a slope of 0.7. A similar dependence of rate on acidity has been reported for the hydration of styrenes,[19] where the use of the H_0 function gave slopes of 1.1–1.3, while plots using the H_R' scale (based on 1,1-diaryl olefins) had slopes of 0.59–0.68.

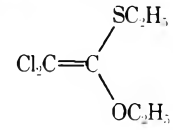
Rate measurements of the hydrolysis of **2** were not carried out at pH > 1 because the acid-catalyzed hydrolysis of

Table I
Rate Constants for Hydrolysis of Ketene Acetals at 30°



[HCl][a]	$k \times 10^3$, sec^{-1}	[HCl][a]	$k \times 10^3$, sec^{-1}
0.0833[b]	0.38	0.833[b]	3.30
0.21[b]	0.85	1.67	9.82
0.417[b]	1.63	3.33	36.5
0.624[b]	2.42		

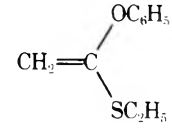
k_H[c] = 4.0×10^{-3} M^{-1} sec^{-1}



[HCl][d]	$k \times 10^3$, sec^{-1}
0.097	0.127
0.146	0.176
0.97	1.15

k_H[c] = 1.22×10^{-3} M^{-1} sec^{-1}

$[HClO_4]$[e]	$k \times 10^3$, sec^{-1}	$[HClO_4]$[e]	$k \times 10^3$, sec^{-1}
0.33	0.283	1.67	4.33
0.518	0.671	2.00	5.34
0.833	1.24	2.59	21.0
1.00	1.45	3.34	46.1
1.25	1.86	4.17	109.0
1.50	2.87	5.00	157.0



pH[f]	$k \times 10^3$, sec^{-1}	pH	$k \times 10^3$, sec^{-1}
2.32[g] (DCl)	75.9	4.48[h]	1.38
3.16 (HCl)	37.3	4.78[i]	0.791
3.36[g] (DCl)	7.03	5.04[h]	0.44
4.21[h]	2.56	5.43[h]	0.178

k_H[j] = 47.0 M^{-1} sec^{-1}, k_D = 16.0 M^{-1} sec^{-1}

[a] 16.7% CH_3CN–H_2O. [b] μ = 0.833 (KCl). [c] Based on hydrogen ion concentration; k_H is calculated from data at [HCl] ≤ 1 *M*. [d] 3.3% CH_3CN–H_2O, μ = 0.97 (LiCl). [e] 10% CH_3CN–H_2O. [f] 10% CH_3CN–H_2O, μ = 0.9 (LiCl). [g] pD = pH meter reading + 0.40. [h] Extrapolated to zero acetate buffer concentration. [i] Constant pH maintained with pH stat [T. C. Bruice and J. R. Maley, *Anal. Biochem.*, 34, 275 (1970)]. [j] Based on hydrogen ion activity.

Table II
Rate Constants for Hydrolysis of Ethyl Dichlorothiolacetate[a,b]

[HCl], M	$k_{obsd} \times 10^5$, sec^{-1}	[HCl], M	$k_{obsd} \times 10^5$, sec^{-1}
0.005	2.99	0.20	3.28
0.01	3.07	0.40	3.10
0.02	3.02	0.50	3.09
0.05	3.13	1.0	3.71
0.10	2.94	2.0	3.74
0.15	3.21	4.0	3.74

k_{av} = 3.25

[$HClO_4$]	$k_{obsd} \times 10^5$, sec^{-1}
1.85	2.07
3.75	1.84
6.95	1.99

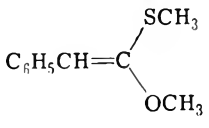
[a] 0.33% CH_3CN–H_2O, 30°. [b] Experiments in HCl solution at 0.005–1.0 M are at μ = 1.0 (LiCl).

the ketene acetal becomes slower than the further hydrolysis of both ethyl dichloroacetate (k_{H_2O} = 5 × 10^{-5} sec^{-1} at 25°)[20] and ethyl dichlorothiolacetate. The rate of hydrolysis of the latter compound is essentially constant over a wide range of acid concentration (Table II). These two esters are the expected products of the hydrolysis of **2**, and it is thus not possible to identify the initial products formed from **2** at pH > 3.

The more reactive ketene *O,S*-acetal **3** could be conveniently studied at pH 2–5. General acid catalysis is observed in acetate buffers, and the rate constants recorded in Table I are extrapolated to zero buffer concentration. At constant buffer ratio, there is a nonlinear dependence of k_{obsd} on acetate buffer concentration (Figure 1 and Table III).[21] Hydrolysis of **3** is slower in D_2O than in H_2O, with k_H/k_D = 3.0.

Products of Hydrolysis. Owing to the ready hydrolysis of phenyl dichloroacetate, the products of the hydrolysis of **1** were determined only in solution more acidic than 0.8 M HCl. In the range of 0.8–3.3 M HCl, the initial products of hydrolysis are phenol (and presumably ethyl dichloroacetate), formed in quantitative yield. This conclusion, based on the final absorbances at 280 nm, is supported by the observation that the hydrolysis of **1** in all cases showed no deviation from first-order kinetics. If appreciable amounts of phenyl dichloroacetate had been formed, the initially rapid hydrolysis of **1** would have been followed by the slower and easily measurable hydrolysis of phenyl dichloroacetate ($t_{1/2}$ 6.4 min).

The yield of thiol ester formed on hydrolysis of **2** rises from 4% in 0.33 N $HClO_4$ to a maximum of 34% in 3.0 N $HClO_4$, then decreases at higher acidity (Table IV). The low yields of thiol ester in dilute acid do not result from subsequent decomposition of initially formed thiol ester, since even in the least acidic solution, the ketene acetal **2** reacts ten times more rapidly than the thiol ester. The behavior of **2** is reminiscent of the hydrolysis[5a] of the phenylketene *O,S*-acetal **4** which showed increasing yields of thiol ester product as the pH was decreased from 3.0 to 1.0.



4

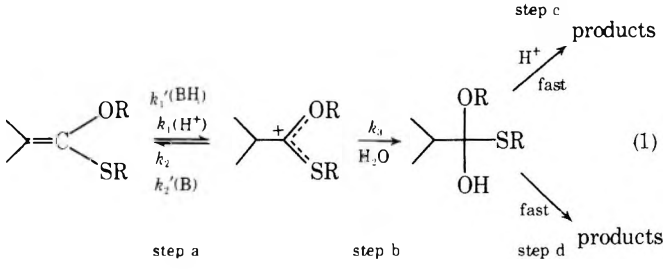
The predominant products of the hydrolysis of **3** are phenol and ethyl thiolacetate. These products, measured by uv spectroscopy, are formed in nearly 100% yield in HCl solution of pH 2–3. In dilute acetate buffers (ca. 0.02 M) at pH 4–5, the spectroscopic method indicates a small decrease in yield of the above products (to about 90%). This observation is corroborated by colorimetric assay for ethanethiol, using the Ellman procedure.[22] The formation of ethanethiol seems to be related to the presence of acetate buffer, and is under investigation.

Discussion

From previous studies, it is believed that the rate-determining step in the hydrolysis of ketene acetals is the protonation of the olefinic function by hydronium ion or general acids, including water.[5a,12-14,23,24] A similar mechanism has been ascribed to the hydrolysis of enol ethers.[25] It is probable that rate-controlling protonation also occurs in the hydrolysis of **1–3** in mineral acid solution, and in the presence of low concentrations of acetate buffers. This conclusion is supported by the observed catalysis by hydronium ion and acetic acid (see below), the sizable solvent deuterium isotope effect (with **3**), and the structural similarity of these compounds to ketene acetals studied earlier. The isotope effect (k_H/k_D = 3.0), which reflects the transfer of a proton in the transition state, may be compared to the values of 2.3–3.0 found for a series of ketene *O,O*-acetals.[14,23]

As expected, the hydrolysis of **1–3** follows the rate law $k_{obsd} = k_H[H^+]$ in dilute acidic solution, indicating the presence of a proton in the transition state. With **2**, the dependence of rate on acidity in perchloric acid solutions of 1–5 M is quite similar to that found in the hydration of styrenes,[19] for which the experimental evidence points strongly to a transition state which includes the hydrated proton.

The nonlinear dependence of rate on acetate buffer concentration (Figure 1) in the hydrolysis of **3** suggests that there occurs a change in rate-determining step with increasing buffer concentration, although other interpretations of the observed curvature are not ruled out by the available data.[26] It is proposed that the conversion of the ketene acetal to the carbonium ion intermediate (eq 1) is



(1)

accelerated as buffer concentration increases, until the reverse step k_2' becomes faster than the subsequent uncatalyzed hydration of the carbonium ion (step k_3). Similar nonlinear dependences of rate on buffer concentration have been frequently reported in nucleophilic addition to the carbonyl or imino group, and have been used as evidence for a change in rate-determining step.[27] Several instances are also known of nonlinear buffer catalysis in electrophilic substitution at the carbon–carbon double bond. In addition to the hydrolysis of **3** and **4**,[5b] downward curvature in plots of k_{obsd} vs. buffer concentration has been reported in the hydrolysis of a vinyl ether,[28] and in the hydrolysis[23] and methanolysis[29] of ketene *O,O*-acetals, and may result from a change in rate-determining step.

If the nonlinear buffer effect on the hydrolysis of **3** is

Table IV
Effect of Acidity on Yield of Thiol Ester Formed in Hydrolysis of 2[a]

$[HClO_4]$	% thiol ester	$[HClO_4]$	% thiol ester
0.333	4.1	3.34	28.8
0.517	8.2	4.17	22.1
0.833	12.1	5.00	20.9
1.00	15.8	6.26	17.7
1.25	19.5	0.313[b]	26.1
1.50	25.8	0.626[b]	25.5
1.67	29.4	1.25[b]	24.8
2.00	33.0	1.88[b]	23.6
2.50	33.4	2.50[b]	22.2
3.00	34.2	3.13[b]	20.9

[a] 10% CH_3CN–H_2O, 30°. [b] μ = 6.26 ($NaClO_4$).

taken as evidence for the existence of a carbonium ion intermediate whose formation is rate limiting at low acetate buffer concentration, and whose hydration becomes rate determining at high buffer concentration, the rate data may be analyzed further. In what follows, some quantitative conclusions concerning the partitioning of the carbonium ion intermediate are presented, keeping in mind the tentative nature of this analysis.

Application of the steady-state approximation to the carbonium ion (eq 1) leads to eq 2 for the dependence of k_{obsd} on buffer concentration ($[B_t] = [BH] + [B]$; $K_a = [B][H^+]/[BH]$). Both at zero buffer concentration (eq 3) and at infinitely high buffer concentration (eq 4), k_{obsd} is proportional to $[H^+]$. The initial slopes of plots of k_{obsd} vs. B_T depend on the mole fraction of buffer in the acidic form (eq 5), and the effectiveness of the buffer may be described by a constant, K_{app}, which is equal to the concentration of buffer required to produce half the maximum possible rate increase (eq 6).

$$k_{obsd} = \frac{\left(k_1[H^+] + \frac{k_1'[H^+]B_T}{[H^+] + K_a}\right)\frac{k_3}{k_2'}\left(\frac{[H^+] + K_a}{K_a}\right)}{\left(\frac{k_2 + k_3}{k_2'}\right)\left(\frac{[H^+] + K_a}{K_a}\right) + B_T} \quad (2)$$

$$k_{obsd} = \frac{k_1k_3[H^+]}{k_2 + k_3} \quad (3)$$

$$k_{max} = \frac{k_1k_3[H^+]}{k_2} \quad (4)$$

$$k_{obsd} = \left(\frac{k_1'k_3}{k_2 + k_3}\right)\left(\frac{[H^+]}{[H^+] + K_a}\right)B_T = \left(\frac{k_1'k_3(1 - \alpha)}{k_2 + k_3}\right)B_T \quad (5)$$

$$K_{app} = \left(\frac{k_2 + k_3}{k_2'}\right)\left(\frac{[H^+] + K_a}{K_a}\right) = \frac{k_2 + k_3}{k_2'\alpha} \quad (6)$$

Values of k_{max} and K_{app} were obtained at four buffer ratios by computer fitting of the data of Figure 1 to the equation for the two-parameter rectangular hyperbola (Table V).[31] The calculations given in Table V sugggest that the effect of acetate buffer in the hydrolysis of **3** conforms approximately to eq 1 and 2. The reason for the lack of constancy of the terms listed in columns 4, 6, and 8 is not clear, and may result from the gradual variation in pH observed on serial dilution of acetate buffers of constant buffer ratios. Taking the average value of $k_{max}/[H^+]$ as 5200 M^{-1} sec^{-1} and $k_1k_3/(k_2 + k_3)$ = 47 M^{-1} sec^{-1} (Table I) leads to a value of 110 for k_3/k_2, which describes the partitioning of the carbonium ion between hydration and proton abstraction. Using previously obtained[5] data on the effect of formate buffer in the hydrolysis of **4** (k_{max} = ca. 0.136 sec^{-1} at pH 3.0) gives an estimate of k_3/k_2 = 11 for that compound. The lower value of k_3/k_2 with **4** (uncorrected for a statistical factor of 2) may reflect (a) the increased driving force for proton abstraction in the case where the developing double bond is conjugated with the β-phenyl substituent, and (b) the greater steric requirements for proton abstraction from **3**.

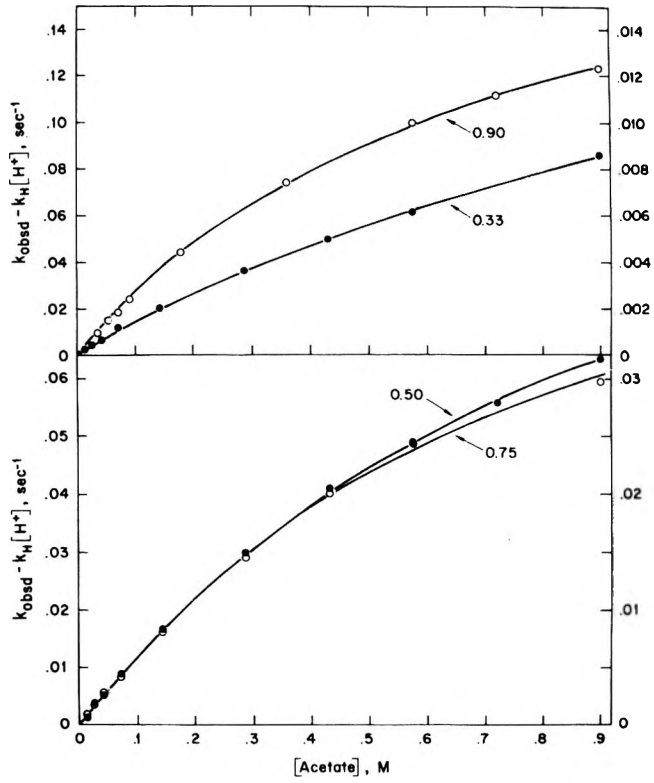


Figure 1. Effect of acetate buffer on the rate of hydrolysis of **3**: ●, left ordinate; ○, right ordinate. The mole fraction of buffer in the free base form is shown. The solid lines are calculated from the expression $k_{obsd} - k_H[H^+] = (k_{max} - k_H[H^+])[buffer]/([buffer] + K_{app})$, using the values of k_{max} and K_{app} in Table V and k_H = 47 M^{-1} sec^{-1}.

Where comparison to other compounds can be made, the observed reactivities of **1**–**3** and **4** (k_H = 12 and 36 M^{-1} sec^{-1} for the two geometric isomers) are reasonable. For example, replacement of the ethoxy group of ethyl vinyl ether by phenoxy reduces the rate of hydrolysis by 530.[25] Similarly, the reactivities of dichloroketene diethyl acetal[14] (25°) and **1** (30°) are in the ratio of 850:1. Also, comparison of the reactivities of ethyl vinyl ether and ethyl styryl ether (both in 80% dioxane) shows that β-phenylation causes a decrease in rate of about 500-fold,[32] while β-dichlorination reduces the rate of hydrolysis by 10^8.[14,25] It follows that replacement of the β-phenyl substituent in vinyl ethers by the dichloro group inhibits reaction by a factor of about 2×10^5. This effect may be compared to the relative reactivities of **4** and **2**, which are in the ratio of $1–3 \times 10^4$. Finally, the similar reactivities of **1** and **2** suggest that replacement of an alkoxy group of a ketene dialkyl acetal by either a phenoxy or an alkylthio function would result in an equivalent decrease in hydrolytic rate of about 10^3, presumably as a result of decreased stabilization of the carbonium ion-like transition state by the electron-withdrawing substituents.

Partitioning of Tetrahedral Intermediates. The products of hydrolysis of the ketene *O,S*-acetal **2** vary with acidity in a manner reminiscent of the behavior of **4**,[5a] though the change in products takes place in more acid solutions (Figure 2). The absence of a correlation between the

Table V
Summary of Parameters for Acetate-Catalyzed Hydrolysis of 3[a]

pH	Intercept $\times 10^3$,[b] sec^{-1}	Initial slope[b] M^{-1} sec^{-1}	Initial slope[c] $/(1-\alpha)$	k_{max},[d] sec^{-1}	$10^{-3}\ k_{max}/[H^+]$, M^{-1} sec^{-1}	K_{app},[e] M	$K_{app}\ \alpha$,[c] M
4.21	2.56	0.146	0.22	0.24	3.9	1.65	0.54
4.48	1.38	0.130	0.26	0.14	4.2	1.05	0.52
5.04	0.44	0.070	0.28	0.06	6.6	0.85	0.64
5.43	0.178	0.030	0.30	0.023	6.2	0.77	0.69

[a] 10% CH_3CN–H_2O. μ = 0.90 (LiCl), 30°. [b] Intercept and initial slope of plots of k_{obsd} vs. total buffer concentration (Figure 1). [c] α = mole fraction acetate ion. [d] Extrapolated rate constant at infinite buffer concentration. [e] See eq 6.

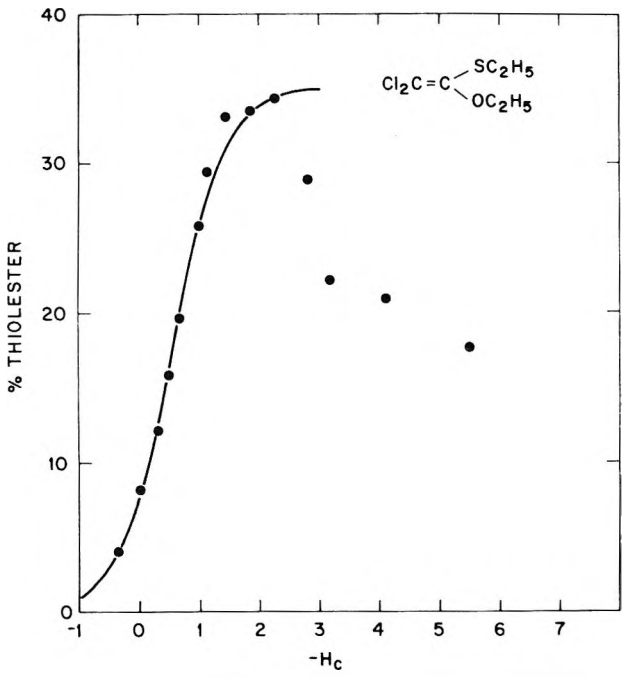
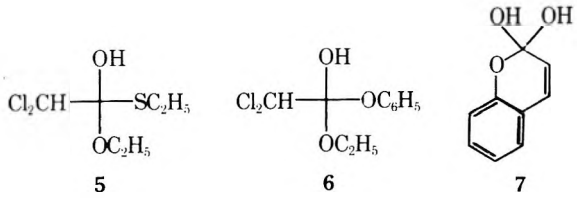


Figure 2. Effect of perchloric acid concentration on the yield of thiol ester formed on hydrolysis of **2**. The line is the calculated titration curve of an acid of pK −0.55, with asymptotes at 0 and 35%.

effect of changing acidity on products and on reaction rate (the plot, not shown, of log k_{obsd} vs. H_c is linear) is evidence for an intermediate whose breakdown to products is acidity dependent. The dependence of the thiol ester yield on H_c at [$HClO_4$] < 3 M is approximately sigmoid with a midpoint at 1.0–1.2 M $HClO_4$. As has been suggested[5a] for **4**, it is likely that a neutral tetrahedral adduct **5** expels predominantly mercaptan and accounts for the products formed at pH > 0. At higher acidity, protonation of **5** yields a cationic intermediate which expels 35% ethanol and 65% ethyl mercaptan. The observed product mix presumably reflects the interplay between the better leaving ability of the protonated thioether group and its lower concentration, relative to the protonated alcohol function.[33] That the product transition with **2** occurs at higher acidity than that of **4** (product transition at pH 1.66) is consistent with the greater acidity of the cationic intermediate derived from **2**. The relatively low yield of thiol ester obtained from **2** in acid (no more than 35%) continues a trend noted earlier which indicates that the partitioning of cationic intermediates related to **5** increasingly favors mercaptan expulsion as electron withdrawal in the acyl group increases.[36] The gradual decrease in thiol ester yield at [$HClO_4$] > 3 M does not seem to be as ionic strength effect (Table IV), but more likely results from the changing relative basicities of ethers and sulfides in concentrated acids.[35] The much greater solvation requirements of the protonated ether favor protonation of the thioether function in strongly acidic media, and may thus affect the partitioning of the cationic intermediate.



Unlike the hydrolysis of methyl thiolformate[5a] and a thiolactonization reaction,[5b] the hydrolysis of ethyl dichlorothiolacetate gives no clear evidence for a change in rate-determining step in acidic solution (Table II). This means either (a) that the tetrahedral intermediate expected to be formed by addition of water to the thiol ester carbonyl group behaves differently from its O-methyl analog derived from **2**; (b) that experimental scatter conceals the at best small deviation from a simple rate law of the type $k_{obsd} = k_H[H^+] + k_{H_2O}$ which would reveal the change in rate-limiting step; or (c) that the rate measurements on the thiol ester, carried out in HCl solutions, are not directly comparable to the product study done in $HClO_4$ for the hydrolysis of **2**.

Although measurements could be made only over a limited range of acidity (0.8–3.3 M HCl), the hydrolysis of **1** was found to yield predominantly phenol as the initial product. Though no direct experimental support is available, it is probable that the hydrolysis of **1** proceeds via tetrahedral intermediates also, so that the mode of breakdown of **6** (and/or of its cationic form) consists solely of the expulsion of phenol. This is in contrast to the pathway of breakdown of the related intermediate **7** derived from coumarinic acid, which expelled phenol from a neutral intermediate and water from the cationic species, with a transition at pH 1–3, depending on the nature of the aromatic substituent.[37] On the other hand, the pH–rate profiles for the hydrolysis of phenyl formate and phenyl dichloroacetate showed no evidence for intermediates at acid pH, suggesting either that intermediates are not formed in these reactions, or, more likely, that the partitioning of the intermediates and hence the nature of the rate-limiting step do not vary significantly over the pH range examined.

The acidic hydrolysis of two unsymmetrical ketene O,O-acetals (2-ethoxydihydropyran and 2-ethoxy-4-methyldihydropyran) has been reported to yield exclusively the ring-opened products. These selective reactions have been ascribed to stereoelectronic control of the decomposition of the tetrahedral intermediates.[38]

Assuming that the hydrolysis of **3** also proceeds via a tetrahedral adduct, it appears that the departure of phenol competes successfully with that of ethyl mercaptan in the range of pH 2–5, possibly from a neutral intermediate analogous to **5**. No conclusions can be drawn concerning the pathways of breakdown of cationic or anionic species of the

intermediate, though the preliminary observations that acetate buffers enhance the expulsion of mercaptan suggest that a change in products may occur at higher pH.

Two different types of evidence indicate the participation of intermediates in the hydrolysis of ketene acetals. (a) The nonlinear effect of buffers on the rate of hydrolysis suggests that a step which is susceptible to buffer catalysis at low buffer is followed by a step which is not catalyzed by buffer and which becomes rate determining at high buffer. The intermediate formed in the first step is presumably a carbonium ion. (b) The independent influences of acidity on the rates and products of the reaction indicate that the product-determining step is different from the rate-determining step. While it is in principle conceivable that the direct conversion of the carbonium ion to products might be pH dependent, it seems chemically more reasonable to postulate that hydration of the carbonium ion to a tetrahedral intermediate is followed by the pH-dependent transformation to products (eq 1). According to this proposal, step a is rate determining when BH = H_3O^+ or H_2O, and at low buffer concentration; step b becomes rate determining at high buffer, and steps c and d are product determining. It seems unlikely that attack of solvent on the carbonium ion would lead directly to ester or thiol ester. While thiol ester formation by direct displacement on the R group of the OR substituent is possible, the kinetically favored process is nucleophilic addition to the electron-deficient central carbon atom.[39]

Experimental Section

2,2-Dichloro-1-ethoxy-1-phenoxyethylene (1) was prepared from 1,1-difluoro-1,2,2-trichloroethane (Pierce Chemical Co.) according to McBee and Bolt:[11] NMR (neat) δ 1.05 (3 H, t), 3.75 (2 H, q), 7.1 (5 H, m); uv max (CH_3CN) 271.5 nm (ϵ 640), 265 (820), 259 (710); mass spectrum molecular ion at *m/e* 232.

2,2-Dichloro-1-ethoxy-1-ethylthioethylene (2). A. 2,2-Dichloro-1,1-difluoro-1-ethylthioethane (8) was prepared by a modification of the procedure of McBee and Bolt.[11] To a suspension of 8.3 g (0.1 mol) of sodium ethylmercaptide in 75 ml of ether–25 ml of acetonitrile was added dropwise 17 g (0.1 mol) of 1,1-difluoro-1,2,2-trichloroethane, and the reaction mixture was stirred overnight. After filtration, the product was obtained as a colorless liquid by fractional distillation: yield 13 g; bp 35–37° (1.3 mm); NMR (CCl_4) δ 1.35 (3 H, t), 2.95 (2 H, q), 5.80 (1 H, t). Anal. Calcd for $C_4H_6Cl_2F_2S$ (195.07): C, 24.62; H, 3.10; Cl, 36.65; S, 16.44. Found: C, 24.82; H, 3.14; Cl, 36.24; S, 16.69.

B. Conversion of **8** to **2** was accomplished by heating a solution of 7 g (0.036 mol) of **8** and 14 g of KOH in 150 ml of ethanol for 24 hr at reflux temperature. After cooling, the reaction mixture was diluted with 200 ml of water and extracted with three 100-ml portions of chloroform. The pooled $CHCl_3$ extracts were dried over anhydrous Na_2CO_3 and distilled at reduced pressure. Redistillation of the fraction boiling at 44–45° (0.2 mm) gave 5 g (69% yield) of a colorless liquid whose ir spectrum was free of carbonyl absorption at 5–6 μ: bp 39° (0.1 mm); NMR (neat) δ 1.25 (6 H, m), 2.75 (2 H, q), 3.9 (2 H, q); uv max (CH_3CN) 257 nm (ϵ 5560); mass spectrum molecular ion at *m/e* 201. Anal. Calcd for $C_6H_{10}Cl_2OS$ (201.12): C, 35.82; H, 5.02; Cl, 35.26; S, 15.94. Found: C, 36.14; H, 5.19; Cl, 34.78; S, 15.54.

1-Ethylthio-1-phenoxyethylene (3). β-Chlorophenetole was converted[40] to phenyl vinyl ether, which was brominated to yield 1,2-dibromo-1-phenoxyethane (**9**), bp 92–98° (0.7–1.0 mm) [lit.[41] bp 129–130° (12 mm)]. To 250–300 ml of liquid NH_3 (Dry Ice) was added 300 mg of $FeCl_3$ followed by 0.5 g of sodium. When a black precipitate had formed, 6.9 g of sodium was added, followed by (after 30 min) 12 g (0.043 mol) of **9**. The solution was stirred for 2 hr and 15 g of ethyl mercaptan was added dropwise over 1 hr. After stirring for 2 hr in a Dry Ice–acetone bath, NH_3 was allowed to evaporate and the reaction flask was flushed with nitrogen overnight. The residue was dissolved in 200 ml of ice water and extracted with five 50-ml portions of ether. The pooled extracts were dried over K_2CO_3 and distilled at reduced pressure, yielding **3** as a faintly yellow liquid (1.8 g, 23%): bp 60–63° (0.3 mm) [lit.[6c] bp 89° (3 mm)]; uv (CH_3CN) λ_{max} 274 nm (ϵ 600), 268 (840), 241 (3600); NMR ($CDCl_3$) δ 1.23 (3 H, t), 2.7 (2 H, q), 4.75 (2 H, m), 7.0 (5 H, m); mass spectrum molecular ion at *m/e* 180.

Phenyl dichloroacetate[15] had mp 47–48°. The preparation of **ethyl dichlorothiolacetate** has been previously described.[36] **Phenyl formate**,[42] prepared using formic–acetic anhydride,[43] had bp 106–108° (70 mm) [lit.[44] bp 90° (30 mm)]. 3,3′-Dithiobis(6-nitrobenzoic acid) was recrystallized from ethyl acetate–ligroin.

Kinetic Methods. Acetonitrile was purified as previously described.[36] Buffers and inorganic salts were of reagent grade and were used without further purification. Glass-distilled water was employed in the preparation of all solutions. D_2O (99.7% D) was obtained from Merck Sharpe and Dohme of Canada.

Stock solutions of the ketene acetals (10^{-2}–10^{-3} *M*) were prepared in dry acetonitrile immediately after synthesis and contained ca. 10^{-3} triethylamine. The rates of hydrolysis of **1**–**3** at 30° in the solvents given in the footnotes to Table I were determined spectrophotometrically by the changes in absorbance at 280, 250, and 270 nm for **1**, **2**, and **3**, respectively. Concentrations of the ketene acetals were 1–2 × 10^{-4} *M*. Reactions were initiated by the addition of a small volume (<0.5 ml) of stock solution of the ketene acetal to the aqueous buffer equilibrated at 30° in the cell compartment of a Cary 15 spectrophotometer. Reactions were followed for at least 3 half-lives and generally for more than 6. The absorbance change involved in the hydrolysis of **1** and **3** was only 0.05–0.1 units, requiring the use of the expanded scale of the Cary spectrophotometer. Rate constants were calculated as previously described.[36]

The hydrolysis of phenyl dichloroacetate and phenyl formate (under the conditions stated in the Results section) were followed at 30° by the increase in absorbance at 270 nm, with ester at 5–6 × 10^{-4} *M*. The details of the hydrolysis of ethyl dichlorothiolacetate have been previously reported.[36]

Product Analysis. The yield of phenol formed on hydrolysis of **1** (10^{-4} *M*) was determined from the infinity absorbance reading of each kinetic experiment at 280 nm where neither ethyl dichloroacetate nor phenyl dichloroacetate have a measurable absorbance at the concentration employed. The release of phenol was found to be invariably first order. The absorbance expected for 100% formation of phenol is about 0.07 units.

The yield of ethyl dichlorothiolacetate produced on hydrolysis of **2** (at 3.5 × 10^{-4} *M*) was based on the measurement of the absorbance at 250 nm after 6 or more half-lives of reaction. At this wavelength, ϵ_{max} for the thiol ester is 4500 and no other product has significant absorbance.

Complete spectra taken on completion of the hydrolysis of **3** (1.5 × 10^{-4} *M*) at pH 2–3 (HCl) were identical with those of an equimolar mixture of ethyl thiolacetate and phenol. When hydrolysis was carried out at pH 4–5 (0.02 *M* acetate buffer), the decreases in the absorption maxima at 235 nm (thiol ester) and 270 nm (phenol) suggested that the yields of phenol and thiol ester were about 90%. Assay of the reaction mixtures using a modification of the Ellman procedure[22] and L-cysteine as a standard indicated a yield of 8–10% of thiol, under conditions where ethyl thiolacetate is stable to hydrolysis.

Acknowledgments. We are grateful to Mr. Tad S. Stashwick for assistance with some of the kinetic experiments and to Mr. John E. Garst for improving the synthesis of 3.

Registry No.—**1**, 55913-32-1; **2**, 55913-33-2; **3**, 25195-35-1; **8**, 5187-60-0; **9**, 42220-93-9; 1,1-difluoro-1,2,2-trichloroethane, 354-21-2; sodium ethylmercaptide, 811-51-8; ethyl dichlorothiolacetate, 41880-03-9.

Supplementary Material Available. Table III will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2940.

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Carbon-13 CIDNP during Photolysis of Di-*tert*-butyl Ketone in Carbon Tetrachloride[1]

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Received February 27, 1975

Carbon-13 Fourier transform (FT) NMR was used to observe CIDNP during the photolytic decomposition of di-*tert*-butyl ketone in CCl_4. Recombination of the triplet *tert*-butyl–pivaloyl radical pair (I) was unambiguously established. The polarizations from 2,2-dimethylpropanal (1) and 2,2-dimethylpropanoic acid chloride (3) also result from triplet radical pair I. Other polarized products may come from singlet or triplet radical pair precursors. The observed polarization signs agreed with those predicted for all identified products.

The use of carbon-13 FT NMR to study CIDNP holds great promise as a mechanistic and kinetic tool for the investigation of radical reactions.[2] The major advantages of studying carbon-13 CIDNP are the large chemical shift range and the ability to make all carbons appear as singlets by proton decoupling. In addition, FT NMR techniques enable the entire spectrum to be recorded in a matter of seconds.

As part of our program of defining the pathways of material degradation, we have examined by carbon-13 FT NMR the CIDNP during the photochemical decomposition of di-*tert*-butyl ketone (DTBK) in CCl_4. Analysis of the polarization signs provided insight into the various degradation steps and the multiplicities of radical pair precursors. Proton CIDNP during the photolysis of DTBK has been previously studied using continuous-wave NMR.[3]

Results

Figure 1 shows proton decoupled carbon-13 FT NMR spectra of a 25% DTBK solution in CCl_4 obtained before, during, and after irradiation. The center spectrum, obtained during the first 1000 sec of photolysis, shows emis-

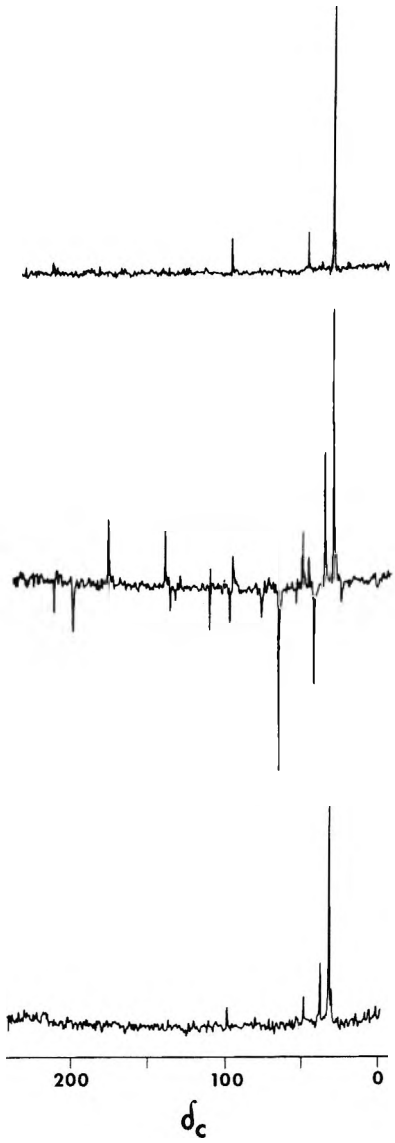


Figure 1. Proton decoupled carbon-13 FT NMR spectra of a 25% DTBK solution in CCl_4 obtained before (top), during (middle), and after (bottom) irradiation. The spectra width is 250 ppm. For each spectrum 100 free induction decays were accumulated at a pulse repetition time of 10 sec.

sion and enhanced absorption signals. These CIDNP signals were assigned to particular carbon atoms by comparing their chemical shifts to those of authentic compounds (Table I). Assignments were aided by observing the carbon–hydrogen splitting patterns in proton coupled spectra. In addition, the proton coupled CIDNP spectra ensured that signals were not being lost in the decoupled spectra due to the exact cancellation of any multiplet effects.

Emission signals occur from C-3 of DTBK, C-1 and C-2 of 2,2-dimethylpropanal (**1**), C-1 of methylpropene (**2**), C-2 of 2-chloro-2-methylpropane (**4**), and $CHCl_3$. The emission signal at 23.9 ppm may be assigned to C-3 of either aldehyde **1** or olefin **2**. Enhanced absorption signals are observed for C-2 of olefin **2**, C-1 of chloride **4**, and all the carbons of 2,2-dimethylpropanoic acid chloride (**3**). Although the signals from C-1 and C-2 of DTBK were affected during photolysis, it was difficult to tell if absorption or emission was occurring because of contributions from unreacted DTBK. Other CIDNP signals of lower intensity were not assignable. The spectrum recorded after photolysis, using the same number of spectral accumulations, contained only signals attributable to C-1 and C-2 of DTBK, C-3 of acid chloride **3**, and C-1 of chloride **4**. Additional signal averaging revealed peaks assigned to $CHCl_3$ and C_2Cl_6.

Table I
Carbon-13 Chemical Shifts of Products Showing CIDNP During the Photolysis of DTBK in CCl_4[a]

Product	Carbon position	Chemical shift, ppm: During photolysis[b]	Chemical shift, ppm: Authentic product[c]
DTBK	1	28.5[d]	28.5
	2	45.3[d]	45.2
	3	215.2 (E)	215.1
1	1	202.4 (E)	202.2
	2	42.2 (E)	42.5
	3	23.9 (E)[e]	24.0
2	1	110.7 (E)	110.6
	2	140.8 (A)	140.7
	3	23.9 (E)[e]	23.8
3	1	178.6 (A)	178.6
	2	48.9 (A)	49.0
	3	27.1 (A)	27.1
4	1	34.5 (A)	34.5
	2	65.7 (E)	65.6
$CHCl_3$	1	77.2 (E)	77.1

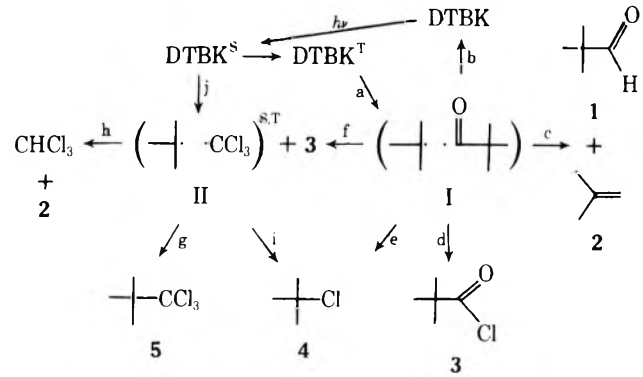
[a] Chemical shifts converted to Me_4Si scale using $\sigma_{Me_4Si} = \delta_{CCl_4} + 96.0$. [b] A = enhanced absorption; E = emission. Unassigned CIDNP signals occurred at 137.8 (E), 111.4 (E), 111.1 (A), 103.4 (E), 98.1 (E), 53.8 (E), 49.7 (A). [c] 25% solutions in CCl_4. [d] Although the intensity of this peak was affected, it was difficult to tell if enhanced absorption or emission was occurring because of signal contribution from unreacted DTBK. [e] This signal may be assigned to C-3 of **1** or **2**.

Products **1**, **3**, **4**, $CHCl_3$, C_2Cl_6 as well as 1,1,1-trichloro-2,2-dimethylpropane (**5**), HC_2Cl_5, and C_2Cl_4 were identified by GC–MS analysis.

Discussion

Interpretation of the polarization signs in terms of the CKO theory[4] of CIDNP suggested the mechanistic pathways shown in Scheme I. All the polarization signs may be

Scheme I



rationalized by initially invoking the triplet *tert*-butyl–pivaloyl radical pair (I). Some of the polarizations, however, are also consistent with reaction from the singlet *tert*-butyl–trichloromethyl radical pair (II).

The polarizations from DTBK, aldehyde **1**, and acid chloride **3** must result from triplet pair I. Olefin **2** and chloride **4** may come from I, from triplet pair II formed by pair substitution[5] (eq f), or from singlet pair II formed by a singlet exciplex reaction (eq j). In addition, trichloropropane **5** and $CHCl_3$ may result from the singlet or triplet pair II.

Table II
Evaluation of Kaptein's Expression for Products Formed During Photolysis of DTBK in CCl_4[a]

Product	Carbon position	Radical formation eq[c]	Radical formation μ	Product formation eq[c]	Product formation ϵ	Δg[d]	A	Polarization[b] Calcd	Polarization[b] Exp
DTBK	1	a	+	b	+	+	−	E	*e*
	2	a	+	b	+	+	+	A	*e*
	3	a	+	b	+	−	+	E	E
1	1	a	+	c	+	−	+	E	E
	2	a	+	c	+	−	+	E	E
	3[f]	a	+	c	+	−	+	E	E
2	1	a	+	c	+	+	−	E	E
		f	+	h	+	+	−	E	E
		j	−	h	+	−	−	E	E
	2	a	+	c	+	+	+	A	A
		f	+	h	+	+	+	A	A
		j	−	h	+	−	+	A	A
	3[f]	a	+	c	+	+	−	E	E
		f	+	h	+	+	−	E	E
		j	−	h	+	−	−	E	E
3	1	a	+	d	−	−	+	A	A
	2	a	+	d	−	−	+	A	A
	3	a	+	d	−	−	+	A	A
4	1	a	+	e	−	+	−	A	A
		f	+	i	−	+	−	A	A
		j	−	i	−	−	−	A	A
	2	a	+	e	−	+	+	E	E
		f	+	i	−	+	+	E	E
		j	−	i	−	−	+	E	E
5	1	f	+	g	+	−	+	E	*g*
		j	−	g	+	+	+	E	*g*
	2	f	+	g	+	+	+	A	*g*
		j	−	g	+	−	+	A	*g*
	3	f	+	g	+	+	−	E	*g*
		j	−	g	+	−	−	E	*g*
$CHCl_3$	1	f	+	h	+	−	+	E	E
		j	−	h	+	+	+	E	E

[a] μ is + for triplet pairs and pairs formed from free radical encounters, − for singlet pairs; ϵ is + for cage products, − for escape products; Δg is + for the radical with the larger g factor, − for the radical with the smaller g factor. [b] A = enhanced absorption; E = emission. [c] Equations of Scheme I. [d] g(pivaloyl) = 2.0008;[16] g(*tert*-butyl) = 2.0026;[16] $g(\cdot CCl_3)$ = 2.0091.[17] [e] See Table I, footnote *d*. [f] See Table I, footnote *e*. [g] The chemical shifts of these carbons have not been determined. However, an emission signal was observed in the region where C-1 would be expected to appear (see ref 8).

Table II evaluates Kaptein's expression,[6] $\Gamma = \mu\epsilon\Delta gA$, for the reaction products formed by the indicated pathways. The four terms determine the sense of the polarization. Thus, Γ is positive for enhanced absorption and negative for emission. The multiplicity of the radical pair is given by μ, the type of product-forming reaction is taken into account by the ϵ term, Δg is the sign of the spectroscopic splitting factor difference, and the sign of the electron-nuclear hyperfine interaction constant, A, directly enters the expression.

Triplet Reactions. Spin selection originating in triplet pair I can rationalize the polarization signs for all identified products. Triplet DTBK undergoes α-cleavage (eq a) to form I, which may recombine (eq b), disproportionate (eq c), lead to escape products (eq d, e), or produce triplet pair II by pair substitution[5] (eq f). Pair II may also collapse (eq g), disproportionate (eq h), or lead to escape products (eq i).

Although all the carbons of DTBK are being affected during photolysis, the emission of C-3 is most distinctive. This emission must result from collapse of triplet radical pair I to regenerate starting DTBK (eq b). Carbon-13 CIDNP provides unambiguous evidence that recombination is occurring. This information is difficult to obtain by other photochemical methods. Furthermore, proton CIDNP studies[3] were unable to reveal this reaction, except under stationary nutation conditions.[7]

Table II shows that the polarization from all the carbons of aldehyde 1 can only result from the disproportionation of triplet radical pair I (eq c). Olefin 2 produced in this same process also shows agreement between the experimental and predicted polarization signs. The polarization of all the carbons of chloride 4 and acid chloride 3 are consistent with spin sorting in triplet radical pair I. Escape of the *tert*-butyl and pivaloyl radicals from this cage followed by abstraction of chlorine from solvent would lead to the observed polarizations (eq d, e).

Triplet pair I may undergo pair substitution[5] to give pair II. In this process one of the members of pair I (most probably the more reactive pivaloyl radical) reacts with CCl_4 and is quickly replaced by the trichloromethyl radical. Since spin multiplicity is conserved in this step, new pair II retains triplet character.

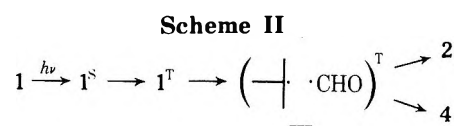
The product from cage collapse of pair II (eq g) is trichloropropane 5. Although an authentic sample of 5 was not available, there is a weak emission signal in the trichloromethyl carbon region which could be assigned to C-1 of 5.[8] The production of 5 was confirmed by GC–MS analysis. The emission signal of $CHCl_3$ (eq h) may also be rationalized by this pair substitution mechanism. Unfortunately, the polarization predictions for olefin 2 and chloride 4 are the same for reactions from triplet pair I or triplet pair II, making a definite mechanistic choice impossible.

Singlet Reactions. It has been shown that photoexcitation of *tert*-butyl ketones leads to both singlet and triplet reactive states.[9] More recent evidence points to formation of a singlet exciplex species when the solvent is CCl_4.[3a,10] Scheme I illustrates the decomposition pathways from a singlet DTBK–CCl_4 exciplex.[11] Simultaneous α-cleavage and chlorine abstraction leads selectively to the *tert*-butyl–trichloromethyl radical pair (II), which still retains singlet character (eq j). The acid chloride (3) produced in this reaction is not expected to be polarized.[10a] As Table II shows, the polarization signs from products 2, 4, 5, and $CHCl_3$ are predicted to be the same for singlet pair II or a triplet pair II formed by pair substitution and a choice between these two radical pairs cannot be made on the basis of these CIDNP results alone.

Other Reactions. In order to see if secondary photochemical reactions were contributing to the observed polarizations, solutions of compounds 1, 2, 3, and 4 in CCl_4 were photolyzed in the spectrometer.[12]

Aldehyde 1 readily photolyzed and gave rise to major CIDNP signals assigned to C-2 (A) of olefin 2, C-1 (A) and C-2 (E) of chloride 4. These polarizations are consistent with reaction from triplet radical pair (III) formed by C–C cleavage (Scheme II). Disproportionation of triplet pair III

Scheme II



III

produces olefin 2 with C-2 in enhanced absorption while escape of *tert*-butyl radicals followed by abstraction gives polarized chloride 4. The polarization signs are identical with those obtained from the photolysis of DTBK and indicate a

possible complexity in the quantitative analysis of these CIDNP intensities.

Polarizations from the carbons of olefin **2** were not observed during irradiation of **2**. Likewise, CIDNP signals were not detected during the photolysis of acid chloride **3** or chloride **4** under the reaction conditions.

Experimental Section

All chemicals were commercially available and were used without further purification. Solutions were deaerated by a stream of high-purity nitrogen. The products of the photolysis were identified with a Hewlett-Packard Model 5700A/5930A GC–MS system in addition to carbon-13 chemical shifts.

Carbon-13 NMR Measurements. Carbon-13 NMR spectra were obtained at 25.15 MHz on a Varian HA-100 spectrometer modified for pulsed operation and equipped with an external fluorine-19 field-frequency lock.[13] Free induction decays were accumulated and Fourier transformed with a NIC-80 data system. Typically, 100 free induction decays were accumulated using a pulse interval of 10 sec. A 90° pulse took 130 μsec. The probe temperature was 44 ± 2° and 7.5 mm o.d. quartz sample tubes were used. Identical phase corrections were applied to spectra obtained before, during, and after irradiation. Chemical shifts were assigned by comparison with spectra of authentic compounds, which were run as 25% solutions in CCl_4. Chemical shifts were converted to the Me_4Si scale using $\delta_{Me_4Si} = \delta_{CCl_4} + 96.0$.

Photolysis Experiments. Light from a 600-W Hg–Xe arc source was focused through a water filter, Corning filters no. CS-056 and CS-954, and onto the polished end of a quartz rod which terminated 1 mm from the bottom of the sample tube. The combined Corning filters had a measured transmittance of greater than 50% at wavelengths longer than 290 nm and less than 1% at wavelengths shorter than 250 nm. Deaerated 25% solutions of DTBK in CCl_4 were used in the photolysis experiments. For the photolysis of compounds **1**, **2**, **3**, and **4**, 10% solutions were used.

INDO Calculations. The signs of the electron–carbon hyperfine interaction constants for the pivaloyl and *tert*-butyl radicals were obtained using the INDO semiempirical method.[14] Standard geometries were assumed and QCPE program 142 was used for the calculations. All the $A(C^{13})$'s for the pivaloyl radical were calculated to be positive while for the *tert*-butyl radical $A(C^{\alpha})$ is positive and $A(C^{\beta})$ is negative. The $A(C^{13})$ for the trichloromethyl radical is positive.[15]

Registry No.—**1**, 630-19-3; **2**, 115-11-7; **3**, 3282-30-2; **4**, 507-20-0; **5**, 56087-10-6; DTBK, 815-24-7; $CHCl_3$, 67-66-3.

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Secondary Deuterium Isotope Effects and the Conformation of Transition States in the Solvolyses of 3α- and 3β-Cholestanyl Brosylates

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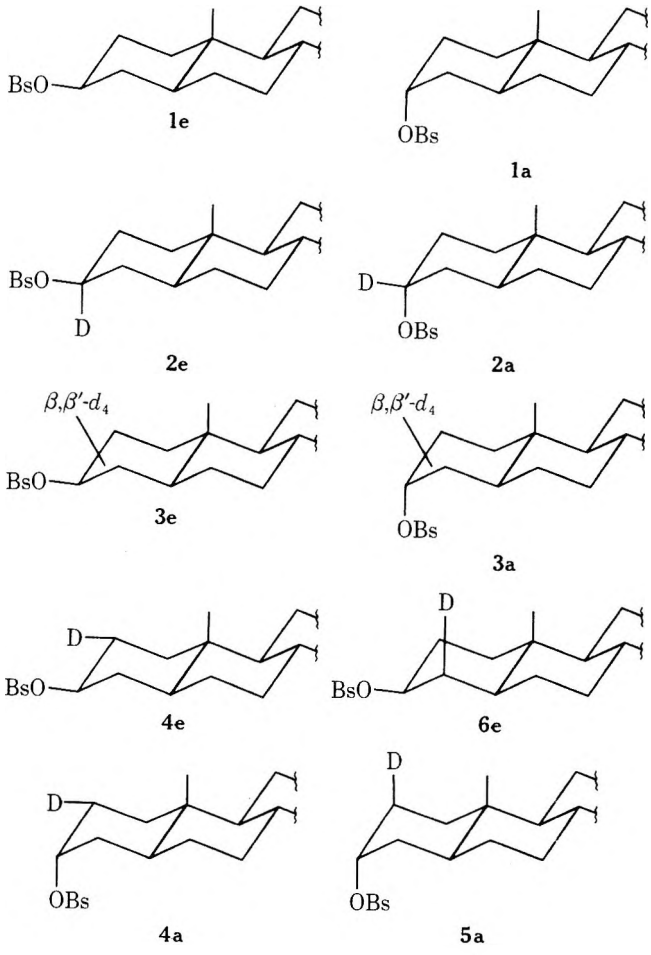
Received March 3, 1975

Secondary deuterium isotope effects in ethanolysis of 3β-cholestanyl-3-d_1 brosylate (**2e**), 3α-cholestanyl-3-d_1 brosylate (**2a**), 3β-cholestanyl-2,2,4,4-d_4 brosylate (**3e**), 3α-cholestanyl-2,2,4,4-d_4 brosylate (**3a**), 3β-cholestanyl-2α-d_1 brosylate (**4e**), 3α-cholestanyl-2α-d_1 brosylate (**4a**), and 3α-cholestanyl-2β-d_1 brosylate (**5a**) were measured. The solvolysis products of unlabeled epimeric brosylates (**1e** and **1a**) were also determined. The deuterium content analyses of olefinic fraction obtained in acetolyses of **3e**, **3a**, **4a**, and **5a** were carried out. The magnitude of the β isotope effects obtained in solvolysis of **3e** ($k_H/k_D = 1.30$), **4e** ($k_H/k_D = 0.95$), and **6e** ($k_H/k_D = 1.18$) leads to the conclusion that the 3β-cholestanyl arensulfonates solvolyze via a chair-like rate-determining transition state. On the other hand, the solvolysis products indicate a half-chair conformation for a product-forming transition state. The isotope effects measured on axial derivatives **3a** ($k_H/k_D = 2.30$), **4a** ($k_H/k_D = 1.13$), and **5a** ($k_H/k_D = 1.60$) discussed together with acetolysis products and the deuterium content of olefins products from **3a**, **4a**, and **5a** suggest a partitioning between k_Δ and k_s processes.

The application of Hammond's postulate[3] to SN1 type reactions implies structural similarities of the cationic intermediate with both ionization and product-forming transition states. One of the best probes of the rate-determining ionization transition state structure are kinetic isotope effects,[4] in particular, owing to their strong conformational dependence, the secondary β-deuterium isotope effects. Product studies, on the other hand, furnish information regarding the structure of the product-forming transition state which, being of lower energy than the rate-determining transition state, resembles the intermediate even more closely.

Recently,[5] we applied both kinetic isotope effects and product analysis in our studies of menthyl tosylate solvoly-

sis. In the present paper we wish to report a case where different structures seem to be involved in the rate-determining transition state and the product-forming intermediate cation, respectively. The reaction studied was the solvolysis of cholestanyl derivatives **1e–6e** and **1a–5a.**



Results

Preparations. The epimeric 3β-cholestanyl brosylate (**1e**) and 3α-cholestanyl brosylate (**1a**) as well as their labeled analogs **2e, 2a, 3e, 3a, 4e, 4a,** and **5a,** were synthesized by the procedures described in the Experimental Section. All compounds except **3e** and **3a** have been known and described previously. The last two were prepared by a modified Djerassi method for the preparation of Δ^4-cholestene-3,6-dione-2,2,7,7-d_4.[6] The configuration of all parent alcohols and their derivatives was determined by NMR spectra and mass spectral and the TLC data, which were compared with either authentic samples or with data reported in the literature. Brosylate esters were obtained by the treatment of alcohols with *p*-bromobenzenesulfonyl chloride in anhydrous pyridine following described procedures. The stereochemistry of C–D bonds in labeled compounds was determined by the ir spectra, which exhibited characteristic streching frequencies for axial or equatorial C–D bonds.[7] The deuterium content and distribution in all labeled compounds came from mass spectral data. The synthesis of **6e** was described in our previous work.[8]

Rates. The rate measurements were performed by the potentiostatic technique at a constant pH of 6.8 for ethanolyses and 2.3 for acetolysis. The liberated acid was titrated with 0.03 *M* sodium ethoxide solution or sodium acetate solution, respectively. Infinity titers were checked and were found to be in accordance with the theoretical values. The solvolysis course was followed in each experiment to 75–80% completion in the case of ethanolysis and to 50–60% in acetolysis. More detailed descriptions about kinetic measurements are given in the Experimental Section. The rate data and calculated isotope effects are listed in Table I.

Solvolysis Products. Although acetolysis products from both **1e** and **1a** have been reported previously,[9] the product composition was checked twice. Slight differences from Baker's results were found in the first experiment so that the product studies were repeated. The data given in Table II are the average values obtained from these two experiments. For a comparison products of **1e** in 89% aqueous acetone were also recorded.

From the acetolysis of tetradeuterated brosylates **3e** and **3a** and monodeuterated 3α-cholestanyl derivatives **4a** and **5a** only the olefinic fraction was isolated. The deuterium content and distribution in alkenes was determined by means of mass spectrometry (Table III). The detailed procedure used in product studies is given in the Experimental Section.

Discussion

The equatorial brosylate **1e** solvolyses in 96% ethanol 6.8 times slower than the axial epimer **1a,**[10] which compares well with the 4.35 rate ratio for epimeric 2-decalyl tosylates.[11] The secondary α isotope effects differ only slightly for the two epimers **2e** and **2a** and are of identical magnitude with those observed in the solvolysis of epimeric cholesteryl tosylates.[8] This can be taken as evidence for similar degrees of bond breaking and/or solvent or neighboring-group participation in the rate-determining transition states.[12]

However, the β-d_4 isotope effect in **3e** (k_H/k_D = 1.30) is significantly smaller in comparison with the d_4 isotope effect in **3a** (k_H/k_D = 2.31). Such small β-d_4 isotope effects have been observed only in solvolysis of menthyl-β,β'-d_3 tosylate[5] and have been explained in terms of a rigid chair-like conformation of the rate-determining ionization transition state. On this basis we exclude for this transition state[13] other conformations of C_2 or C_s symmetry in the cyclohexane ring A[5], which is also in accordance with the suggestion "that equatorial tosylates do not have to assume an axial orientation (either in another chair form or twist form) for solvolyses".[14] This rigidity, which cannot be found in other related cyclohexyl derivatives,[15] must be due to the trans fusion of rings A and B in **1e.** In this respect this ring fusion in positions 3 and 4 relative to the reaction center probably plays a similar role as the two alkyl groups in positions 2 and 5 in menthyl tosylate.[5] Further support for a chair-like transition state in solvolysis of **1e** is furnished from rate data in the solvolysis of **4e** and **6e.** While conformationally flexible cyclohexyl derivatives show very similar normal (k_H/k_D > 1) isotope effects[15a,16–18] for both axial and equatorial deuteriums in β positions,[7] the effect observed with **4e** is inverse (k_H/k_D = 0.944). This can only be caused by a dihedral angle of ca. 90° between the developing p orbital at C-3 and the equatorial C–D bond on carbon atom 2.[19] At the same time this orientation allows a good hyperconjugative overlap with the axial C–D bond on C-4 as demonstrated by the effect in **6e** (k_H/k_D = 1.20).

The product composition in the acetolysis of **1e** is practically identical with the results reported by Baker et al.[9] The amount of inverted substitution product (39.7%) is solvent dependent as it was shown in the solvolysis of **1e** in 89% aqueous acetone (Table II). Under these conditions 64% of inverted cholestanol was formed.

From the magnitude and practical identity of β-d_4 isotope effects in both acetolysis and ethanolysis of **3e** we as-

Table I
Deuterium Isotope Effects in the Solvolysis of the Cholestanyl Brosylates

Compd	Solvent	Deuterium content, %	Temp, °C	k, sec^{-1} [a]	k_H/k_D
2e	96 E[b]	0.99	60.1	$(2.771 \times 10^{-5}) \pm 0.020$[c]	1.130 ± 0.010
				$(2.460 \times 10^{-5}) \pm 0.013$	
2a	96 E	0.99	60.0	$(1.890 \times 10^{-4}) \pm 0.012$[c]	1.099 ± 0.009
				$(1.720 \times 10^{-4}) \pm 0.009$	
3e	96 E	0.89	60.0	$(2.670 \times 10^{-5}) \pm 0.027$[c]	1.296 ± 0.022[d]
				$(2.060 \times 10^{-5}) \pm 0.016$	
	AcOH		70.5	$(3.310 \times 10^{-5}) \pm 0.145$[c]	1.288 ± 0.045
				$(7.230 \times 10^{-5}) \pm 0.201$	
3a	96 E	0.89	60.0	$(1.890 \times 10^{-4}) \pm 0.017$[c]	2.307 ± 0.019[e]
				$(0.858 \times 10^{-4}) \pm 0.026$	
4e	96 E	0.98	60.0	$(2.644 \times 10^{-5}) \pm 0.029$[c]	0.944 ± 0.016
				$(2.799 \times 10^{-5}) \pm 0.011$	
4a	96 E	0.98	60.3	$(2.134 \times 10^{-4}) \pm 0.014$[c]	1.130 ± 0.019
				$(1.888 \times 10^{-4}) \pm 0.142$	
5a	96 E	0.98	60.3	$(2.134 \times 10^{-4}) \pm 0.014$[c]	1.599 ± 0.013
				$(1.334 \times 10^{-4}) \pm 0.044$	
6e	96 E	0.88	60.3	$(3.040 \times 10^{-5}) \pm 0.015$[c]	1.174 ± 0.020[f,g]
				$(2.590 \times 10^{-5}) \pm 0.028$	

[a] Uncertainties are standard errors. [b] 96% v/v EtOH. [c] The values correspond to undeuterated compound. [d] Isotope effect corrected to 100% deuterium content is 1.36. [e] Isotope effect corrected to 100% deuterium content is 2.56. [f] Isotope effect corrected to 100% deuterium content is 1.195. [g] Reference 8.

Table II
Products in the Solvolysis of Epimeric Cholestanyl Derivatives [a]

Compd	1e	1e	1a	
Solvent	AcOH	89% (v/v) aq acetone	AcOH	Products, %
	39.70	63.94	6.00	3α-Cholestanol
	2.03	0.22	7.91	3β-Cholestanol
	0.45			2α-Cholestanol
			0.99	2β-Cholestanol
	55.92	33.73	82.29	Δ^2- + Δ^3-Cholestene
	98.10	97.99	97.19	Total

[a] From the acetolysis of tetradeuterated brosylates 3e and 3a and monodeuterated 3α-cholestanyl derivatives 4a and 5a only the olefinic fraction was isolated. The deuterium content and distribution in alkenes was determined by means of mass spectrometry (Table III). The detailed procedure used in product studies is given in the Experimental Section.

sume that, in these solvents, the ionization step is rate determining. Despite the large olefin fraction (56% in ethanol, Table II) these effects are clearly too small for a rate-determining elimination and are more characteristic for an ionization transition state.[5,15]

A comparison of the product composition found in the acetolysis of **1e** with the solvolytic product of menthyl tosylate[5] reveals a significant difference with respect to the configuration of substitution products. While the identity of kinetic β isotope effects data for both systems indicates similar chair-like transition states, the stereochemical outcome from the product-determining step in solvolysis of **1e** suggests that the geometry of the latter is half-chair or bent chair.[5] Such a conformation is required for a back-side solvent attack leading to products of inverted configuration on the C-3 atom.

The small amount of rearranged 2β product probably arises from a 1,2-hydrogen migration in a half-chair product transition state. This migration can be detected by the deuterium content of olefins formed from **3e** which show 2.29% of d_4 molecules (Table III).

The large β,β′-d_4 isotope effect in the solvolysis of **3a** can be attributed to a primary isotope effect due to rate-determining hydrogen participation and/or β-elimination.[15a,20-22] According to Streitwieser[23] "the tendency for participation by an axial hydrogen adjacent to an axial leaving group appears to be general". A chair-like transition state of ring A in the solvolysis of **1a** fulfills this requirement. It has been shown that even more flexible axial cyclohexyl derivatives solvolyze via a chair-like transition state.[5a]

Table III
Mass Spectral Analysis of Olefins Formed in the Acetolysis of Specifically Deuterated 3α- and 3β-Cholestanyl Brosylates

Substrate		
Compd	Deuterium content	Deuterium content in olefinic products
3e	70.30 d_4	2.29 d_4
	19.35 d_3	70.46 d_3
3a	70.30 d_4	48.56 d_4
	19.35 d_3	13.24 d_3
4a	0.98 D	0.67 D
5a	0.98 D	0.83 D

The isotope effect observed in the solvolysis of **5a** (k_H/k_D = 1.60) is too large to be of hyperconjugative origin only,[22] and is, as in neomenthyl tosylate,[21] likely due to hydrogen participation. The β effect observed with **4a** (k_H/k_D = 1.13)

has to be considered as an α effect with the migrating hydrogen as the leaving group.

The observation of 1% of the rearranged 2β-substitution product and the fact that 69% of deuterium originally present in **3a** remains in the isolated olefin(s) is indicative of a hydrogen-bridged cationic intermediate. This intermediate is probably also the precursor of the retained substitution product. Thus, a 1,2-hydrogen shift probably occurs from this intermediate in one of the subsequent steps. Unfortunately, the incomplete deuteration of **3a** precludes a more detailed mechanistic interpretation. Also, here the situation is less clear because product studies were made in a different solvent than the rate studies.

Additional information can, to a certain extent, be gained by inspecting the elimination products in the solvolysis of **4a** and **5a** (Table III). Here deuteration of the starting ester was complete (0.98 atom D per molecule). The olefin from **4a** showed only 0.67 atom D per molecule, while 83% of deuterium remained in the alkene formed from **5a**. The loss of deuterium from the equatorial position probably occurs in a k_s process (competitive solvent-promoted elimination and back-side substitution on the intimate ion pair).

The relatively smaller loss of the axial deuterium in **5a** during the elimination process implies that an E2-type elimination does not play a substantial role.

The best rationalization of these results is, in our opinion, the formation of a hydrogen-bridged intermediate in the k_Δ process in competition with the k_s solvolytic pathway.

The ratio of inverted to retained unrearranged substitution products from **1a** (1.33) is slightly lower than that reported by Baker et al.[9] (3.53) and can also be explained in terms of two separate paths, i.e., k_Δ, yielding the retained product, and k_s, proceeding with inversion on the C-3 atom.

Experimental Section

General. Melting points were taken on a Kofler block and are uncorrected. Mass spectra were measured on a Bell and Howell CEC-21-110C spectrometer. Infrared spectra were recordered on a Perkin-Elmer 211 spectrophotometer using KBr pellets. The NMR spectra were taken on a Varian A-60A spectrophotometer in $CDCl_3$ solutions with internal Me_4Si. Optical rotations were determined with a Carl Zeiss polarimeter in chloroform solutions. Thin layer chromatography was carried out with silica gel G (Merck) and spots were located with uv light or by spraying plates with dilute H_2SO_4. Column chromatography was performed on silica gel (Merck) or alumina activity II/III (Merck). In chromatographic separations on silica gel benzene–ethyl acetate (9:1 v/v) was used as eluent.

All chemicals used were reagent grade.

3β-Cholestanyl Brosylate (1e). Commercial 3β-cholesterol was converted to 3β-cholestanol as described in the literature[24] (94%). The saturated alcohol was oxidized using a known procedure and gave cholestan-3-one[25] (88%): mp 127–129.5° (lit.[25] mp 128–129°); $[\alpha]D$ +41.4° (lit.[25] $[\alpha]D$ +41.5°); ir ν 1720 cm^{-1} (C=O). The reduction of the ketone with lithium aluminum hydride gave a mixture of 3β-cholestanol and 3α-cholestanol[26] (93%) in the ratio 87.4:9.3. The epimers were separated and purified by column chromatography over silica gel:[27] 3β-cholestanol, mp 143–144° (lit.[26] mp 140–141°); $[\alpha]D$ +23.3° (lit.[28] $[\alpha]D$ +22°); NMR δ 1.67 (s, 1, –OH), 3.63 (m, 1, >CHOH); ir ν 3500 cm^{-1} (O–H); 3α-cholestanol, mp 183–185.5° (lit.[29] mp 184–185°); $[\alpha]D$ +24.2° (lit.[29] $[\alpha]D$ +24°); NMR δ 1.48 (s, 1, –OH), 4.05 (m, 1, >CHOH); ir ν 3500 cm^{-1} (O–H). 3β-Cholestanyl brosylate (**1e**) was prepared[30] by treatment of the corresponding alcohol in anhydrous pyridine with BsCl at 0° for 48 hr (81%): mp 123–124° (lit.[28] mp 120–122°); NMR δ 4.41 (m, 1, >CHOBs), 7.62 (m, 4, C_6H_4). According to TLC analysis the product was free from both unreacted alcohol and brosyl chloride.

3α-Cholestanyl Brosylate (1a). The axial alcohol was converted to the corresponding brosylate in the usual manner[31] (54%): mp 133–135 (lit.[31] mp 132–133°); NMR δ 4.45 (m, 1, >CHOBs), 7.65 (m, 4, C_6H_4). The NMR spectrum and TLC analysis did not show the presence of alkenes, free alcohol, or BsCl.

3β-Cholestanyl-*3*-d_1 Brosylate (2e) and 3α-Cholestanyl-*3*-d_1 Brosylate (2a). Monodeuterated brosylates **2e** and **2a** were synthesised by methods described for the preparation of unlabeled compounds. The reduction of cholestan-3-one was performed using lithium aluminum deuteride instead of $LiAlH_4$.[26] The NMR spectra of both brosylates did not show signals corresponding to protons on the C-3 atom. According to TLC both compounds were more than 98% pure. From mass spectral data the deuterium content in both esters was calculated as 0.99 atom D per molecule.

3β-Cholestanyl-*2,2,4,4*-d_4 Brosylate (3e) and 3α-Cholestanyl-*2,2,4,4*-d_4 Brosylate (3a). According to Djerassi's procedure for the preparation of β-tetradeuterio ketones,[6] cholestan-3-one[25] (5.0 g, 12.5 mmol) was dissolved in AcOD (100 ml) and D_2O (180 ml) and the mixture was refluxed for 4 hr under a slight stream of dry nitrogen. Solvent was removed under high vacuum and this operation was repeated three times. The residue was dissolved in ether (previously saturated with D_2O) and the organic solution was washed with D_2O (2 × 50 ml), a saturated solution of $NaHCO_3$ in D_2O (2 × 50 ml), and again with heavy water (2 × 25 ml). The organic layer was dried over anhydrous $MgSO_4$ and solvent was removed in vacuo. The crude cholestan-3-one-*2,2,4,4*-d_4 was subjected to low-temperature recrystalization from MeOD. The yield was 4.60 g (91.5%): mp 129–130.5;[25] $[\alpha]D$ +41.7°;[25] ir ν 2140, 2175 cm^{-1} (axial and equatorial C–D bond streching frequencies[7]). The deuterium distribution was determined by mass spectral analysis: d_4, 70.30%; d_3, 19.35%; d_2, 7.55%; d_1, 1.36%; total 3.56 atoms D per molecule. Reduction of β-perdeuteriocholestan-3-one with $LiAlH_4$ in anhydrous ether[26] gave a mixture (95.4%) of 3β-cholestanol-*2,2,4,4*-d_4 and 3α-cholestanol-*2,2,4,4*-d_4 in the ratio 87.4:9.2. Separation over silica gel[27] yielded the pure epimeric tetradeuterioalcohols. Mass spectra of both compounds were in full accordance with the deuterium content and distribution found in the parent ketone. The perdeuterio alcohols were converted to the corresponding brosylates in a manner used for the preparation of unlabeled esters **1e**[30] and **1a**.[31] Both **3e** and **3a** did not show the change in the deuterium content in respect with the data obtained from the epimeric alcohols. According to TLC analysis and NMR spectra **3a** and **3e** were 98% pure.

3α-Cholestanyl-*2*β-d_1 Brosylate (5a). A sample of 3β-cholestanol[24] was treated with TsCl in anhydrous pyridine in a usual manner,[30] yielding 3β-cholestanyl tosylate (62.6%), mp 135–137.5° (lit.[28] mp 135–137°). The purity of the tosylate was checked by NMR and TLC techniques. A sample of 3β-cholestanyl tosylate was kept in benzene over basic Al_2O_3 for 2 days.[32] After filtration benzene was removed under high vacuum. The crude product was recrystallized from acetone, yielding 2-cholestene (69%): mp 74.5–75° (lit.[33] mp 73–75°); $[\alpha]D$ +69.1° (lit.[32] $[\alpha]D$ +64°).

2α,3α-Epoxycholestane was prepared by treatment of 2-cholestene with perbenzoic acid[34] in chloroform at −10° for 20 hr.[35] The mixture was then worked up as usual.[35] The crude product was recrystallized (86%) from ether–ethanol mixture: mp 102–104° (lit.[35] mp 105–106°); $[\alpha]D$ +36.2° (lit.[35] $[\alpha]D$ 36.0–36.9°). The epoxide was refluxed with lithium aluminum deuteride in spectrograde dioxane for 90 hr.[36] The excess of deuteride was destroyed with water. The usual work-up[36] gave a white solid which showed on TLC several spots. By column chromatography on alumina (II/III) unindentified impurities were removed with petroleum ether (bp 45–60°). Pure 3α-cholestanol-2β-d_1 (53%) was obtained using petroleum ether–benzene (90:10) as eluent: mp 184–186° (lit.[36] mp 184–186°); $[\alpha]D$ +24.2° (lit.[29] $[\alpha]D$ +24°). The mass spectrum showed 0.98 atom D per molecule. The corresponding brosylate was prepared by a standard procedure[31] (59%): mp 132.5–134° (lit.[31] mp 132–133°); ir ν 2140 cm^{-1} (axial C–D bond frequency[7]). The deuterium content was the same as in the parent alcohol.

3β-Cholestanyl-*2*α-d_1 Brosylate (4e). Deuterioboration of 2-cholestene with $LiAlD_4$ and freshly distilled BF_3-Et_2O complex in dry ether was carried out over dry and oxygen-free nitrogen for 15 hr.[36] After usual treatment with H_2O_2,[36] the crude product was chromatographied over Al_2O_3 (II/III).[36] The unreacted alkene (12%) was eluted with petroleum ether. Pure 3α-cholestanol-2α-d_1[36] (21.7%) was obtained using petroleum ether–benzene (40:60): mp 183–185°; ir ν 2150, 2175 cm^{-1} (equatorial C–D bond frequency[7]). The mass spectrum showed 0.98 atom D per molecule. Elution with petroleum ether–benzene (30:70) gave 2α-cholestanol-3α-d_1 (12.6%), mp 177–180° (lit.[36] mp 177–180°). Using benzene–ether (80:20) 3β-cholestanol-2α-d_1 (18.0%) was isolated: mp 142–144°; ir ν 2150, 2175 cm^{-1} (equatorial C–D bond frequency[7]). The mass spectral data showed 0.98 atom D per molecule. Using the

standard procedure,[30] 3β-cholestanol-2α-d_1 was converted to the brosylate (54%). Deuterium content in **4e** was the same as determined in the parent alcohol. According to NMR and TLC analysis ester was 98% pure.

3α-Cholestanyl-2α-d_1 Brosylate (4a). Treatment of 3α-cholestanol-2α-d_1 with BsCl in dry pyridine at 0° for 5 days gave the corresponding brosylate[31] (44%), mp 132–134° (lit.[31] mp 132–133°). According to mass spectrum 0.98 atom D per molecule was found.

Kinetic Measurements. Reagent grade acetic acid was redistilled over $KMnO_4$ and P_2O_5, respectively, prior to use as a solvolytic solvent. Spectrograde ethanol, 96% v/v (Merck), was redistilled. The middle fraction was used as solvent in solvolyses.

Measurements of the titrimetric rates were carried out by means of a pH-stat. Radiometer, Copenhagen, SBR 2c titrigraph with PHM 25 and TTT 11. The titrimetric cell with solvent was allowed to stabilize at the desired temperature prior to addition of substrate. The concentration of arensulfonate esters was 1.5–2.0 mmol in all experiments. Six to nine kinetic measurements were performed for each compounds alternating the solvolysis of labeled and unlabeled substance. Rate data were evaluated by a nonlinear least-squares sum-fitting program. The rate constants did not exhibit any trend between 15 and 75% of the solvolysis completion.

Solvolysis Products. In a typical acetolysis run, the brosylate **1a** or **1e** (3.7 g, 6.04 mmol) was dissolved in anhydrous acetic acid (600 ml) containing anhydrous sodium acetate (5.85 g, 3.75 mmol). The resulting solution was refluxed for 36 hr. After removal of solvent under high vacuum the residue was dissolved in petroleum ether (bp 30–45°). The organic solution was washed repeatedly with aqueous $NaHCO_3$ until neutral reaction and dried over $MgSO_4$. Evaporation of the solvent gave crude product, which after the usual treatment with lithium aluminum hydride gave a mixture of alkenes and alcohols. Products were separated over alumina (II/III); elution with petroleum ether yielded the olefinic fraction; petroleum ether–benzene (85:15) gave 2β-cholestanol (if present); the use of petroleum ether–benzene (70:30) resulted in the collection of 3α-cholestanol; elution with petroleum ether–benzene (50:50) gave 2α-cholestanol (if present); the last elution using pure benzene yielded 3β-cholestanol. The products were identified by TLC, NMR, and ir spectra, as well as by measurements of their optical rotations and melting points.

Olefinic products (mp 72–74°, $[\alpha]D$ +64.8°) were almost pure 2-cholestene, compared with data from the literature (mp 73–75°,[33] $[\alpha]D$ +64°[32]). Mass spectral analysis, with respect to previously reported results,[9] supported this conclusion. The low-pressure hydrogenation of the isolated olefinic products from both **1a** and **1e** gave pure cholestane: mp 78–80° (lit.[37] mp 79.5–80°); $[\alpha]D$ +25.1° (lit.[37] $[\alpha]D$ +25°); NMR spectrum of the hydrogenated product did not show a signal corresponding to olefinic protons. By this experiment the absence of 4-cholestene in the solvolysis products was confirmed.[38]

Isolated alkenes treated under identical solvolytic conditions as described above in AcOD (0.97 atom D per molecule) did not show after reisolation any deuterium incorporation. This experiment was performed to show that olefins formed in acetolysis of both **1e** and **1a** are primary solvolytic products.

The mass spectra made on olefinic products isolated in solvolysis of labeled substrates gave the amount and distribution of deuterium.

The hydrolysis in 89% aqueous acetone was run in the same manner as the acetolysis using 4000 ml of solvent together with 15 g of $CaCO_3$ as a base. Brosylate **1e** (8.0 g, 13.1 mmol) was refluxed for 72 hr. The resulting mixture gave olefins and alcohols as products. Separation over alumina (II/III) and product identification were performed in a manner described for the acetolysis.

Acknowledgment. This investigation was supported by the Research Council of Croatia and by Grant 02-011-1 (PL 480) administered by the National Institutes of Health. The authors are grateful to Mrs. Sanja Hiršl-Starčević, who carried out some of the preliminary experiments in this study, and to Professor V. J. Shiner, Jr., for numerous helpful discussions.

Registry No.—**1e,** 35596-32-8; **1a,** 56083-04-6; **2e,** 55925-56-9; **2a,** 56083-05-7; **3e,** 55925-57-0; **3a,** 55954-88-0; **4e,** 55954-89-7; **4a,** 55954-90-0; **5a,** 56083-06-8; **6e,** 55954-49-9; 3β-cholestanol, 80-97-7; 3α-cholestanol, 516-95-0; cholestan-3-one, 15600-08-5; lithum aluminum deuteride, 14128-54-2; cholestan-3-one-2,2,4,4-d_4, 13976-58-4; 2α,3α-epoxycholestane, 1753-61-3; 2-cholestene, 570-73-0.

References and Notes

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Notes

Secondary Deuterium Isotope Effects as a Sensitive Probe for Double Bond Participation. The Structure of the Cholesteryl Cation[1]

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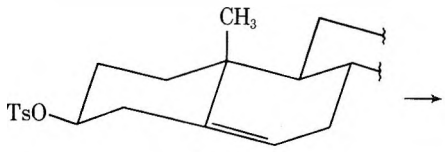
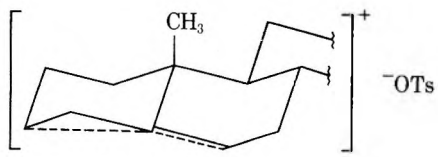
Received March 3, 1975

More than two decades ago Winstein concluded from the kinetic analysis of the solvolysis of cholesteryl *p*-toluenesulfonate (**1**) that "the relatively high rates of acetolysis and alcoholysis of **1** and other indication of high reactivity of Δ^5 materials show that the double bond furnishes a substantial driving force".[3]

Originally structure **2** has been proposed for the intermediate resonance-stabilized homoallylic cation and consequently for the transition state leading to it.[3,4a] Later[4b]

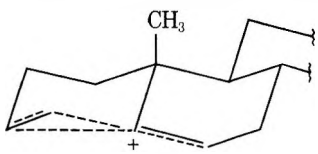


1

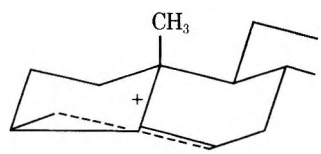


2

both symmetrical (**3**) and unsymmetrical (**4**) intermediates have been suggested and their relative merits discussed.[4c,d]



3



4

In this paper we would like to present evidence in favor of the unsymmetrical structure **2**. Our conclusions are based on secondary deuterium isotope effect measurements which have been shown to be sensitive to neighboring group participation and thus can be successfully applied for the elucidation of transition state structures in anchimerically assisted reactions.[5,6] Specifically deuterated cholesteryl (**5–8**) and cholestanyl (**9, 10**)[6b] derivatives were prepared according to the procedures described in the Experimental Section and their solvolysis rates were measured. The kinetic data are given in Tables I and II. The α effects in both epimers are similar and rather small. Such low effects could be due either to an intervening SN2 reaction or to ion-pair return. In **6** a direct displacement by solvent at C-3 can be excluded on the basis of the observation that the methanolysis of *epi*-cholesteryl tosylate affords only rearranged substitution products, i.e., 4β-methoxycholest-5-ene and 6β-methoxycholest-4-ene and cholesta-3,5-diene as the elimination product.[7] There is also no evidence for a direct displacement in **5**, which leaves a significant ion-pair return[4b] as the alternative explanation for the low α effects in the solvolysis of both **5** and **6**.

The β effects in solvolysis of the anchimerically assisted tosylate **7** and the saturated analog **9** differ markedly. The negligible slightly inverse effect in **7** is in our opinion a consequence of double bond participation and bridging which counteracts the hyperconjugative electron release from the β C–D bond.[5,8] Also the geometry at C-3 which is oriented for overlap with C_5 is wrong for hyperconjugation with the C_4–H(D) bond.[4b] The only other case where such drastic reduction in magnitude of the usual value for β-D effects (1.15–1.20)[9] was observed is the solvolysis of 5-methoxy-2-pentyl-*1,1,1-d*$_3$ brosylate, a strongly n-participating system.[10–12]

In nonparticipating systems small or even inverse β effects have been observed only when the dihedral angle between the developing empty p orbital and the adjacent C–D bond is close to 90°.[14]

Participation of a double bond in ring B can also be considered as the reason for the observance of an inverse isotope effect in the solvolysis of **8**. Bridging between C-3 and C-5 (but not C-4) and the nucleophilic attack on C-6 are probably already well advanced in the transition state. The result is an overall force field increase in the originally sp^2 hybridized carbon atom 6, concurrent with a force field decrease on C-3 atom. In this respect the bridged ion **2** resembles a transition state in addition reactions to olefins, where substrates deuterated at the unsaturated carbon atom yield inverse effects.[15] This effect supports the idea of a significant ion-pair return[4b] with the nucleophilic attack by ethanol at C-6 in the tight ion as the rate-determining step.

The absence of a β isotope effect in **7** rules out significant bond weakening between C-4 and C-5 as implied by structures **3** and **4**. Also, as Winstein pointed out, the C-3 is secondary in **2**, while C-4 is primary in **4** rendering the latter less stable.[4b]

The results described in this paper seem to prefer, in harmony with arguments put forward by Story and Clark,[4d] the unsymmetrical structure **2** for the intermediate cation.

The slightly inverse isotope effect observed in the solvolysis of **10** is apparently of an inductive origin. Such remote inverse effects have been observed in the solvolysis of cyclopentyl-*3,3,4,4-d*$_4$ tosylate.[16]

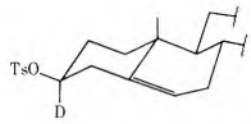
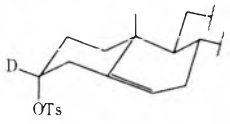
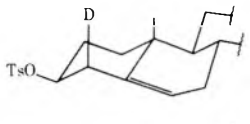
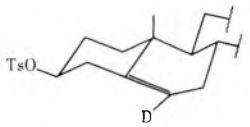
Experimental Section

General. Melting points (uncorrected) were taken on a Kofler apparatus. Proton magnetic resonance spectra were obtained using a Varian A-60A spectrophotometer in $CDCl_3$ solutions with internal tetramethylsilane. The ir spectra were recorded using potassium bromide pellets. The mass spectral data came from a Bell and Howell CEC-21-110C mass spectrometer. Optical rotations were determined with a Carl Zeiss polarimeter in chloroform solutions. Thin layer chromatography plates were prepared from silica gel G (Merck) and column chromatography was performed on silica gel (Merck). In the chromatograms of both types benzene–ethyl acetate (9:1 v/v) was used as solvent. Compounds and reaction mixtures were routinely checked by TLC prior to purification.

All chemicals were reagent grade. Spectrophotometric grade ethanol (Merck), 96%, v/v, was distilled twice prior to use as solvent in kinetic measurements.

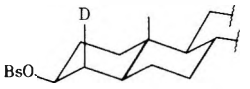
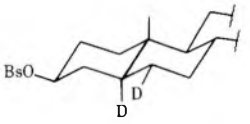
3β-Cholesteryl Tosylate (1). Commercial 3β-cholesterol was converted to 5α,6β-dibromocholesterol using the described procedure.[17] Oxidation of the crude product yielded 5α,6β-dibromocholesten-3-one[17] (64%): mp 71–74° (lit.[17] mp 73–75°); $[\alpha]_D$ −45.9° (lit.[17] $[\alpha]_D$ −47.0°). Debromination afforded cholesten-3-one[17]

Table I
Deuterium Isotope Effects in the Solvolysis of Cholesteryl Tosylates in 95% (v/v) Ethanol

Compd	Compd no.	Deuterium content, %	Temp, °C	k, sec^{-1} [a]	k_H/k_D
	5	99	50.2	$(2.400 \pm 0.016) \times 10^{-4}$ [b] $(2.120 \pm 0.010) \times 10^{-4}$	1.132 ± 0.008
	6	99	50.0	$(3.480 \pm 0.016) \times 10^{-5}$ [b] $(3.150 \pm 0.009) \times 10^{-5}$	1.104 ± 0.010
	7	91	50.0	$(2.150 \pm 0.020) \times 10^{-4}$ [b] $(2.173 \pm 0.020) \times 10^{-4}$	0.989 ± 0.018
	8	91	50.0	$(2.150 \pm 0.020) \times 10^{-4}$ [b] $(2.295 \pm 0.020) \times 10^{-4}$	0.937 ± 0.014

[a] Uncertainties are standard errors. [b] The values correspond to undeuterated compounds.

Table II
Deuterium Isotope Effects in the Solvolysis of 3β-Cholestanyl Brosylates in 95% (v/v) Ethanol

Compd	Compd no.	Deuterium content, %	Temp, °C	k, sec^{-1} [a]	k_H/k_D
	9	90	60.3	$(3.040 \pm 0.015) \times 10^{-5}$ [b] $(2.590 \pm 0.028) \times 10^{-5}$	1.174 ± 0.020[c]
	10	1.01	60.4	$(3.185 \pm 0.165) \times 10^{-5}$ [b] $(3.268 \pm 0.051) \times 10^{-5}$	0.974 ± 0.021

[a] Uncertainties are standard errors. [b] The values correspond to undeuterated compounds. [c] Isotope effect corrected to 100% deuterium content is 1.195.

(78%): mp 124–127° (lit.[17] mp 124–129°); $[\alpha]_D$ −2.3° (lit.[17] $[\alpha]_D$ −2.5°). Reduction of the ketone with lithium aluminum hydride gave a mixture of 3β-cholesterol and 3α-cholesterol[18] (97.6%) in the ratio 89.2:8.4 The epimers were separated and purified by column chromatography over silica gel:[19] 3β-cholesterol, mp 148–149° (lit.[19] mp 149–149.5°); $[\alpha]_D$ −39.1°; NMR δ 2.5 (s, 1, –OH), 3.52 (m, 1, >CHOH), 5.35 (m, 1, vinyl); ir ν 3500 cm^{-1} (O–H); 3α-cholesterol, mp 140–141° (lit.[18] mp 140°); $[\alpha]_D$ −32.2°; NMR δ 1.68 (s, 1, –OH), 4.05 (m, 1, >CHOH), 5.45 (m, 1, vinyl); ir ν 3500 cm^{-1} (O–H). 3β-Cholesteryl tosylate was prepared by a standard procedure[20] (56%): mp 129–131° (lit.[20] mp 131.7–132.6°); NMR δ 2.35 (s, 3, $-CH_3$), 4.26 (m, 1 >CHOTs), 5.22 (m, 1, vinyl), 7.20, 7.70 (d, d, 2, 2, C_6H_4). Data obtained from TLC confirmed the absence of the unreacted alcohol in the tosylate.

3α-Cholesteryl Tosylate (11). 3α-Cholesterol was converted to the corresponding tosylate using a previously described procedure[20] (54%): mp 94–95° (lit.[20] mp 96°); $[\alpha]_D$ +7.2° (lit.[20] $[\alpha]_D$ +6.5 ± 2°); NMR δ 2.32 (s, 3, $-CH_3$), 4.71 (m, 1, >CHOTs), 5.20 (m, 1, vinyl), 7.21, 7.72 (d, d, 2, 2, C_6H_4). The purity of the tosylate was confirmed, with respect to unreacted alcohol or olefinic by-products, by TLC analysis.

3β-Cholesteryl-*3*-d_1 Tosylate (5) and 3α-Cholesteryl-*3*-d_1 Tosylate (6). Monodeuterated tosylate esters **5** and **6** were prepared in the same manner as the unlabeled analogs[17–21] using lithium aluminum deuteride instead of $LiAlH_4$ in the reduction of cholesten-3-one. The ^1H NMR spectra of both deuterated esters did not show signals corresponding to the proton on C-3. Mass spectral data showed the presence of 0.99 D in both 3α-cholestanyl-*3*-d_1 and 3β-cholestanyl-*3*-d_1 tosylate.

3β-Cholesteryl-*4β*-d_1 Tosylate (7). 3β-Cholesteryl benzoate (mp 146–147°, $[\alpha]_D$ −13.7°) was converted by a standard procedure[22] to 4β-hydroxy-3β-cholesteryl benzoate (68%): mp 205–206° (lit.[22] mp 209–210°); $[\alpha]_D$ −30.7° (lit.[22] $[\alpha]_D$ −30.7°). The product was treated according to Young et al.[23] with tri-*n*-butylamine, gaseous HCl and freshly distilled thionyl chloride, yielding (84%) 6β-chloro-Δ⁴-cholesten-3β-benzoate: mp 125–127° (lit.[23] mp 122–128°); $[\alpha]_D$ −82.8° (lit.[23] $[\alpha]_D$ −82.6°). Reduction of the latter with lithium aluminum deuteride gave 3β-cholesterol-*4β*-d_1[23] (88%): mp 147–149°; $[\alpha]_D$ −39.4°. The ir spectrum showed an absorption band at 2140 cm^{-1}, characteristic for the axial C–D stretching.[23] The deuterium content as calculated from the mass spectrum was 0.91 atom D per molecule. 3β-Cholesteryl-*4β*-d_1 tosylate was prepared in the same manner as described for the unlabeled tosylate[20] (56%): mp 131–131.5°.

3β-Cholesteryl-*6*-*d* Tosylate (8). 3β-Cholesterol-*6*-*d*[24,25] was treated with tosyl chloride in the usual manner.[20] The crude **8** was recrystallized at low temperature from ether–pentane mixture (61%): mp 131–132°; NMR δ 2.32 (s, 3, $-CH_3$), 4.26 (m, 1, >CHOTs), 7.20, 7.70 (d, d, 2, 2, C_6H_4). The mass spectral data showed 0.91 atom D per molecule.

3β-Cholestanyl Brosylate (12). Catalytic hydrogenation of 3β-cholesterol over Adams catalyst in glacial acetic acid yielded partially acetylated 3β-cholestanol.[26] The crude product was purified by removal of the remaining cholesterol with concentrated H_2SO_4, hydrolysis with NaOH in EtOH, and filtration through an Al_2O_3 column (II/III) with CCl_4 as an eluent. After recrystallization from anhydrous EtOH 3β-cholestanol was obtained (69%): mp 142–144°; $[\alpha]_D$ +23.3°; NMR δ 1.67 (s, 1, –OH), 3.65 (m, 1, >CHOH); ir ν 3500 cm^{-1} (O–H). 3β-Cholestanyl brosylate was prepared by treatment of the alcohol in dry pyridine with brosyl chlo-

ride at 0° for 2 days.[27] After the usual work-up procedure[27] the crude product was recrystallized from ether–ligroin mixture (82%): mp 119–121° (lit.[28] mp 120–122°); NMR δ 4.4 (m, 1, >CHOTs), 7.66 (m, 4, C_6H_4).

3β-Cholestanyl-4β-d_1 Brosylate (9). The mixture containing 3β-cholesterol-4β-d_1 and freshly distilled acetic anhydride was refluxed in dry pyridine for 20 hr.[29] After addition of ether (200 ml) the resulting solution was washed with water until neutral reaction. The organic layer was dried over $MgSO_4$ and filtered. Solvent was removed under reduced pressure and crude 3β-acetoxycholesterol-4β-d_1 was recrystallized from EtOH (91%): mp 113–115.5° (lit.[29] mp 114.5–116.5°); NMR δ 2.00 (s, 3, $-CH_3$), 4.70 (m, 1, >CHOAc).

Acetylated 3β-cholesterol-4β-d_1 was catalytically hydrogenated over Pt (Adams catalyst) in glacial acetic acid at 65° for 36 hr. This method does not lead to deuterium scrambling.[30] After the usual work-up the crude product was refluxed in an alkaline ethanol solution for 1 hr.[30] Purification and recrystallization from acetone yielded 3β-cholestanol-4β-d_1 (80%): mp 142–144°; $[\alpha]D$ +23.4°; ir ν 2140 cm^{-1} (C–D).[23] The alcohol was converted to the corresponding brosylate **9** by the known procedure[27] (53%), mp 121–122°. Mass spectral data did not indicate deuterium scrambling. The deuterium content was determined as 0.91 atom D per molecule. The ir spectrum supported the presence of a 4β C–D bond in the substrate.[23]

3β-Cholestanyl-5α,6α-d_2 Brosylate (10). 3β-Acetoxycholesterol[29] was catalytically deuterated over Pt in AcOH-d_1 as previously described.[30] The reaction mixture was treated as usual,[30] yielding 3β-cholesterol-5α,6α-d_2 (91%): mp 142.5–144°; $[\alpha]D$ +23.1°; ^1H NMR spectrum did not show the signal corresponding to a vinyl proton (δ 5.35). The deuterium distribution according to the mass spectrum was d_3, 3%; d_2, 96%; d_1, 1%; total 2.02 atoms D per molecule. The deuterated alcohol was converted to the brosylate **10** in a described manner[27] (67%), mp 120.5–122°.

Kinetic Measurements. The titrimetric rates were obtained using the automatic potentiometric titration method by means of a pH-stat, Radiometer, Copenhagen, SBR-2/TTT 11, maintaining a constant "pH setting" of 6.8. The substrate concentration was 1.5 mmol in all experiments. Six to eight solvolyses were performed for each sulfonate ester, alternating the measurement of the labeled and unlabeled derivative. The rate data were calculated from the standard integrated first-order law and evaluated using a nonlinear least-squares program. No trend was observed in the rate constants between 15 and 80% of the solvolysis completion.

Acknowledgment. We are indebted to Professor V. J. Shiner, Jr., Indiana University, for helpful and stimulating discussions.

Registry No.—**1**, 1182-65-6; **2**, 56227-24-3; **5**, 55913-52-5; **6**, 55913-53-6; **7**, 55954-48-8; **8**, 55913-54-7; **9**, 55954-49-9; **10**, 55954-50-2; **11**, 3381-56-4; **12**, 35596-32-8; 3β-cholesterol, 57-88-5; 3α-cholesterol, 474-77-1; 3β-cholesteryl benzoate, 604-32-0; 3β-cholesterol-4β-d_1, 1973-68-8; 3β-cholesterol-6-d, 16374-87-1; 3β-cholestanol, 80-97-7; 3β-acetoxycholesterol-4β-d_1, 1973-64-4; 3β-cholestanol-4β-d_1, 55954-51-3; 3β-cholestanol-5α,6α-d_2, 55954-52-4.

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Configuration of 5-Cholestene Hydrochloride

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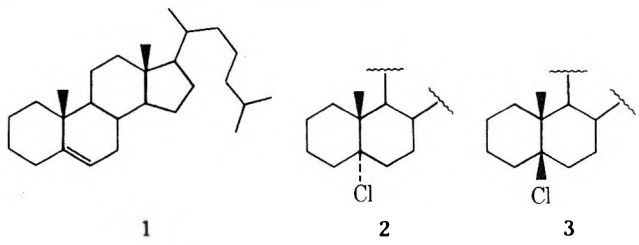
Received April 8, 1975

The addition of hydrogen chloride to 5-cholestene (**1**) was reported long before the constitution of the steroid nucleus was established.[2] The major product (prisms, mp 97°, $[\alpha]D$ +4.7°) has been described as 5α-chlorocholestane (**2**), rather than the 5β isomer (**3**),[3] and reference has been made[4] to a structure determination using X-ray diffraction techniques.[5]

The structure of the major product ("Mauthner's hydrochloride") was, however, not solved. The crystallographic investigation was limited to the determination of the point group and dimensions of the unit cell. As pointed out by Bernal,[5] these data are not sufficient to be considered diagnostic as to the stereochemistry of the ring junction.

Subsequent experiments on the addition of hydrogen chloride to **1** substantiated Mauthner's observations but lacked rigorous proof of stereochemistry.[6] The major product (prisms, mp 96–97°, $[\alpha]D$ +6.4°) was separated mechanically from a minor product (plates, mp 94–95°, $[\alpha]D$



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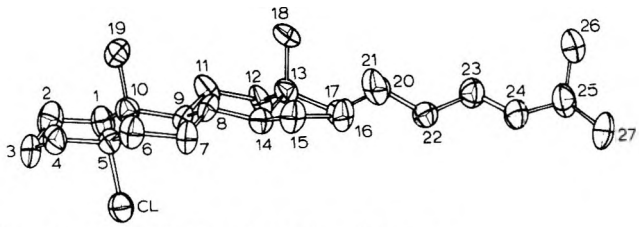

Figure 1. ORTEP view of 5α-chlorocholestane.

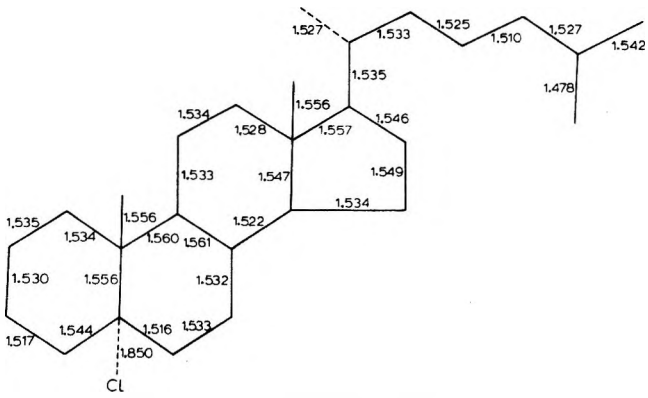

Figure 2. Bond lengths of 5α-chlorocholestane. The average standard deviation of a C–C bond is 0.008 Å.

+37°). The minor product was assigned the 5β configuration **3**.

Recent interest in the stereochemical and conformational aspects of decalyl cations[7] led us to question the structure of Mauthner's hydrochloride. The reasoning which prompts this reconsideration is based on the numerous observations of competitive, sometimes dominant capture of decalyl cations by nucleophiles to afford products having cis ring fusions.[7–9]

Addition of hydrogen chloride to **1** in chloroform at 25° afforded prisms, mp 96.0–96.5°, $[\alpha]D$ +3°, as the only crystallizable product. These constants correspond well to those reported and the physical appearance of the crystals matched those of a diagram of Mauthner's hydrochloride.[5]

Since the chemical shift of the 19-methyl group in steroids is sensitive to the presence of substituents elsewhere in the molecule and the stereochemistry of the A/B ring junction,[10] an attempt was made to deduce the structure of the product from its NMR spectrum. A singlet 1.04 ppm downfield from internal tetramethylsilane was readily assignable to the 19-methyl group. The chemical shift of 0.26 ppm to lower field relative to 5α-cholestane is in good agreement with the 0.21–0.27-ppm shift predicted from the Zurcher rules. In spite of the observed correspondence, the 5β-chloro stereochemistry could not be rigorously excluded because of the lack of data available with which to make a prediction for this substitution pattern. The observed signal is 0.12 ppm downfield from the 19-methyl signal of 5β-cholestane and a shift of this magnitude appears not unreasonable. It is relevant to note that the chemical shifts of the methyl groups of *cis*- and *trans*-9-chloro-10-methyldecalin are identical within experimental error (1.11 ppm).[11]

With only one isomer in hand, recourse was made to an unambiguous determination of structure by X-ray crystallographic methods. The structure was solved by standard Patterson heavy atom techniques, and refined by block-diagonal least-squares calculations. The coordinates of all hydrogen atoms were found in a Fourier difference map. The final conventional R factor was 4.6%, weighted R was 3.4%.

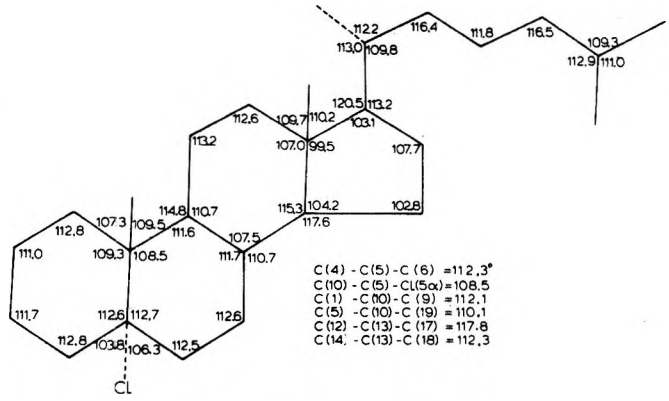

Figure 3. Valence angles of 5α-chlorocholestane. The average standard deviation in a valence angle is 0.6°.

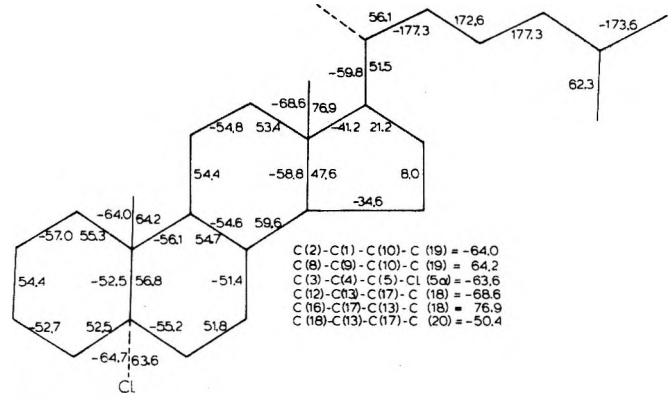

Figure 4. Torsion angles of 5α-chlorocholestane.

Final positional and thermal parameters are listed in Tables I and II (supplementary material). Figure 1 shows an ORTEP drawing (50% probability thermal ellipsoids) of the steroid skeleton. Figures 2, 3, and 4 depict the bond distances, angles, and torsion angles, respectively, of the steroid skeleton. *The chlorine is clearly in the α position on C(5).* Figures 5 and 6 show the packing in the 100 and 001 projections, respectively (supplementary material). The side chains pack over one another and the steroid skeletons pack over one another with normal van der Waals contacts.

Experimental Section

NMR spectra were recorded on a Jeol PS-FT spectrometer at 100 MHz in $CDCl_3$ and chemical shifts are reported in parts per million from internal tetramethylsilane. Melting points are corrected and were determined on a Thomas-Hoover apparatus.

Hydrochlorination of 5-Cholestene. Hydrogen chloride was passed through a solution of 1.02 g (2.77 mmol) of 5-cholestene in chloroform for 2 hr. The solution was allowed to stand at 25° for 2 days, the solvent was evaporated, and the resulting product was taken up in ether dried over magnesium sulfate. The ether was evaporated and the residue was then dissolved in the minimum quantity of anhydrous ether and allowed to stand at 25°. After 2 days the crystalline product (139 mg, 12%) was collected: mp 96–96.5°; $[\alpha]D$ +3° (chloroform); NMR ($CDCl_3$) 0.65 (s, 3, C-18 methyl), 0.86 (d, 6, J = 6 Hz, C-25 methyls), 0.90 (d, 3, J = 6 Hz, C-20 methyl), 1.04 (s, 3, C-19 methyl), and 1.0–2.1 ppm (m).

Crystal Data. $C_{27}H_{47}Cl$, mol wt 407.1, a = 14.444 (3) Å, b = 19.264 (6) Å, c = 8.976 (2) Å; space group, $P2_12_12_1$, orthorhombic, Z = 4, V = 2495.5 Å^3.

Crystallographic Measurements. The unit cell parameters were determined by a least-squares refinement of 20 values of 15 well-centered reflections with 30° < 2θ < 50°. An initial set of three-dimensional data (2444 reflections, 1056 observed) was collected with a GE-XRD-5 diffractometer. The data did not refine well, so another set of data was collected with an Enraf-Nonius CAD-4 automated diffractometer using Mo Kα (λ 0.71069 Å) ra-

diation with a graphite monochromator (4104 reflections, 1533 observed). Only the latter data set was used in the refinement reported here.

Acknowledgments. This research was supported in part by a USPHS Grant (CA-10906) to the Medical Foundation of Buffalo.

Registry No.—**1**, 570-74-1; **2**, 56114-17-1; hydrogen chloride, 7647-01-0.

Supplementary Material Available. Tables of coordinates, thermal parameters, structure factors, and packing diagrams (Figures 5 and 6) will appear following these pages in the microfilm edition of the volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th Street, N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2956.

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Isolation and Structure of 1-Hydroxy-7-methoxy-4-isopropyl-1,6-dimethyl-2(1*H*)-naphthalenone from Cotton

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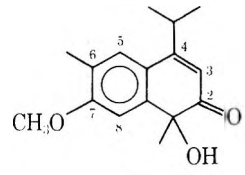
Received May 6, 1975

Previous work from this laboratory has been concerned with attempts to identify the components in the cotton plant *Gossypium hirsutum* which are implicated in producing the clinical symptoms of the disease byssinosis.[1] In this earlier study we reported preliminary characterization of a column chromatographic fraction from cotton dust or cotton bracts which exhibited chemotactic activity with human polymorphonucleur cells. Purification of this fraction by preparative layer chromatography afforded 70 μg of a compound exhibiting a strong yellow-green fluorescence under 254-nm ultraviolet light which was tentatively assigned a molecular weight of 260 from mass spectral examination.

Reisolation of 20 mg of this compound has now permitted its characterization as 1-hydroxy-7-methoxy-4-isopropyl-1,6-dimethyl-2(1*H*)-naphthalenone (**1**).



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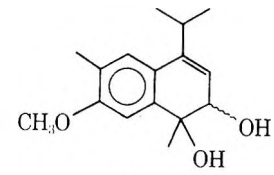

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The initial isolation studies of the fluorescent component were directed toward examination of the volatile fraction on the basis that steam treatment of cotton is reported to reduce or destroy the byssinosis factor when measured by the response of susceptible workers.[2] The yields of the fluorescent fraction obtained by this procedure were extremely low (~10 μg/kg) and alternative sources and methods of isolation were examined. Using the fluorescence properties as a guide to the presence of active material, it was found that aged cotton bracts contained more than fresh bracts and that fresh leaves and stems contained only insignificant amounts of this material.

Extensive purification of an aqueous acetone extract of aged cotton bracts by column chromatography afforded a crude fraction containing the yellow-green fluorescent component. Preparative layer chromatography of this fraction on silica gel in chloroform–5% methanol gave a pure compound, mp 100–102°, which proved identical in its chromatographic and mass spectral characteristics with that previously obtained.

An exact mass measurement of the molecular ion, *m/e* 260, from the electron impact (EI) spectrum established the molecular formula as $C_{16}H_{20}O_3$. Verification that the ion *m/e* 260 was indeed the molecular ion was obtained from the chemical ionization (CI) spectrum, which showed a quasimolecular ion at *m/e* 261 (100).

The CI spectrum was remarkably simple in that in addition to the QM^+ ion the only ions of significant intensity appear at $(QM^+ + 1)$, $(QM^+ - OH)$, and $(QM^+ - H_2O)$ and account for 90% of the total ion current. In contrast, the high-resolution EI spectrum contained many ions of which those corresponding to $M^+ - CH_3$ at *m/e* 245 and $M^+ - CO$ at *m/e* 232 were present. The loss of CH_3 from the *m/e* 232 ion to a fragment ion of *m/e* 217, when taken in conjunction with the appearance of an ion at *m/e* 202, suggested the presence of two methyl groups and a ketone. In addition, the base peak at *m/e* 189 ($C_{12}H_{13}O_2$) and an ion at *m/e* 175 ($C_{11}H_{11}O_2$) were the only other ions of any significance at high mass. The occurrence of absorption bands at 1670 and 3490 cm^{-1} in the ir spectrum of **1** confirmed the presence of an unsaturated carbonyl and hydroxyl functions, respectively.[3] The invariance of the OH band at 3490 cm^{-1} with increasing dilution in CCl_4 solution demonstrated that the OH group was intramolecularly hydrogen bonded and the frequency of the absorption was consistent with that expected for an α-hydroxy ketone.[4]

In agreement with the fluorescence properties of **1**, the uv spectrum in cyclohexane showed evidence for extended conjugation with bands at 222 nm (ε 9100), 227 (10,400), 252 (10,800), 258 (11,300), 335 (4730), and 365 (2730). An indication that the latter was consistent with a β-aryl-α,β-unsaturated ketone chromophore was supported by a comparison of its spectrum in ethanol, which was much less detailed than in cyclohexane, with the uv of other 2(1*H*)-naphthalenones[5] and by the marked change in the uv spec-

trum associated with the reduction of 1 to its dihydro derivative 2 with sodium borohydride (see Experimental Section).

The 100-MHz ^1H and the ^{13}C spectra of the fluorescent component provided considerable structural information. These data when considered in conjunction with other spectral results were sufficient to permit an assignment of structure. A pair of 3 H doublets (J = 7.0 Hz) at δ 1.24 and 1.26 which were coupled (DNMR) to a 1 H multiplet at δ 3.14 was observed in the ^1H NMR spectrum of 1 and indicated the presence of an isopropyl group in which the methyl groups are diastereotopic. Carbon resonances[6] at δ 21.8 and 22.1 for the methyls and δ 28.2 for the methine carbon supported the presence of an isopropyl group.[8] Methyl resonances in the proton spectrum occurred as singlets at δ 1.52, 2.22, and 3.88 and, in conjunction with the corresponding carbon resonances at 33.4,[8] 16.1,[9] and 55.5[9] ppm, allowed their assignment to a methyl on a carbon containing an hydroxyl group, an aromatic methyl, and an aromatic methoxyl. One-proton singlets at δ 6.08, 7.23, and 7.34 were attributable to the α hydrogen of an α,β-unsaturated ketone and aromatic hydrogens in a para relationship, respectively. A DNMR experiment showed that the low-field aromatic signal was slightly broadened through coupling to the methyl at δ 2.22. Support for the presence of a β-substituted enenone system was provided by the carbon signals at 125 and 164.1 ppm. The highly deshielded position of the latter is in agreement with the expected position of the β carbon of a β-substituted α,β-unsaturated ketone system.[10]

Although the foregoing spectral data are consistent with structure 1, there are several alternatives which cannot be excluded from consideration. These structures differ from 1 by interchanging the position of the aromatic substituents and the isopropyl group. Two of these alternative structures could be discounted from the observation that compound 1 is recovered from an acidic solution and therefore it is not in accord with the properties expected for a β-diketone enol ether.[11] The structural possibilities are reduced to that proposed and the biogenetically less attractive alternative in which the position of the methoxyl and aromatic methyl are interchanged.

A decision in favor of structure 1 was provided by a lanthanide shift study. The small coupling observed between the methyl group on the aromatic ring and the aromatic hydrogen associated with the signal of δ 7.34 indicates that the aromatic signal at δ 7.23 originates from the hydrogen ortho to the methoxyl group. During additions of incremental amounts of Eu(fod)$_3$ to a sample of 1, the largest $\Delta\delta$ was observed for the methyl signal of δ 1.52 in agreement with the expected complexation of the europium at the hydroxyl group.[12] Of the two aromatic hydrogen signals, the low-field signal at δ 7.34 remains essentially unchanged upon addition of Eu(fod)$_3$ while the signal at δ 7.23 is shifted appreciably. This finding clearly is consistent with structure 1 and suffices to rule out the alternative structure in which the positions of the methyl and methoxyl on the aromatic ring are reversed. This compound represents a further example of the sesquiterpenes found in cotton which are based upon the cadanane skeleton.[13] Despite the fact that structure 1 is chiral, examination of the CD and ORD spectra indicated that 1 is produced in the racemic form. At this stage the role of 1 in causing the onset of symptoms associated with byssinosis is under active investigation. The increased incidence of 1 in aged bracts and its absence from fresh plant material may indicate that its occurrence is linked to the presence of contaminating microorganisms. A recent report[14] has described the occurrence of isohemigossypol as a phytoalexin in cotton plants infected with *Verticillium dahliae*.

Experimental Section

Melting points were determined on a Kofler hot-stage apparatus. Infrared spectra were obtained in chloroform solutions on a Perkin-Elmer Model 621 spectrophotometer. Ultraviolet spectra were measured in cyclohexane unless otherwise noted on a Cary 15 spectrophotometer. Proton nuclear magnetic resonance (NMR) spectra were recorded at 90 MHz on a Bruker HFX-90 and at 100 MHz on a Jeol MH-100 in $CDCl_3$ solution containing Me_4Si. The Fourier transform carbon-13 spectrum was obtained on a Jeol PS-100 through the courtesy of I. Carrol, Research Triangle Institute. The spectrometer was operated at 25.0292 MHz and was equipped with a high-sensitivity insert. The Fourier transforms were based upon 8K data points and employed the absorption spectrum. A sample concentration of 18 mg in 0.3 ml of $CDCl_3$ (containing 1% Me_4Si) contained in a 5-mm sample tube was used. The spectrum was recorded with noise decoupling in the proton region. A total of 64K transients were accumulated under conditions using a pulse width of 12.5 μsec and a repetition rate of 1.0 sec. High-resolution mass spectra were obtained on an MS-902 at 70 eV using a direct insertion probe. Chemical ionization spectra were obtained on a Finnigan 3300 quadrupole mass spectrometer operating in the CI mode with electron energy of 125 eV at a source pressure of 500 μ of isobutane and a source temperature of 125°. Circular dichroism spectra were obtained on a Jasco ORD/CD spectropolarimeter. Gas–liquid chromatography (GLC) was carried out on a Hewlett-Packard 402 instrument with 8 ft × 0.125 in. glass columns packed with 3% OV-17, 3% QF-1, or 3% SE-30 on Gas-Chrom Q (100–120 mesh) operating at 200°.

Isolation. The cotton stems and bracts (3.65 kg) obtained from the inclined cleaner of a cotton mill were ground in a blender at high speed for ca. 1–2 min with acetone–water (85:15) (12 ml/g) and was then filtered over Celite. The filtrate was treated with lead acetate solution;[7] one part of the lead acetate solution was added to four parts of deionized water which was then added to an equal volume of the cotton filtrate, and the resulting suspension was filtered over Celite. This filtrate was extracted with an equal volume of chloroform, the organic layer was taken to dryness under reduced pressure, and the resulting oil (26 g) was applied to a column (27 × 2.75 in.) containing 1.3 kg of neutral alumina (activity 1). The column was eluted sequentially with benzene (3 l.), a continuous gradient of benzene–chloroform (6 l.), chloroform (3 l.), a continuous gradient of chloroform–methanol (6 l.), and methanol (3 l.). The desired yellow fluorescent material along with a blue fluorescent compound and second yellow fluorescent component were eluted with methanol. Purification of this fraction by preparative layer chromatography (PLC) on silica gel in $CHCl_3$–MeOH (20:1) gave a major component at R_f 0.93 which was further purified by PLC on silica gel in benzene–ether (4:6) to give 20 mg of 1 which crystallized slowly from CCl_4: mp 100–102°; ir ($CHCl_3$) 3490 (OH), and 1670 cm^{-1} (CO), the 3490-cm^{-1} band was not affected by dilution of the sample to concentrations of 1×10^{-4} M; uv (hexane) 222 nm (ϵ 9100), 227 (10,400), 252 (11,800), 258 (11,360), 335 (4730), 335 (2730); uv (95% EtOH) 228 (10,200), 248 (10,300), 339 (4300), 370 (sh); ^1H NMR (100 MHz) δ 1.24 (d, J = 7.0 Hz, 3), 1.26 (d, J = 7.0 Hz, 3), 1.52 (s, 3), 2.22 (s, 3), 3.14 (m, 1), 3.88 (s, 3), 6.08 (s, 1), 7.23 (s, 1), 7.34 (s, 1); ^{13}C NMR (25.029 MHz) 16.1, 21.8, 22.1, 28.2, 29.6, 33.9, 55.5, 75.6, 107.2, 114.7, 125.2, 125.5, 127.5, 145.4, 164.1 ppm (C=O signal was saturated under the operating conditions used); mass spectrum (70 eV) m/e (rel intensity) 260 (40, M$^+$), 245 (6, M − CH_3), 232 (30, M − 60), 217 (66, M − CO + CH_3), 202 (21, M − CO + 2CH_3), 189 (100, $C_{12}H_{13}O_2$). GLC on QF-1 or SE-30 columns gave a single peak. Compound 1 was also isolated from cotton dust obtained from the floor sweepings of a cotton mill. A similar extraction of fresh leaves and bracts gave no evidence for the presence of 1.

Anal. Calcd for $C_{16}H_{20}O_3$: m/e 260.1412. Found: m/e 260.1416.

Borohydride Reduction of 1. A solution of 1 (2.89 mg, 11 μmol) in 2-propanol (1 ml) was added to a stirred solution of $NaBH_4$ (2 mg) in 2-propanol (1 ml) over a period of 45 min at room temperature. Preparative layer chromatography on silica gel in $CHCl_3$–MeOH (20:1) gave the dihydro compound 2: mp 172–174°; R_f 0.45; ir 3558 cm^{-1} (OH), no C=O; uv 258 nm (3200), 284 (3870); mass spectrum m/e (rel intensity) 262 (44, M$^+$), 244 (23, M − 18), 219 (47, M − 43), 201 (53), 159 (100).

Anal. Calcd for $C_{16}H_{22}O_3$: m/e 262.1568. Found: m/e 262.1564.

Attempted Hydrolysis of 1. A solution of 1 (3 mg) in dioxane (2.5 ml) was heated with 2.5 ml of 1 *N* HCl and the reaction was monitored by GLC on a SE-30 column periodically for 1 hr. No change in the intensity of the peak associated with 1 was observed during this time period.

Acknowledgments. This research was supported through the award of a training grant in Environmental Sciences from the National Institute of Environmental Health Sciences (5-TOJ-ES-00124) and a Biological Sciences Support Grant to Duke University. High-resolution mass spectral results were provided by the Research Triangle Institute of Mass Spectrometry through the courtesy of Dr. David Rosenthal and Mr. Fred Williams. Dr. P. E. Sasser and Mr. W. Taylor, Cotton Inc., kindly provided the cotton plant material and samples of cotton dust.

Registry No.—1, 56051-00-4; 2, 56051-01-5.

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α-Chlorination of Aliphatic Acids by Molecular Chlorine

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Received March 21, 1975

We have previously reported that enolizing catalysts such as H_2SO_4, HCl, or $FeCl_3$ together with *m*-dinitrobenzene as a radical trapper increase the ratio of α- vs. β-chlorination of propionic acid by molecular chlorine.[1]

As an extension of this study concerning the effect of catalyst, the authors discovered that aliphatic acids can be effectively α-chlorinated in the presence of molecular oxygen as a radical trapper, which was pointed out in the Cl_2 addition to double bond[2] and in the phosphorus chloride catalyzed chlorination of alkanes.[3] The significant effect of molecular oxygen on the α-chlorination in the presence of 95% H_2SO_4 is listed in Table I.

Table I
Effect of Radical Trappers on the Chlorination Product of Butyric Acid[a]

Radical trapper	(mol %)	Registry no.	Yield, % α-Chloro acid	Yield, % β-Chloro acid
m-$C_6H_4(NO_2)_2$	(7.0)	99-65-0	6.7	1.4
O_2[b]		7782-44-7	22.3	0

[a] Chlorine gas was continuously introduced into the substrate at the flow rate of 200 ml/min at 120° for 3 hr in the dark with initial amounts of butyric acid (0.2 mol) and H_2SO_4 (0.02 mol). [b] The flow rate of O_2 was 200 ml/min.

The authors discovered also that the yield of α-chlorinated product further increases by the use of chlorosulfonic acid instead of concentrated H_2SO_4 as an enolizing catalyst. The remarkable effect of chlorosulfonic acid is probably due to the ability of formation of a more homogenous mixture and to the stronger acidity compared with that of H_2SO_4. Moreover, the authors examined the ability of some radical trappers and found that chloranil has an apparent effect on the α-chlorination.[4] These results are summarized in Table II for the chlorination of isovaleric acid as a substrate.

Table II
Effect of Chlorosulfonic Acid and Chloranil on Chlorination of Isovaleric Acid[a]

O_2:Cl_2 mol ratio[b]	Chloranil, mmol	Enolizing catalyst (mmol)	Yield, % α-Chloro acid	Yield, % β-Chloro acid
1:2	0.04	95% H_2SO_4 (171)	23.0	1.2
1:2	0.04	$ClSO_3H$ (60)	70.6	0.0
1:2	0	$ClSO_3H$ (60)	72.8	0.0
No O_2	0	$ClSO_3H$ (60)	41.6	2.7
No O_2	3	$ClSO_3H$ (60)	65.6	7.3

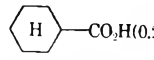
[a] Dark reaction at 140° for 3 hr with an initial amount of isovaleric acid of 600 mmol. [b] The flow rates of Cl_2 and O_2 gas were 100 and 50 ml/min, respectively.

Table II shows that the most effective α-chlorination of isovaleric acid by molecular chlorine in the dark is possible in the presence of chlorosulfonic acid, molecular oxygen, and chloranil at 140°. The chlorination in the absence of these three addenda gave a mixture of several chloro acids.

Various aliphatic acids can be similarly α-chlorinated in the presence of the above catalysts ($ClSO_3H$, O_2, and chloranil) to give its corresponding α-chloro acids alone in excellent yields (Table III). No β-chloro acid is detected except with isobutyric, *n*-butyric, and isocaproic acid, which produce only a trace of the corresponding β-chloro acid. It is of interest to note that the α-chlorination is predominant even in the presence of tertiary hydrogen, e.g., isovaleric acid. These products were characterized on the basis of boiling point, ir, and NMR spectra of the corresponding methyl ester which is prepared by H_2SO_4-catalyzed esterification with a mixture of methyl alcohol and ethylene dichloride[5] (Table IV).

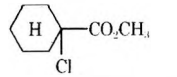
The authors already proposed that the acid-catalyzed chlorination of aliphatic acid by molecular chlorine in the dark may proceed via the ionic chlorination of enolized aliphatic acid, $RCH{=}C(OH)_2$, where the radical trappers minimize the radical chlorination.[1,6] The above results

Table III
Yields of α- and β-Chloro Acids with Various Substrates

Registry no.	Substrate (mol)	Reaction time, hr[b]	Reaction temp, °C	Yield, % α-Chloro acid	Yield, % β-Chloro acid	α-Chloro acid registry no.
79-31-2	$(CH_3)_2CHCO_2H$ (0.45)	2.5	120	74.6	0.3	594-58-1
107-92-6	$CH_3(CH_2)_2CO_2H$ (0.45)	2.5	120	82.0	1.6	4170-24-5
97-61-0	$CH_3(CH_2)_2CHCO_2H$ (0.35), CH_3	2.0	120	81.1	0.0	55905-12-9
105-43-1	$CH_3CH_2CHCH_2CO_2H$ (0.18), CH_3	1.0	120	78.1	0.0	921-48-2
646-07-1	$CH_3CH(CH_2)_2CO_2H$ (0.16), CH_3	1.0	120	78.6	6.4	29671-29-2
98-89-5	 (0.23)	2.0	110[c]	73.4	0.0	25882-61-5

[a] Reactions were carried out with a 4:1:0.04 mole ratio of aliphatic acid:$ClSO_3H$:chloranil. A mixture of Cl_2 and O_2 gas (2:1 mole ratio) was introduced into the substrate in the dark at 120°. [b] Although the reaction was continued for 3 hr, the maximum yield of α-chloro acid was obtained at this reaction time. [c] The reaction temperature was lowered to 110° for the comparison with the literature. According to the literature,[7] the yield of α-chlorocyclohexanecarboxylic acid at 110° was less than 10% in PCl_3-catalyzed chlorination by molecular chlorine.

Table IV
Physical Properties and Identification of Methyl Esters of Produced Chloro Acids

Registry no.	Compd	Bp, °C (mm)	Ir, $\nu_{C=O}$, cm^{-1}[a]	NMR chemical shift[b]
26464-32-4	$CH_3CH_2CHCO_2CH_3$, Cl	87–88 (82)[c]	1750[d]	3.68 (s, 3 H, OCH_3), 4.20 (t, 1 H, J = 7.0, α-H), 1.92 (quintet, 2 H, J = 7.0, β-H), 1.00 (t, 3 H, J = 7.0, γ-H)
55905-13-0	$(CH_3)_2CHCHCO_2CH_3$, Cl	152–153	1740	3.72 (s, 3 H, OCH_3), 4.00 (d, 1 H, J = 6.8, α-H), 2.20 (octet, 1 H, J = 6.8, β-H), 0.94 (d, 6 H, J = 6.8, γ-H)
22421-97-2	$(CH_3)_2CCO_2CH_3$, Cl	29–31 (50–52)[e]	1734[f]	3.62 (s, 3 H, OCH_3), 1.63 (s, 6 H, β-H)
55905-14-1	$CH_3(CH_2)_2CCO_2CH_3$, Cl, CH_3	66–67 (11)	1747	3.73 (s, 3 H, OCH_3), 1.80–2.20 (m, 2 H, β-H), 1.68 (s, 3 H, α-Me), 1.10–1.60 (m, 2 H, γ-H), 0.97 (t, 3 H, J = 6.0, γ-Me)
55905-15-2	$CH_3CH_2CHCHCO_2CH_3$, Cl, CH_3	71–72 (10)	1750	3.70 (s, 3 H, OCH_3), 3.98–4.32 (two doublets,[g] 1 H, J = 5.7 and 8.4, α-H), 1.72–2.30 (m, 1 H, β-H), 1.20–1.72 (c, 2 H, γ-H), 0.85–1.20 (c, 6 H, β- and γ-Me)
55905-16-3	$CH_3CHCH_2CHCO_2CH_3$, Cl, CH_3	71–72 (11)	1750	3.74 (s, 3 H, OCH_3), 4.20 (t, 1 H, J = 8.0, α-H), 1.60–2.10 (c, 3 H, β- and γ-H), 0.96 (d, 6 H, J = 6.0, γ-Me)
25882-62-6		64 (2)	1750[h]	3.82[i] (s, 3 H, OCH_3), 1.81–2.34 (br, 4 H, β-H), 1.17–1.81 (br, 6 H, γ- and δ-H)

[a] Neat. [b] The NMR spectra were measured by a 60-MHz Jeol C-60 HL NMR spectrometer at 25° as ca. 30% solutions in CCl_4. Chemical shifts are given in parts per million relative to internal Me_4Si on the δ scale and coupling constants are reported in hertz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, unresolved multiplet; c, complex; br, broad. [c] Lit.[8] bp 146–150°. [d] Lit.[8] 1750 cm^{-1}. [e] Lit.[8] bp 150°. [f] Lit.[8] 1735 cm^{-1}. [g] Two doublets are probably due to the asymmetric C_α and C_β carbons. [h] Lit.[7] 1748 cm^{-1}. [i] Lit.[7] 3.78 (s) as ca. 20% solutions in CCl_4.

seem to give further support to this mechanism, i.e., the chlorination of aliphatic acids by molecular chlorine in the presence of molecular oxygen, chlorosulfonic acid, and chloranil in the dark may proceed via this enol form or ketene, RCH=C=O, to give α-chloro acid selectively.

Experimental Section

General. All aliphatic acids and chlorosulfonic acid were the best commercial grade available and distilled before use. Commercial chloranil and *m*-dinitrobenzene were purified by recrystallization. Ir spectra were measured by a Perkin-Elmer Model 337 spec-

Table V
Elemental Analyses of New Compounds

Compd	% calcd C	% calcd H	Mol formula	% found C	% found H
$(CH_3)_2CHCHCO_2CH_3$ (Cl)	47.85	7.36	$C_6H_{11}O_2Cl$	46.55	7.52
$CH_3(CH_2)_2CCO_2CH_3$ (Cl)	51.07	7.96	$C_7H_{13}O_2Cl$	50.80	8.22
$CH_3CH_2CHCHCO_2CH_3$ (CH_3, Cl)	51.07	7.96	$C_7H_{13}O_2Cl$	50.97	8.06
$CH_3CHCH_2CHCO_2CH_3$ (Cl, CH_3)	51.07	7.96	$C_7H_{13}O_2Cl$	51.17	7.86

trophotometer and NMR spectra were measured on a 60-MHz Jeol C-60 HL NMR spectrometer at 25° using Me_4Si as an internal standard. Reaction products analyses were done on a Yanagimoto Model GCG 550 gas chromatograph employing a flame ionization detector and a 1.5 m × 3 mm copper column packed with Apiezon grease L 15% on Celite 545 of 80–100 mesh. The column was operated at 50–200°, with nitrogen as a carrier (30 ml/min) and hydrogen of flow rate 30 ml/min. The yields shown in Tables I–III were determined by the internal standard method.

Typical Procedure for the Chlorination in Table I. Butyric acid (17.62 g, 0.2 mol), concentrated H_2SO_4 (1.96 g, 0.02 mol), and *m*-dinitrobenzene (2.78 g, 0.017 mol) were placed in a 100-ml four-necked flask fitted with a Dimroth condenser, a thermometer, and a gas inlet tube with sponge glass end. After gaseous N_2 was passed through the reaction mixture for ca. 30 min to expel oxygen, the butyric acid was chlorinated at 120° for 3 hr by bubbling a mixture of gaseous chlorine (flow rate ca. 100 ml/min) and oxygen (200 ml/min) dried with concentrated H_2SO_4 with magnetic stirring in the dark. After completion of the reaction, chlorine remaining in the solution was expelled out by bubbling N_2 gas into it for ca. 30 min. In general, a fraction of the reaction mixture (0.5–1.5 g) was added with water (10 ml) and extracted three times with chloroform (each 10–20 ml). The dried chloroform extract, after being dried with anhydrous Na_2SO_4 and vacuum distilled, was esterified with diazomethane in ether and the ether solution was analyzed by GLC.

Typical Procedure for the Chlorination in Tables II and III. In a 300-ml four-necked flask fitted with a Dimroth condenser, a thermometer, and a gas inlet tube were placed isovaleric acid (61.2 g, 0.6 mol), chlorosulfonic acid (6.20 g, 0.06 mol) as an acid catalyst, and chloranil (0.743 g, 0.003 mol). After being passed with N_2 gas for ca. 30 min to expel oxygen, a mixture of Cl_2 and O_2 gas (in a mole ratio of 2:1) were introduced into the substrate in the dark at 140°. Aliquots (2 ml) of the reaction mixture were taken out at given intervals of time and esterified by refluxing with a mixture of concentrated H_2SO_4 (0.05 ml), methyl alcohol (3 ml), and ethylene dichloride (8 ml) for 10 hr. The cooled mixture was separated and the organic layer was washed successively with water, aqueous $NaHCO_3$, and again with water. The organic solution was dried over anhydrous Na_2SO_4 and then analyzed by GLC.

The analogous work-up was applied to other acids. The elemental analysis data for new compounds among obtained α-chloro acids are shown in Table V.

Registry No.—Chlorosulfonic acid, 7790-94-5; chloranil, 118-75-2; isovaleric acid, 503-74-2; α-chloroisovaleric acid, 921-08-4.

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An Acid Protecting Group

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Received May 13, 1975

In some related work we were interested in utilizing an acid protecting[2] group that could be readily cleaved under mild acidic conditions as well as under catalytic-reductive conditions. The model studies reported herein indicate that an acid protected as its benzyloxymethyl ester can fulfill these two requirements.

The benzyloxymethyl esters can be synthesized in good yields by reaction of the sodium salt of the acid with benzyl chloromethyl ether in hexamethylphosphoramide[3,4] at room temperature. Employing these reaction conditions,

$$\underset{\text{I or II}}{R\text{—}\overset{O}{\overset{\|}{C}}ONa} + PhCH_2OCH_2Cl \xrightarrow[\text{room temp}]{HMPA} \underset{\text{III or IV}}{R\text{—}\overset{O}{\overset{\|}{C}}OCH_2OCH_2Ph}$$

I, R = n-C_5H_{11}; II, R = Ph

III, R = n-C_5H_{11}; IV, R = Ph

benzyloxymethyl hexanoate (III) and benzyloxymethyl benzoate (IV) were prepared in 73 and 68% yields, respectively.

Hydrolysis of the benzyloxymethyl esters III and IV with an aqueous HCl–THF solution at room temperature for 2 hr afforded the corresponding acids hexanoic V and benzoic VI in good yields.

$$\underset{\text{III or IV}}{R\text{—}\overset{O}{\overset{\|}{C}}OCH_2OCH_2Ph} \xrightarrow[\text{room temp. 2 hr}]{\text{aq HCl-THF}} \underset{\text{V or VI}}{R\text{—}\overset{O}{\overset{\|}{C}}OH}$$

V, R = n-C_5H_{11}; VI, R = Ph

$$\text{III or IV} \xrightarrow[\substack{\text{ETOH, 1 atm}\\ \text{room temp}}]{5\%\ Pd/C\text{-}H_2} \text{V or VI}$$

Reductive removal of the benzyloxymethyl group in esters III and IV was readily achieved by reduction of III and IV, respectively, with 5% Pd/C in ethanol in the presence of hydrogen at 1 atm at room temperature. These results are summarized in Table I.

Experimental Section

Benzyloxymethyl Hexanoate (III). Sodium hexanoate (13.8 g, 0.1 mol), benzyl chloromethyl ether (15.7 g, 0.1 mol), and hexamethylphosphoramide (80 ml) were placed in a 250-ml flask fitted with a stopper and the resulting mixture was allowed to stir at room temperature for 2 days. The reaction mixture was poured into 700 ml of water and extracted with 2 × 500 ml of hexanes. The hexane extracts were combined and washed consecutively with a

Table I
Hydrolysis and Catalytic Reduction of Benzyloxy Esters

Esters	Hydrolysis	Catalytic reduction	Product	% yield
$PhCO_2CH_2OCH_2Ph$	aq HCl–THF		$PhCO_2H$	98
$PhCO_2CH_2OCH_2Ph$		5% Pd/C–H_2	$PhCO_2H$	100
$C_5H_{11}CO_2CH_2OCH_2Ph$	aq HCl–THF		$C_5H_{11}CO_2H$	75
$C_5H_{11}CO_2CH_2OCH_2Ph$		5% Pd/C–H_2	$C_5H_{11}CO_2H$	69

5% sodium bicarbonate solution (500 ml) and water (500 ml) and dried over anhydrous magnesium sulfate. Filtration and concentration of the organic phase on a rotary evaporator yielded an oil. Distillation of the oil afforded 17.2 g (73%) of benzyloxymethyl hexanoate: bp 101–104° (0.08 mm); ir (neat) ester band at 1750 cm^{-1}; NMR (CCl_4) δ 7.44 (s, 5 H), 5.4 (s, 2 H), 4.71 (s, 2 H), 2.25 (t, 2 H), 1.1–2 (m, 6 H) and 0.9 (t, 3 H).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.31; H, 8.41.

Benzyloxymethyl Benzoate (IV). Sodium benzoate (18.7 g, 0.13 mol), benzyl chloromethyl ether (20.2 g, 0.13 mol), and hexamethylphosphoramide (75 ml) were stirred at room temperature for 48 hr and the reaction mixture was worked up by the above procedure. Distillation afforded 21.2 g (68%) of benzyloxymethyl benzoate: bp 122–124° (0.06 mm); ir (neat) ester band at 1725 cm^{-1}; NMR (CCl_4) δ 4.74 (s, 2 H), 5.67 (s, 2 H), 8.02–8.22 (m, 2 H), 7.20–7.50 (m) and 7.30 (s) [(m) + (s), 8 H].

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.52; H, 5.89.

Ester Hydrolysis. Benzoic Acid VI. Benzyloxymethyl benzoate (IV, 1.0 g, 0.0041 mol) was dissolved in an aqueous HCl–THF solution (8 ml of concentrated HCl, 6 ml of H_2O, and 36 ml of THF) and the resulting solution was stirred at room temperature for 2 hr. The reaction solution was poured into 100 ml of H_2O and extracted with 2 × 100 ml of ether. The ether extracts were combined and extracted with 3 × 25 ml of 10% $NaHCO_3$. The aqueous basic layers were combined and washed with 75 ml of ether and then acidified carefully with concentrated HCl. The acidic layer was then extracted with 3 × 75 ml of $CHCl_3$ and the chloroform extracts were combined and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent on a rotary evaporator afforded 490 mg (98%) of benzoic acid, mp 121–122° (lit.[5] mp 122.4°). The NMR and ir spectra of benzoic acid were identical with those of an authentic sample.

Hexanoic Acid V. Benzyloxymethyl hexanoate (III, 3.0 g, 0.0126 mol) was dissolved in an aqueous HCl–THF solution (6 ml of H_2O, 8 ml of concentrated HCl, and 51 ml of THF), the resulting solution was stirred at room temperature for 2 hr, and the reaction mixture was worked up by the above procedure. The organic solvent was removed by distillation at 1 atm and the resulting oil was then distilled under vacuum to afford 1.1 g (75%) of hexanoic acid, bp 115–123° (40 mm) [lit.[6] bp 107° (15 mm)]. The NMR and ir spectra of hexanoic acid were identical with those of an authentic sample.

Catalytic Reduction. Benzoic Acid VI. To a solution of benzyloxymethyl benzoate (1.0 g, 0.0041 mol) in absolute ethanol (15 ml) was added 5% Pd/C (400 mg) and the resulting mixture was reduced with H_2 at 1 atm at room temperature. After a hydrogen uptake of 97.6 ml, the reaction mixture was filtered through Celite 545 and the Celite was washed with additional ethanol. The organic filtrate was dried over anhydrous magnesium sulfate; filtration followed by removal of the solvent afforded 500 mg (100%) of benzoic acid, mp 121.6–122.3° (lit.[5] mp 122.4°). The NMR and ir spectra of benzoic acid were identical with those of an authentic sample.

Catalytic Reduction. Hexanoic Acid V. To a solution of benzyloxymethyl hexanoate (III, 3.0 g, 0.0126 mol) in absolute ethanol (20 ml) was added 400 mg of 5% Pd/C, the resulting mixture was reduced at 1 atm at room temperature, and the reaction mixture was worked up by the above procedure. The organic solvent was removed by distillation at 1 atm. The oil residue was dissolved in 10% $NaHCO_3$ (50 ml) and extracted with 100 ml of ether. The ether phase was extracted with 35 ml of 10% $NaHCO_3$ and the basic layers were combined and carefully acidified with concentrated HCl. The acidified mixture was extracted with 3 × 150 ml of chloroform. The chloroform extracts were combined and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent at 1 atm afforded an oil. Vacuum distillation of the oil afforded 1.0 g (69%) of hexanoic acid, bp 115–118° [lit.[6] bp 107° (15 mm)]. The NMR and ir spectra of hexanoic acid were identical with those of an authentic sample.

Registry No.—I, 10051-44-2; II, 532-32-1; III, 55887-43-9; IV, 55887-44-0; V, 142-62-1; VI, 65-85-0; benzyl chloromethyl ether, 3587-60-8.

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Reactions of Oxetane with Imine Salts Derived from Cyclohexanone

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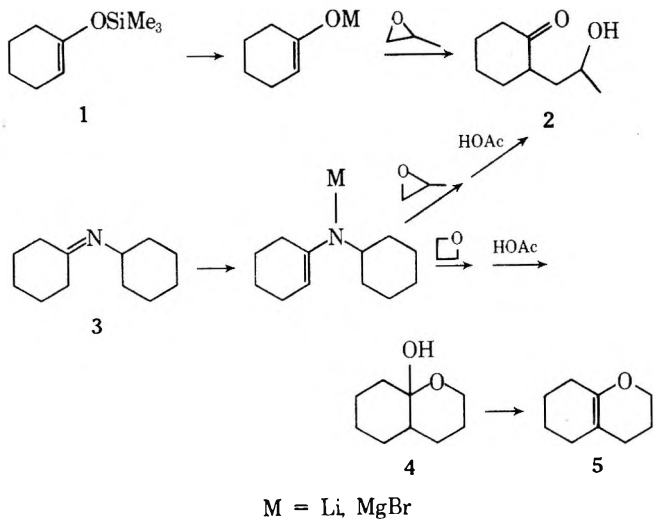
Received May 1, 1975

In connection with our interest in the use of α-methyleneoxetane[1] in nucleophilic ring-opening reactions, e.g., in the Robinson annelation, we have investigated the possibility of alkylating enolates or imine salts with oxetane (trimethylene oxide). For comparison, we have also studied the analogous reactions with an epoxide, propylene oxide. Ring-opening reactions of oxetanes with Grignard,[2-4] organolithium,[3,5] and organoaluminum[6] reagents are known, but few reactions with C-functional nucleophiles are reported.[7] Many nucleophilic ring-opening reactions of epoxides are reported, including reactions with imine salts and with enolates of β-dicarbonyl compounds.[7c,d,8-10]

We have been able to alkylate enolates of cyclohexanone with propylene oxide, but not with oxetane. However, we have found that the imine salt[11] of cyclohexanone is alkylated by both oxetane and propylene oxide in good yields.

When propylene oxide was treated with the lithium or bromomagnesium enolates of cyclohexanone,[12a] the alkylated product **2**[9b,10,14] was formed in low to moderate yields. However, when oxetane was treated with these enolates[12] under a variety of conditions, none of the expected alkylation products, **4**[15] or **5**,[15,16] was detected.[17]

The reaction of oxetane with the bromomagnesium salt of the imine (**3**) of cyclohexanone, followed by acetic acid hydrolysis,[11e] gave the hemiketal **4** in 80% isolated yield. A



similar reaction with the lithium salt of **3** gave a 38% yield by VPC.[18] The corresponding reactions of propylene oxide with the bromomagnesium and lithium imine salts produced keto alcohol **2** in 75% (isolated) and 43% (VPC) yields, respectively.

Harvey and Tarbell have reported the reaction of propylene oxide with the bromomagnesium salt of **3** followed by hydrochloric acid hydrolysis, giving **2** in only 36% yield.[10] In our initial studies of the reactions of oxetane with imine salts of **3**, we employed the hydrochloric acid hydrolysis procedure and obtained quite low (~20%) yields. The milder acetic acid hydrolysis method[11e] is clearly superior.

Nucleophilic ring-opening reactions of both oxetanes and epoxides are known to be greatly facilitated by coordination of the oxygen atom with Lewis acids.[19,20] In the reactions reported here, lithium and magnesium may facilitate the ring openings by acting as Lewis acids.[22] Although alkylations of oxetanes (and epoxides) with simple ketone enolates appear to have little synthetic value, alkylations with the more nucleophilic imine salts clearly have potential synthetic utility.

Experimental Section

Oxetane (Aldrich) and propylene oxide (Eastman) were used as received. Tetrahydrofuran (THF) was distilled from a deep purple solution prepared from sodium and benzophenone. 1,2-Dimethoxyethane (glyme) was distilled from lithium aluminum hydride. Petroleum ether was washed with sulfuric acid, dried (K_2CO_3), and distilled; the fraction of bp 38–41.5° was used. Methyllithium and butyllithium were obtained from Alfa Inorganics.

All reactions were carried out under a nitrogen atmosphere. Melting points were determined on a Fisher-Johns hot stage melting point apparatus. Infrared (ir) spectra were obtained using a Perkin-Elmer Model 137 spectrometer. Nuclear magnetic resonance (NMR) spectra were obtained using a Varian T-60 spectrometer, using tetramethylsilane as the internal reference. Vapor phase chromatographic (VPC) analyses were performed on a Varian Aerograph Model 90-P instrument.[23]

Purification of Authentic Samples of Hemiketal 4 and Enol Ether 5. Following the procedure of Borowitz,[15] hemiketal **4** was obtained as a colorless oil which crystallized on standing: ir (CCl_4) 2.79, 2.95, 3.39, 3.50, 5.88 (very weak), 6.94, 9.28, 10.57 μ; NMR (CCl_4) δ 1.0–2.4 (broad, 13.8 H), 3.3–4.3 (broad, 2 H); 2,4-dinitrophenylhydrazone (from ethanol) mp 127.5–128.5° (lit.[16c] mp 126–128°). Portions of the product were recrystallized from pentane (yielding white crystals, mp 67–69°) and from aqueous ethanol (yielding white crystals, mp 75–78°). VPC analysis (145°)[23a] showed two peaks at 1.2 and 2.2 min in a ratio of 1:4.[8] The two components were separated by preparative VPC. The first, which on reinjection showed only one peak at 1.2 min, was identified as the enol ether **5**: ir (film) 5.91, 8.08, 8.69 μ; the NMR spectrum was identical with that reported.[16b-e] The second component was identified as hemiketal **4** (contaminated with a little **5**) by its ir and NMR spectra; on reinjection in the VPC, it showed two peaks at 1.2 and 2.2 min, indicating partial dehydration to the enol ether **5**.[18]

Propylene Oxide with Enolates of Cyclohexanone. A. Lithium Enolate. To a stirred solution of 30 ml (48 mmol) of methyllithium (1.6 *M* in ether) in 50 ml of glyme was added a solution of 6.22 g (36.5 mmol) of the silyl enol ether **1**[24] in 50 ml of glyme over a period of 1 hr.[12a] After 5 min, 5 ml (4.3 g, 74 mmol) of propylene oxide was added, and the resulting solution was stirred at room temperature for 48 hr. The reaction mixture was poured into saturated $NaHCO_3$ and extracted with three 100-ml portions of ether, and the combined extracts were washed with water, dried (Na_2SO_4, $MgSO_4$), concentrated, and distilled, yielding 1.716 g (30%) of **2** as a colorless liquid: bp 70–75° (0.2 mm) [lit.[10] bp 73–75° (0.2 mm)]; 2,4-dinitrophenylhydrazone (from ethanol) mp 106–109° (lit.[9b] mp 105–108°). VPC analysis (105°)[23a] of **2** showed one major peak (93% pure) at a retention time of 1.7 min. The ir and NMR spectra of **2** were essentially identical with those of an authentic sample of **2** prepared by the method of Harvey and Tarbell.[10]

VPC analysis[23b] of the product of a similar reaction employing decane as an internal standard indicated that a 40% yield of **2** was formed after 48 hr at room temperature.[25]

B. Bromomagnesium Enolate. The bromomagnesium enolate was prepared by treating the silyl enol ether **1**[24] with methylmagnesium bromide in refluxing glyme–HMPA (20:1 v/v) for 55 hr.[12a] Treatment of propylene oxide with this enolate (room temperature, 6 hr) in the presence of decane (internal standard) gave a 19% yield of **2** by VPC.[23b,25]

Oxetane with Imine Salts of Cyclohexanone. A solution of 10.87 g (60.7 mmol) of the imine **3**[26] in 40 ml of THF was added to 35 ml (70 mmol) of ethylmagnesium bromide (about 2 *M* in THF) heated at reflux. After 2 hr, the solution was cooled to 0°, and 5.5 ml (4.9 g, 84.7 mmol) of oxetane was added. The resulting yellow solution was stirred at 25° for 19 hr, then partitioned between ether and brine. The layers were separated and the brine layer was reextracted twice with ether. The combined ether layers were dried (Na_2SO_4) and concentrated, then stirred with 80 ml of petroleum ether and 100 ml of 1 *M* acetic acid for 2 hr at room temperature.[11e] Sodium chloride was added to saturate the aqueous layer, the layers were separated, and the aqueous layer was reextracted twice with ether. The combined organic layers were washed with saturated $NaHCO_3$ and brine, and were dried (Na_2SO_4, $MgSO_4$) and concentrated, yielding 9.5 g of brown oil which crystallized. The solid was separated and washed with petroleum ether, producing 5.57 g of white crystals, mp 74–76°. The combined mother liquor and washing liquid were concentrated, giving oil and crystals. The crystals were distilled (bulb to bulb, oven temperature 110°, oil pump vacuum) giving 1.13 g of white crystals, mp 67–70°; the oil was similarly distilled, giving 0.90 g of white, crystalline solid, mp 61–66° (total yield 80%). The ir spectra of all three fractions were identical with each other and with that of the authentic sample of hemiketal **4** (above). The NMR spectra were equivalent to that of **4**.

VPC analysis[23b] of the product of a similar reaction employing dodecane as an internal standard indicated that an 88% yield of enol ether **5**[18] was formed after 18 hr at 25°.[25]

VPC analysis[23b] of the product of the reaction of oxetane with the lithium salt of **3** (from **3** and *n*-butyllithium at 0°) employing dodecane as an internal standard indicated that a 38% yield of enol ether **5**[18] was formed after 18 hr at 25°.[25]

Propylene Oxide with Imine Salts of Cyclohexanone. A solution of 10.986 g (61.3 mmol) of the imine **3**[26] in 40 ml of THF was added to 35 ml (70 mmol) of ethylmagnesium bromide (about 2 *M* in THF) heated at reflux. After 2 hr, the solution was cooled to 0°, and 6.4 ml (5.5 g, 94.7 mmol) of propylene oxide was added. The resulting yellow solution was stirred for 1 hr at 0° and 1 hr at room temperature, then worked up and hydrolyzed by a procedure identical with that described for the reaction of oxetane with the bromomagnesium salt of **3** (above). The resulting brown oil was distilled through a 7-cm Vigreux column, producing 7.20 g (75% yield) of **2** as a colorless liquid, bp 66–73° (0.50 mm) [lit.[10] bp 73–75° (0.2 mm)]. VPC analysis (130°)[23b] showed one major peak (95% pure) at a retention time of 4.0 min. The ir and NMR spectra were identical with those of an authentic sample of **2** prepared by the method of Harvey and Tarbell.[10]

VPC analysis[23b] of the product of a similar reaction run at 25°, employing decane as an internal standard, indicated that a 67% yield of **2** was formed after 2 hr.[25]

VPC analysis[23b] of the product of the reaction of propylene oxide with the lithium salt of **3** (from **3** and *n*-butyllithium at 0°),

employing decane as an internal standard, indicated that a 43% yield of 2 was formed after 1 hr at 25°.[25]

Acknowledgments. We are grateful to the Colgate-Palmolive Co. for a Fellowship to C.-N. W. We thank the National Science Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Research Corporation, and the Research Council of Rutgers University for support of this research.

Registry No.—1, 6651-36-1; 2, 6126-52-9; 2 DNPH, 23260-65-3; 3, 10468-40-3; 4, 13377-10-1; 5, 7106-07-2; methyllithium, 917-54-4; propylene oxide, 75-56-9; methyl bromide, 74-83-9; ethyl bromide, 74-96-4; oxetane, 503-30-0.

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(20) Ring-opening reactions of oxetanes might be expected to be less facile than those of epoxides because of the difference in strain; however, catalysis by Lewis acids might be more effective with oxetanes, since oxetanes have been shown to be more basic than epoxides.[21]
(21) S. Searles and M. Tamres, *J. Am. Chem. Soc.*, **73**, 3704 (1951); see also S. Searles, Jr., and M. Tamres in ref 19d, pp 243–308.
(22) Several attempts to use compounds of aluminum, boron, or zinc in the reactions with oxetane were not fruitful.
(23) The following aluminum columns were used for VPC analysis: (a) 5% SE-30 on Chromosorb W, 5 ft × 0.25 in.; (b) 10% SE-30 on Chromosorb W, 10 ft × 0.25 in.
(24) (a) Belgian Patent 670,769 (1966); *Chem. Abstr.*, **65**, 5487*d* (1966); (b) A. Bazouin, J. Dunogues, and M. Lefort, French Patent 1,436,568 (1966); *Chem. Abstr.*, **66**, 18764z (1967).
(25) Analysis of several aliquots taken at different times suggested that this was approximately the optimum reaction time.
(26) E. D. Bergmann, E. Zimkin, and S. Pinchas, *Recl. Trav. Chim. Pays-Bas*, **71**, 168 (1952).

An Efficient Synthesis of 4,5-Benzotropone from o-Xylylene Dibromide

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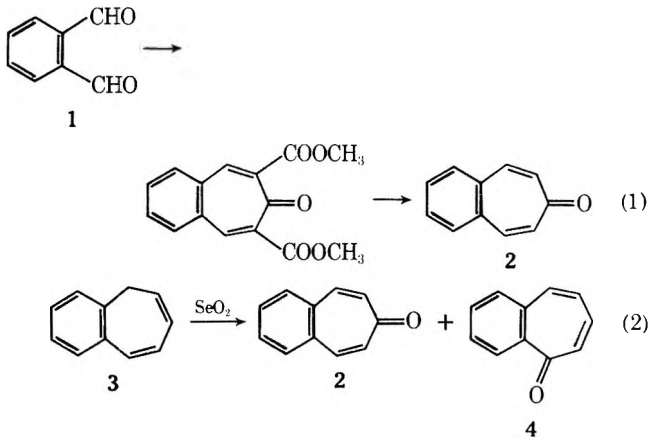
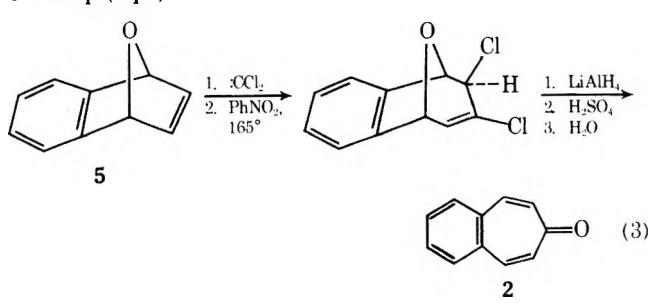
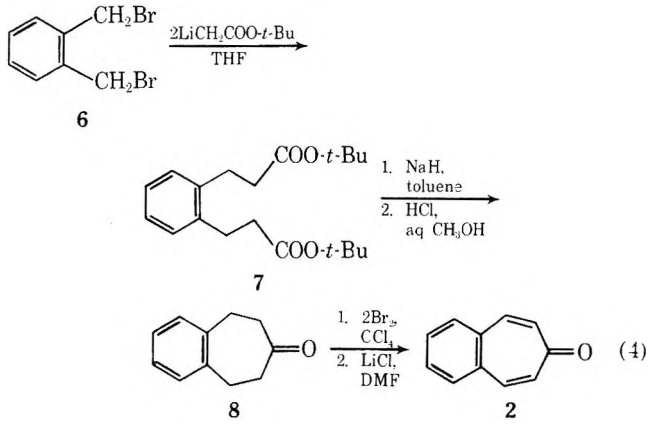
Received June 6, 1975

Our study of the chemical properties of benzazocine[1] and homobenzazocine systems[2] necessitated inter alia the availability of a ready, inexpensive, and plentiful source of 4,5-benzotropone (2). The original procedure of Thiele and Wertz[3,4] involves condensation of *o*-phthaldialdehyde (1) with dimethyl acetonedicarboxylate and subsequent hydrolysis and decarboxylation (eq 1). For large-scale synthesis, however, the cost of 1 becomes prohibitive and the requirements of an autoclave and 200° in the final stage is an unattractive feature. Srivastava and Dev[5] have examined selenium dioxide oxidation of benzocycloheptatriene (3) as a route to 2. Although 4,5-benzotropone is indeed formed (27%), the 2,3 isomer (4, 13% yield) contaminates the product (eq 2). Also, hydrocarbon 3 is not readily available. Battiste's recently discovered multistep route from the benzyne–furan adduct 5 to 2,[6] while novel and elegant in concept, has in our hands not proven amenable to convenient scale-up (eq 3).





In the present approach, we have focused on the fact that 2 is a bisdehydro derivative of 4,5-benzocycloheptenone (8), and have gained simple access to 8 in 51% overall yield by bisalkylation of the readily available *o*-xylylene dibromide (6)[7] with lithio *tert*-butyl acetate[8] and subsequent Dieckmann cyclization[9] (eq 4). Addition of 6 to a cold



(−78°) solution of the lithium enolate in anhydrous tetrahydrofuran followed by gradual warming to room temperature during 3 hr routinely afforded >90% yield of di-*tert*-butyl ester 7 of purity adequate for direct cyclization. A comparable attempt to employ lithio ethyl acetate[10] was unsuccessful. Bromination of 8 with molecular bromine in carbon tetrachloride solution can be conveniently arrested at the α,α'-dibromo ketone stage, since this dibromide precipitates from solution when formed. Direct dehydrobromination of this solid with lithium chloride in dimethylformamide solvent[11] provides 2 in 85% isolated yield. Benzylic bromination with *N*-bromosuccinimide is not equally successful because the ready elimination of hydrogen bromide which ensues has an appreciable deleterious effect. Acid scavengers are seemingly of little value.

In summary, the scheme illustrated by eq 4 has proven to be an especially reliable route to quantities of the title ketone.

Experimental Section

4,5-Benzocycloheptenone (8). To a cold (−78°) solution of 206.4 g (1.10 mol) of *N*-isopropylcyclohexylamine in 700 ml of dry tetrahydrofuran was added 1 mol of *n*-butyllithium in hexane (Alfa Inorganics) via cannula. After being stirred for 20 min at this temperature, the solution was treated dropwise with 127.8 g (1.1 mol) of *tert*-butyl acetate[12] at such a rate that the temperature did not exceed −68°. Some solid which had precipitated earlier was now totally redissolved. After an additional 20 min at −78°, a solution of 110.0 g (0.416 mol) of 6[7] in 500 ml of the same solvent was added below −68°. When all had been introduced, the mixture was allowed to warm to −23° and stirred for 2.5 hr at this temperature. The cooling bath was removed and when 25° was attained, 1 l. of cold hydrochloric acid (100 ml of concentrated HCl diluted to volume) was added and the mixture was poured into 1 l. of brine. The organic layer was separated and combined with the ethereal extracts (3 × 500 ml) of the aqueous phase before washing with 1 *M* hydrochloric acid, drying, and evaporation. There was obtained 130 g (93.5%) of 7 as a light orange oil which was utilized directly; ^{1}H NMR ($CDCl_3$) δ 7.13 (s, 4), 2.75–3.15 (m, 4), 2.3–2.7 (m, 4), and 1.43 (s, 18).

A 5-l., three-necked Morton flask was fitted with a mechanical stirrer, high-dilution adapter to which a condenser was attached,[13] constant addition funnel, and nitrogen inlet tube. Sodium hydride (48.0 g of 50% mineral oil dispersion freed of oil by washing with toluene, 1 mol) was introduced, followed by 1.4 l. of dry toluene and 5 ml of dry *tert*-butyl alcohol. After being blanketed by nitrogen, this slurry was brought to reflux with rapid stirring. A solution of the unpurified 7 in 1.5 l. of dry toluene was added slowly during 3–4 days; subsequently, heating was maintained for an additional 3–4 hr. After cooling, glacial acetic acid (90.0 g, 1.5 mol) was introduced dropwise (some thickening occurs), followed by rapid addition of 1 l. of ice water. The layers were separated and the organic phase was washed with brine, dried, and evaporated.

To the residue was added 400 ml of methanol and 200 ml of 6 *N* hydrochloric acid and this mixture was refluxed for 3 hr, poured onto ice, and extracted with ether. After washing with saturated sodium bicarbonate solution, the organic phase was dried and evaporated. Distillation of the residue afforded 34 g (51% overall from 6) of 4,5-benzocycloheptenone, bp 88° (0.3 mm), mp 41–42° (lit.[14,15] mp 41–42°, 42–43°).

4,5-Benzotropone (2). A magnetically stirred solution of 8 (17.3 g, 0.108 mol) in 325 ml of carbon tetrachloride was treated dropwise with 34.5 g (0.216 mol) of bromine dissolved in 195 ml of the same solvent. Upon completion of the addition, the mixture was brought briefly to reflux. The solvent was removed in vacuo and the off-white solid residue was added to 975 ml of dry dimethylformamide containing 13.05 g (0.308 mol) of lithium chloride. After 1 hr at the reflux temperature under nitrogen, the dimethylformamide was removed in vacuo and the residue was partitioned between ether (400 ml) and water (200 ml). The organic layer was washed with water (3 × 250 ml), dried, and evaporated. Trituration of the residue with boiling pentane afforded 14.3 g (85%) of 4,5-benzotropone as yellow flakes, mp 68–69° (lit.[3,4,6] mp 66–67°, 67.5–68.5°, 69°).

Acknowledgment. The authors thank the National Science Foundation for their support of this investigation.

Registry No.—**2**, 4443-91-8; **6**, 91-13-4; **8**, 37949-03-4; *N*-isopropylcyclohexylamine, 1195-42-2; *tert*-butyl acetate, 540-88-5.

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Reactions of Glycyrrhetic Acid Derivatives with Trifluoromethyl Hypofluorite. Preparation of a New Triterpenoid System

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Received September 4, 1973

Revised June 3, 1975

Trifluoromethyl hypofluorite, CF_3OF, is known to give with some types of double bonds addition products which, after a brief treatment with bases, produce monofluoro compounds.[1] We have investigated the reaction of this reagent with a conjugated enone and with an enol acetate derived from glycyrrhetic acid (1). This is the first attempt to

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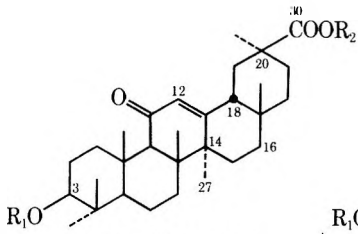
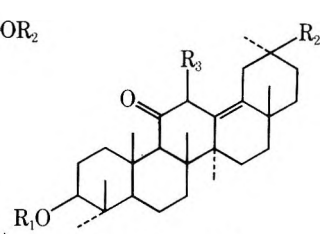
use this reagent in the triterpenoid field. The action of an excess of CF_3OF on methyl 3-*O*-acetylglycyrrhetate (**2**) at room temperature is violent and brings about a far-reaching destruction of the molecule. However, at −70° and with an excess of only 4 equiv of CF_3OF, a single fluorinated compound is obtained in high yield. From the carbonyl absorption ($\tilde{\nu}$ 1715 cm^{-1}) it is clear that the enone double bond has been saturated. The uv spectrum shows a maximum at 290 nm (ϵ 800), which compares well with that of olean-13(18)-en-11-one (**3**) [λ_{max} 286–290 nm (ϵ 600)[2]]. The NMR spectrum shows a hydrogen atom at δ 4.52 ppm (d, J = 49 Hz) while in the ^{19}F NMR spectrum the fluorine atom resonates at relatively low field (117 ppm) as a doublet (J = 49 Hz). These data suggest the presence of a secondary allylic fluorine atom which is also in the α position to a carbonyl. This, and other facts, make it clear that methyl 12-fluoroolean-13(18)-en-11-on-30-oat-3β-yl acetate (**4**) has been formed.



1, $R_1 = H; R_2 = H$
2, $R_1 = Ac; R_2 = Me$

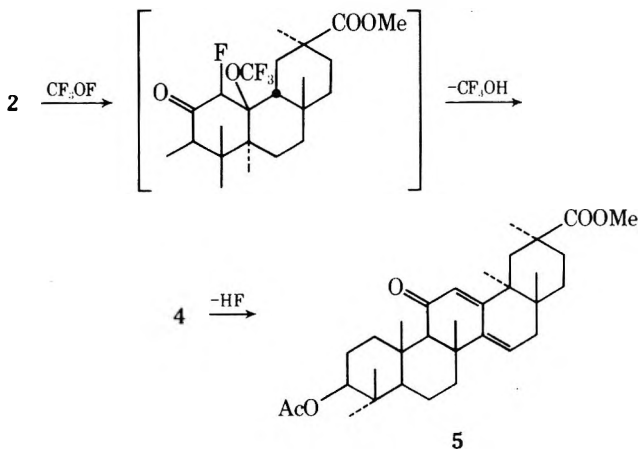


3, $R_1 = R_3 = H; R_2 = CH_3$
4, $R_1 = Ac; R_2 = COOCH_3; R_3 = F$

The β configuration for the fluorine atom is deduced mainly from the ir spectrum. Barton[2] reported for **3** $\tilde{\nu}_{max}$ 1700 cm^{-1}; the fluorine atom thus causes a shift of +15 cm^{-1} and must thus be in the equatorial position.[3] The negative optical rotation ($[\alpha]D$ −37.8°) and the strongly negative background in the ORD spectrum, already apparent at 420 nm, are characteristic of a 13(18) double bond.[4,5] The CD spectrum shows relatively small amplitudes [$\Delta\epsilon_{max}$(355) −0.54, $\Delta\epsilon_{max}$(282) −0.93] in agreement with the geometry of **4**, which does not permit an interaction between the n electrons of the carbonyl and the π electrons of the double bond.[6] Thus the negative Cotton effects could be predicted by application of the ordinary octant rule to the 11-keto group.

It seems that **4** was formed by addition of CF_3OF to the 12 double bond, followed by extrusion of CF_3OH.

In the solid state, **4** is a fairly stable compound, but in polar solvents or when absorbed on silica gel, it decomposes with the loss of the elements of HF to give **5** quantitatively.

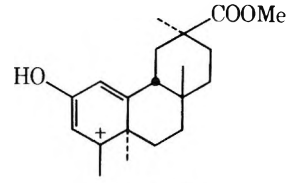


This reaction is hindered by traces of base; otherwise it appears to depend on the polarity of the solvent. In boiling methanol, for example, the transformation requires 30 min as against 2–3 days in chloroform, methylene chloride, or acetone at room temperature. On the other hand, nonpolar solvents such as benzene do not affect **4** at all.

For the reasons detailed below we conclude that **5** is a new triterpenoidal system: methyl 27-nor-18α-methyl-olean-12,14(15)-dien-11-on-30-oat-3β-yl acetate.

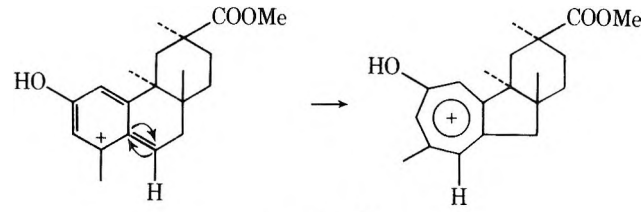
The uv spectrum has a maximum at 293–295 nm (ϵ 0.6 × 10^4), which fits well with the presence of a dienone system. The NMR of **5** shows two vinylic protons of which one, at 5.70 ppm (singlet), is obviously the C-12 hydrogen, while the second at 5.24 ppm is a triplet (J = 7 Hz) and corresponds to the C-15 hydrogen atom. An allylic methylene group is also observed. These two C-16 protons appear as doublets (J = 7 Hz) at 3.04 (H_{eq}) and 2.90 ppm (H_{ax}). Double irradiation of the vinylic hydrogen at 5.24 ppm changes these doublets to singlets. Proton 9α can be observed as a singlet in the region 2.35–2.45 ppm in all glycyrrhetic acid derivatives which possess the enone system at ring C. In compound **5** this proton is shifted to lower field, 2.75 ppm. In the methyl area of the NMR spectrum a methyl is found that resonates at 0.72 ppm, which is the highest recorded value for a methyl in any known glycyrrhetic acid derivative. As can be seen from Dreiding models, C-18 is the only carbon in rings C, D, E that is not affected by the enone system; thus a methyl at C-18 would not suffer any deshielding effects. On the other hand, the C-28 methyl is shifted to lower field (from its usual position of 0.82 ppm to 0.90 ppm), a shift due to the deshielding effect of the dienone system.[7]

The suggested structure is further supported by the mass spectrum. One of the typical ions of the methyl olean-12-en-11-one system is of type a, m/e 317.[8]



a, m/e 317

In the tens of glycyrrhetic acid derivatives which we have studied, this ion has never been found to be the most intense fragment. Only in the mass spectrum of **5** the ion of type a′ is found (at m/e 315) as the most intense one. This

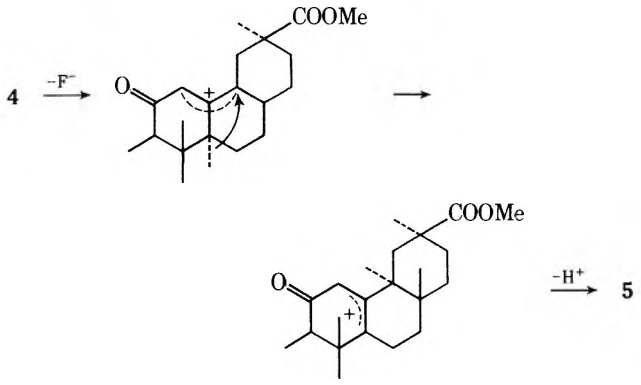


a′, m/e 315

can be explained by the high stability this ion should have; perhaps its formation is followed by isomerization to the corresponding tropylium ion.

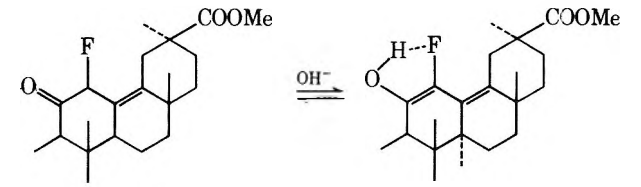
The CD of **5** supports the presence of a conjugated dienone system. The outstanding features of the spectrum are the large bathochromic shift of the Cotton effects and their very large amplitudes:[9] $\Delta\epsilon_{347.5}$ −2.17, $\Delta\epsilon_{283}$ −33.40. The negative sign of the n → π^* region at 347.5 nm is in agreement with Snatzke's "inverse octane rule".[10] We cannot decide what is the source of the second Cotton effect (π → π^*) beyond stating that it may be associated either with the second double bond, at 14(15)[9] or with the transoid junction of the D/E rings.

Some thought should be devoted to the curious migration of the 27 methyl group to C-18. As we cannot explain it by two consecutive [1,2] rearrangements we assume that the whole process is concerted, and [1,3] sigmatropic rearrangement of the methyl group takes place according to the following scheme.



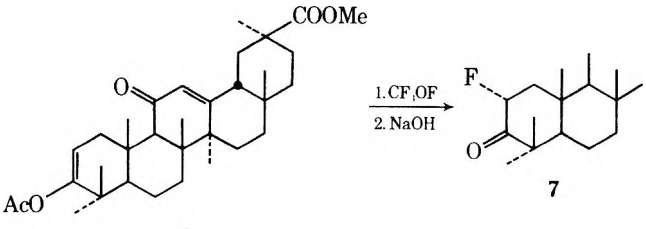
As such rearrangements in small or medium rings can only be suprafacial, it is obvious that the moving methyl would adopt the 18α configuration. As far as we know, this is the first case of a methyl undergoing a [1,3] sigmatropic shift.

We have mentioned that alkali has a retarding effect on the dehydrofluorination of 4. It seems that this is due to the alkali causing enolization, so that a hydrogen bond to the fluorine atom can be formed. The latter is thus stabilized.



4

Trifluoromethyl hypofluorite was also applied to methyl olean-2,12(13)-dien-11-on-30-oat-3β-yl acetate (**6**). Under sufficiently mild conditions, only the enol acetate system reacts, while the double bond at the 12(13) position remains unaffected. After treatment of the crude product with base, methyl 2α-fluoroolean-12-ene-3,11-dion-30-oate (**7**) was obtained in good yield.



6

The NMR spectrum of 7 shows a proton split into a doublet (J = 48 Hz), each half of which is split further into four lines of equal intensity. It is easily found that $J_{H_2H_{1eq}} = 6$, $J_{H_2H_{1ax}} = 12$ Hz and thus it is clear that the hydrogen at C-2 is axial. The ^{19}F NMR spectrum shows double triplets (J_1 = 48, J_2 = 10 Hz) centered at 187 ppm. This splitting can be explained if $J_{F,H\text{-}1ax} = J_{F,H\text{-}1eq}$. Such an equality is only possible for an equatorial fluorine atom.

Experimental Section

General. 18β-Glycyrrhetic acid was kindly supplied to us by D. Grediger of Chemicals and Phosphates Ltd., Haifa, Israel. NMR spectra were measured with a Varian HA-100 instrument, $CDCl_3$ serving as solvent, Me_4Si as internal standard, and $CHCl_3$ as lock signal. Fluorine NMR spectra were determined on the same instrument in $CDCl_3$ solutions at 94.1 MHz using $CFCl_3$ as an external standard. Chemical shifts are reported in parts per million upfield from this standard. Optical rotations were determined in chloroform (c 1.0) with a Perkin-Elmer 141 polarimeter, ir spectra in Nujol mulls, ORD and CD spectra with a Cary 60 spectropolarimeter, and melting points on a Thomas-Hoover capillary apparatus.

The term "treated in the usual way" refers to the treatment of extracts and indicates that they were washed with water till neutral, dried over magnesium sulfate, and evaporated to dryness in vacuo. Solutions of CF_3OF in $CFCl_3$ were prepared as indicated in ref 12.

Methyl 12-Fluoroolean-13(18)-en-11-on-30-oat-3β-yl Acetate (4). To a solution of 4 molar equiv of CF_3OF in 150 ml of $CFCl_3$, cooled at −75°, a solution of 2 g of 2[11] in 50 ml of chloroform was added slowly and the mixture was stirred for 2 hr at that temperature. The excess of the fluorinating reagent was removed with argon and the solvent was evaporated. Trituration of the residue with hexane containing a small amount of benzene gave 1.9 g (92%) of 4: mp 205°; $[\alpha]^{25}D$ −37.8°; ir $\tilde{\nu}_{max}$ 1730, 1715, 1625, and 1250 cm^{-1}; NMR 4.52 (d, 1 H, H-12, J = 49 Hz), 4.47 (q-like, 1 H, H-3α), 3.67 (s, 3 H, methyl ester group), 2.03 (s, 3 H, acetyl protons), 1.26, 1.17, 1.14, 1.14, 0.86, 0.86, 0.86 ppm for methyls 26, 27, 25, 29, 24, 23, and 28, respectively; CD (c 0.21, dioxane) 25° θ_{400} 0, θ_{355} −1790, θ_{330} +52, $\theta_{282.5}$ −3061, θ_{240} −104, θ_{230} −311, θ_{225} −156, $\theta_{217.5}$ −415. For other spectral data see the discussion.

Anal. Calcd for $C_{33}H_{49}FO_5$: C, 72.8; H, 9.0; F, 3.5; mol wt, 544. Found: C, 72.5; H, 8.9; F, 3.8; mol wt, 544 (mass spectrum).

Methyl 27-Nor-18α-methylolean-14(15),12-dien-11-on-30-oat-3β-yl Acetate (5). Treating 4 with boiling methanol for 0.5 hr or dissolving it in methanol, acetone, chloroform, or methylene chloride for a period not longer than 4 days gave a quantitative yield of 5. The same transformation takes place on silica gel: mp 200°; ir $\tilde{\nu}_{max}$ 1725, 1640 (shoulder), 1630, 1250 cm^{-1}; $[\alpha]D$ −358.9°; NMR 3.68 (s, 3 H, methyl ester group), 2.04 (s, 3 H, acetyl protons), 1.43. 1.26, 1.13, 0.86, 0.86, 0.90, and 0.72 ppm for methyls 26, 25, 29, 24, 23, 28, and the 18α methyl, respectively; ORD (c 0.204, dioxane) 25° Φ_{420} −6870, Φ_{305} −57,425, $\Phi_{257.5}$ +89,211, Φ_{240} +70,750; CD (c 0.204, dioxane) 25° θ_{410} 0, $\theta_{347.5}$ −7178, θ_{330} −5845, θ_{283} = −110,235, θ_{240} 0. For other spectral data see the discussion.

Anal. Calcd for $C_{33}H_{48}O_5$: C, 75.4; H, 9.0; mol wt, 524. Found: C, 75.6; H, 9.1; mol wt, 524 (mass spectrum).

Methyl Olean-2(3),12-dien-11-on-30-oat-3β-yl Acetate (6).[13] Methyl 3-deoxy-3-oxoglycyrrhetate[14] (3 g), 60 ml of isopropenyl acetate, and a few drops of concentrated H_2SO_4 were stirred at 70° for 15 hr. About 20 ml of this mixture were distilled off and the residue was poured into water, extracted with chloroform, and treated as usual: yield 2.4 g (74%); mp 249° (from methanol and methylene chloride); ir $\tilde{\nu}_{max}$ 1750, 1735, 1690, 1660, 1620, and 1220 cm^{-1}; $[\alpha]D$ +211°.

Anal. Calcd for $C_{33}H_{48}O_5$: C, 75.6; H, 9.2. Found: C, 75.9, H, 9.3.

Methyl 2α-Fluoroolean-12-ene-3,11-dion-30-oate (7). To a solution of 4 mmol of CF_3OF in 150 ml of $CFCl_3$ at −75°, 1.4 g (2.7 mmol) of 6 in 40 ml of chloroform was added. After 12 min, the excess of the reagent was removed with argon and the solvent was evaporated. The crude product was dissolved in 120 ml of methanol, which contained 6 g of NaOH and 20 ml of water. Dioxane and chloroform were added until the reaction mixture became homogeneous. After stirring for 12 hr, the mixture was poured into dilute hydrochloric acid, extracted with $CHCl_3$, and treated as usual.

Crystallization from methanol gave 1.1 g (82%) of 7: mp 265°; $[\alpha]^{25}D$ = +163.3°; ir $\tilde{\nu}$ 1735 (shoulder), 1725, and 1655 cm^{-1}; NMR 5.71 (s, 1 H, H-12), 5.24 (d, q-like, 1 H, H-2, J_1 = 6, J_2 = 12 Hz), 3.70 ppm (s, 3 H, methyl ester group). For other spectral data see the discussion.

Anal. Calcd for $C_{31}H_{45}FO_4$: C, 74.4; H, 9.0; F, 3.8; mol wt, 500. Found: C, 74.3; H, 9.0; F, 4.0; mol wt, 500 (mass spectrum).

Registry No.—**2**, 10301-74-3; **4**, 56114-28-4; **5**, 56114-29-5; **6**, 38736-92-4; **7**, 56114-30-8; trifluoromethyl hypofluorite, 373-91-1; methyl 3-deoxy-3-oxoglycyrrhetate, 5195-71-1.

References and Notes

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Preparation of Activated Cyclopropanes by Phase Transfer Alkylation

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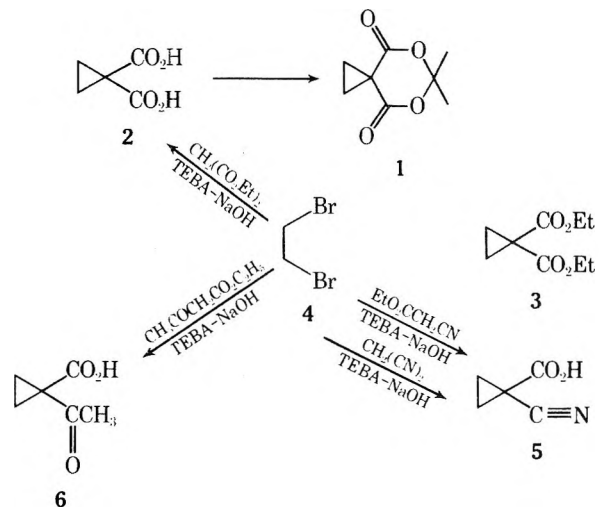
Received April 17, 1975

Recently we described the extreme vulnerability of the spiro acylal 1 to homoconjugate ring opening via nucleophilic attack.[2] Compound 1 has been demonstrated to be a useful synthetic equivalent of $^{+}CH_2CH_2CH(CO_2H)_2$ and $^{+}CH_2(CH_2)_2CO_2H$.

Our route to 1 involved reaction of cyclopropane-1,1-dicarboxylic acid (2) with isopropenyl acetate under the influence of concentrated H_2SO_4. This can be achieved in high (86%) yield. Compound 2 is obtained by saponification of the diester 3. However, the preparation of 3 via the base-induced alkylation of diethyl malonate with 1,2-dibromoethane (4) has hitherto been accomplished in only poor yield.[3,4,5] Furthermore, the inefficiency of this double alkylation necessitates a complicated separation of 3 from diethyl malonate.[4]

In the light of some rather dramatic successes which have been recorded for the alkylation of carbonyl compounds by extractive alkylation through the action of quaternary ammonium hydroxides,[6] it seemed reasonable to study the application of this technology to the synthesis of 1,1-diactivated cyclopropanes.[7] Below we describe what we believe to be the most effective method for the preparation of these valuable synthetic reagents.

We find that reaction of diethyl malonate with 1,2-dibromoethane catalyzed by triethylbenzylammonium hydroxide [generated from the reaction of triethylbenzylammonium chloride (TEBA) and 50% sodium hydroxide] provides a 75% yield of the homogeneous crystalline diacid 2 without need for any purification. Apparently the reaction sequence starts with alkylation of the diester followed by saponification. We are unable to achieve this alkylation when malonic acid is the starting material, presumably because of the difficulties involved in generating synthetically usable concentrations of the required trianion. It is likely that saponification occurs most readily at the stage where enolization of the malonic ester is prevented by disubstitution, i.e., 3. In any case, the phase transfer method has rendered compound 2 and, thus, 1, readily available.



By a similar technology, ethyl cyanoacetate was transformed in 86% yield directly to the crystalline 1-cyanocyclopropanecarboxylic acid (5). Under these conditions, there is no indication for the formation of any diacid, 2. Reaction of ethyl acetoacetate with 4 in the presence of aqueous sodium hydroxide–TEBA gives 1-acetylcyclopropane-1-carboxylic acid (6) in 69% yield after distillation. Unlike reported results in other cases,[6b] better yields were obtained using 4 rather than 1,2-dichloroethane as the alkylating agent.

It is interesting to note that alkylation of malononitrile under phase transfer conditions with 4 gives a 49% yield of the acid 5. We find no indication either in this case or in that starting from ethyl cyanoacetate for the formation of 2.

This methodology should now render diactivated cyclopropanes readily available compounds for organic synthesis.

Experimental Section[8]

Preparation of Cyclopropane-1,1-dicarboxylic Acid (2). To 30 ml of a stirred solution of 50% aqueous sodium hydroxide was added TEBA (3.54 g, 0.015 mol) followed by diethyl malonate (2.40 g, 0.015 mol) and dibromide 4 (4.23 g, 0.023 mol). The reaction mixture was stirred for 1 hr. After dilution with 75 ml of water, the system was extracted with ether. The aqueous layer was acidified with 40 ml of concentrated HCl and extracted with ether. The ether layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave 1.74 g (75%) of 2, mp 134–136° (lit.[9] mp 139–141°), λ_{max} ($CHCl_3$) 5.69, 5.78 μ, whose NMR spectrum [δ $(CD_3)_2CO$ 1.70 (s, 2), 9.50 ppm (s, 1)] indicates it to be homogeneous.

Preparation of Spiro[2.5]-5,7-dioxa-6,6-dimethyloctane-4,8-dione (1). To a stirred suspension of compound 2 (1.30 g, 0.01 mol) and isopropenyl acetate (1.20 g, 0.012 mol) was added dropwise over 30 min 0.181 g of concentrated H_2SO_4. The resulting clear solution was stirred for an additional 30 min and maintained at 0° overnight. Upon dilution with 20 ml of cold water, a solid was obtained by filtration. The solid was twice washed with 5-ml portions of cold water and dried to afford pure 1, 1.40 g (86%), mp 63.5–64.5°.

An analytical sample was obtained by recrystallization from acetone–water: λ_{max} ($CHCl_3$) 5.64, 5.70 μ; δ ($CDCl_3$) 1.82 (s, 3), 1.97 ppm (s, 2).

Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.46; H, 5.98.

Preparation of Cyanocyclopropane-1-carboxylic acid (5). A. From Ethyl Cyanoacetate. To a stirred solution of 40 ml of 50% aqueous sodium hydroxide was added TEBA (4.55 g, 0.02 mol) and a mixture of ethyl cyanoacetate (2.26 g, 0.02 mol) and 1,2-dibromoethane (7.52 g, 0.04 mol). Evolution of heat was noted and the ambient temperature was maintained by external cooling.[10] Stirring was continued for 1 hr. After dilution with 100 ml of water, the system was extracted with ether. The aqueous layer was acidified with 50 ml of concentrated HCl and extracted with ether.

The ether layer was washed with brine and dried over $MgSO_4$. Removal of the solvent at the water pump gave 1.91 g (86%) of **5**: mp 142–144° (lit.[11] mp 145–147°); λ_{max} ($CHCl_3$) 4.43, 5.60, 5.81 μ; δ $(CD_3)_2CO$ 1.65 (s, 4), 11.24 ppm (s, 1).

B. From Malononitrile. The reaction was carried out under conditions similar to those described above, except that the reaction time was reduced to 15 min. Thus 1.32 g (0.02 mol) of malononitrile gave 1.09 g (49%) of **5**, mp 142–144°.

Preparation of Acetylcyclopropane-1-carboxylic Acid (6). To 40 ml of a 50% solution of aqueous sodium hydroxide at 60° was added TEBA (2.27 g, 0.01 mol) following a solution of ethyl acetoacetate (2.60 g, 0.02 mol) and 1,2-dibromoethane (7.52 g, 0.04 mol). The resultant clear mixture was stirred for 1 hr, diluted with 100 ml of water, and extracted with ether. The aqueous layer was acidified with concentrated HCl and extracted with ether. The ether layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent at the water pump left a residue which was evaporatively distilled (bp ca. 110°, 0.3 mm) to give **6**:[12] 1.77 g (69%); λ_{max} ($CHCl_3$) 5.71, 5.90 μ; δ ($CDCl_3$) 1.69–1.78 (m, 4), 2.28 (s, 3), 12.07 ppm (s, 1).

Acknowledgments. This research was supported by an Andrew Mellon Foundation Postdoctoral Fellowship to R.K.S. and by PHS Grant CA-12107-10. NMR spectra facilities were supported by PHS Grant RR-00292-03.

Registry No.—**1**, 5617-70-9; **2**, 598-10-7; **4**, 106-93-4; **5**, 6914-79-0; **6**, 56172-71-5; diethyl malonate, 105-53-3; isopropenyl acetate, 108-22-5; ethyl cyanoacetate, 105-56-6; malononitrile, 109-77-3; ethyl acetoacetate, 141-97-9.

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Synthesis of δ-Lactones from Cyclohexenones. Preparation of a Vernolepin Analog

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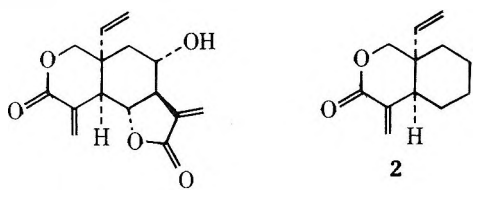
Received April 23, 1975

Lactone **2**, a prototype of the sesquiterpenoid antitumor agent vernolepin (**1**),[1] has been prepared by several workers[2] and has been found to show weak to moderate in vitro cytotoxicity in the CCNSC KB cell culture screen.[2f] The suggestion that the α-methylene δ-lactone moiety of vernolepin may contribute to this molecule's physiological activity is interesting and has prompted us to prepare other related α-methylene δ-lactones for evaluation. Since the angular vinyl group is apparently not crucial to activity (vernolepin and dihydrovernolepin have essentially the same activity),[3] lactones **3** and **4** have been selected for physiological evaluation. Lactone **3** is available by a route involving ozonolytic cleavage of a silyloxyalkene.[2b] In this paper, we report the preparation of the isomeric lactone **4** by a route which shows some generality for the preparation of δ-lactones.



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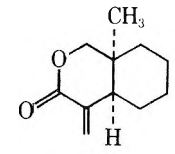

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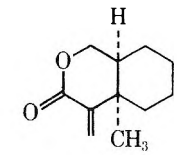
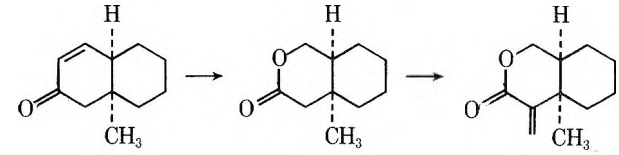


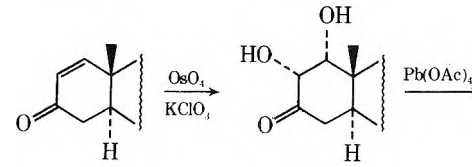
4

Ozonolysis of octalone **5**[4] in methanol solution at −60°, followed by the addition of excess sodium borohydride at 0°, afforded δ-lactone **6** in 45% yield. Introduction of the α-methylene unit by Grieco's two-step procedure[2a,5] (57% overall yield) afforded α-methylene δ-lactone **4**.



5 6 4

The conversion of **5** to **6** represents a convenient method for the synthesis of a δ-lactone when the corresponding cyclohexenone is available. While the yield in this case is only fair (although it has not been optimized), the conversion is a "one-flask" process, and may be generally useful in cases where the requisite cyclohexenone is not especially precious. Pappo has accomplished the same conversion by the following multistep procedure.[6] Overall yields in the Pappo procedure are 50–60%, and the process requires use of the toxic and expensive reagent osmium tetroxide.[7] Consequently, we have examined the generality of our ozonolytic procedure with several other cyclic enones. The results obtained are shown in Table I.



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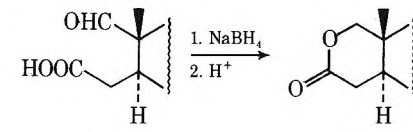


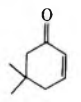
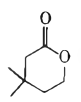
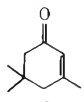
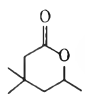
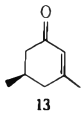
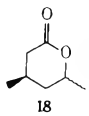
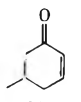
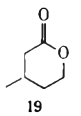
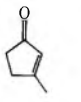
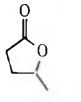
9 10

As can be seen in Table I, modest yields of δ-lactones may be obtained by this process in some cases. The single cyclopentenone tested (compound **15**) gave only an insignificant amount of γ-lactone **20**.

Experimental Section

Synthesis of 8aα-Octahydro-4aα-methyl-3*H*-2-benzopyran-3-one (6). A solution of octalone **5**[4] (1.074 g, 6.55 mmol) in methanol (15 ml) was ozonized at −60° with a Welsbach generator until 2 equiv of ozone had been added. After flushing with nitrogen, the solution was placed in an ice bath (0°) and sodium borohydride

Table I
Lactones from α,β-Unsaturated Ketones

α,β-Unsaturated ketone	Lactone (yield, %)
 11	 16 (58)[a]
 12	 17 (47)[a]
 13	 18 (42)[a,b]
 14	 19 (<25)[c]
 15	 20 (<10)[d]

[a] Distilled yield. [b] Approximately a 1:1 mixture of cis and trans isomers as determined by ^{1}H NMR. [c] Determined by spectral and elemental analyses and GLC. [d] Determined by spectral analysis and comparison with a known sample.

(244 mg, 6.5 mmol) was carefully added. The solution was stirred at 0° for 1 hr, sodium borohydride (244 mg) was again added, the solution was stirred at 0° for an additional 1 hr, and a final batch of sodium borohydride (244 mg) was added. The solution was then stirred at room temperature overnight. The methanol was evaporated off, 20 ml of 10% aqueous HCl was added, and the crude product was isolated by routine ether extraction. Column chromatography [40 g Silicar CC-7, 200–325 mesh, ether–hexanes (1:9)] afforded 490 mg (45%) of lactone **6**: ^{1}H NMR ($CDCl_3$) δ 4.34 (AB q, 2, J = 12 Hz, fine splitting for A and B, $\Delta\nu_{AB}$ = 26.1 Hz), 2.37 (AB q, 2, J = 18 Hz, $\Delta\nu_{AB}$ = 34.9 Hz), 1.0–2.0 (m, 9), 1.17 (s, 3); ir (film) 1742, 1227, 1196, 1092 cm^{-1}; calcd m/e 168.1150 (M^+), found 168.1187 ($C_{10}H_{16}O_2$).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.18; H, 9.73.

Synthesis of 8aα-Octahydro-4aα-methyl-4-methylene-3*H*-2-benzopyran-3-one (4). Lactone **6** (200 mg, 1.19 mmol) was α-methylenated by Grieco's α-hydroxymethylation procedure,[5] yielding 122 mg (57%) of the desired α-methylene lactone (**4**): ^{1}H NMR ($CDCl_3$) δ 6.70 (d, 1, J = 1 Hz), 5.70 (d, 1, J = 1 Hz), 4.37 (AB q, 2, J = 11 Hz, fine splitting for A and B, $\Delta\nu_{AB}$ = 32.2 Hz), 1.3–2.1 (m, 9), 1.30 (s, 3); ir (film) 1727, 1618, 1186, 810 cm^{-1}; calcd m/e 180.1150 (M^+), found 180.1147 ($C_{11}H_{16}O_2$).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found C, 73.08; H, 9.02.

General Procedure for the Preparation of δ-Lactones from Cyclohexenones. A solution of 16.1 mmol of enone in 25 ml of methanol was ozonized at −60° until 1.1 equiv of ozone had been added. After nitrogen flushing, 3 × 600 mg (16 mmol) of sodium borohydride was carefully added over 1-hr intervals at 0°, and the mixture was then stirred at room temperature overnight. The methanol was evaporated off, 40 ml of 10% aqueous HCl was added, and the product was isolated by routine ether extraction (three times). The following compounds were prepared in this manner.

5-Hydroxy-3,3-dimethylpentanoic acid δ-lactone (16) was obtained in 58% yield by bulb-to-bulb distillation [oven temperature 85–95° (0.3 mm)]: ^{1}H NMR ($CDCl_3$) δ 4.40 (t, 2, J = 6 Hz), 2.33 (s, 2), 1.72 (t, 2, J = 6 Hz), 1.13 (s, 6); ir ($CHCl_3$) 1739, 1250, 1078 cm^{-1}; m/e 128 (M^+).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.33; H, 9.50.

5-Hydroxy-3,3-dimethylhexanoic acid δ-lactone (17) was obtained in 47% yield after bulb-to-bulb distillation [oven temperature 85–95° (0.5 mm)]: ^{1}H NMR ($CDCl_3$) δ 4.50 (m, 1), 2.27 (m, 2), 1.6 (m, 2), 1.37 (d, 3, J = 6 Hz), 1.10 (s, 3), 1.07 (s, 3); ir (film) 1736, 1235, 1042, 805 cm^{-1}.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.42; H, 9.76.

5-Hydroxy-3-methylhexanoic acid δ-lactone (18) was obtained in 42% yield after bulb-to-bulb distillation [oven temperature 85–95° (0.5 mm)]: ^{1}H NMR ($CDCl_3$) δ 4.47 (m, 1), 1.40–2.80 (m, 5), 1.40 (d, 3, J = 6 Hz), 1.07 (m, 3); ir (film) 1736, 1244, 1092 cm^{-1}.

Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.27; H, 9.17.

5-Hydroxy-3-methylpentanoic acid δ-lactone (19) was obtained in less than 25% overall yield, as determined by ^{1}H NMR and GLC (crude recovery was only 50%): ^{1}H NMR ($CDCl_3$) δ 4.33 (m, 2), 1.2–3.0 (m, 5), 1.08 (d, 3, J = 6 Hz); ir (film) 1733, 1227, 1092 cm^{-1}; m/e 114 (M^+).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.21; H, 8.84.

4-Hydroxypentanoic acid γ-lactone (20) was obtained in less than 10% overall yield, as determined by ^{1}H NMR and GLC (crude recovery was 36%). ^{1}H NMR and ir revealed absorptions identical with those for commercially available γ-valerolactone (Aldrich); m/e 100 (M^+), 85 ($M^+ - CH_3$).

Acknowledgment. We gratefully acknowledge the National Institutes of Health (CA 12617) for financial support.

Registry No.—**4**, 56247-19-9; **5**, 32980-06-6; **6**, 56247-20-2; **11**, 4694-17-1; **12**, 78-59-1; **13**, 1123-09-7; **14**, 7214-50-8; **15**, 2758-18-1; **16**, 22791-80-6; **17**, 10603-06-2; *cis*-**18**, 24405-13-8; *trans*-**18**, 24405-14-9; **19**, 1121-84-2; **20**, 108-29-2.

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A Facile Synthesis of 1-β-D-Arabinofuranosyl-2-seleno- and -4-selenouracil and Related Compounds

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Received March 28, 1975

2-Thiouridine and 4-thiouridine have been characterized as minor nucleoside components of transfer ribonucleic acid (t-RNA).[1,2] Later several thiopyrimidine nucleosides have been isolated or prepared by multistep syntheses.[3-12] Recently, a facile method was reported by Ueda et al.[13] for the synthesis of 4-thiopyrimidine or 6-thiopurine nucleosides. The selenc analogs, 4-selenouridine and 2-selenouridine, were also synthesized through a coupling method.[14] We have described in recent articles a one-step synthesis of

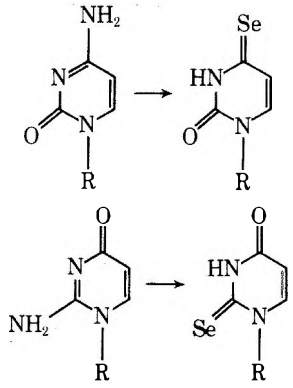
Table I
NMR Data of Some Seleno- and Thiopyrimidines and Pyrimidine Nucleosides

Compd	Registry no.	Chemical shift, ppm (coupling constants, Hz) H-6	H-5	H-1'	Solvent
1-β-D-Arabinofuranosyl-4-selenouracil (I)	56114-31-9	7.69 (7)	6.62 (7)	5.95 (4)	Me_2SO-d_6
1-β-D-Arabinofuranosyl-2-selenouracil (II)	56114-32-0	7.78 (7)	6.08 (7)	6.88 (4)	Me_2SO-d_6
4-Selenouracil (III)	56114-33-1	7.41 (7)	6.49 (7)		Me_2SO-d_6
2-Selenouracil (IV)	16724-03-1	7.35 (7)	5.95 (7)		Me_2SO-d_6
4-Selenouridine (V)	40555-30-4	7.93 (7)	6.63 (7)	5.72 (4)	Me_2SO-d_6
2-Selenouridine (VI)	40555-29-1	8.18 (7)	6.17 (7)	6.72 (4)	Me_2SO-d_6
4-Seleno-2'-deoxyuridine (VII)	56114-34-2	7.87 (7)	6.58 (7)	6.02 (6)	Me_2SO-d_6
4-Thio-2'-deoxyuridine (VIII)	5580-20-1	7.78 (7)	6.33 (7)	6.13 (6)	Me_2SO-d_6
4-Thiouridine	13957-31-8	7.85 (7)	6.33 (7)	5.80 (4)	Me_2SO-d_6
		7.85 (7)	6.63 (7)	5.97 (4)	D_2O
1-β-D-Arabinofuranosyl-4-thiouracil	32754-06-6	7.58 (7)	6.29 (7)	5.99 (4)	Me_2SO-d_6
		7.83 (7)	6.68 (7)	6.27 (4)	D_2O
4-Thiouracil[a]	591-28-6	7.33 (7)	6.18 (7)		Me_2SO-d_6
2'-Deoxycytidine	951-77-9	7.80 (7)	5.75 (7)	6.18 (6)	Me_2SO-d_6
Cytidine	65-46-3	8.17[b]	6.03[b]	6.03[b]	Me_2SO-d_6
		7.90 (7)	6.13 (7)	6.00 (4)	D_2O
1-β-D-Arabinofuranosylcytosine	147-94-4	7.68[c]	5.80[c]	6.03[c]	Me_2SO-d_6
		8.10 (7)	6.28 (7)	6.23 (4)	D_2O
Cytosine	71-30-7	7.72 (7)	5.93 (7)		D_2O-NaOD
Cytidine 5'-monophosphate-Na_2	6757-06-8	8.16 (7)	6.21 (7)	6.10 (4)	D_2O

[a] The compound was synthesized by the method of Y. Mizuno, M. Ikehara, and K. A. Watanake, *Chem. Pharm. Bull.*, **10**, 647 (1962). [b] L. B. Townsend in "Synthetic Procedures in Nucleic Acid Chemistry", Vol. 2, W. Zorbach and R. S. Tipson, Ed., Wiley-Interscience, New York, N.Y., 1973, p 310. [c] Footnote *b*, p 312.

several 6-substituted selenopurine nucleosides and cyclic nucleotides.[15,16] In this paper we describe the application of this new synthetic method to the synthesis of selenopyrimidine and related compounds.

Treatment of 1-β-D-arabinofuranosylcytosine with excess of H_2Se in pyridine–ethylene glycol monomethyl ether at room temperature overnight afforded 1-β-D-arabinofuranosyl-4-selenouracil (I) in 20% yield. In a similar manner, treatment of 1-β-D-arabinofuranosylisocytosine[17,18] with excess of H_2Se in pyridine–DMF at room temperature for 4 days afforded 1-β-D-arabinofuranosyl-2-selenouracil (II) in 26% yield. Cytosine reacted with H_2Se to give 4-selenouracil (III) as expected. Isocytosine, however, was inert to H_2Se in DMF–pyridine, but reacted with H_2Se in pyridine–H_2O to give 2-selenouracil (IV).[19]



R = ribofuranosyl, arabinofuranosyl, 2'-deoxyribofuranosyl, or H

A mechanism of this reaction was proposed[15] and can be correlated to the method of preparation of seleno esters by the selenohydrolysis of imino esters.[20–23]

The advantages of this synthetic procedure are that it can prevent side reactions and the yields are higher than those of the conventional method.

Structures of these selenopyrimidine nucleosides were verified by elemental analysis, uv, and NMR data. The C-6 protons of selenouridines[14] were deshielded as compared with those of arabinofuranosylselenouracils. In order to generalize this effect, 4-selenouridine (V),[14] 2-selenouridine (VI),[14] 4-seleno-2'-deoxyuridine (VII), 4-thio-2'-deoxyuridine (VIII),[24] 1-β-D-arabinofuranosyl-4-thiouracil,[25] and 4-thiouridine[3,13,26] were synthesized. Treatment of cytidine with excess of H_2Se in pyridine–DMF at room temperature for 3 days gave 4-selenouridine (V) in 42% yield. Isocytidine[27] and 2'-deoxycytidine reacted with H_2Se to give 2-selenouridine (VI) and 4-seleno-2'-deoxyuridine (VII), respectively. 4-Thio-2'-deoxyuridine (VIII), 1-β-D-arabinofuranosyl-4-thiouracil, and 4-thiouridine were synthesized from the known method.[13,25] NMR data of these thio- and selenopyrimidines are listed in Table I.

The C-6 protons of the pyrimidine nucleosides are deshielded as compared with those of the corresponding arabinosyl derivatives in Me_2SO solution. Table I also indicates that the C-6 protons of arabinosyl derivatives experience a downfield shift in D_2O solution while there is almost no change for the corresponding nucleosides. This suggests that the arabinosyl derivatives of pyrimidine nucleosides exist in different conformations in Me_2SO and D_2O while pyrimidine nucleosides exist only in one conformation.

In order to determine the conformation of these pyrimidine nucleosides and the arabinosyl derivatives in both Me_2SO and D_2O, it was of interest to compare the chemical shifts of the C-6 protons of these pyrimidine nucleosides with those of known conformation. 4-Thiouridine and 4-thiouridine 5'-phosphate are known to exist in the anti con-

formation in solution.[28,29] Table I reveals that the chemical shift of the C-6 proton of 4-thiouridine in D_2O and Me_2SO is the same while it varies for 1-β-D-arabinofuranosyl-4-thiouracil. It also indicates that the chemical shifts of the C-6 protons for 4-thiouridine and the corresponding arabinosyl derivative are the same in D_2O solution. Thus, 1-β-D-arabinofuranosyl-4-thiouracil, like 4-thiouridine, exists mostly in the anti conformation in D_2O solution, while it probably exists in the syn conformation in Me_2SO. The reason for this conformational change is not clear. It is probably due to the presence of intramolecular hydrogen bonding between the 2′-OH group and the 2-keto (thio or seleno) group of pyrimidine nucleosides containing the 1-β-D-arabinofuranosyl moiety in Me_2SO. This possibility is supported by the NMR data of 4-thio-2′-deoxyuridine and 4-seleno-2′-deoxyuridine. These deoxyuridines, because of the absent of intramolecular hydrogen bonding between 2′-H and the 2-keto group, exist like 4-thiouridine, only in the anti conformation.

The deshielding of the C-6 proton in these pyrimidine nucleosides is probably due to the interaction of the 5′-OH group with the C-6 protons. Pyrimidine nucleosides containing the 1-β-D-arabinofuranosyl moiety in Me_2SO exist in the syn conformation which is free of interaction between the 5′-OH group and the C-6 proton. Similar phenomena were observed by Schweizer et al.,[30] who concluded that the 5′-phosphoryl group in nucleotides with the anti conformation exerts a specific deshielding effect on the H-8 proton of 5′-purine nucleotides and on the H-6 proton (and not H-5) of 5′-pyrimidine nucleotides. Thus the NMR spectra may provide a simple means for distinguishing between nucleosides and arabinonucleosides in pyrimidines.

Table I also indicates a deshielding effect on the anomeric proton of 2-selenouridine and 1-β-D-arabinofuranosyl-2-selenouracil as compared with the corresponding 4-seleno analogs. This is probably due to the anisotropy effect of the seleno group as suggested by Long and Townsend[31] for the thione group.

Interestingly, these selenopyrimidines were stable at pH 7 and 1 while relatively unstable at pH 11. The half-life of 1-β-D-arabinofuranosyl-2-selenouracil (II) at pH 11 is 30 min while 2-selenouridine (VI) is stable for more than 2 weeks. The instability of II in alkali is probably due to attack of the 2′-hydroxyl anion on C-2. The pK_a's of 2-seleno- and 4-selenopyrimidine nucleosides are nearly the same (7.5–7.6), but they are more acidic than their sulfur analogs (pK_a = 8.1–8.2)[9,32] and in turn more acidic than uridine (pK_a = 9.2).[33]

Experimental Section

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Ultraviolet spectra were determined on a Perkin-Elmer Model 402 spectrophotometer. NMR spectra were measured on a Varian A-60A spectrometer in DMSO-d_6 or D_2O with Me_4Si as the internal standard. pK_a values were determined by potentiometric titration using a Radiometer pH meter 26. Elemental analyses were performed by Midwest Microlab, Indianapolis, Ind.

1-β-D-Arabinofuranosyl-4-selenouracil (I). A solution of 550 mg (2 mmol) of arabinofuranosylcytosine in 4 ml of pyridine, 15 ml of ethylene glycol monomethyl ether, and excess of H_2Se was kept at room temperature overnight. The solution was then evaporated to dryness and the residue was dissolved in H_2O. The solution was passed through a Dowex 50 (H^+) column and eluted with H_2O. Evaporation of the solution gave 130 mg (20%) of I: mp 130° dec; uv λ_{max} (H_2O) 261 nm (ε 5131), 366 (16,482); λ_{max} (pH 1) 262 nm (ε 3798), 366 (18,355); λ_{max} (pH 11) 240 nm (ε 7095), 340 (14,915); pK_a = 7.39.

Anal. Calcd for $C_9H_{12}N_2O_5Se \cdot 0.75H_2O$: C, 33.71; H, 4.24; N, 8.74. Found: C, 34.08; H, 4.49; N, 8.32.

1-β-D-Arabinofuranosyl-2-selenouracil (II). A mixture of 170 mg (0.7 mmol) of arabinofuranosylisocytosine in 10 ml of pyridine, 10 ml of DMF, and 0.4 ml of H_2Se was stirred at room temperature for 4 days. The solution was evaporated to dryness. The residue was dissolved in H_2O and filtered. The filtrate was passed through a Dowex 50 (H^+) column and eluted with H_2O. Evaporation of the appropriate fractions and drying in vacuo gave 60 mg (26%) of II: mp 130° dec; uv λ_{max} (H_2O) 223 nm (ε 14,308), 308 (9756); λ_{max} (pH 1) 224 nm (ε 11,488), 308 (7599); λ_{max} (pH 11) 241 nm (ε 13,871), 292 (7316); pK_a = 7.53.

Anal. Calcd for $C_9H_{12}N_2O_5Se \cdot H_2O$: C, 33.24; H, 4.34; N, 8.62. Found: C, 33.10; H, 4.60; N, 8.43.

4-Selenouracil (III). A solution of 300 mg (2.8 mmol) of cytosine in 10 ml of pyridine, 25 ml of H_2O, and 0.7 ml of H_2Se was kept at 70° for 5 days. The mixture was evaporated to dryness. The residue was dissolved in H_2O and filtered. The filtrate was passed through a Dowex 50 (H^+) column and eluted with H_2O. Evaporation of the solution and drying in vacuo at 100° gave 60 mg (12%) of III: mp 235° dec; uv λ_{max} (H_2O) 260 nm (ε 7069), 368 (18,625); λ_{max} (pH 1) 260 nm (ε 6763), 368 (16,708); λ_{max} (pH 11) 235 nm (ε 7722), 348 (14,415).

Anal. Calcd for $C_4H_4N_2OSe$: C, 27.45; H, 2.30; N, 16.00. Found: C, 27.42; H, 2.45; N, 15.78.

2-Selenouracil (IV).[19] A solution of 300 mg (2.7 mmol) of isocytosine in 10 ml of H_2O, 5 ml of pyridine, and excess of H_2Se was kept at 70° for 4.5 days. The solution was evaporated to dryness. The residue was dissolved in H_2O and filtered. The filtrate was passed through a Dowex 50 (H^+) column and eluted with H_2O. The eluent was evaporated to dryness. The residue was recrystallized from EtOH to give 60 mg of IV. The filtrate was evaporated to dryness and dried in vacuo to give additional 110 mg of IV, uv λ_{max} (EtOH) 312 nm (ε 12,313).

4-Selenouridine (V).[14] A solution of 450 mg (1.85 mmol) of cytidine in 20 ml of DMF, 20 ml of pyridine, and 0.7 ml of H_2Se was kept at room temperature for 3 days and then evaporated to dryness. The residue was dissolved in H_2O and passed through a Dowex 50 (H^+) column. The column was eluted with H_2O. The solution was evaporated to dryness. The residue was dissolved in MeOH and filtered. The filtrate was evaporated to dryness and dried in vacuo to give 262 mg (42%) of V. The analytical sample was purified with Avicel plates (1000 μm) and developed with H_2O. The bands containing the compound were scraped out, dissolved in H_2O, and filtered. The filtrate was evaporated to dryness, coevaporated with EtOH, and dried in vacuo: mp 105° dec [lit.[14] mp 150–151° (anhydrous)]; uv λ_{max} (H_2O) 260 nm (ε 4532), 366 (16,332); λ_{max} (pH 1) 260 nm (ε 4320), 366 (16,362); λ_{max} (pH 11) 240 nm (ε 7401), 340 (13,568); pK_a = 7.60.

Anal. Calcd for $C_9H_{12}N_2O_5Se \cdot 0.5EtOH$: C, 36.37; H, 4.58; N, 8.48. Found: C, 35.94; H, 4.51; N, 8.71.

2-Selenouridine (VI).[14] A solution of 450 mg (1.85 mmol) of isocytidine in 10 ml of DMF, 10 ml of pyridine, and 0.6 ml of H_2Se was kept at room temperature for 3 days. The solution was evaporated to dryness. The residue was dissolved in H_2O and passed through a Dowex 50 (H^+) column. The column was eluted with H_2O. Evaporation of the appropriate fractions gave 270 mg (47%) of VI. The compound was suspended in a small amount of MeOH, filtered, and dried in vacuo to give the analytical sample: mp 170° dec [lit.[14] mp 197° dec (anhydrous)]; 225 nm (ε 16,150), 308 (13,650); λ_{max} (pH 1) 223 nm (ε 17,246), 308 (14,856); λ_{max} (pH 11) 240 nm (ε 13,988), 293 (9294); pK_a = 7.57.

Anal. Calcd for $C_9H_{12}N_2O_5Se \cdot 0.25H_2O$: C, 34.68; H, 4.04; N, 8.99. Found: C, 34.85; H, 4.30; N, 8.64.

4-Seleno-2′-deoxyuridine (VII). A solution of 300 mg (1.32 mmol) of 2′-deoxycytidine in 10 ml of DMF, 5 ml of pyridine, and excess of H_2Se was kept at room temperature for 2 days. The solvent was evaporated to dryness. The residue was dissolved in H_2O and passed through a Dowex 50 (H^+) column. The compound was eluted with H_2O. Evaporation of the solution gave 120 mg (31%) of VII: mp 135° dec; uv λ_{max} (H_2O) 260 nm (ε 3142), 368 (11,783); λ_{max} (pH 1) 260 nm (ε 2686), 368 (10,663); λ_{max} (pH 11) 239 nm (ε 5854), 340 (8960).

Anal. Calcd for $C_9H_{12}N_2O_4Se \cdot 0.5EtOH$: C, 38.23; H, 4.81; N, 8.92. Found: C, 38.16; H, 5.21; N, 9.16.

4-Thio-2′-deoxyuridine (VIII).[24] A mixture of 300 mg (1.32 mmol) of 2′-deoxycytidine in 10 ml of DMF, 5 ml of pyridine, and 5 ml of H_2S was kept at 70° for 3 days. The solution was evaporated and coevaporated with EtOH to dryness. The residue was dissolved in H_2O and passed through a Dowex 50 (H^+) column. The compound was eluted with H_2O. The solution was evaporated, coevaporated with EtOH, and dried. The residue was recrystallized from EtOH–Et_2O to give 150 mg (47%) of compound VII: mp

145–147° dec; uv λ_{max} (H_2O) 248 nm (ε 3638), 333 (20,789); λ_{max} (pH 1) 246 nm (ε 4020), 335 (21,026); λ_{max} (pH 11) 318 nm (ε 20,906).

Anal. Calcd for $C_9H_{12}N_2O_4S$: C, 44.25; H, 4.95; N, 11.47. Found: C, 44.49; H, 5.15; N, 11.51.

Acknowledgments. This work has been generously supported by Grants CA 12591-03A1 and CA 13943 from the U.S. Public Health Service. The authors are indebted to Drs. R. E. Parks, Jr., and P. Calabresi for their encouragement during the course of this investigation. The authors also thank Dr. Ronald G. Lawler of the Chemistry Department for helpful discussions on NMR data.

Registry No.—Arabinofuranosylisocytosine, 10212-30-3; isocytosine, 674-97-5; isocytidine, 489-59-8; H_2Se, 7783-07-5.

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Indeno[1,2-*c*]isocoumarin

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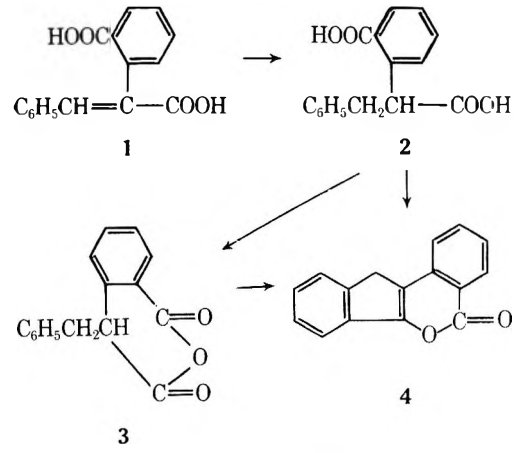
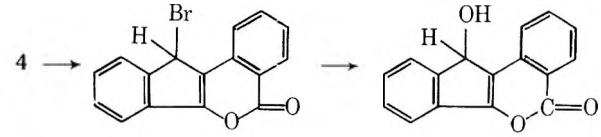
Received May 13, 1975

In studies dealing with the preparation of stabilized 2-arylindenones,[2,3] the synthesis of 2-*o*-carboxyphenylindanone, the precursor of 2-*o*-carboxyphenylindenone, from α-(*o*-carboxyphenyl)cinnamic acid (1) was investigated and found to give indeno[1,2-*c*]isocoumarin (4) instead of the desired product. α-(*o*-Carboxyphenyl)cinnamic acid (1) was prepared in two ways by the hydrolysis of α-(*o*-carboxyphenyl)cinnamonitrile and by the condensation of *o*-carboxyphenylacetic acid with benzaldehyde. Reduction of 1 with Raney nickel alloy in alkali gave α-(*o*-carboxyphenyl)-β-phenylpropionic acid (2), which was converted to the anhydride 3 by heating in toluene. Treatment of the acid 2 with polyphosphoric acid gave indeno[1,2-*c*]isocoumarin (4). The same product was formed by treating the anhydride 3 with aluminum chloride. Proofs for structure 4 were



1 2 3 4

the spectral data and the conversion of 4 to the known 11-keto[1,2-*c*]isocoumarin.[4] Bromination of 4 with *N*-bromosuccinimide gave 11-bromoindeno[1,2-c]isocoumarin (5), which when treated with alkali gave upon acidification 11-hydroxyindeno[1,2-*c*]isocoumarin (6). Evidence for this



5 6

structure was the NMR spectrum, which showed two doublets for the alcohol grouping. These doublets became a singlet in the presence of deuterium oxide.

The infrared spectrum in Nujol for 6 varied with the solvent used for recrystallization of this compound. A sample from benzene showed a sharp free hydroxyl absorption at 3484 cm^{-1} and carbonyl absorptions at 1739 and 1706 cm^{-1} with a shoulder at 1681 cm^{-1}. Compound 6 from ethanol gave two broad absorptions for the hydroxyl at 3268 and 3125 cm^{-1} and carbonyl absorptions at 1761 and 1712 cm^{-1}; the carbonyl at 1712 cm^{-1} was very small. Both samples, however, showed an absorption for the carbon–carbon double bond at 1637 cm^{-1}; its intensity when compared with that for the aromatic double bond at 1616 cm^{-1} was the same. One percent solutions of both samples in tetrahydrofuran, however, gave identical infrared spectra between 2.5 and 7 μ.

The alcohol 6 dissolved in alkali and the resulting solution when allowed to stand exposed to air for 7 days and then acidified gave 11-ketoindeno[1,2-c]isocoumarin.

Compound 6 was also formed by the reduction of 11-ketoindeno[1,2-c]isocoumarin with zinc and acetic acid.

Experimental Section

Melting points are corrected. The ir spectra were recorded with Model 21 and 137 Perkin-Elmer spectrometers, and the NMR spectra were obtained with a Varian A-60 spectrometer.

α-(*o*-Carboxyphenyl)cinnamonitrile. This nitrile was prepared from *o*-carboxyphenylacetonitrile[5] and benzaldehyde using the directions given for the preparation of α-phenylcinnamoni-

trile.[6] Recrystallization from 50% ethanol gave a 73% yield of a pale yellow solid, mp 170–171°.

Anal. Calcd for $C_{16}H_{11}O_2N$: C, 77.09; H, 4.45; N, 5.62. Found: C, 77.00; H, 4.75; N, 5.72.

α-(o-Carboxyphenyl)cinnamic Acid (1). A. α-(o-Carboxyphenyl)cinnamonitrile (11.4 g) was refluxed with concentrated hydrochloric acid (300 ml) for 48 hr. The mixture upon cooling gave a pale yellow solid, mp 197–201°. Purification by dissolving the solid in 10% sodium hydroxide, decolorizing with decolorizing carbon, and acidifying with hydrochloric acid gave 8.8 g of a white solid melting at 215–216°.

Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51. Found: C, 71.69; H, 4.29.

B. A mixture of o-carboxyphenylacetic acid (36.0 g), benzaldehyde (75 ml), and acetic anhydride (28.4 ml) at 70–80° was treated dropwise with triethylamine (50 ml) over a period of 1.5 hr. Heating and stirring were continued for another 4 hr and the resulting dark brown mixture was poured into 10% hydrochloric acid (700 ml) and allowed to stand overnight at 0°. The resulting brown oil was separated and dissolved in benzene (300 ml). Extraction with 5% sodium hydroxide followed by acidification gave a resinous solid which was filtered and treated with benzene (400 ml). The resulting pale tan solid melted at 185–190° and was purified by the method used in part A. The white solid melted at 215–216°, yield 25.8 g.

α-(o-Carboxyphenyl)-β-phenylpropionic Acid (2). α-(o-Carboxyphenyl)cinnamic acid (**1**, 15.5 g) was dissolved in 10% sodium hydroxide (275 ml) and the resulting solution was treated at 90° with small amounts of nickel–aluminum alloy (Raney catalyst, 27 g) during the course of 2 hr. The mixture was heated for an additional 1 hr and filtered, and the residue was washed with hot 10% sodium hydroxide (25 ml) and hot water (50 ml). The filtrate was added dropwise with stirring to 150 ml of concentrated hydrochloric acid at a rate such that the temperature did not exceed 80–85°. The resulting acid (13.5 g) melted at 166–167°.

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.79; H, 5.31.

α-(o-Carboxyphenyl)-β-phenylpropionic Anhydride (3). α-(o-Carboxyphenyl-β-phenylpropionic acid (**2**, 27.0 g) was refluxed with toluene in a flask fitted with a Dean-Stark for 24 hr or until 1.82 ml of water was formed. Removal of the toluene gave a quantitative yield of the anhydride **3**, mp 114–116°, ir (Nujol) 1780, 1740 cm^{-1} (anhydride).

Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.17; H, 4.79. Found: C, 75.97; H, 4.55.

Indeno[1,2-c]isocoumarin (4). A. A solution of α-(o-carboxyphenyl)-β-phenylpropronic acid anhydride (**3**, 5.0 g) in nitrobenzene (100 ml) was treated with aluminum chloride (10.7 g) and heated at 60° for 15 min. The resulting mixture was poured into dilute hydrochloric acid (300 ml) containing ice and then steam distilled to remove the nitrobenzene. The resulting solid was filtered and purified by dissolving in 10% sodium carbonate, treating the solution with decolorizing carbon, and acidifying. The crude product upon recrystallization from 70% ethanol gave 0.88 g of indeno[1,2-c]isocoumarin (**4**) melting at 175–176°; ir (Nujol) 1740 (C=O), 1685 cm^{-1} (C=C); NMR ($CDCl_3$) δ 4.10 (s, 2, CH_2), 7.68 (m, 8, aromatic H).

Anal. Calcd for $C_{16}H_{10}O_2$: C, 81.06; H, 4.53. Found: C, 81.16; H, 4.32.

B. α-(o-Carboxyphenyl)-β-phenylpropionic acid (**2**, 10 g) was added quickly with stirring to a mixture of concentrated phosphoric acid (80 g) and phosphorus pentoxide (80 g) at 160° and maintained at this temperature for 12 hr. The mixture was cooled and added to water (300 ml) and ice (300 g) and the resuling solid was extracted with ether. Removal of the ether gave a product which upon crystallization from 70% ethanol gave 5.14 g of indeno[1,2-c]isocoumarin (**4**), mp 175–176°.

11-Bromoindeno[1,2-c]isocoumarin (5). A solution of **4** (0.60 g) in carbon tetrachloride (15 ml) was treated with *N*-bromosuccinimide (0.46 g) and a trace of benzoyl peroxide and the resulting mixture was refluxed and irradiated for 6 hr. Upon cooling a pale yellow solid (0.8 g) was obtained and purified by stirring with water (20 ml) for 2 hours and recrystallizing from hexane: yield 0.49 g; mp 216–217°; ir (Nujol) 1760 (C=O), 1705 cm^{-1} (C=C); NMR ($CDCl_3$) δ 4.44 (s, 1 H, CHBr), 7.67 (m, 8, aromatic protons).

Anal. Calcd for $C_{16}H_9BrO_2$: C, 59.82; H, 3.01. Found: C, 59.71; H, 2.96.

6a,11a-Dihydro-11-ketoindeno[1,2-c]isocoumarin (6). A. A solution of **5** (0.25 g) in absolute ethanol (15 ml) was stirred at room temperature with 10% sodium hydroxide (1 ml) for 12 hr. Acidification with dilute hydrochloric acid gave a pale orange solid which upon recrystallization from benzene gave a pale green solid melting at 183–184°; yield 0.15 g. Two recrystallizations from ethanol gave a white solid melting at 186–187°; ir (1% in tetrahydrofuran) 3367 (OH), 1754, 1695 (very small, CO), 1639 (C=C), 1645 cm^{-1} (aromatic C=C); NMR (Me_2SO-d_6) δ 5.48 (d, 1, CH, J = 8 Hz), 5.97 (d, 1, OH, J = 8 Hz), 7.17–8.25 (m, 8, aromatic); NMR (Me_2SO-d_6 + D_2O) δ 5.45 (s, 1, CH), 7.17–8.25 (m, 8, aromatic).

Anal. Calcd for $C_{16}H_{10}O_3$: C, 76.79; H, 4.03. Found: C, 76.83; H, 4.23.

B. A solution of 11-ketoindeno[1,2-c]isocoumarin, (0.2 g) in glacial acetic (30 ml) was treated at reflux with zinc dust until the orange color of the solution disappeared. The resulting mixture was filtered into water (70 ml) and the solid formed was recrystallized from benzene, yield 0.14 g, mp 183–184°. A mixture melting point with the sample prepared in procedure A melted at the same point.

11-Ketoindeno[1,2-c]isocoumarin[4]. A solution of **6** in ethanol (15 ml) and 10% sodium hydroxide (1 ml) was stirred at room temperature for 7 days. Acidification with hydrochloric acid gave an orange solid which when recrystallized from benzene melted at 260–261°. A mixture melting point with an authentic sample melted at the same point.

Registry No.—**1**, 39585-13-2; **2**, 2897-88-3; **3**, 2897-89-4; **4**, 5651-52-5; **5**, 5614-25-1; **6**, 56114-26-2; α-(o-carboxyphenyl)cinnamonitrile, 5614-27-3; o-carboxyphenylacetonitrile, 6627-91-4; benzaldehyde, 100-52-7; o-carboxyphenylacetic acid, 89-51-0; *N*-bromosuccinimide, 128-08-5; 11-ketoindeno[1,2-c]isocoumarin, 5651-60-5.

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The *O*,2-Dilithio Derivative of Allyl Alcohol, a Useful Synthetic Reagent

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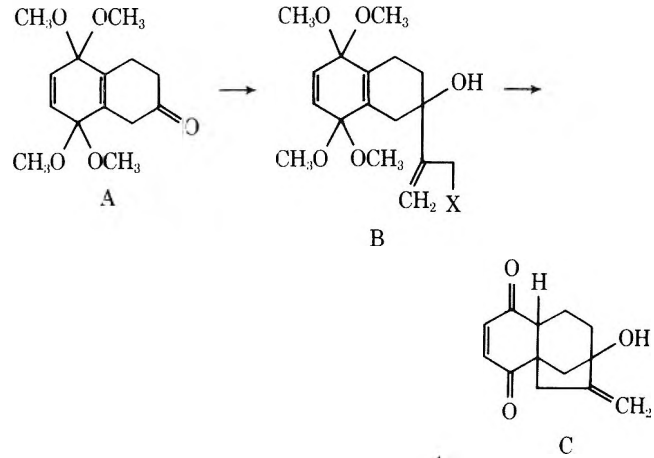
Received April 24, 1975

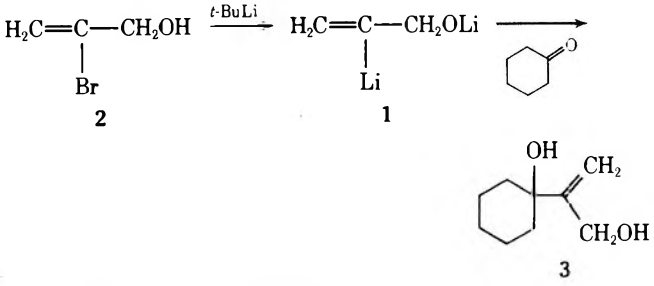
In connection with research directed toward a synthesis of gibberellic acid,[1] a reagent was required for effecting the sequence A → B → C. The ideal candidate seemed to be



the previously unknown *O*,2-dilithio derivative of allyl alcohol, $H_2C{=}C(Li)CH_2O^-Li^+$ (**1**). A similar reagent,

$H_2C{=}C(Li)CH_2N(CH_3)_2$, had been generated and utilized advantageously in earlier work in these laboratories.[2] It was also known that the reaction of metals such as magnesium with ethers of 2-bromoallyl alcohol leads rapidly to allene presumably via the intermediate $H_2C{=}C(Met)CH_2OR$.[3] The generation of 1 has in fact been found to be quite straightforward. Communication of our results at this time has been prompted by the obvious practicality and usefulness of 1 and also by the appearance of a recent paper[4] dealing with two reagents of the same general type (substituted 2-oxido vinyllithium derivatives).

Treatment of the readily available[5] 2-bromoallyl alcohol (2) in ether with 2.5 equiv of *tert*-butyllithium[6] at −78 to 0° resulted in formation of 1 as evidenced by the isolation of the adduct 3 in 73% yield after reaction with cyclohexanone.



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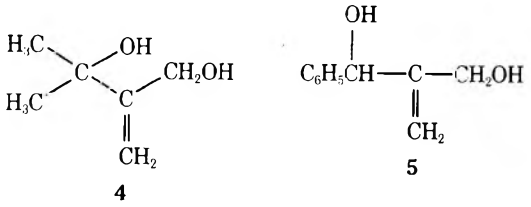

4 5

Experimental Section

General Method. 2-(1′-Hydroxycyclohexyl)allyl Alcohol (3). To a solution of 413 mg (3.01 mmol) of 2-bromoallyl alcohol in 8 ml of ether at −78° was added slowly 7.65 ml of 0.99 *M* *tert*-butyllithium in pentane. The solution was quickly warmed to 0° and stirred for 4 hr. Cyclohexanone (98.5 μl, 1.0 mmol) was added to the reaction solution and stirring was continued for an additional 1 hr at 0°. The reaction was hydrolyzed with methanol and a minimal amount of water, and the aqueous phase was extracted with ether. The ethereal extracts were combined with the organic phase of the reaction, dried (brine and Na_2SO_4), and concentrated. Preparative TLC (silica gel, 1:1 benzene–ether, R_f 0.25) of the residue gave 113 mg of diol 3 as a clear, colorless oil (73%): ir (film) 3600–3100, 2930, 2855, 1640, 1030, 960, and 905 cm^{-1}; NMR ($CDCl_3$) δ 5.13 (2 H, s, =CH), 4.28 (2 H, s, $-OCH_2-$), 3.03 (2 H, br, OH), and 2.1–1.4 (10 H, br s, $-CH_2-$). After recrystallization from hexane–ether, crystalline 3, mp 48.5–50°, was obtained, mass spectrum *m/e* (% of base peak) 156 (4), 138 (19), 95 (64), 81 (64), 67 (90), 55 (100).

Spectroscopic data for 4: ir ($CHCl_3$) 3600–3100, 2970, 1640, 1460, 1375, 1365, 1155, 1010, 915 cm^{-1}; NMR ($CDCl_3$) δ 5.15 (2 H, s, =CH), 4.32 (2 H, s, $-OCH_2-$), 3.47 (2 H, br, OH), 1.60 (6 H, s, $-CH_3$); mass spectrum *m/e* (% of base peak) 101 (69), 83 (39), 59 (100).

Spectroscopic data for 5: ir (film) 3600–3100, 3025, 2870, 1650, 1490, 1450, 1020, 915, 700 cm^{-1}; NMR ($CDCl_3$) δ 7.32 (5 H, s, ArH), 5.25 (1 H, s, ArCHO), 5.15 (2 H, s, =CH), 3.98 (2 H, s, OCH_2), 3.52 (2 H, br, OH); mass spectrum *m/e* (% of base peak) 164 (0.6), 146 (96), 97 (80), 79 (100), 77 (97).

Registry No.—1, 56030-45-6; 2, 598-19-6; 3, 56030-46-7; 4, 56030-47-8; 5, 56030-48-9; *tert*-butyllithium, 594-19-4.

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(6) See E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, **94**, 7210 (1972), for the generation of vinylic lithium derivatives using 2 equiv of *n*-butyllithium. In this case the use of somewhat larger amounts of *tert*-butyllithium was found to result in higher yields of 1, perhaps owing to competing reaction(s) of *tert*-butyllithium (e.g., with solvent or with 2 to form lithiated allenes).

(7) This work was assisted financially by a grant from the National Science Foundation.

Dehydrobromination of α-Bromo Ketones with Palladium Tetrakis(triphenylphosphine)

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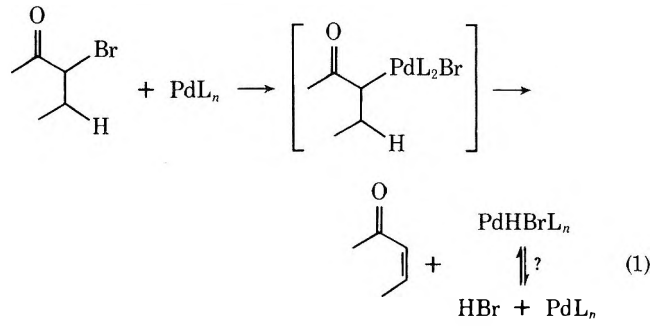
Received March 25, 1975

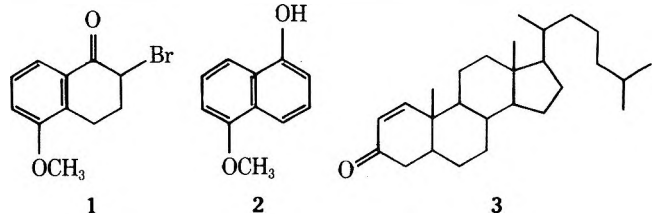
The conversion of ketones to α,β-unsaturated ketones is important in organic synthesis. The most widely used pathway for this transformation has consisted in preparation and dehydrohalogenation of intermediate α-bromo ketones. These dehydrobrominations usually require quite vigorous conditions.[1] This note reports our attempts to develop a mild method for this type of elimination using palladium tetrakis(triphenylphosphine).[2]

It was hoped that $Pd(PPh_3)_4$ would undergo facile oxidative addition with α-bromo ketones just as Pd(0) complexes do with other organic halides.[3] The resulting species, for which one possible representation is shown in eq 1,[4,5] might be expected to expel a β hydrogen along with palladium to form enone.[6] Presumably, the intermediate(s) involved would be similar to those in the direct oxidation of ketones to enones using Pd(II) salts.[7-9] The proposed method offers the potential advantage of regioselectivity in enone formation and could, in principle, be catalytic in palladium without added Cu(II) salts.[7,9]



(1)

The method works well in the case of 2-bromo-1-tetralones, where the initially formed enone can aromatize simply by tautomerization. When 5-methoxy-2-bromo-1-tetralone (1) is treated with 1 equiv of $Pd(PPh_3)_4$ in benzene under nitrogen, it is converted to 5-methoxy-1-naphthol (2)



1 2 3

Table I
Dehydrobromination of α-Bromo Ketones with $Pd(Ph_3P)_4$

α-Bromo ketone (registry no.)	Product(s) (% yield)	Conditions[a]
1	2[b] (94)	PhH, N_2, Et_3N (1.1 equiv),[c] 40°, 1.5 hr[c]
2-Bromo-1-tetralone (13672-07-6)	1-Naphthol[b] (90-15-3)	PhH, N_2, room temp, 3 min[d]
2α-Bromocholestan-3-one (23737-88-4)	3 (~40) Cholest-4-en-3-one (~15) Cholestan-3-one (~35)	PhH, N_2, 80°, 2 hr
4α-Bromocholestan-3-one (56245-74-0)	Cholest-4-en-3-one (36) Mixture of 3 and cholestan-3-one (45)	PhH, N_2, 50°, 12 hr[e]
2-Bromocyclododecane (31236-94-9)	Mixture of *cis*- and *trans*-cyclododecenone (~50)	PhH, N_2, Et_3N (1.3 equiv),[c] room temp, 6 hr
2-Bromocyclohexanone (822-85-5)	Cyclohexenone (70)[f] Cyclohexanone (22)[f]	PhH, N_2, room temp, 8 hr

[a] 1 equiv $Pd(PPh_3)_4$ unless otherwise noted. [b] Only product by TLC. Registry number of 1-naphthol is in parentheses. [c] Reference 8. [d] Time of reaction varied considerably depending on the $Pd(PPh_3)_4$ used. [e] 2 equiv of $Pd(PPh_3)_4$. [f] GLC yield, not isolated.

quantitatively by TLC (94% isolated yield) with a reaction time varying from 3 min to 2 hr depending on the particular preparation of $Pd(PPh_3)_4$ used. 2-Bromo-1-tetralone is equally effectively dehydrobrominated to 1-naphthol. Appropriate control reactions were run to determine that the palladium reagent is indeed essential for the dehydrobrominations.

The method is less successful, however, with α-bromo ketones which cannot lead directly to phenolic products. Treatment of 2-bromocyclohexanone with $Pd(PPh_3)_4$ at room temperature for 8 hr gave 70% cyclohexenone and 22% cyclohexanone (GLC yields). Other examples are given in Table I. The steroidal cases, it should be noted, required more vigorous conditions and gave useless mixtures of products, with a disappointing lack of regiospecificity.

Numerous experiments were tried in an effort to make the nontetralone dehydrohalogenations efficient. For example, triethylamine was added to take up hydrogen bromide, which could act as a proton source to facilitate formation of saturated ketone, but this had no effect.[10] Similarly, addition of norbornadiene to take up hydrogen had no effect. Other Pd(0) and Pd(II) complexes, e.g., palladium bis(dibenzylideneacetone)[11] and palladium acetoacetonate,[12] were ineffective even for dehydrobromination of 1. Pure cholest-1-en-3-one (3) was placed in a reaction of 1 with $Pd(PPh_3)_4$ to see if reversibility of hydrogen loss (which would be indicated by formation of cholestan-3-one) in systems which cannot go on to naphthol might be responsible for the low yield of enone in the steroidal cases, but the 3 was recovered unchanged. Use of less than 1 equiv of $Pd(PPh_3)_4$ in reaction with 1 resulted in lower yields of 2; dehydrobromination catalytic in palladium was not observed.

Several interesting unanswered questions remain concerning the potential of this dehydrobromination method. In particular, one would like to know why the tetralones undergo elimination uniquely effectively among the substances used.[13] However, our motivation to pursue this research further was significantly reduced by the recent reports of the development of an efficient, mild, and apparently versatile preparation of α,β-unsaturated ketones from ketones via α-selenium derivatives.[14-16]

Experimental Section

Melting points were determined in open capillaries on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 137 or 333 spectrometer. The benzene used was distilled and stored over 4 Å molecular sieves, and had nitrogen bubbled through it before use.

Palladium Tetrakis(triphenylphosphine). The $Pd(PPh_3)_4$ was prepared either by Fitton's modification[17] of the procedure of Malatesta and Angoletta,[2] or, more conveniently, by the method of Takahashi,[18] which is described here. The recent preparation reported by Coulson[19] would presumably be the current method of choice. A mixture of 0.533 g (0.96 mmol) of palladium bis(dibenzylideneacetone)[11] and 2.133 g (8.1 mmol) of triphenylphosphine in 25 ml of benzene was stirred for 1 hr. The mixture was evaporated in vacuo and the residue was washed with 4 × 10 ml of anhydrous ether to afford 0.970 g (89%) of $Pd(PPh_3)_4$ as a bright yellow powder: mp 109–115° dec (lit.[18] mp 106° dec, lit.[20] mp 104–106° dec, lit.[19] mp 116° dec); ir essentially identical with that of PPh_3 from 4000 to 650 cm^{-1}, but has single band at 500 cm^{-1} vs. bands at 510 and 490 cm^{-1} for PPh_3. The $Pd(PPh_3)_4$ was usually used as prepared, since recrystallization[18] proved troublesome in our hands. Representative dehydrobromination experiments follow.

Conversion of 2-Bromo-5-methoxy-1-tetralone (1) to 5-Methoxy-1-naphthol (2). A mixture of 0.123 g (0.48 mmol) of 1, mp 91–93°,[21] 0.558 g (0.50 mmol) of $Pd(PPh_3)_4$, and 0.53 g (0.53 mmol) of distilled triethylamine in 20 ml of benzene was stirred under nitrogen at 50° for 1.5 hr. The mixture was diluted with ether and extracted three times with 1 *M* NaOH solution. The extracts were acidified to pH 1 with 6 *M* HCl and extracted three times with ether. The ether layers were washed with brine, dried ($MgSO_4$), and evaporated to afford 0.078 g (94%) of 2, which had an ir spectrum identical with that of an authentic sample.[22]

Conversion of 2-Bromocyclohexanone to Cyclohexenone. A mixture of 0.143 g (0.81 mmol) of 2-bromocyclohexanone[23] and 0.933 g (0.81 mmol) of $Pd(PPh_3)_4$ in 30 ml of benzene was stirred under nitrogen at room temperature for 8 hr. The mixture was filtered to remove 0.196 g of a yellow-orange precipitate, tentatively identified as $Pd(PPh_3)_2Br_2$ by the similarity of its ir spectrum to that of $Pd(PPh_3)_2Cl_2$[24] and by mp 270–275° dec (lit.[25] ca. 250° dec). The filtrate was reduced in volume to ca. 15 ml by distillation and 0.082 g of *o*-dichlorobenzene was added as an internal standard previously calibrated with known mixtures[26] for instrument response in GLC analysis. Using a Perkin-Elmer Model 154 vapor fractometer with a 20% SE-30 column at 130°, the GLC analysis indicated that the product contained 70% cyclohexenone and 22% cyclohexanone by comparison of retention times with those of authentic samples.[26]

Conversion of 4α-Bromocholestan-3-one to Cholest-4-en-3-one. A mixture of 0.120 g (0.26 mmol) of 4α-bromocholestan-3-one[27] and 0.601 g (0.52 mmol) of $Pd(PPh_3)_4$ in 25 ml of benzene was stirred under nitrogen at 50° for 12 hr. TLC indicated three principal products: cholestan-3-one, cholest-1-en-3-one, and cholest-4-en-3-one. The reaction mixture was filtered, and the filtrate was diluted with hot hexane and washed with 2 × 100 ml of hot water. The water was extracted with hot hexane and the combined organic layers (ca. 300 ml) were washed with brine, filtered, and evaporated to afford 0.522 g of yellow-brown solid, which ir indi-

cated was mostly triphenylphosphine oxide. A 0.190-g portion of this material was subjected to preparative TLC on silica gel, using 1:4 ether–hexane three times, to afford 0.012 g (36%) of cholest-4-en-3-one, mp 69–73° (lit.[28] mp 81–82°), identified by ir spectrum. From the preparative TLC there was also obtained 0.016 g of a mixture of cholestan-3-one and cholest-1-en-3-one.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—1, 31236-91-6; 2, 3588-80-5; palladium tetrakis(triphenylphosphine), 14421-01-3.

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Complex Formation Between Potassium Acetate and a Simple Triol

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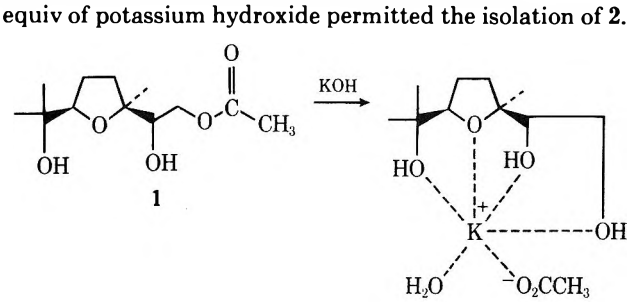
Received January 13, 1975

Complexes of organic compounds with metal ions have been known and studied for many years, but alkali metal ions have not been prominent in these studies until recently. The crown ethers[1] have been in the forefront of research on alkali metal ion complexes, and the first crown ethers have spawned a host of related compounds.[2,3] Other organic compounds[4–7] have shown a more limited capacity for complexing with alkali metal ions, and a number of naturally occurring polyether antibiotics[8–10] have shown remarkable selectivity for specific ions.

Most of the polyether molecules have a systematic configuration of ether, carbonyl, hydroxyl, and/or carboxyl groups that hold the ion in place, while the rest of the molecule serves to shield the ion, and give the overall complex more lipophilic character. X-Ray analysis of the structures of these complexes shows that often six ligand atoms are used in holding sodium and potassium ions. Six is not a magic number, but seems to be the frequent compromise between steric and electrostatic factors. An increasing number of ligands gives a more diffuse electrostatic interaction, but this is countered by the steric requirement of the ligands and their need to approach within a given distance of the ion.[11] The ligand atoms are frequently separated by two-carbon bridges. These consistent elements of structure[12] have made it possible to devise new compounds that show the capacity to complex, and this in part explains the proliferation of activity in this area.

We have observed a potassium acetate complex **2** involving a very small organic compound that has little more than the necessary elements of structure of the polyether ionophores. The four oxygen atoms in the triol have the characteristic two-carbon separations, with a water molecule and the acetate ion apparently functioning as additional ligands. The synthesis of **1** has been previously reported[13] using a neutral permanganate oxidation of geranyl acetate. These workers hydrolyzed **1** to the free triol using a fractional amount of potassium hydroxide. Our use of **1** equiv of potassium hydroxide permitted the isolation of **2**.



1 2

The presence of the water molecule is clearly noted in the ^1H NMR spectrum and confirmed by the microanalysis. It is assumed to be present only to give maximum steric and electrostatic stability to the complex. No attempt was made to remove the water. When the ^1H NMR sample is exchanged with D_2O, the spectrum reverts to that of the triol, which can be recovered from the chloroform solution.

The complex **2** could also be formed by addition of potassium acetate to the free triol. No complex formation could be detected between sodium acetate and the triol. It should be noted that there are only seven oxygens as possible ligands in this complex. The mole of water would seem to be necessary, although this has not been definitively shown. The acetate ion apparently functions similarly to the intramolecular carboxyl group in some ionophorous antibiotics.[9-10]

Experimental Section

Preparation of the Complex 2 by Hydrolysis. The acetate **1** (5 g, mp 107–108°) was treated with 1 equiv of potassium hydroxide in 1:1 MeOH–H_2O (30 ml) at room temperature overnight. The solvents were removed under vacuum, $CHCl_3$ was added, and the solution was filtered. Removal of the $CHCl_3$ under vacuum gave an oil which could be crystallized by dissolving in a minimum volume of MeOH, adding five volumes of ether, and cooling. The complex separated slowly as flocculent, white crystals, mp 53–56° (2 g). Addition of a larger volume of ether caused separation of potassium acetate. The complex could be recrystallized from $CHCl_3$–ether, mp 56–58°. The free triol could be obtained from the first mother liquors and had mp 98–99°.

The complex **2** has ^1H NMR ($CDCl_3$) δ 4.91, s (5 H), 3.65, m (4 H), 1.92, broad s (7 H), 1.24, s (3 H), 1.13, s (3 H), and 1.08, s (3 H). D_2O exchange causes decomposition of the complex as shown by removal of the absorption at δ 4.91, decrease of the integration for the peak at δ 1.92 to four protons, and reversion of the spectrum to that of the triol: δ 3.8, sharpened multiplet (4 H), 1.4–2.4, multiplet (4 H), 1.27, s (3 H), 1.18, s (3 H), and 1.09, s (3 H). Titration of the complex gave a pK_a of 4.55 and a mol wt of 322. The calculated mol wt is 320. Combustion Anal. Calcd for $C_{12}H_{25}KO_7$: C, 44.98; H, 7.86. Found: C, 45.04; H, 7.67. Atomic Absorption Anal. Calcd: K, 12.2. Found: K, 11.7.

Formation of the Complex 2 from the Triol. The parent triol (5.01 g, 25 mmol), potassium acetate (2.45 g, 25 mmol), and water (0.45 ml) were stirred in MeOH (50 ml) until everything went into solution (about 20 min). The solvent was removed under vacuum, MeOH (10 ml) was added, and after filtration, ether (50 ml) was added. The solution was cooled for 24 hr at −25°, and white crystals (2.5 g) were collected, mp 55–57°.

Acknowledgments. I thank Professor Jack Baldwin for his valuable suggestions and Messrs. G. M. Maciak and R. L. Wilson for analytical measurements.

Registry No.—**1**, 4031-49-6; **2**, 56050-93-2; potassium hydroxide, 1310-58-3; *cis*-tetrahydro-α^2-(hydroxymethyl)-2α,α^5,α^5-trimethyl-2β,5β-furandimethanol, 4031-50-9; potassium acetate, 127-08-2.

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The Carbon–Nitrogen Rotational Barrier as a Stereochemical Probe of Benzamidoximes

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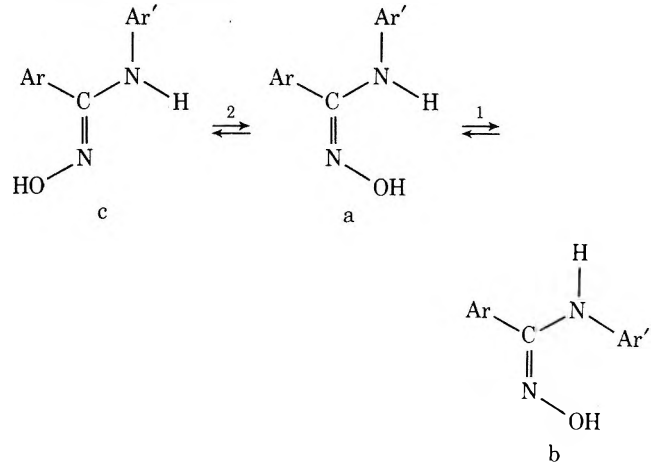
Received February 24, 1975

The stereochemistry of benzamidoximes has been recently investigated by electric dipole moment measurements and NMR spectroscopy.[1] The results of these two independent experimental approaches were complementary and conclusive enough to support the existence of the amino oxime tautomeric structure as well as the *Z* configuration on the C=N bond (structure a and b). However, a further point which remained to be clarified concerns the nature of the two isomers observed in the NMR spectra of some compounds. In principle the two species could derive either from restricted rotation around the amidic bond (equilibrium 1) which creates a barrier for the a ⇄ b transformation, or from inversion around the oximino bond (equilibrium 2); it has been already suggested that the first model should apply.[1]



In order to provide further evidence in favor of this interpretation, we have measured the activation parameters for the reversible conversion of these isomers, since it was thought that a quantitative estimate of the energy involved in this process could discriminate between the two possibilities. In fact it is well known that the rotational barriers around the amidic bond amount[2] to 15–24 kcal mol^{-1} in different environments, whereas the inversion of the carbon-nitrogen double bond of oximes[3] and related compounds[4] should require a much larger energy since syn–anti thermal isomerization is difficult and isomers can be separated.[5]

Among the compounds previously examined,[1] those bearing ortho methyl groups in Ar gave NMR spectra indicating the presence of two isomers whereas only one species was observed for Ar = Ar′ = Ph. We have therefore selected compounds **1** (Ar = 3,5-Cl_2-2,4,6-Me_3C_6; Ar′ = Ph) and **2** (Ar = 2-MeC_6H_4; Ar′ = Ph) and their NMR spectra were recorded at various temperatures. Ortho-methyl substituted benzamidoximes were suitable for a line-shape study since, owing to the lacking of exchange at room temperature, the methyl groups give enough separated sharp singlets. The same nonequivalence was observed also for the amidic and hydroxylic protons, which, however, were less reliable for this study since they can be involved in intra- and intermolecular exchange phenomena. The signals of

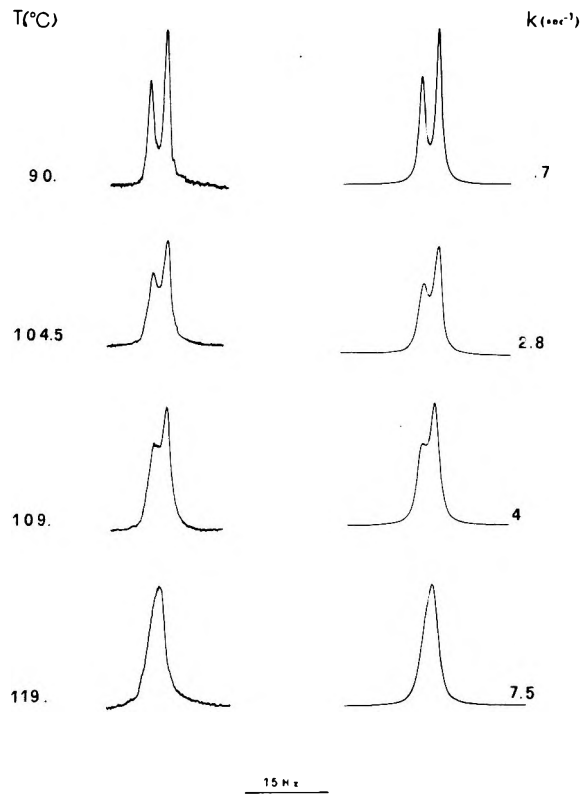


Figure 1. Experimental (left) and simulated (right) 60-MHz spectra of 1 at various temperatures.

the ortho-methyl groups of 1 (Figure 1), which show unequal intensities owing to the different amounts of the two isomers, begin to broaden at about 90° and coalesce into a single line at about 110°. In Figure 1 are also reported for comparison some of the experimental and calculated methyl signals of 1, the latter being obtained by the DNMR computer program[6] assuming appropriate rate constants. The thermodynamic parameters evaluated from the Eyring and Arrhenius equations[7] are collected in Table I. The activation entropies very close to zero are consistent with both rotational and syn–anti isomerization processes;[8] on the other hand, the relatively low values of the activation energies give evidence in favor of the existence of equilibrium 1 rather than 2. As the *Z* configuration on the C=N has been previously established,[1] it may be inferred from steric considerations that a is the preferred conformer whereas b can be observed when the size of Ar is increased by introducing one or two ortho-methyl groups. This fact forces Ar′ in the conformation b to an extent which is proportional to the ortho substitution (10 and 40% for 2 and 1, respectively). If the opposite situation would apply (b more stable than a) it is difficult for us to find conceivable reasons to explain the above change of isomer ratio. Furthermore, it may be observed that conformation a, where H faces the OH group,[8] is expected to be sterically more favored than b. This is supported by the observation that substitution of the amidic hydrogen in PhC(NHPh)=NOH with a methyl group [3, PhC(NMePh)=NOH] induces the formation of the second isomer in a relatively lower amount (30%), owing to the increased steric interaction between Me and OH which destabilizes isomer a. Unfortunately, the activation parameters could not be measured in this case, since the two methyl signals, which are well separated at room temperature, become incidentally equivalent before any broadening is observed.

Table I
Activation Parameters[a] for the C–N Rotation in Benzamidoximes 1 and 2 in Me_2SO-d_6

Amidoxime	E_a, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	$\Delta F^{\ddagger}$, kcal/mol
1	21.9 ± 0.7	21.1 ± 0.7	−1.1 ± 1.8	21.54 ± 0.04
2	21.8 ± 0.5	21.1 ± 0.5	3.4 ± 1.3	19.91 ± 0.05

[a] The data refer to the forward process a → b, where a and b are the more and less stable isomers, respectively. $\Delta F^{\ddagger}$ values are the average from values calculated at ten different temperatures.

Experimental Section

The variable-temperature NMR spectra were recorded in Me_2SO-d_6 by a 60-MHz instrument. Temperatures were determined before and after each measurement by a suitable thermometer placed inside the NMR probe. Spectra were simulated (see Figure 1) by the DNMR program[6] run on a CDC 6600 computer.

Benzamidoximes 3–5 were prepared by addition of the proper amine to benzonitrile *N*-oxide as described[1] for compounds 1 and 2. The products were separated from the excess of amine and diphenylfurazan *N*-oxide by chromatography on a silica gel column [eluents, benzene and then ethyl ehter for 4 and 5; eluent, benzene-ethyl ether (95:5) for 3] and after crystallization from proper solvent were analytically pure and gave ir spectra (CCl_4–C_2Cl_4–CS_2) showing characteristic bands at 3600 (OH), 3400 (NH) (absent in 3), ca. 3300 broad (OH), and 1630 cm^{-1} (C=N). ***N*-Methylphenylbenzamide oxime** (3) had mp 110° (from benzene–petroleum ether); NMR (Me_2SO-d_6) δ 10.8 (s, 1, OH), 7.5–6.3 (m, 10, aromatic protons), 3.2 and 3.1 (s, 3, Me). Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.35; H, 6.27; N, 12.49. ***N*-*o*-Tolylbenzamide Oxime** (4) had mp 148–149° (from benzene-petroleum ether); NMR (CS_2) δ 10–8 (very broad, 1, OH), 7.5–6.0 (m, 10, NH and aromatic protons), 2.25 (s, 3, Me). Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.26; H, 6.20; N, 12.35. ***N*-Mesitylbenzamide oxime** (5) had mp 184–185° (from ethanol); NMR (CS_2) δ 9.5–8.0 (very broad, 1, OH), 7.0 (s, 5, aromatic protons), 6.5 (s, 2, aromatic protons), 2.0 (s, 6, ortho Me), 2.05 (s, 3, para Me), the NH signal was between the two aromatic proton signals. Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.65; H, 7.14; N, 11.10.

Registry No.—1, 56050-94-3; 2, 56050-95-4; 3, 56050-96-5; 4, 56050-97-6; 5, 56050-98-7; benzonitrile *N*-oxide, 873-67-6; *N*-methylbenzenamine, 100-61-8; 2-methylbenzenamine, 95-53-4; 2,4,6-trimethylbenzenamine, 88-05-1.

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(5) The thermal syn–anti isomerization of oximes is usually very slow and $\Delta F^{\ddagger}$ values are too high to be measured before considerable decomposition takes place. However, a $\Delta F^{\ddagger}$ value as low as 32 kcal/mol is reported for a typical case: E. G. Vassian and R. K. Murmann, *J. Org. Chem.*, **27**, 4309 (1962). In principle, it is possible that the barrier to syn–anti isomerization of oximes may be lowered by a heteroatom bonded to the azomethine carbon in place of a carbon of an alkyl or aryl group, as observed for other compounds containing the C=N double bond (ref 3, p 404). However, the existence of stable syn and anti isomers at room temperature even for this type of oximes, such as ethyl benzohydroximates [I. K. Larsen and O. Exner, *Chem. Commun.*, 254 (1970)], seems to indicate that the interconversion energy is still much higher than 30 kcal/mol. Furthermore, also the well-established amino oxime form of amidoximes[1] makes it unlikely that a partial single bond character of the C=N bond may lower the energy of the syn–anti isomerization to the observed values.
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(8) When ortho methyl groups are in Ar′ [4, PhC(NHC$_6$H$_4$-Me-2)=NOH; 5, PhC(NHMes)=NOH], a single methyl signal is observed. In principle this could be due either to a fast rotation around the carbon–nitrogen bond or to the presence of only one isomer. In view of the high activation energies measured for compounds 1 and 2, the second hypothesis seems more likely, but we cannot assign the structure of the conformer in these cases.

Synthetic Reactions by Complex Catalysts. XXXVII. A Novel and Versatile Method of Carbodiimide Synthesis. Oxidation of Carbene Palladium(II) Complex with Silver Oxide

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For several years, there has been much interest in metal–carbene complexes.[1] However, most studies are concerned with the isolation and characterization of stable metal–carbene complexes[1] and with the mechanism of reactions involving transient metal–carbene intermediates.[2] Studies of the synthetic applications of metal–carbene complexes are scanty. In preceding papers, we have reported that Cu(I), Ag(I), and Au(III) salts catalyze the insertion reactions of isonitriles with amines,[3] alcohols,[4] and thiols,[5] and that Ag(I),[6] Cu(I),[6] and Pd(II)[7] salts catalyze the cyclization reaction of isonitriles with diamines, amino alcohols, and amino thiols. It has been established[8] that all these reactions involved the heteratom-substituted carbene–metal complexes as the key intermediates.

Herein we wish to report a versatile synthetic method for symmetrical and unsymmetrical carbodiimides (**2**), in which the N,N′-disubstituted diaminocarbene Pd(II) complex (**1**)[9] prepared from primary amine and $Pd(II)Cl_2(RNC)_2$ is oxidized with Ag_2O (Table I). The isolation of carbene Pd(II) complex **1** is not necessarily required for the carbodiimide synthesis. In practice, the synthesis of carbodiimides is accomplished just by stirring a heterogeneous mixture of primary amine, isonitrile, Ag_2O, and a catalytic amount of $Pd(II)Cl_2$ at room temperature or an elevated temperature (Table II). Thus, the present reaction presents a general convenient preparative method of carbodiimide.

$$RNH_2 + R'NC \xrightarrow{Pd(II)Cl_2} Pd(II)Cl_2(R'NC)\left(:C\begin{matrix}NHR\\NHR'\end{matrix}\right)$$

1

$$\xrightarrow[-H_2O]{Ag_2O} RN{=}C{=}NR'$$

2

In the stoichiometric reaction of diaminocarbene Pd(II) complex (**1**) with Ag_2O, the desired carbodiimide (**2**) was obtained as a sole product (76–96% yields) (Table I). In the $Pd(II)Cl_2$-catalyzed reaction of amine and isonitrile with Ag_2O, on the other hand, product of carbodiimide (**2**) was always accompanied by the corresponding urea (RNHCONHR′), which is derived from the carbodiimide (**2**) and water produced. The use of molecular sieve or anhydrous Na_2SO_4 in the reaction helped to exclude the formation of the urea.

The products of carbodiimides were identified by elemental analysis, ir (an absorption at 2110 cm^{-1} characteristic of –N=C=N–), NMR, and a chemical conversion to the corresponding ureas which were compared with the authentic samples.

The previous carbodiimide synthesis[10] from isocyanate requires phosgene in the preparation of precursor of isocyanate. This new method has the advantages of the higher yields of carbodiimides and the simplicity of manipulation. Further studies are in progress to extend the potential of

Table I
Reaction of N,N′-Disubstituted Diaminocarbene Pd(II) Complex 1 with Ag_2O

Carbene Pd(II) complex **1**[a]	Reaction time,[b] hr	Product, (%)[c,d]
$PdCl_2(t\text{-}C_4H_9NC)\left(:C\begin{matrix}NHC_4H_9\text{-}t\\NHC_4H_9\text{-}n\end{matrix}\right)$	3	$t\text{-}C_4H_9{-}N{=}C{=}N{-}C_4H_9\text{-}n$ (82)
$PdCl_2(t\text{-}C_4H_9NC)\left(:C\begin{matrix}NHC_4H_9\text{-}t\\NHC_6H_5\end{matrix}\right)$	4	$t\text{-}C_4H_9{-}N{=}C{=}N{-}C_6H_5$ (93)
$PdCl_2(t\text{-}C_4H_9NC)\left(:C\begin{matrix}NHC_4H_9\text{-}t\\NHCH_2CH{=}CH_2\end{matrix}\right)$	2	$t\text{-}C_4H_9{-}N{=}C{=}N{-}CH_2CH{=}CH_2$ (76)
$PdCl_2(t\text{-}C_4H_9NC)\left(:C\begin{matrix}NHC_4H_9\text{-}t\\NHCH(CH_3)CO_2C_2H_5\end{matrix}\right)$	4	$t\text{-}C_4H_9{-}N{=}C{=}N{-}CH(CH_3)CO_2C_2H_5$ (96)

[a] Registry numbers are, respectively, 56195-59-6, 56195-63-2, 56195-64-3, and 56195-58-5. [b] 20°. [c] Yields were determined by GLC. [d] Registry numbers are, respectively, 56195-54-1, 2219-34-3, 56195-55-2, and 56195-56-3.

Table II
Synthesis of Carbodiimides

$$RNH_2 + R'NC + Ag_2O \xrightarrow[-H_2O]{\text{cat. } Pd(II)Cl_2} RN{=}C{=}NR' + RNHCONHR'$$

Amine[a] (RNH_2)	Isonitrile (R′NC)	Reaction[b] Temp, °C	Reaction[b] Time, hr	RN=C=NR′, %[c]	RNHCONHR′, %
$n\text{-}C_4H_9NH_2$	$t\text{-}C_4H_9NC$[d]	20	3	93 (85)[e]	<3
$c\text{-}C_6H_{11}NH_2$	$t\text{-}C_5H_9NC$	20	4	94	0
$c\text{-}C_6H_{11}NH_2$	$c\text{-}C_6H_{11}NC$[f]	67	0.5	77 (68)[e]	0
$C_6H_5NH_2$	$t\text{-}C_4H_9NC$	80	4	72	0
$C_6H_5NH_2$	$t\text{-}C_4H_9NC$	80	3[g]	77	<3
$CH_2{=}CHCH_2NH_2$	$t\text{-}C_4H_9NC$	20	3	77	<3
$CH_3CH(NH_2)CO_2C_2H_5$	$t\text{-}C_4H_9NC$	20	7	80	8

[a] Registry numbers are, respectively, 109-73-9, 108-91-8, 62-53-3, 107-11-9, 56195-57-4, 630-18-2, and 766-05-2. [b] No attempts have been made to optimize the reaction conditions. Molecular sieves were added as a dehydrating agent. [c] Yields were determined by GLC. [d] Registry number, 1202-53-5. [e] Isolated yields. [f] Registry number, 538-75-0. [g] Anhydrous sodium sulfate was added in place of molecular sieves.

this synthetic method and to investigate the reaction mechanism.

Experimental Section

The general experimental procedure is as follows.

A. A Stoichiometric Reaction of Diaminocarbene Pd(II) Complex (1) with Ag_2O. A heterogeneous mixture of complex 1[9] (1 mmol) and Ag_2O (1 mmol) in benzene (10 ml) was stirred at room temperature for 2–4 hr. The reaction mixture was worked up by filtration to remove insoluble inorganic materials and solvent distillation in vacuo, leaving the desired carbodiimide as a sole product (76–96% yields) (Table I).

B. A $Pd(II)Cl_2$-Catalyzed Reaction of Amine and Isonitrile with Ag_2O. A heterogeneous mixture of primary amine (5 mmol), isonitrile (6 mmol), and Ag_2O (5 mmol) in benzene (10 ml) was stirred in the presence of $Pd(II)Cl_2$ (0.5 mmol) and molecular sieve (1.5 g) or anhydrous Na_2SO_4 (1.5 mmol) at room temperature or an elevated temperature. The reaction mixture was filtered to remove inorganic materials, and then distilled in vacuo to give the corresponding carbodiimide in good yield (Table II).

Registry No.—Ag_2O, 20667-12-3.

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A Novel Reaction of 5*H*-Dibenzo[*a*,*d*]cyclohepten-5-one with Hydrazine

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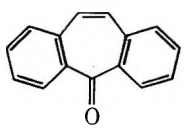
Received May 15, 1975

Recently, various transannular reactions producing a variety of bridged dibenzsuberans have been reported.[1-3] During the course of our investigation into the reactions of dibenzocycloheptenone (1) we discovered an interesting and, what we believe to be, novel reaction.



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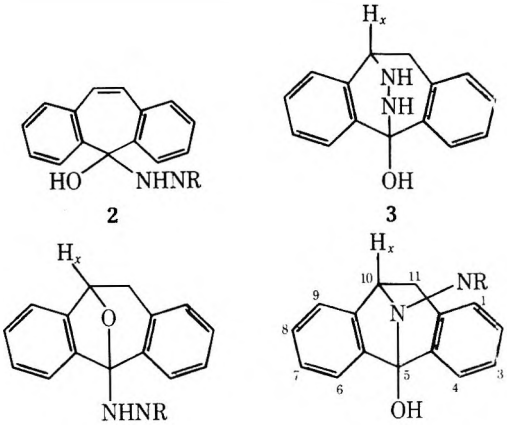
When 1 was treated with anhydrous hydrazine at elevated temperature, a stable product was isolated whose infrared spectrum lacked a carbonyl absorption and elemental composition indicated an addition of hydrazine without concomitant loss of water.

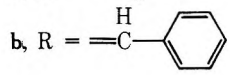
Four possible structures can be postulated for such a product (**2a–5a**). Structure 2 can be ruled out because of the unlikelihood of its stability and the distinct absence of the olefinic proton signal in the NMR.



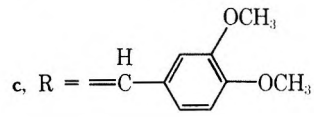
2 3

4 5

a, R = $=H_2$



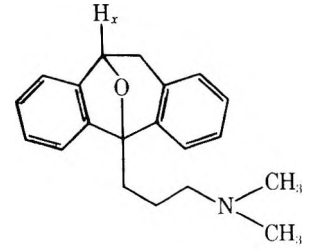
b, R = $=C$



c, R = $=C$

We attempted to elucidate the structure of the adduct by further functionalizing the compound on the hydrazino group. It was found that treatment of the adduct with various aldehydes produced corresponding hydrazones in good yields (R = **b** and **c**).[4] Disappointingly, no firm structure proof was obtained as not even the use of shift reagents in proton NMR led to a clear conclusion.

Therefore, it was then necessary to compare the NMR spectra of all the compounds to that of a known model[5] **6**. A noticeable difference was observed in the shift of the low-field H_x doublet of AMX spin system of **6** in comparison to our adduct. Upon conversion of the adduct to the benzylidene derivatives, H_x is drastically shifted, appearing close to that of the model compound **6**. The respective chemical shift values of H_x are 5.55 ppm for compound **6**, 5.36 ppm for **b**, 5.26 ppm for **c**, and 4.38 ppm for **a**.



6

The large shift difference noticed when the benzylidene derivative (R = **b**, **c**) and model compound **6** are compared to the adduct where R = H_2 can be rationalized by two possible explanations: (1) introduction of the benzylidene function into the substrate causes a rearrangement from the N-bridged structure **3** or **5** to the O-bridged structure **4**, or (2) the benzylidene function is directly added to the $N-NH_2$ bridge in structure **5a**.

To distinguish between these two possibilities the structure elucidation was continued with the help of ^{13}C NMR spectroscopy. Should the first explanation be correct, a

downfield shift of the bridgehead carbon atom at position 10 would be expected because of the replacement of the nitrogen (bonded to this carbon) with the more strongly deshielding oxygen. If the second explanation is correct, carbon atom 10 would receive an additional γ carbon and therefore experience an upfield shift owing to the γ effect. It was found that introduction of the benzylidene function caused an upfield shift of the C-10 doublet from 63 to 59 ppm, indicating that **5a** is the most probable structure.

It was also observed that the proton and carbon spectra of **5a** were broadened at room temperature. Quantitative work on temperature dependence was not performed, but sharp spectra were obtained at 80–120°. The origin of broadening may be either slow flipping of the seven-membered carbocyclic ring[6] or a slow pyramidal inversion of the bridge nitrogen. Formation of the benzalhydrazone derivative would be expected to flatten the nitrogen by conjugation, but encumber ring flipping somewhat. The fact that sharp spectra on the hydrazones were obtained at room temperature suggests that in their precursors slow pyrimidal inversion rather than slow ring flipping was responsible for broadening.

Experimental Section[7]

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 237 and 457 spectrophotometers. All pure materials were run as Nujol or halocarbon mulls. Nuclear magnetic resonance spectra were determined on Varian A-60 and T-60 spectrophotometers using tetramethylsilane as an internal reference. ^{13}C NMR spectra were determined on a Varian XL-100 spectrophotometer. Mass spectra were recorded on an LKB 9000 spectrometer.

Interpretation of NMR data: δ, chemical shift in parts per million (multiplicity, number of protons, coupling constant, proton assignment); s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

12-Amino-10,11-dihydro-5,10-imino-5*H*-dibenzo[*a,d*]cycloheptene-5-ol (5a). A suspension of 30.0 g of **1** in 150 ml of anhydrous hydrazine was refluxed for 4 hr. The excess hydrazine was removed under reduced pressure and methylene chloride was added to the residue. The resulting solid was filtered, washed twice with ethanol and then with ether to yield 26.8 g (77%) of **5a**, mp 191–194°. An analytical sample was recrystallized from methanol: mp 192–194°; NMR (Me_2SO) δ 7.8–6.5 (m, 8), 4.4 (d, 1, J = 5 Hz, NCH), 3.4 (q, 1, J = 5 Hz, 17, CHH′), 3.5 (s, broad, 3, OH, NH_2), 2.4 (d, 1, J = 17 Hz, CHH′); ^{13}C NMR (Me_2SO) δ 62.8 (CH), 28.1 (CH_2).

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.6; H, 5.9; N, 11.8. Found: C, 75.2; H, 6.3; N, 12.0.

12-Benzylideneamino-10,11-dihydro-5,10-imino-5*H*-dibenzo[*a,d*]cyclohepten-5-ol (5b). To a hot solution of 0.5 g of **5a** in 30 ml of methanol was added 1.0 ml of benzaldehyde. The solution was refluxed for 5 min. Upon cooling, a crystalline precipitate formed and was filtered and washed twice with ethanol and then with ether to yield 0.55 g (81%) of **5b**: mp 158–161°; NMR (Me_2SO) δ 8.3 (s, 1, N=CH), 7.9–6.7 (m, 13), 5.4 (d, 1, J = 4 Hz, NCH), 3.5 (m, 1, J = 4, 17 Hz, CHH′), 3.4 (s, 1, OH), 2.5 (d, 1, J = 17 Hz, CHH′); ^{13}C NMR (Me_2SO) δ 59.8 (CH), 27.9 (CH_2).

Anal. Calcd for $C_{22}H_{18}N_2O$: C, 81.0; H, 5.6; N, 8.6. Found: C, 81.1; H, 5.7; N, 8.4.

12-(3,4-Dimethoxybenzylidene)amino-10,11-dihydro-5,10-imino-5*H*-dibenzo[*a,d*] cyclohepten-5-ol (5c). To a hot solution of 10.0 g of **5a** in 400 ml of methanol was added 5.0 g of 3,4-dimethoxybenzaldehyde. The solution was refluxed for 6 hr (after 1 hr a precipitate forms). Upon cooling, the solid was filtered and washed twice with methanol and then with ether to yield 9.0 g (56%) of **5c**: mp 152–155°; NMR (Me_2SO) δ 8.2 (s, 1, N=CH), 7.9–6.8 (m, 11), 5.3 (d, 1, J = 4 Hz, NCH), 3.7 (s, 6, OCH_3), 3.4 (s, 1, OH), 3.35 (q, 1, J = 4, 17 Hz, CHH′), 2.4 (d, 1, J = 17 Hz, CHH′).

Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.6; H, 5.7; N, 7.3. Found: C, 75.0; H, 5.9; N, 7.3.

Acknowledgments. The authors wish to thank Mrs. Alicia Kahle and Mrs. Susan DiCataldo for running all NMR spectra and Mr. William Bonkoski and associates for performing the microanalyses. The authors also wish to express their gratitude to Dr. Byron H. Arison (Merck Institute) for supplying spectral data for compound **6**.

Registry No.—1, 2222-33-5; **5a,** 55991-62-3; **5b,** 55991-63-4; **5c,** 55991-64-5; hydrazine, 302-01-2; benzaldehyde, 100-52-7; 3,4-dimethoxybenzaldehyde, 120-14-9.

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Changing the Reaction Paths of a Metathesis Catalyst

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Received May 9, 1975

Numerous papers and several reviews have been published on the metathesis of olefins.[1–7] This reaction has also been called olefin "dismutation" or "disproportionation", and involves breaking carbon double bonds and rejoining the fragments: $2RCH{=}CHR' \rightleftharpoons RCH{=}CHR + R'CH{=}CHR'$. We have observed a new phenomenon in catalysis of this kind: the transformation of a metathesizing system into a dimerizing system simply by increasing the amount of aluminum component in the catalyst. Ligands also play an important role in such processes, completely changing the course of the reaction.

Table I shows the importance of the order in which reagents are combined in this metathesizing system.

Table I
Metathesis of Mixed 2-Pentenes
(0.2 m*M* WCl_6, 10 m*M* olefin, 0.3 m*M* $PhNH_2$, 0.3 m*M* $Et_3Al_2Cl_3$)

Injection order[a]	1	2	3	4
Conversion, %	55	51	50	61
Selectivity to 3-hexene, mol %	46	50	53	41
Selectivity to 2-butene, mol %	36	40	44	28
Total selectivity, %	82	90	97	69
2-Pentene, *trans-/cis*[b]	4.9	5.6	5.2	6.1
2-Butene, *trans-/cis-*	2.5	2.0	2.0	2.6

[a] Injection order: 1, W + 2-pentenes (2-P) + aniline ($PhNH_2$) + Al; 2, W + $PhNH_2$ + 2-P + Al; 3, W + $PhNH_2$ + Al + 2-P; 4, W + Al + $PhNH_2$ + 2-P. [b] Initial trans/cis ratio of 2-pentene was 0.59.

Most critical is the interaction of WCl_6 and the aniline ligand: nearest approach to theoretical equilibration was attained when this interaction was most direct, as in injection orders 2 and 3. The poorest selectivity was observed in order 4, where $Et_3Al_2Cl_3$ had reacted with WCl_6 before ani-

line was added. The importance of the ligand is further illustrated in Table II, where the catalysts with no ligand, or with ethanol, both convert propylene or 2-pentene quantitatively to oligomers or alkylates.

Table II
Metathesis by $Et_3Al_2Cl_3$–WCl_6 and Ligands

Olefin	Ligand	% conversion	% metathesis
2-Pentene[a]	None	100	0
2-Pentene	Aniline	22	100
Propylene[b]	None	99	0
Propylene	Ethanol	99	0
Propylene	Aniline	27	75

[a] 0.2 m*M* WCl_6 in benzene, 10 m*M* 2-pentene in *n*-pentane, 0.4 m*M* neat ligand, 0.2 m*M* $Et_3Al_2Cl_3$, in that order. [b] 0.2 m*M* WCl_6, 0.3 m*M* ligand, 0.2 m*M* $Et_3Al_2Cl_3$, 20 m*M* propylene, in that order, all in chlorobenzene.

In contrast, addition of aniline led exclusively to metathesis. Separate experiments with propylene at Al/W = 10 showed a similar pattern, except that dimerization occurred exclusively, rather than metathesis. The failure of ethanol to modify the catalyst may be due to elimination of ethyl chloride, and the formation of tungsten oxytetrachloride, thus losing any steric or electronic control by the ethoxy group.

A dark brown precipitate was formed upon addition of the aniline. This solid was almost entirely dissolved by the alkylaluminum halide, but complete homogeneity was uncertain.

Figure 1 shows the sharp change from metathesis to dimerization. At Al/W = 1.5, metathesis accounts for almost

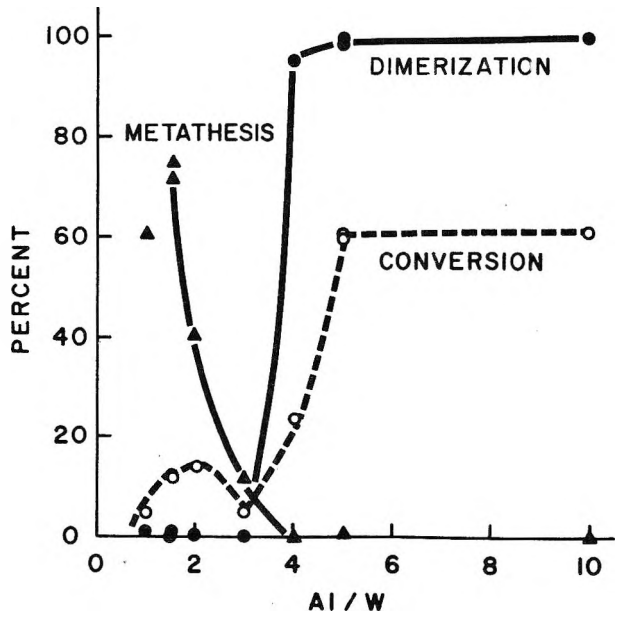


Figure 1. Propylene and $Et_3Al_2Cl_3$.

all the propylene converted (to 2-butenes, ethylene, and some 1-butene). As the amount of $Et_3Al_2Cl_3$ was increased to Al/W = 3.0, both conversion and selectivity toward metathesis fell steeply to zero. From this point on, conversion rose sharply, with dimerization the exclusive reaction. The dimer mixture was composed largely of 2-methyl-1-pentene and 2,3-dimethyl-1-butene.

When $EtAlCl_2$ was employed as cocatalyst, and a chlorinated aniline as ligand, virtually all the ethylene was consumed as fast as it was formed. Figure 2 represents this product mixture, which had the representative composition 22% 1-butene, 17% *trans*-2-butene, 25% *cis*-2-butene, 19% 3-methyl-1-butene, and 15% 2-methyl-1-butene. As Al/W was increased, dimerization again predominated, giving a mixture of branched hexenes.

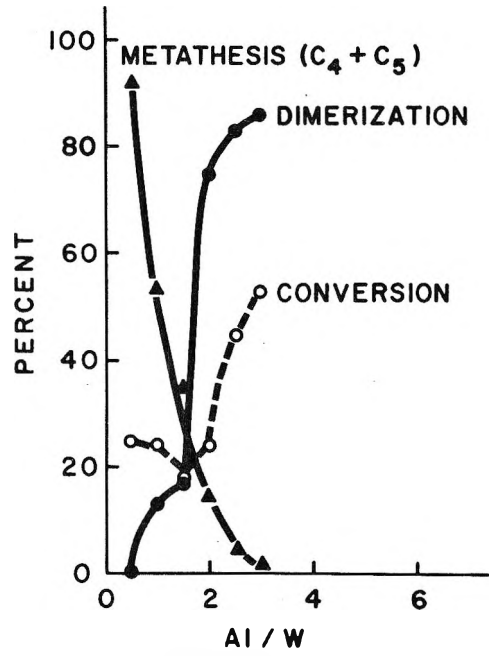
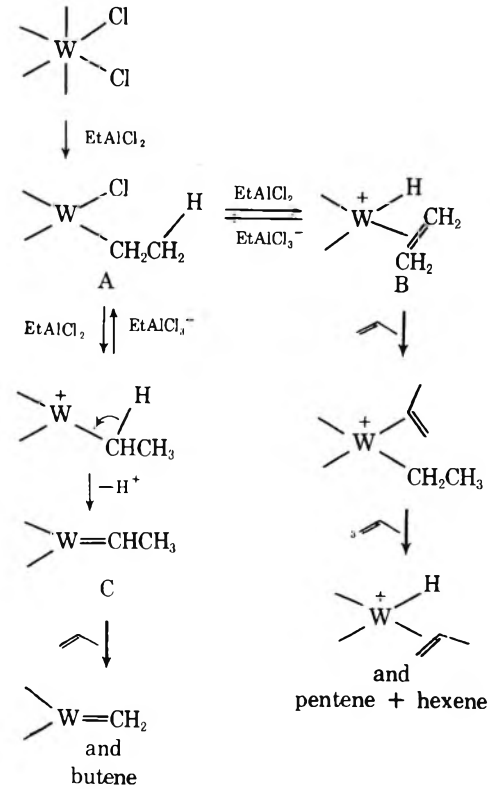


Figure 2. Propylene and $EtAlCl_2$.

Figure 3 shows a similar pattern for 2-pentene, except that essentially no reaction occurred at aluminum/tungsten ratios greater than 5. In earlier work, 2-butene showed the same behavior at such levels of aluminum. For our catalyst, this indicates an intermediate allowing coordination of internal and terminal olefins in the metathesis process, but only terminal olefins in dimerization. This may be explained by the mechanism suggested



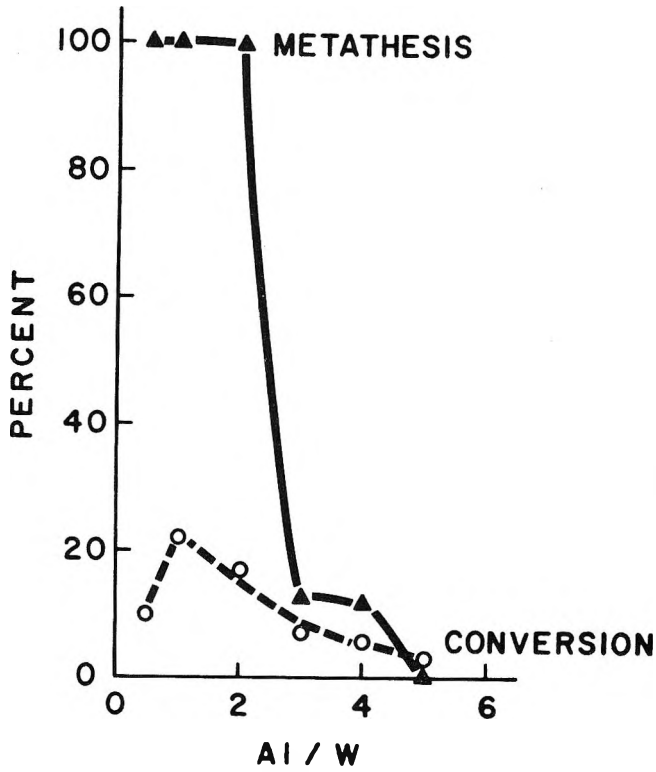


Figure 3. 2-Pentene-2 and $Et_3Al_2Cl_3$.

where intermediate C, with one less ligand, would allow more facile coordination of an internal olefin than B.

Similar results would be observed if the terminal olefin sustained a nonproductive metathesis, such as the exchange of methylene groups only. However, this possibility seems unlikely.

When the tungsten atom of intermediate A is in a relatively high oxidation state (perhaps IV or V), the pathway to the carbene C affords relief to electron-deficient tungsten by expulsion of H^+. When tungsten has been reduced further (perhaps III or IV), the route through intermediate B, where W is relatively electron rich, affords stabilization of the olefin complexes shown. Somewhere in between, A becomes stable and little reaction occurs. Complexes of the type A and B have been reported,[8] and the carbene mechanism for metathesis has been suggested.[9] The route to metathesis should be favored by small amounts of Lewis acid, and we have observed such an effect previously.[5] More basic reductants such as butyllithium may abstract the α proton from A first, followed by ejection of chloride ion.

Experimental Section

2-Pentene was distilled from sodium bisulfite under nitrogen, and propylene was dried through a bed of 3-A molecular sieves. Aniline was vacuum distilled from sodium. Solvents were carefully dried over sodium or silica gel. Tungsten hexachloride was dissolved and used as received, and the ethylaluminum chlorides were diluted to 2 *M* in benzene or chlorobenzene.

Propane as an internal standard was added to the propylene–chlorobenzene solutions, which were about 0.5 *M*.

Transfers of olefin solutions and chemical reagents were done by hypodermic syringes. Reactions were carried out for 1 hr in 4-oz glass bottles at room temperature, agitated on a Burrell shaker, and terminated by 1 ml of isopropyl alcohol. Then the reaction mixtures were cooled before VPC analysis.

For 2-pentene, analyses were done on a 42-ft Tergitol column at 60°, using *n*-pentane as internal standard. For the propylene work, analyses were done on a 60-ft β,β-oxydipropionitrile column at 30° or Tergitol at 30°. Using propane as an internal standard, the weight of propylene converted (expressed in peak area) was calculated and compared to ½ the observed areas for the 2-butene isomers (since some of the ethylene went on to form 1-butene, etc.). Thus, conversion and total selectivities were simply calculated.

Acknowledgment. We would like to thank Mr. Frank Cinocca for his capable assistance in performing much of the work described here, and also The Goodyear Tire & Rubber Co. for permission to publish. Thanks to Drs. J. G. Bryson and M. F. Farona for a helpful discussion on mechanism.

Registry No.—*trans*-2-Pentene, 646-04-8; *cis*-2-pentene, 627-20-3; *trans*-2-butene, 624-64-6; *cis*-2-butene, 590-18-1; propylene, 115-07-1; WCl_6, 13283-01-7; $PhNH_2$, 62-53-3; $Et_3Al_2Cl_3$, 12075-68-2; ethanol, 64-17-5; $EtAlCl_2$, 563-43-9.

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Reaction of Diphenylcyclopropenone with Pyridinium *N*-Imine in Protic Media. The Quenching of a Reactive Intermediate

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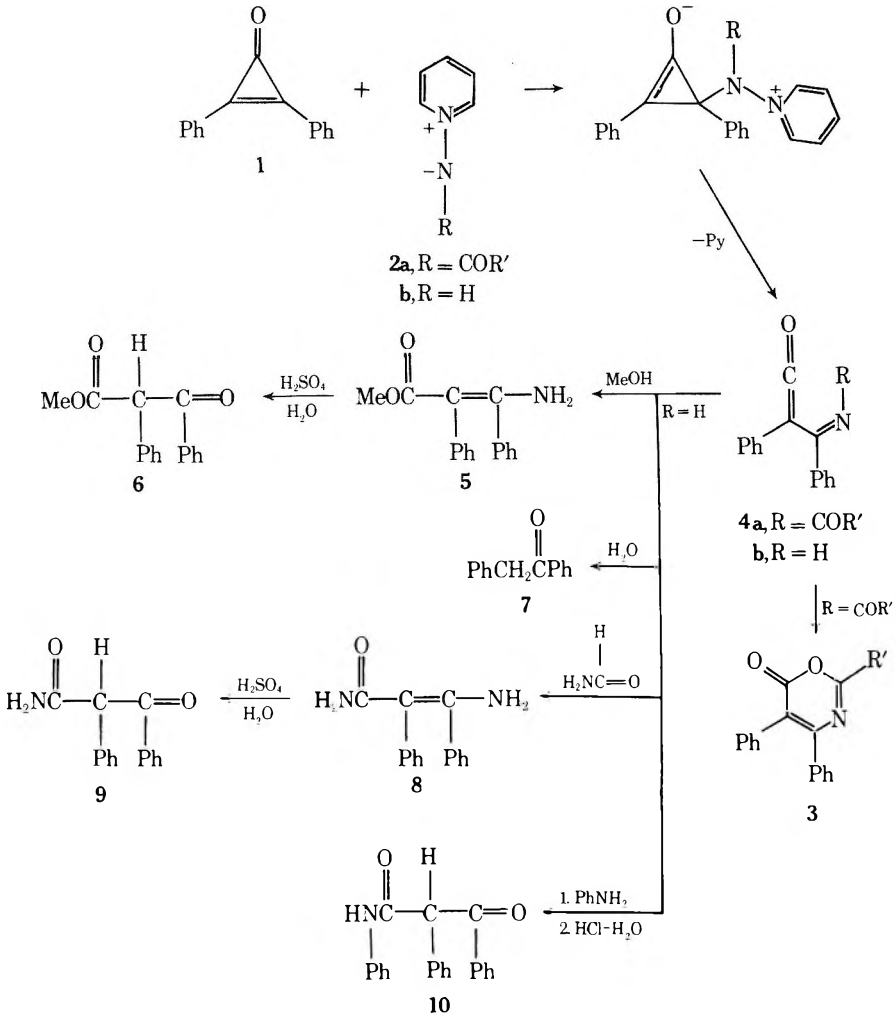
Received May 6, 1975

The reaction of diphenylcyclopropenone (**1**) with *N*-acyl pyridinium imines (**2a**) has been reported to produce 2,4,5-trisubstituted 6*H*-1,3-oxazin-6-ones (**3**).[1,2] A pathway involving formation of a ketene[3] intermediate (**4a**) was suggested for the process. However, attempts to quench this intermediate with methanol were unsuccessful, possibly because the intramolecular cyclization process is rapid compared with intermolecular reaction of the ketene with solvent.[1] In this case, absence of the N substituent should permit addition of a protic solvent to the intermediate.

We have, therefore, investigated some reactions of diphenylcyclopropenone with *N*-aminopyridinium iodide, in protic media, in the presence of a tertiary amine (diisopropylethylamine and triethylamine were found to be equally effective). A methanol solution of these reagents developed a wine-red coloring during several hours at room temperature. After 17 hr, the methanol was evaporated and the residue was purified by extraction and precipitation to give **5** as a crystalline solid in 95% yield. The structure assignment was suggested by the NMR spectrum ($CDCl_3$) which showed a sharp 3 H singlet at δ 3.65 (methyl ester), and by the infrared spectrum ($CHCl_3$), which exhibited prominent absorption at 3490, 3304, and 1660 cm^{-1}. A mild acid hydrolysis of **5** produced the known[4] β-keto ester **6**. Primary enamines analogous to **5** have been reported in the reactions of diphenylcyclopropenone with aziridines[5] and ammonia,[6] the cis configuration being assigned in both cases. Evidence has been presented[6] to suggest that the trans isomer, if formed in the reaction, would be expected to isomerize readily in solution.

The formation of **5** in the present study may be visualized as occurring by way of a 1,2 or 1,4 addition of methanol to an iminoketene intermediate (**4b**), formed by initial conjugate addition of **2b** on **1**. The general applicability of the reaction was demonstrated by considering various protic media. Thus, reaction in aqueous dioxane gave deoxy-



benzoin (**7**, 30%), the expected decarboxylation–hydrolysis product of H_2O addition to **4b**. Reaction in formamide produced amide **8** (50%), presumably via a decarbonylation of the formamide adduct under the reaction conditions. The structure of **8** was confirmed by mild acid hydrolysis to the known[7] β-keto amide **9**. Some deoxybenzoin (**7**) always accompanied the formation of **8**, and probably arises from the presence of traces of water in the formamide. Finally, reaction in aniline, followed by a work-up with concentrated HCl, afforded directly the hydrolysis product **10** (57%), an alternate preparation of which has been described elsewhere.[7]

Experimental Section

All melting points were obtained on a Mettler FP52 melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 337 spectrophotometer. NMR spectra were recorded with a Varian T-60 spectrometer using tetramethylsilane as an internal standard. The elemental analyses were performed by Alfred Bernhardt Laboratories, West Germany.

Reaction of Diphenylcyclopropenone (1) with *N*-Aminopyridinium Iodide in the Presence of Triethylamine. A. In Methanol. A solution of *N*-aminopyridinium iodide[8] (0.444 g, 2 mmol), triethylamine (0.6 ml, 4 mmol), and diphenylcyclopropenone (0.206 g, 1 mmol) in 60 ml of dry methanol was allowed to stand at room temperature. After 17 hr, the solvent was evaporated at reduced pressure, and the resulting residue was extracted with methylene chloride (60 ml). The extract was concentrated to 30 ml and pentane (30 ml) was added to precipitate dissolved salts. Evaporation of the solvent left a pale yellow solid, which upon recrystallization from cyclohexane afforded 0.240 g (95%) of **5** as white needles: mp 113–114°; ir ($CHCl_3$) 3490, 3304, 1650, 1600, 1575 cm^{-1}; NMR ($CDCl_3$) δ 3.65 (3 H, singlet), 7.00 and 7.10 (singlets, the region 6.0–8.0 integrating as 12 H, diminishing to 10 H upon D_2O exchange).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.73; H, 6.04; N, 5.69.

B. In Aqueous Dioxane. A solution of *N*-aminopyridinium iodide (0.666 g, 3 mmol), triethylamine (1.2 ml, 8 mmol), and diphenylcyclopropenone (0.412 g, 2 mmol) in 20 ml of 50% aqueous dioxane was allowed to stand at room temperature. After 20 hr, water (50 ml) was added and the resulting mixture was extracted with methylene chloride. The organic layer was washed several times with water, dried over $MgSO_4$, and evaporated at reduced pressure to yield 0.500 g of a yellow oil. Addition of benzene (50 ml) left an insoluble solid residue (0.100 g), which was not identified. The benzene-soluble material was chromatographed on a neutral alumina column (benzene) to afford 0.120 g (30%) of pure **7**, mp 56°.

C. In Formamide. A solution of *N*-aminopyridinium iodide (0.222 g, 1 mmol), triethylamine (0.3 ml, 2 mmol), and diphenylcyclopropenone (0.128 g, 0.62 mmol) in 30 ml of formamide (Fisher reagent grade, dried over type 3A molecular sieve) was allowed to stand at room temperature. After 17 hr, the solution was treated with 100 ml of water and worked up as in B to give 0.121 g of a solid residue which was recrystallized from methylene chloride–pentane to afford 0.074 g (50%) of **8**: mp 149–151°; ir ($CHCl_3$) 3525, 3480, 3405, 1630, 1600, 1565 cm^{-1}; NMR ($CDCl_3$) δ 5.20 (2 H, broad), 7.10 and 7.13 (sharp singlets, the region 6.5–7.5 integrating as 12 H).

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.65; H, 6.07; N, 11.62.

Evaporation of the mother liquor left a yellow oil which was crystallized from cyclohexane to give 0.012 g (10%) of **7**, mp 55–56°. The infrared spectrum of this material ($CHCl_3$) was identical with that of an authentic sample.

D. In Aniline. A solution of *N*-aminopyridinium iodide (0.666 g, 3 mmol), triethylamine (1.2 ml, 8 mmol), and diphenylcyclopropenone (0.412 g, 2 mmol) in 30 ml of freshly distilled aniline was allowed to stand at room temperature. After 20 hr, 200 ml of ether was added followed by the dropwise addition of concentrated HCl (21 ml). The salts were removed by filtration. The organic layer

was washed several times with water, dried over $MgSO_4$, and reduced to 30 ml, whereupon a white solid precipitated. An equal volume of pentane was added to give a total of 0.360 g (57%) of pure **10**, mp 168–169° (lit.[7] mp 168–169°).

Acid Hydrolysis of 5 to Form 6. A solution of **5** (0.163 g, 0.64 mmol) in 6 ml of dioxane was treated with 6 ml of 10% H_2SO_4. After 21 hr at room temperature, the mixture was diluted with 30 ml of water and extracted with methylene chloride. The organic layer was washed with water, dried over $MgSO_4$, and evaporated at reduced pressure to yield 0.150 g of an oily solid. Recrystallization from pentane afforded 0.120 g (73%) of **6**, mp 73–74° (lit.[4] mp 75°).

Acid Hydrolysis of 8 to Form 9. A solution of **8** (0.071 g, 0.29 mmol) in 3 ml of benzene was treated with 3 ml of 10% H_2SO_4 with stirring. Stirring was continued for 47 hr, after which time work-up as above gave **9** (0.035 g, 50%), mp 176–177° (lit.[7] mp 174–176°).[9]

Acknowledgment. The authors gratefully acknowledge the financial assistance of FINEP (Financiadora de Estudos e Projetos).

Registry No.—**1**, 886-38-4; **5**, 55991-26-9; **6**, 54108-62-2; **7**, 451-40-1; **8**, 55991-27-0; **9**, 35061-99-5; **10**, 22468-40-2; *N*-aminopyridinium iodide, 6295-87-0.

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(9) A mild, heterogeneous hydrolysis of **5**, as described for **8**, gave a mixture of **5** and **6**, even after 47 hr at room temperature. The possibility that such a mixture forms in the case of **8** cannot be ruled out, inasmuch as only 50% of the material was recovered.

Optically Active Heteroaromatic Compounds. VII. Synthesis of the Three Optically Active *sec*-Butylpyridines

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Received February 25, 1975

As a part of a synthesis project for optically active vinylpyridines, a relatively simple and expeditious method for obtaining chiral alkylpyridines with rather high enantiomeric purity was needed.

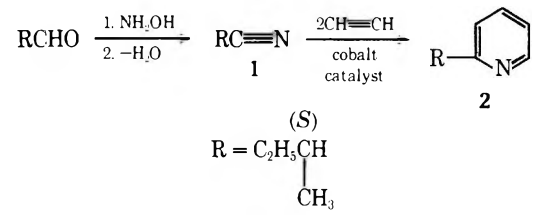
The only known optically active alkylpyridine is 2-*sec*-butylpyridine, which was obtained by resolution of racemic compound with dibenzoyl-(+)-tartaric acid.[1] The value of the specific rotation of the most highly resolved sample was rather high ($[\alpha]^{25}D$ −30°), but neither the absolute configuration of the prevailing enantiomer nor the minimum optical purity was reported.

In this paper we report results obtained (1) in the synthesis of all isomeric chiral *sec*-butylpyridines and (2) in the determination of the relationship between the sign of the rotatory power and the absolute configuration, and of the minimum optical purity.

The reaction sequence leading to (+)-(*S*)-2-*sec*-butylpyridine is depicted in Scheme I.

The necessary optically active nitrile **1** was obtained by dehydration of the known (+)-(*S*)-2-methylbutanal oxime[2] using *N,N'*-carbonyldiimidazole[3] with nearly quantitative yields; moreover, because of the very mild conditions used, the optical yield was very high (≥95%).

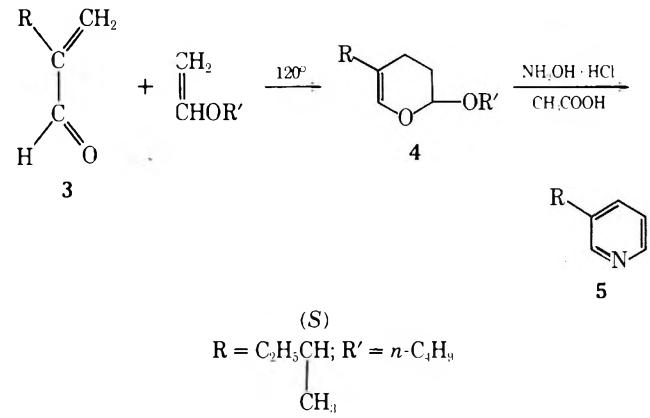
Scheme I



Cyclization of **1** with acetylene[4] at a pressure of ≥6 atm and 140° using π-cyclopentadienylcobalt cyclooctadiene[5] as the catalyst brought about the formation of the desired pyridine derivative in 95% yield.

Different reaction sequences are used for the preparation of (+)-(*S*)-3-(**5**) and (+)-(*S*)-4-*sec*-butylpyridine (**12**) (Schemes II and III). The chiral starting product for both

Scheme II



syntheses was (+)-(*S*)-2-methylene-3-methylpentanal (**3**).[6] In the first case **3** represented the diene partner for the well-known cycloaddition to vinyl butyl ether[7] to form (+)-2-butoxy-5-*sec*-butyl-3,4-dihydro-2*H*-pyran, which is a very suitable precursor for pyridine ring formation.[8] In a second case **3** was transformed through a five-step sequence (Scheme III) into (*S*)-3-*sec*-butylglutaraldehyde (**10**) and hence to the corresponding (+)-(*S*)-4-*sec*-butylpyridine (**12**). Some investigations on reaction conditions have been made in order to obtain higher yields of dihydropyran derivative **4** (Scheme II).

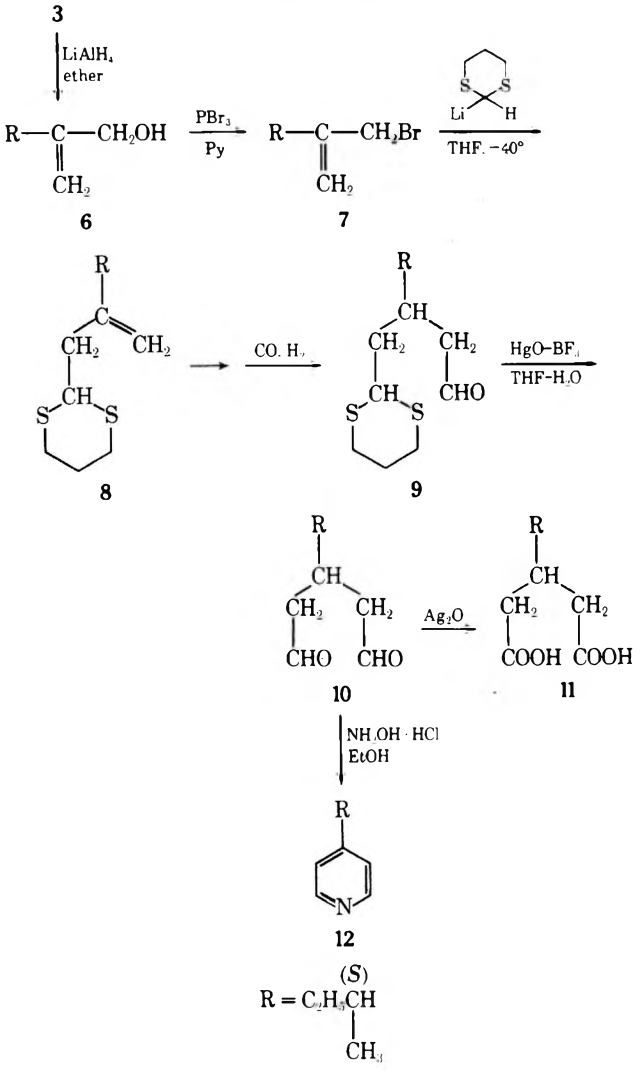
From the results obtained in several runs, it can be concluded that, with comparable conversion of the unsaturated aldehyde **3** (~90%), the best yield of **4** (70%) is achieved operating in a steel autoclave at 120° and 1–2 atm of nitrogen for 24 hr with a vinyl ether to acrolein molar ratio of 2.0. The secondary reactions, namely, isomerization and dimerization of the substrate, were under these conditions 20–22 and 7–8%, respectively.

Cyclization of **4** with hydroxylamine hydrochloride in acetic acid according to a known procedure[9] gave a high yield of the corresponding pyridine (**5**) (80–86%), free from isomeric products (GLC and NMR analysis).

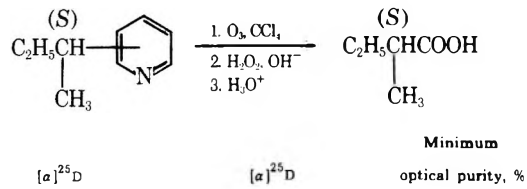
For the synthesis of optically active 4-*sec*-butylpyridine we preferred to develop a general route, not involving a dihydropyran derivative, because of the absence in the literature of any data about optically active β-*sec*-butyl acroleins necessary for cycloaddition to the vinyl ethers.

For the preparation of a suitable precursor to pyridine, e.g., an optically active alkyl-substituted glutaraldehyde, we considered the hydroformylation of acetal of β,γ-unsaturated aldehydes[10] as a concrete possibility, an analogous procedure having given good results in the synthesis of

Scheme III



Scheme IV



	$[\alpha]^{25}D$	$[\alpha]^{25}D$	Minimum optical purity, %
2	+25.78° (ethanol)	+15.8° (*n*-heptane)	80
5	+26.7° (neat)	+11.9° (neat)	60
12	+23.4° (*n*-heptane)	+17.9° (ethyl ether)	89

1,4-dialdehydes from acetal of α,β-unsaturated aldehydes.[12]

The suitable substrate for hydroformylation **8** was obtained by alkylation of 2-lithium-1,3-dithiane[13] with (+)-(*S*)-2-*sec*-butylallyl bromide (**7**) (Scheme III), easily obtained from (+)-(*S*)-2-*sec*-butylacrolein through the corresponding alcohol.[14] Hydroformylation of **8** was accomplished conveniently using $HRh(CO)(PPh_3)_3$ or $RhCl(CO)(PPh_3)_2$ as the catalyst,[12] and the monothioacetal of 3-*sec*-butylglutaraldehyde (**9**) was formed as the only reaction product (GLC and NMR analysis). Treatment of **9** with $HgO–BF_3·Et_2O$ system in $THF–H_2O$ solution at room temperature[15] resulted in rapid formation of the 3-*sec*-butylglutaraldehyde (**10**). An attempt to purify this compound by vacuum distillation was unsuccessful. To confirm its identity, **10** was converted by silver oxide oxidation into the corresponding (+)-(*S*)-3-*sec*-butylglutaric acid (**11**) (Scheme III).

Cyclization of crude **10** with hydroxylamine hydrochloride in boiling ethanol produced (+)-(*S*)-4-*sec*-butylpyridine (**12**) in 40–66% yield.[16] 3-Substituted isomer (up to 4%) also was found in the reaction product, as shown by comparison with the mass spectra, GLC analyses, and NMR spectra of an authentic sample.[17] The minimum optical purity of the prepared alkylpyridines was determined by the method of standard cleavage of the heterocyclic nucleus to (+)-(*S*)-2-methylbutanoic acid (Scheme IV).[2,19] The values of optical purity found for the recovered samples of this acid were assumed as the minimum for the optical purity of the relative pyridines, as the cleavage procedure employed by us should occur without remarkable racemization.[2,12]

Thus, it can be established that cyclization of (+)-(*S*)-2-methylbutanenitrile to (+)-(*S*)-2-*sec*-butylpyridine (Scheme I) takes place with ~9% racemization, indicating that the asymmetric center, even if directly bound with the cyano group, is not involved in the intermediary reaction complex.

Furthermore, while the reaction we have adopted for the synthesis of (+)-(*S*)-4-*sec*-butylpyridine (**12**) (Scheme III) occurs with a very low degree of racemization (~3%), we found for the (+)-(*S*)-3-*sec*-butylpyridine a minimum optical purity of 60%, corresponding to 35% loss of optical activity with respect to the starting (+)-(*S*)-2-*sec*-butylacrolein (**3**) (Scheme II).

It appears very unlikely that racemization takes place during the cycloaddition of **3** to butyl vinyl ether as shown by analogous reaction of (+)-(*S*)-*sec*-butyl-1,3-butadiene with ethylene, even under much more drastic reaction conditions.[21] Moreover, as **5**, when kept for 4 hr under the same conditions used for cyclization, does not racemize, it can be assumed that the loss of optical activity occurs practically only during the formation of pyridine ring from the dihydropyran **4**. Other examples illustrating improvements and extentions of these routes to alkylpyridines will be described in due course.

Experimental Section

Boiling points are uncorrected. GLC analyses were perfcrmed on the Perkin-Elmer F-11 and 990 gas chromatographs, using the columns and the temperatures specified. NMR spectra at 60 MHz were obtained with a Varian T-60 spectrometer, and at 100 MHz with a Varian HA-100 spectrometer, in CCl_4 solutions with tetramethylsilane as an internal standard (δ 0). Optical rotations were taken on a Perkin-Elmer 141 polarimeter in 1- or 0.1-dm tubes. Mass spectra were obtained with an Hitachi Perkin-Elmer RMU-6L mass spectrometer. Microanalyses were performed by the Microanalytical Laboratory of the Technical-Chemical Laboratory of the E. T. H. (Zurich, Switzerland).

Materials. Butyl vinyl ether from Fluka AG (purum grade) was distilled on sodium metal before use. (+)-(*S*)-2-*sec*-Butylacrolein (**3**) and (+)-(*S*)-2-*sec*-butylallyl alcohol (**6**) were prepared by methods described in the literature.[6,14] 1,3-Dithiane from Fluka AG (purum grade) was used without further purification. The synthesis of racemic 2-*sec*-butylpyridine was accomplished by the reaction of pyridine and *sec*-butyllithium.[1]

(+)-(*S*)-2-Methylbutanenitrile (1). To a solution of 18.6 g (0.114 mol) of 1,1-dicarbonylbiimidazole in 56 ml of CH_2Cl_2, 11.8 g (0.114 mol) of (+)-(*S*)-2-methylbutanal oxime,[2] $[\alpha]^{25}D$ + 23.1° (*c* 4.084, *n*-heptane), was added at room temperature during 0.5 hr.[3] After stirring for 0.5 additional hr the reaction mixture, solvent, and reaction product were distilled in vacuo (0.1 mm) and collected in a trap cooled at −70°. Fractional distillation gave a practically quantitative yield of pure (+)-(*S*)-2-methylbutanenitrile (**1**), bp 125° (750 mm), $[\alpha]^{25}D$ +34.18° (neat), corresponding to a minimum optical purity of 87.4%.[22] In another experiment, **1**, $[A]^{25}D$ +32.7° (neat) (83.4% optical purity), was prepared with 95% yield by dehydration of (+)-(*S*)-2-methylbutanal oxime, $[\alpha]^{25}D$ +23.5° (*c* 4.00, *n*-heptane).

(+)-(*S*)-2-sec-Butylpyridine (2). π-Cyclopentadienylcobalt cyclooctadiene[5] (0.700 g) was dissolved in 8 g (0.096 mol) of (+)-(*S*)-2-methylbutanenitrile (which was distilled under nitrogen), $[\alpha]^{25}D$ +33.2° (85.2% optical purity), at room temperature, still maintaining the nitrogen atmosphere. This brown solution was introduced by suction into a 0.2-l. autoclave, evacuated from air (0.1 mm). The autoclave was pressurized to 8 atm with acetylene and then shaken and heated to 140°. Reaction started immediately. Whenever the pressure (14 atm) dropped to 6 atm, acetylene was introduced to the upper pressure limit. Four hours was required for the adsorption of the theoretical amount of gas.

After cooling and releasing of residual gas, the brown reaction mixture was distilled under reduced pressure to give 12.3 g (0.091 mol, 95% yield) of pure **2**, bp 73° (15 mm) [lit.[1] bp 74° (18 mm) for the racemic compound], $[\alpha]^{25}D$ +31.96° (neat), d_4^{25} 0.904, $[\alpha]^{25}D$ +25.78° (c 1.706, ethanol).

2 gave one peak by GLC analysis (2 m × 2.5 mm column, SP 1000 2.5% on Chromosorb G at 130°) and was identified by comparison of mass spectrum and NMR spectrum with those of an authentic sample.

(+)-2-Butoxy-5-*sec*-butyl-2*H*-pyran (4). A typical procedure is described. A mixture of 5.2 g (0.05 mol) of (+)-(*S*)-2-sec-butylacrolein (**3**) (95–96% optical purity),[6] 10.2 g (0.1 mol) of freshly distilled butyl vinyl ether, and 0.150 g of hydrochinone was heated in a rocking steel autoclave at 120° and 2 atm of nitrogen for 24 hr. GLC analysis of the reaction mixture (on a 2 m × 2.2 mm 15% polyglycol 4000 on Kieselgur column, heated at 200°) showed that 90% of **3** had reacted and the following composition: 70% of cycloaddition product **4**, 20% of isomeric products derived from **3**, 7–8% of dimerization products of **3**. Fractional distillation gave 7.0 g of pure **4**, bp 116° (11 mm), $\alpha^{25}D$ +27.5° (*l* 1, neat). The mass spectrum showed the molecular ion *m/e* 212; NMR ($CDCl_3$) 6.12 (m, H-6), 4.95 (m, H-2), 1.9 ppm (m, 2 H-3 and 2 H-4).

In another experiment from 16.5 g (0.16 mol) of **3**, using the same reaction conditions but 130° reaction temperature, **4** was obtained with 69% yield, $\alpha^{25}D$ +31.05° (*l* 1, neat) after 15 hr reaction time.

(+)-(*S*)-3-sec-Butylpyridine (5). **4** (22.0 g, 0.103 mol), $\alpha^{25}D$ +31.0° (*l* 1, neat), in 200 ml of pure acetic acid was refluxed under nitrogen for 2 hr. After cooling, this solution was added to a boiling mixture of 21.5 g (0.31 mol) of hydroxylamine hydrochloride and 100 ml of acetic acid.[9] Heating was continued for 4 additional hr, then most of the solvent was evaporated in vacuo (12–13 mm). Cold water (100 ml) was added and the resulting mixture was alkalized with 10% sodium hydroxide (pH ~10). Extraction with ether, drying (Na_2SO_4), and fractional distillation yielded 11.0 g (80% yield) of pure **5**: bp 74° (15 mm); $n^{20}D$ 1.4942; d_4^{25} 0.914; $[\alpha]^{25}D$ +27.0° (neat). The mass spectrum showed the molecular ion *m/e* 135; NMR (100 MHz, CCl_4) 8.31 (m, H-2 and H-6), 7.38 (m, H-4), 7.11 (m, H-5), 2.62 (m, 1 H, CH), 1.28 (d, 3 H, CH_3), 0.84 ppm (t, 3 H, CH_3).

In another experiment, **5**, $[\alpha]^{25}D$ 26.7° (neat), was prepared in 80% yield by cyclization of **4**, $\alpha^{25}D$ 27.5° (*l* 1, neat), using the same reaction conditions.

(+)-(*S*)-2-*sec*-Butylallyl Bromide (7). Phosphorus tribromide (21.9 g, 0.08 mol) was added dropwise to a stirred solution of 23 g (0.2 mol) of (+)-(*S*)-2-sec-butylallyl alcohol (**6**), $[\alpha]^{25}D$ +20.3° (minimum optical purity ~95%[14]), and 5.5 g (0.06 mol) pyridine cooled to 0°. After stirring at 0° for 4 hr, then at room temperature for 2 hr, the mixture was poured into ice and the product was extracted with ether. The ether solution was neutralized with 5% sodium bicarbonate, dried over Na_2SO_4, and, after removal of the solvent, distilled in vacuo. The yield of **7** was 25.5 g (72%), bp 52° (12 mm), $[\alpha]^{25}D$ + 25.76° (*c* 4.27, *n*-heptane).

(+)-(*S*)-2-(2-*sec*-Butylallyl)-1,3-dithiane (8). 1,3-Dithiane (17 g, 0.14 mol) was treated with 5% excess of butyllithium in 430 ml of THF at −40°.[13] After addition of 25.5 g (0.14 mol) of **7**, the mixture was stirred at −40° for 6 hr and at −20 to −15° for 18 hr. Working up according to Seebach[13] and distillation gave 25.0 g (82% yield) of **8**, bp 112–114° (0.2 mm), $[\alpha]^{25}D$ +21.23° (*c* 3.344, *n*-heptane).

In another experiment **8**, $[\alpha]^{25}D$ +20.74° (c 2.3, *n*-heptane), was prepared from **7** (0.15 mol), $[\alpha]^{25}D$ +26.06° (c 1.174, *n*-heptane), with 75% yield.

(+)-(*S*)-3-*sec*-Butyl-4-(1,3-dithian-2-yl)butanal (9). **8** (23.8 g, 0.11 mol) in 100 ml of dry benzene was hydroformylated with a mixture of CO and H_2 (1:1) at 100 atm and 100° in the presence of 0.20 g of $HRh(CO)(PPh_3)_3$ according to the procedure described elsewhere.[12] After 30 hr, >90% of the substrate had reacted (GLC). After cooling and releasing of the pressure, the reaction mixture was evaporated under reduced pressure (20 mm) and the residual aldehyde was directly purified through its bisulfite derivative. Quite pure **9** (18.9 g, 70%) was recovered by distillation in vacuo as a pale yellow oil, bp 128–130° (0:04 mm), $[\alpha]^{25}D$ +4.65° (*c* 2.406, *n*-heptane).

In another preparation 8 (0.11 mol), $[\alpha]^{25}D$ +20.74° (*n*-heptane), was hydroformylated at 100° and 105 atm of a mixture of CO and H_2 (1:1) using 0.400 g of $RhCl(CO)(PPh_3)_2$ and 0.5 ml of triethylamine. After a reaction time of 40 hr **9** was obtained by usual working up of the reaction mixture with 66% yield.

(*S*)-3-*sec*-Butylglutaraldehyde (10). A typical procedure is described. Red mercuric oxide (4.3 g, 0.02 mol) and 2.8 g (0.02 mol) of boron trifluoride etherate in 24 ml of 15% aqueous THF were stirred vigorously under nitrogen. A solution of 2.5 g (0.01 mol) of the dithiane **9** in 2 ml of THF was added dropwise and the mixture was stirred at room temperature for 2 hr.[15] The crude reaction product (1.3 g, 80% yield) was obtained as a slightly yellow oil by working up of the reaction mixture[15] and gave one peak by GLC analysis (2 m × 2 mm column, silicone SF 96, 2.5% on Chromosorb G at 150°). The molecular weight was 156 (mass spectroscopy).

(+)-(*S*)-3-*sec*-Butylglutaric Acid (11). Crude dialdehyde **10** (1.0 g) was added slowly at 0° to a stirred suspensn of 12.5 g (5.3 mmol) of silver oxide in 20 ml of water containing 0.3 g of NaOH. After 8 hr the filtered solution was worked up in the usual way[23] to give a slightly yellow oil. After addition of dry pentane the crude acid was allowed to stand for 2 hr at room temperature. The white crystals formed were filtered, washed with pentane, and dried under vacuum. **11** (0.6 g) was obtained, mp 82°, $[\alpha]^{25}D$ +12.3° (*c* 2.048, chloroform), neut equiv 98 (lit.[24] mp 68–70° for racemic compound).

Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.34; H, 8.44.

(+)-(*S*)-4-*sec*-Butylpyridine (12). $NH_2OH·HCl$ (1.2 g) was added to a boiling solution of 1.2 g (0.08 mol) of crude **10** in 20 ml of ethanol. After 0.5 hr the mixture was alkalized with 5% sodium hydroxide and the product was extracted with ether. Drying over Na_2SO_4 and distillation yielded 0.45 g (0.032 mol, 40% yield) of **12**, bp 128° (100 mm) [lit.[25] bp 128–130° (100 mm) for racemic compound], $[\alpha]^{25}D$ +23.36° (*c* 1.524, *n*-heptane), which was shown to contain ~4% of 3-sec-butylpyridine by GLC analysis (2 m × 2.5 mm column, SP 1000, 2.5% on Chromosorb G at 100°). The mass spectrum showed the molecular ion *m/e* 135; NMR (CCl_4) 8.4 (m, H-2 and H-6), 7.1 (m, H-3 and H-5), 2.58 (m, 1 H, CH), 1.27 (d, 3 H, CH_3), 0.85 ppm (t, 3 H, CH_3).

In another cyclization experiment **12** (containing ~4% of **5**), $[\alpha]^{25}D$ +23.8° (*c* 1.310, *n*-heptane), was obtained from **9** (0.038 mol) with 66% yield. Isomers **12** and **5** were separated by preparative GLC on a 5 m × 8 mm column, SP 1000, 15% on Chromosorb G at 180°. Pure **12** showed $[\alpha]^{25}D$ 20.2° (*c* 2.29, *n*-heptane).

Ozonization of (+)-(*S*)-*sec*-Butylpyridines to (+)-(*S*)-2-Methylbutanoic Acid. A typical experiment is described.[2] **12** (0.5 g, 3.7 mmol), $[\alpha]^{25}D$ 23.4° (*c* 1.524, *n*-heptane), in 15 ml of CCl_4 was ozonized at room temperature for 18 hr. After replacement of the solvent by the same volume of ethanol, 5 ml of 5% sodium hydroxide and 2 ml of 35% hydrogen peroxide were added slowly at 0°. The mixture was refluxed for 3 hr and the acid was isolated by the usual procedure.[2] (+)-(*S*)-2-Methylbutanoic acid (98 mg) was obtained (26% yield), $[\alpha]^{25}D$ +17.9° (*c* 0.91, ethyl ether) (89% minimum optical purity).

From **5** (4.0 g, 0.03 mol), $[\alpha]^{25}D$ +26.7° (neat), 0.5 g of the same acid was obtained, $[\alpha]^{25}D$ 11.9° (neat) (60% minimum optical purity). From **2**, $[\alpha]^{25}D$ +25.78° (*c* 1.706, ethanol), (+)-(*S*)-2-methylbutanoic acid was obtained, $[\alpha]^{25}D$ +15.8° (*c* 0.974, *n*-heptane) (80% minmum optical purity).

Racemization Experiment with (+)-(*S*)-3-*sec*-Butylpyridine (5). **5**, $[\alpha]^{25}D$ +25.75° (neat), was refluxed for 4 hr in 75 ml of dry acetic acid containing 5.3 g of 37% hydrochloric acid. The pyridine, recovered by already reported working up of the mixture, showed $[\alpha]^{25}D$ +25.53° (neat).

Acknowledgment. The authors are grateful to H. Bönnemann for sending a substantial amount of π-cyclopentadienylcobalt cyclooctadiene and to P. Pino for reading and commenting on the manuscript.

Registry No.—**1**, 25570-03-0; **2**, 55740-78-8; **3**, 10203-77-7; **4**, 55740-79-9; **5**, 55740-80-2; **6**, 39497-65-9; **7**, 55740-81-3; **8**, 55740-82-4; **9**, 55740-83-5; **10**, 55740-84-6; **11**, 55740-85-7; **12**, 55740-86-8; (+)-(*S*)-2-methylbutanol oxime, 16885-26-0; phosphorus tribro-

mide 7789-60-8; 1,3-dithiane, 505-23-7; (+)-(S)-2-methylbutanoic acid, 1730-91-2.

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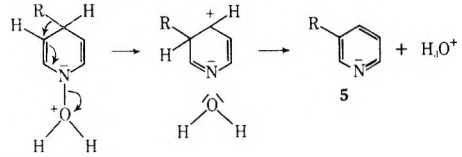
(16) An attempt to obtain **12** by direct cyclization of **9** afforded a very low yield of the expected alkylpyridine and other unidentified products.
(17) A sample containing ~80% of **5** was obtained by preparative GLC. The rotatory power of this sample ($[\alpha]^{25}D$ ~+30°) showed that **5** is also optically active. On this basis, and taking into account the reaction intermediates suggested for the cyclization of 1,4-dioxo compounds with hydroxylamine,[18] a possible pathway for the formation of **5** from **10** can be formulated as follows.



(18) See ref 8, p 279.
(19) The optical purity was determined in case of chiral 2-*sec*-butylpyridine (**2**) by NMR analysis in the presence of tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III).[20] From the NMR results obtained on a solution containing 35.3 mg of (−)-(*R*)-**2**, $[\alpha]^{25}D$ −12.8° (ethanol), prepared by resolution of racemic compound with dibenzoyl-(+)-tartaric acid,[1] and 59.9 mg of the europium complex, $[\alpha]D$ +196° (carbon tetrachloride), in 0.7 ml of carbon tetrachloride, looking at the signals of the H-2 ring proton and of the methyl group protons nearer to the asymmetric center, a value of 29 (ethanol) for the maximum rotatory power of **2** was extrapolated. This value is in satisfactory agreement with that obtained through the cleavage method, $[\alpha]^{25}D$ +32.2° (ethanol) (Scheme IV), considering that the precision of the NMR method is about ±10%.
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Reaction of Azomethine Ylides with Sulfur Ylides. A Novel Azetidine Synthesis

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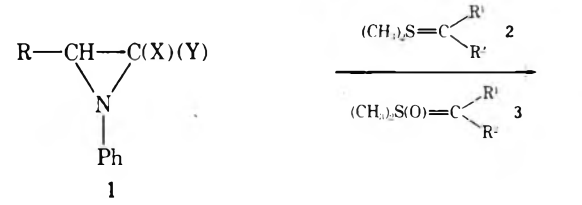
Received February 13, 1975

Aziridines represent versatile substrates which can serve as azomethine ylide precursors. We have shown an unusual feature of these ylides: they are able to react with both electrophilic and nucleophilic reagents.[1-4] Not the least interesting of these last are sulfur ylides which lead to azetidines in a novel way.[5] As a result of a continuing study of this last reaction we wish to report some new information and experimental details which were not given in the preliminary note.[5]

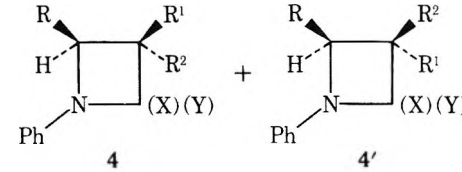
The various azetidines which were prepared are shown in Scheme I.

Scheme I[6]



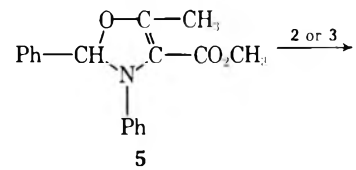
1a, R = Ph; X = Y = CO_2CH_3
1b, R = X = Y = CO_2CH_3
1c, R = Ph; X = H; Y = $CO_2C_2H_5$

2a or **3a**, $R^1 = R^2$ = H
2b, R^1 = H; $R^2 = CO_2CH_3$
2c, R^1 = H; $R^2 = CO_2C_2H_5$
2d or **3d**, R^1 = H; R^2 = COPh
2e, $R^1, R^2 = C_{13}H_{18}$[a]
2f, R^1 = Cl; $R^2 = CO_2C_2H_5$
2g, R^1 = Br; $R^2 = CO_2C_2H_5$

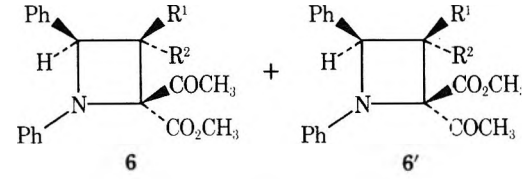


4 a-g
4′ R = Ph; X = Y = CO_2CH_3

4d and **4′d**, R = X = Y = CO_2CH_3



5



6 **6′**

6b or **6′b**; **6d** or **6′d**; **6e** or **6′e**; **6f** or **6′f**

[a] Fluorenylidene.

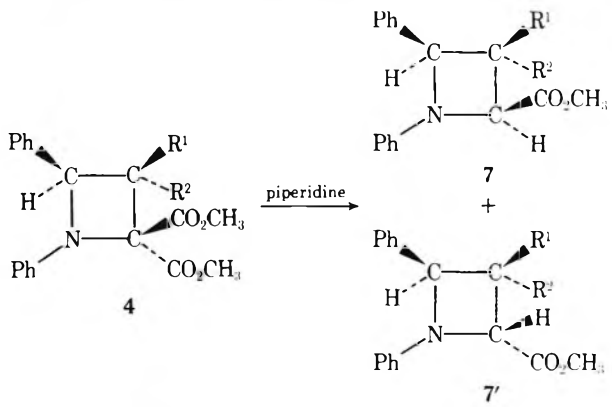
In the reactions of ethyl chloro- (or bromo-) (dimethylsulfuranylidene)acetate (**2f** or **2g**) with aziridine **1a** and 4-oxazoline **5**, we expected competition between dimethyl sulfide (DMS) and bromide or chloride elimination. However, in each case, DMS is a better leaving group than the halide and we observe only formation of the epimeric halogenated azetidines **4f, 4′f; 4g, 4′g;** and **6f, 6′f.** In an attempt to prepare the C_2 monosubstituted azetidines, the sulfonium ylides were heated with aziridine **1c** in boiling benzene (under these conditions, **1c** is in equilibrium with the corresponding azomethine ylide[2,3,7]) but no reaction occurs, except the isomerization of **1c** and the partial decomposition of the sulfur ylide. We have no explanation for this failure; it is not due to instability of the sulfonium ylide, which is still present after 8 hr of reaction. Nevertheless it is possible to get the C_2 monosubstituted azetidines in good yield by demethoxycarbonylation of compounds **4** with piperi-

Table I
Ir and NMR Data of 7 and 7′

Compd	R^1	R^2	Ir, cm^{-1} $\nu_{C=O}$	NMR, δ(Me_4Si) H_2	H_3	H_4	J_{23}, Hz	J_{34}, Hz	CO_2CH_3 ($CO_2CH_2CH_3$)	Rel %
7a	H	H	1744	4.45	2.42[a]	4.82	8.8	8.4	3.83	90
					2.97		7.4	7.6		
7′a	H	H		4.14	2.58	5.36	*b*	*b*	3.69	10
					2.30					
7b	H	CO_2CH_3	1744	4.68 d	3.50 t	4.93 d	7.0	7.0	3.84	≥90[c]
									3.74	
7c	H	$CO_2C_2H_5$	1740	4.76 d	3.50 t	5.03 d	7.0	7.0	3.92	≥90[c]
									(1.27)	
7d	H	COPh	1678	4.91 d	4.42 t	5.00 d	7.0	7.0	3.86	≥90[c]
			1740							
7e	*d*		1754	5.01 s		5.51 s			3.24	91
7′e	*d*			4.85 s		5.39 s			3.20	9

[a] J_{gem} = 11.0 Hz. [b] The mixture **7a** + **7′a** has a satisfactory elementary analysis. It is not possible to measure the coupling constants of **7′a** on the spectra of this mixture. The given δ is the position of the multiplet's center. [c] Near **7** it is possible to detect (NMR) the presence of some impurities bearing ester groups. The integration of the methoxycarbonyl methyl protons allows us to give the ratio of **7**. These impurities are not identified. [d] Azetidine resulting from the demethoxycarbonylation of **4e**.

dine in boiling toluene or xylene. Here this reaction, which gives fairly good results for five-membered heterocycles,[8] successfully applied to four-membered rings.



In the resulting mixtures, compounds **7** are always the major products (≥90%); they are isolated and purified by recrystallization. Compounds **7′a** and **7′e** are identified by NMR (Table I); **7′b**, **7′c**, and **7′d**, which are formed in small quantities (≤10%), are not identified with certainty.

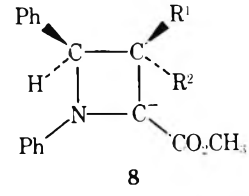
The values of J_{23} and J_{34} in compounds **7** (≤7, 6 Hz) indicate that H_2 and $R^1 = H_3$ are trans and the same for H_4 and $R^1 = H_3$.

The assignment of formula **7e** to the major product arising from **4e** is realized by assuming that this compound behaves as the other azetidines **4**.

Compounds **7a–c** and **7e** are recovered unchanged after boiling with piperidine in toluene. When treated with *N*-deuteriopiperidine, **7b** and **7c** are unchanged; there is no isomerization or deuterium exchange with H_2 or H_3. Furthermore, the *N*-deuteriopiperidine converts **4b** to **7b** with a deuterium on C_2 only, providing a simple method to deuterate the azetidines on C_2. These results indicate that the demethoxycarbonylation of **4a–c** and **4e** is under kinetic control and takes place without changing the configuration at carbon 3.

4d (R = Ph) is a special case since H_3 is acidic enough to be replaced by deuterium, owing to the presence of a benzoyl group. Thus the reaction of **4d** with *N*-deuteriopiperidine in boiling toluene leads to a deuterated compound on C_3 and not on C_2. Furthermore, demethoxycarbonylation of pure **4′d** gives the same mixture as **4d**. Demethoxycarbonylation of **4d** is slower than the isomerization of **4′d** to **4d**.

These results may be rationalized as follows: the demethoxycarbonylation proceeds through the intermediate carbanion **8**, which undergoes a kinetic protonation. These carbanions with an α nitrogen atom are likely to be pyramidal.[9] There are two carbanions epimeric on C_2 which are easily interconverted and which are protonated to give **7** and **7′** in a ratio which depends on the relative stabilities of the epimeric carbanions.



Experimental Section[10]

The sulfur ylides were prepared by known procedures: **2a** and **3a**,[11] **2b** and **2c**,[12] **2d**,[13] **2e**,[14] **2f** and **2g**,[15] **3d**.[16]

The aziridines **1a** and **1b** and 4-oxazoline **5** were obtained by thermolysis of the corresponding triazolines under nitrogen.[3,17] The neat triazoline was thermolyzed under nitrogen (**1a**, 180° for 15 min; **1b**, 145° for 20 min; **5**, 155° for 20 min). When the evolution of N_2 had ceased, the resulting aziridines or 4-oxazoline were dissolved in anhydrous benzene or THF.

The addition of the sulfur ylides to aziridines **1** or 4-oxazolines **5** was always realized under nitrogen and anhydrous solvents were used.

Azetidine Synthesis. As an example, we will describe the reaction between aziridine **1a** and dimethylphenacylidene sulfurane (**2d**). All other reactions were done following a similar procedure and we will indicate only the modifications of experimental conditions in each case. Furthermore, we will report the experimental and spectroscopic data related to the compounds which were not already published,[5] i.e., reactions with halogenated sulfuranes and also reactions with the trimethoxycarbonyl aziridine **1b**.

3-Benzoyl-2,2-dimethoxycarbonyl-1,4-diphenylazetidines 4d and 4′d (R = Ph; X = Y = CO_2CH_3). Aziridine **1a**, resulting from the thermolysis of 2.1 g (6 mmol) of the corresponding triazoline, was dissolved in 40 ml of benzene. Then 1.08 g (6 mmol) of the sulfurane **2d** in 20 ml of benzene was added dropwise. When the addition was complete, the reaction mixture was allowed to stand for 2 hr at room temperature before removing the solvent in vacuo. The reaction led to a quantitative yield (NMR) of the mixture **4d** + **4′d**. Recrystallization from methanol gave 85% (2.3 g) of **4d** + **4′d** (79:21). Fractional crystallization from benzene–petroleum ether afforded 0.6 g of **4d**, mp 152°, and 0.2 g of **4′d**, mp 200°.

Compounds **4b**, **4′b**, **4c**, and **4′c** were obtained by this procedure. For compounds **4a** and **4e** the reaction was carried out in the mixture THF–Me_2SO (4:1) at room temperature. All these products

were recrystallized in boiling methanol except for compound **4e** (benzene–petroleum ether).

3-Chloro-2-2-dimethoxycarbonyl-1,4-diphenyl-3-ethoxycarbonylazetidines 4f and 4'f. Using the same procedure, the reaction led to a quantitative yield (NMR) of the mixture **4f** + **4'f** (87:13).

Recrystallization from methanol afforded **4f** in a 72% yield: mp 154°; ir 1736, 1756 cm^{-1} (ester C=O); NMR ($CDCl_3$) δ 5.94 (1 H, s), 3.97 (3 H, s), 3.54 (3 H, s), 1.30 (3 H, t), 4.30 (2 H, q), 6.40–7.60 (10 H, m). **4'f** (isomer only identified by NMR): δ 5.68 (1 H, s), 3.81 (3 H, s), 3.64 (3 H, s), 0.82 (3 H, t), 3.70 (2 H, q), 6.40–7.60 (10 H, m).

The chemical shift of the methyl of the ethoxycarbonyl group on carbon 3 indicates that **4f** has the trans configuration (phenyl and ester group on C_3 and C_4). It is the same for azetidine **4g** (see ref 5).

3-Bromo-2,2-dimethoxycarbonyl-1,4-diphenyl-3-ethoxycarbonylazetidine 4g. A solution containing 1.36 g (6 mmol) of ethyl bromo(dimethylsulfuranylidene)acetate (**2g**) in 25 ml of chloroform was added at 0–5° to a solution of 6 mmol of **1a** in 10 ml of chloroform. After standing for 4 hr at room temperature, the solution was washed with water and dried (Na_2SO_4). Removal of $CHCl_3$ in vacuo led to 2.5 g of an oily residue which contained (NMR) only the isomer **4g** (85%), benzaldehyde, and methyl anilinomalonate (these two last products result from the hydrolysis of unreacted **1a**, 15%). Recrystallization from methanol led to azetidine **4g**: 1.5 g (52%); mp 150°; ir 1738, 1760 cm^{-1} (C=O); NMR ($CDCl_3$) δ 5.88 (1 H, s), 4.04 (3 H, s), 3.61 (3 H, s), 1.33 (3 H, t), 4.36 (2 H, q), 6.60–7.70 (10 H, m).

3-Benzoyl-1-phenyl-2,2,4-trimethoxycarbonylazetidines 4d and 4'd (R = X = Y = CO_2CH_3). The equilibrium between aziridine **1b** and the corresponding azomethine ylide is established only at the reflux of toluene. So the reaction between **1b** and sulfurane **2d** was run in boiling toluene for 3 hr. The reaction led to a quantitative yield (NMR) of the mixture **4d** + **4'd** (48:52). Recrystallization from methanol gave pure **4'd** (38%): mp 164°; ir 1670 (C=O ketone), 1724, 1734, 1760 cm^{-1} (C=O esters); NMR ($CDCl_3$) δ 5.00 (1 H, d, J = 8.9 Hz), 5.27 (1 H, d, J = 8.9 Hz), 3.60 (3 H, s) 3.64 (3 H, s), 3.70 (3 H, s), 6.60–7.90 (10 H, m); **4d** (isomer only identified by NMR) δ 5.15 (1 H, d, J = 7.0 Hz), 5.39 (1 H, d, J = 7.0 Hz), 3.71 (3 H, s), 3.79 (3 H, s), 4.03 (3 H, s).

The stereochemical assignment is based on J_{34} values:[5] **4'd** is the cis compound (J_{34} = 8.9 Hz) and **4d** the trans compound (J_{34} = 7.0 Hz).

2-Acetyl-3-chloro-1,4-diphenyl-3-ethoxycarbonyl-2-methoxycarbonylazetidines 6f and 6'f. The sulfonium ylide **2f** (1.1 g, 6 mmol) was added to a 30-ml benzene solution of 6 mmol of **4**-oxazoline **5** (obtained from 2 g of the corresponding triazoline). After standing for 18 hr at room temperature the benzene was removed in vacuo. The reaction led (NMR) to a mixture **6f** + **6'f** (75:25). Recrystallization from methanol gave 0.3 g of **6f** + **6'f** (83:17). Fractional crystallization in benzene–petroleum ether led to **6f** (or **6'f**), mp 126°. A second crop of 0.4 g, containing **6f** + **6'f** (35:65), was obtained from methanol, overall yield 28%: **6f** (or **6'f**) ir 1702, 1740, 1756 cm^{-1} (C=O); NMR ($CDCl_3$) δ 5.94 (1 H, s), 4.03 (3 H, s), 2.33 (3 H, s), 1.33 (3 H, t), 4.27 (2 H, q), 6.40–7.70 (10 H, m); **6'f** (or **6f**), NMR ($CDCl_3$) δ 5.90 (1 H, s), 3.59 (3 H, s), 2.57 (3 H, s), 1.36 (3 H, t), 4.42 (2 H, q), 6.40–7.70 (10 H, m).

6d and **6'd** were obtained by the same procedure. For compounds **6e** and **6'e** the reaction was carried out in the mixture THF–Me_2SO (4:1) at room temperature. For **6b** or **6'b** the reaction was run in boiling benzene (2 hr). All these compounds were recrystallized in methanol except for **6e** or **6'e** (acetone).

Demethoxycarbonylation of Azetidines 4. Piperidine (1 ml) was added to 1 g of azetidine **4** in 20 ml of anhydrous toluene or xylene and the mixture was usually refluxed for 24 hr (the reaction was followed by NMR). When **4** had completely disappeared, the solvent and excess of piperidine were distilled under reduced pressure (3 mm).

I. Demethoxycarbonylation of 4a. **4a** gave a quantitative yield of **7a** + **7'a** (90:10) after 140 hr of reaction in boiling xylene. The mixture **7a** + **7'a** was purified by distillation under vacuum, bp 150–155° (0.015 mm). Addition of ethanol yielded **7a** (30%), mp 74°.

II. Demethoxycarbonylation of 4b–e. The crude reaction mixtures were analyzed by NMR. Compounds **7** were isolated and purified: **7b**, mp 102° (ether), 74% yield; **7c**, mp 60° (ether–petroleum ether), 58% yield; **7d**, mp 118° (ethanol), 74% yield; **7e**, mp 192° (ether–petroleum ether), 68% yield.

III. Demethoxycarbonylation of 4'd. Piperidine (0.2 ml) was added to the solution of 0.1 g of **4'd** in 10 ml of anhydrous toluene. After 8 hr of reflux, the NMR indicated that 52% of **7d** was formed and that the remaining 48% was **4d** (and not the starting **4'd**). This shows that **4'd** is isomerized to **4d** in the reaction. After 24 hr the reaction was complete and gave the same mixture as **4d**.

IV. Evidence for Kinetic Control of the Reaction. A. Reaction of 7a–c and 7e with Piperidine. Piperidine (0.1 g) was added to the solution of 0.1 g of azetidine in 10 ml of anhydrous toluene. After distillation of toluene in vacuo, the starting azetidine was recovered without any change.

B. Preparation of *N*-Deuteriopiperidine. Piperidine (10 ml) distilled over KOH was mixed with 10 ml of D_2O (98%). After standing for 0.5 hr under nitrogen the piperidine was extracted with ether (saturated with D_2O). The ether layer was dried over anhydrous K_2CO_3 and then distilled at atmospheric pressure, giving 8 ml of piperidine deuterated to the extent of 65% (NMR).

Piperidine N-deuterated to 95% was obtained in the following way. In a two-neck flask fitted with a dropping funnel and a Dean-Stark trap, 50 ml of anhydrous toluene, 1 g of *N*-deuteriopiperidine (65%), and 1 g of D_2O (99.5%) were introduced under nitrogen. The mixture was heated to reflux and water was eliminated by azeotropic distillation with toluene and then the compound to be demethoxycarbonylated was added in toluene solution.

C. Reaction of 4b with *N*-Deuteriopiperidine. **4b** (1 g) in toluene solution (10 ml) was added under nitrogen to 1 g of piperidine-*1-d* in toluene (10 ml). After 24 hr of reflux, distillation under reduced pressure gave an oily residue which crystallized by addition of hot methanol. **7b** deuterated on C_2 to the extent of 95% (mp 102°, 70% yield) was obtained.

D. Reaction of 7d with *N*-Deuteriopiperidine. **7d** (1 g) was treated with 1 g of piperidine-*1-d* (65%) in boiling toluene for 24 hr. Distillation of toluene and excess of piperidine in vacuo gave **7d** deuterated on C_3. **7d** was recrystallized from boiling methanol. The NMR showed that it was a mixture of deuterated and nondeuterated compounds in equivalent amount.

Registry No.—**1a**, 34671-09-5; **1b**, 51597-29-6; **1c**, 49790-76-3; **2a**, 6814-64-8; **2b**, 18915-90-7; **2c**, 7380-81-6; **2d**, 5633-34-1; **2e**, 55800-52-7; **2f**, 16980-47-5; **2g**, 55800-53-8; **3a**, 5367-24-8; **3d**, 20718-17-6; **4a**, 43113-13-9; **4b**, 43113-14-0; **4c**, 43113-16-2; **4d**, 55800-57-2; **4e**, 5580-54-9; **4f**, 55800-55-0; **4g**, 55800-56-1; **4'b**, 43113-15-1; **4'c**, 43113-17-3; **4'd**, 55800-58-3; **4'f**, 55800-59-4; **4'g**, 55800-60-7; **5**, 4311-18-4; **6b**, 55869-69-7; **6d**, 55869-70-0; **6e**, 55800-61-8; **6f**, 55800-62-9; **6'b**, 55869-71-1; **6'd**, 55869-72-2; **6'e**, 55800-63-0; **6'f**, 55869-73-3; **7a**, 55800-64-1; **7b**, 55800-65-2; **7b** deuterated on C_2, 55869-74-4; **7c**, 55800-66-3; **7d**, 55800-67-4; **7d** deuterated on C_3, 55869-75-5; **7e**, 55800-68-5; **7'a**, 55800-69-6; **7'e**, 55800-70-9; piperidine, 110-89-4; *N*-deuteriopiperidine, 694-58-6.

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Preferred Conformer Assignments of Diaryl Sulfoxides Employing Aromatic Solvent Induced Shifts

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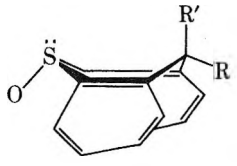
Received May 26, 1975

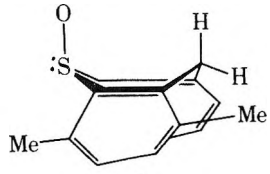
The changes in proton chemical shifts of a solute molecule on passing from a (presumably) noninteracting solvent (e.g., carbon tetrachloride or deuteriochloroform) to an aromatic solvent (e.g., benzene or toluene) are assumed to arise from long-range magnetic anisotropic effects of the solvent specifically solvated to solute molecules.[2] It is the general contention that aromatic solvent induced shifts (ASIS)[3] emanate from a number of factors including (a) solute–solvent collision complexes with time-averaged structures,[4] (b) clustering of partially oriented solvent molecules about polar sites of the solute,[5] and (c) charge-transfer interactions between solvent and solute.[2] In this manuscript we report a generalized application of ASIS to the determination of the stereochemistry of some diaryl sulfoxides.

From numerous citations[6] of aromatic anisotropic effects reflecting both steric and electronic factors of solute and/or solvent,[6a,b] we anticipated that the molecular dipoles of contrasting sulfoxides should experience different degrees of solvation (hence, shielding) in benzene solution.[6] Thus, the relative shielding effects experienced by a sensor proton might serve as a diagnostic probe for sulfoxides possessing a pseudo-axial (a′) or pseudo-equatorial (e′) sulfinyl oxygen atom conformation.

In an earlier report[7] we had shown that the preferred conformation of the sulfinyl oxygen atom in thioxanthene *S*-oxide (**1**) was 10e′ whereas that of the anancomeric 1,4-dimethylthioxanthene *S*-oxide (**2**) was 10a′. In both cases



1, R = R′ = H
cis-**3**, R = Me; R′ = H
trans-**3**, R = H; R′ = Me
4, R = R′ = Me



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the peri protons (H_4, H_5) are deshielded ($CDCl_3$) relative to the remaining aryl protons.[8] This shielding effect is considered to result from the combined inductive and anisotropic effect of the sulfinyl group.[9] However, in perdeuteriobenzene (C_6D_6)[10] the peri protons (H_4, H_5) of **1** are less shielded than the H_5 peri proton of **2**; in deuteriochloroform they are virtually identical ($\Delta\delta_{CDCl_3}$ 0.02 ppm). Hence, the observed chemical shift difference ($\Delta\delta_{C_6D_6}$ 0.40 ppm) between the peri protons of **1** and **2** in C_6D_6 clearly reflects differences in anisotropic effects of "complexed" benzene in diastereomeric environments.

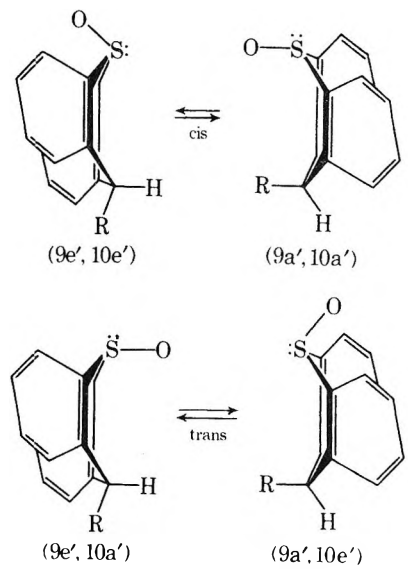
A simple analysis of the data of the aryl protons in $CDCl_3$ would not allow for a firm conclusion regarding the preferred conformation of the sulfinyl oxygen atom; however, the sign and magnitude of the ASIS value (Δ) does provide valuable insight into this problem. Since the preferred conformations of the *cis*- and *trans*-9-methylthioxanthene *S*-oxide (**3**)[7,11,12] and 9,9-dimethylthioxanthene *S*-oxide (**4**)[7,11] have already been determined, it was clear to us that the success of the ASIS technique applied to these systems (with **1** and **2** as model compounds) would be based on a corroborative prediction of sulfinyl conformational preferences which had been previously ascertained by independent schemes.

In Table I, the Δ value (−0.18) for **1** indicates less shielding of the $H_{4,5}$ protons in C_6D_6 than in $CDCl_3$ solution whereas the opposite is observed for the H_5 proton of **2** (Δ 0.20). The conclusion drawn from these data is that benzene causes a downfield shift of the proximal peri protons when solvating an e′ sulfinyl group but an upfield shift of the proximal peri protons when solvating an a′ sulfinyl group.

Both **4** and *cis*- and *trans*-**3** exist in preferred conformations with 10e′ sulfinyl oxygen atoms and it is evident from Table I that the Δ values correlate well with these previously established sulfinyl oxygen orientations. In the *cis*- and *trans*-9-ethylthioxanthene *S*-oxide (**5**) series, the Δ value for the trans isomer is characteristic of an e′ sulfinyl oxygen atom conformation while the Δ value for the cis isomer is similar to that found for a diaryl sulfoxide with an a′ sulfinyl oxygen, e.g., 1,4-dimethylthioxanthene *S*-oxide (Δ +0.21). A similar trend is observed for the cis and trans forms of 9-isopropylthioxanthene sulfoxide (**6**). The results indicate that the sulfinyl group occupies the a′ conformation in the cis forms and the e′ conformation in the trans forms of **5** and **6**. This conclusion is to be contrasted to that obtained for the diastereomers of **3**, where both diastereomers exist with the sulfinyl oxygen in the e′ conformation.[7]

In a previous report[13] we noted that alkyl groups larger than methyl at C-9 overwhelmingly prefer the 9a′ conformation in the sulfide and from these results we suggest that the preferred conformations of the diastereomers of **5** and **6** are *cis*-(9a′,10a′) and *trans*-(9a′,10e′).[14,15]

These conclusions are in harmony with those arrived at by Michaelis et al.[16] regarding the cis and trans *S*-oxides of 9-[(*N*-methyl-3′-piperidyl)methyl]thioxanthene. Employing ir, uv, and ^1H NMR spectroscopy, Michaelis et al.[16] assigned the dipseudo-axial conformation (9a′,10a′) to the cis form and the 9a′,10e′ conformation to the trans diastereoisomer.

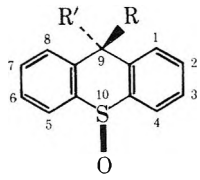


Experimental Section[17]

The preparations of the sulfides and thioxanthene *S*-oxide, 1,4-dimethylthioxanthene *S*-oxide, *cis*- and *trans*-9-methylthioxanthene *S*-oxide, and 9,9-dimethylthioxanthene *S*-oxide have been described elsewhere.[7,14]

***cis*- and *trans*-9-Ethylthioxanthene *S*-Oxides (5).** A solution of *m*-chloroperoxybenzoic acid (7.68 g, 44.6 mmol) in CH_2Cl_2 (125

Table I
Proton Magnetic Resonance Parameters[a] of Substituted Thioxanthene *S*-Oxides



Compd	Solvent	$C_{1,2,3,6,7,8}$ H[b]	$C_{4,5}$ H[c]	ΔASIS[d]
Thioxanthene *S*-oxide (**1**)	$CDCl_3$	7.35	7.86	−0.18
R = R' = H	C_6D_6	6.96	8.04	
1,4-Dimethylthioxanthene *S*-oxide (**2**)	$CDCl_3$	7.46	7.84	+0.20
R = R' = H	C_6D_6	6.96	7.64	
cis-9-Methylthioxanthene *S*-oxide	$CDCl_3$	7.40	7.88	−0.15
(*cis*-**3**) R = Me; R' = H	C_6D_6	6.96	8.03	
trans-9-Methylthioxanthene *S*-oxide	$CDCl_3$	7.42	7.96	−0.16
(*trans*-**3**) R = H'; R' = Me	C_6D_6	6.94	8.12	
9,9-Dimethylthioxanthene *S*-oxide (**4**)	$CDCl_3$	7.44	7.98	−0.22
R = R' = Me	C_6D_6	7.06	8.20	
cis-9-Ethylthioxanthene *S*-oxide	$CDCl_3$	7.43	7.88	+0.21
(*cis*-**5**) R = Et; R' = H	C_6D_6	6.94	7.67	
trans-9-Ethylthioxanthene *S*-oxide	$CDCl_3$	7.35	7.96	−0.15
(*trans*-**5**) R = H; R' = Et	C_6D_6	6.99	8.11	
cis-9-Isopropylthioxanthene *S*-oxide	$CDCl_3$	7.38	7.80	+0.25
(*cis*-**6**) R = *i*-Pr; R' = H	C_6D_6	6.94	7.55	
trans-9-Isopropylthioxanthene *S*-oxide	$CDCl_3$	7.34	7.97	−0.15
(*trans*-**6**) R = H; R' = *i*-Pr	C_6D_6	7.00	8.12	
9,9-Dimethylthioxanthene[e]	$CDCl_3$	7.15	7.43	+0.31
	C_6D_6	6.97	7.12	

[a] Chemical shifts (δ) are reported in parts per million downfield from internal tetramethylsilane and were obtained at 60 and/or 100 MHz. [b] Only the center of the absorption resulting from these protons is reported and these data are included in this table to show the consistent upfield shifting effect of C_6D_6 on protons removed from the sulfinyl environment. [c] The chemical shifts reported here represent the arithmetic mean of the $C_{4,5}$ H multiplet. [d] ASIS = $\Delta_{C_{4,5}H} = \delta_{CDCl_3} - \delta_{C_6D_6}$ at ambient temperature. [e] This derivative is included to show that all protons are shielded in C_6D_6 solution.

ml) was added dropwise to a cold (ice bath) solution of 9-ethylthioxanthene (8.10 g, 35.7 mmol) in 150 ml of CH_2Cl_2. The resulting solution was stirred at 0–5° for 6 hr, allowed to warm to room temperature, treated with a saturated solution of $NaHCO_3$ (4 × 100 ml), and washed with water (100 ml). Drying ($MgSO_4$) and evaporation of the solvent (N_2 gas) gave 8.58 g of crude *S*-oxides. TLC indicated only a trace of 9-ethylthioxanthene.

***cis*-9-Ethylthioxanthene *S*-Oxide (*cis*-5).** The yellow solid (diastereoisomeric sulfoxides) was dissolved in *n*-hexane and slow evaporation of the solvent gave colorless needles of *cis*-9-ethylthioxanthene *S*-oxide. The mother liquor was decanted, concentrated, and seeded with crystals of *cis*-**5** to afford more colorless crystals. This process was repeated several times and two recrystallizations of the combined solids from ethyl acetate gave 910 mg (3.76 mmol, 10.5% yield) of pure *cis*-**5**: mp 111.0–112.0°; ir (Nujol) 8.44, 9.33, 9.74, and 9.68 μm. Anal. Calcd for $C_{15}H_{14}OS$: C, 73.34; H, 5.82; S, 13.23. Found: C, 74.41; H, 6.03; S, 13.19.

***trans*-9-Ethylthioxanthene *S*-Oxide (*trans*-5).** The hexane mother liquor resulting from the separation of *cis*-**5** was evaporated to dryness (N_2 gas stream), the crystals were redissolved in 95% ethanol, and the solution was allowed to evaporate slowly. This process gave ca. 3.6 g of an inhomogeneous material which was recrystallized from ethyl acetate to afford 1.07 g (4.43 mmol, 12.3% yield) of pure *trans*-**5**: mp 119.0–120.0°; ir (Nujol) 9.65 and 9.17 μm. Anal. Found: C, 74.66; H, 5.93; S, 13.28.

***cis*- and *trans*-9-Isopropylthioxanthene *S*-Oxides (6).** A solution of *m*-chloroperoxybenzoic acid (7.68 g, 44.6 mmol) in CH_2Cl_2 (150 ml) was added dropwise to a cold solution (ice bath) of 9-isopropylthioxanthene (10.0 g, 40.7 mmol) in CH_2Cl_2 (200 ml). The resulting solution was stirred at 0–5° for 48 hr, washed with a saturated solution of $NaHCO_3$ (4 × 100 ml) and water (2 × 100 ml), dried ($MgSO_4$), and concentrated to dryness (N_2 gas) to give 11.2 g of crude material. This material was dissolved in *n*-hexane and as the solvent slowly evaporated two distinct crystalline forms crystallized in the flask. Manual separation gave two batches of crystals.

***cis*-9-Isopropylthioxanthene *S*-Oxide (*cis*-6).** The batch of needles was recrystallized from hexane to afford 1.36 g (5.32 mmol, 12.7%) of colorless, pure *cis*-**6**: mp 101.0–102.5°; ir (Nujol) 9.86, 9.71, 9.63, and 9.91 μm. Anal. Calcd for $C_{16}H_{16}OS$: C, 74.96; H, 6.29; S, 12.50. Found: C, 74.92; H, 6.32; S, 12.61.

***trans*-9-Isopropylthioxanthene *S*-Oxide (*trans*-6).** The batch of rectangular blocks was recrystallized from hexane to yield 2.87 g (11.2 mmol, 26.8%) of homogeneous *trans*-**6**: mp 166.0–166.5°; ir (Nujol) 9.67 and 9.26 μm. Anal. Found: C, 74.94; H, 6.24; S, 12.30.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. The portion of this work carried out at the University of Texas at Arlington was supported by Grant Y-484 from the Robert A. Welch Foundation. Funds for a Varian Model HA-100 at UTA were provided by the Research Corporation.

Registry No.—**1**, 1011-81-0; **2**, 51517-43-2; *cis*-**3**, 19018-80-5; *trans*-**3**, 19018-81-6; **4**, 19019-06-8; *cis*-**5**, 56195-77-8; *trans*-**5**, 56195-78-9; *cis*-**6**, 55235-94-4; *trans*-**6**, 56195-79-0; 9,9-dimethyl-T, 19019-10-4; *m*-chloroperoxybenzoic acid, 937-14-4; 9-ethyl-T, 28612-38-6; 9-isopropyl-T, 28612-39-7.

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p-(Aminomethyl)phenoxymethyl Polymer for Solid Phase Synthesis of Protected Peptide Amides[1]

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Received March 31, 1975

We have previously[2] reported on the use of *p*-methoxybenzyl (pmb) as an amido protecting group and on the synthesis of a related *p*-alkoxybenzylamine support for the preparation of C-terminal peptide amides. Attempts to prepare peptide amides using this polymer as a substitute of the benzhydryl amino polymer[3] showed that the anchoring bond between the first amino acid and the polymer is not stable in the conditions normally associated with the removal of *N-tert*-butyloxycarbonyl (Boc). Thus, when the Boc-Ala-*p*-alkoxybenzylamine resin, Boc-Ala-NH-resin, was treated with 50% (v/v) trifluoroacetic acid in methylene chloride or 1 *N* HCl–acetic acid to remove the Boc group, alanine amide was released in 80% yield. A similar result has been obtained by the use of Boc-Val-NH-resin and Boc-Gly-NH-resin. This experimental finding led us to use this support for the preparation of small protected peptide amides suitable for conventional peptide synthesis. This approach has been already described[4] and is very important, since the two most necessary requirements for the successful synthesis of pure long peptide chains by the solid phase peptide technique, i.e., nearly 100% stepwise yields and careful choice of protecting groups, are often difficult to meet.

This paper describes the preparation of the *p*-(aminomethyl)phenoxymethyl polymer (*p*-alkoxybenzylamine polymer) and its application to the synthesis of three protected peptide amides using for amino protection the very acid labile 2-phenylisopropyloxycarbonyl group (Ppoc).[5]

Two synthetic routes to this support are outlined in Scheme I.

Initial preparation was carried out by reaction of the Merrifield resin (IV) with *p*-cyanophenol followed by reduction with $LiAlH_4$ in presence of ammonia. A second procedure involved the treatment of the *p*-alkoxybenzyl alcohol resin[6] with HBr in methylene chloride to give the *p*-alkoxybenzyl bromide polymer, which was converted to the desired amine derivative by reaction with ammonia in methylene chloride.

The first method required accurately controlled conditions because of the possible concurrent formation of the *p*-alkoxybenzyl alcohol polymer. To overcome this drawback the cyano polymer, obtained by treating the Merrifield resin with a large excess of *p*-cyanophenol for short reaction times, was reduced in a stream of dry ammonia. This difficulty did not occur in the preparation of the *p*-alkoxybenzylamine polymer starting from the *p*-alkoxybenzyl alcohol support. However, this route was discarded since the sequence of reactions, i.e., preparation of the *p*-alkoxybenzyl alcohol polymer, conversion to the corresponding bromide derivative, and final amination, was long and tedious. For this reason the synthesis of our models was carried out on the polymer prepared by the first procedure. Ppoc-amino acids were attached to the amine support via DCC. The degree of substitution was 0.4–0.5 mequiv/g; the remaining free amino groups were blocked by acylation. The Ppoc group was removed by 30-min exposure to 1% (v/v) trifluoroacetic acid in methylene chloride.[5] During this time there was hardly any free amide released from the resin, indicating that the anchoring bond was largely stable under these conditions.

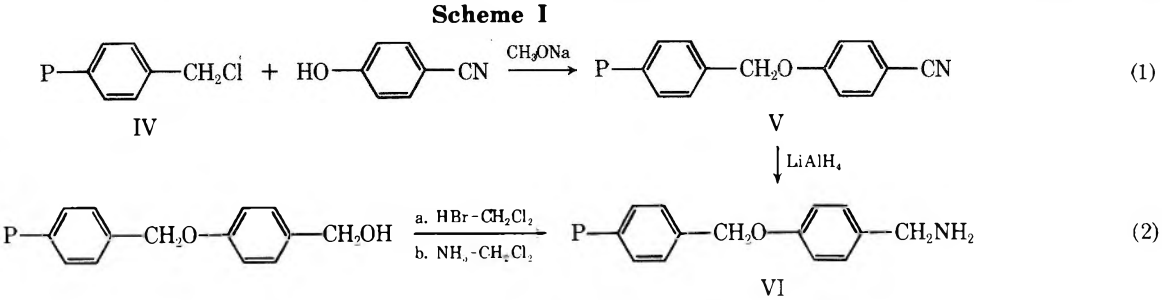
The following protected peptide amides were prepared on the *p*-alkoxybenzylamine support: Z-Pro-Leu-Gly-NH_2 (I), Z-Ala-Phe-Gly-Leu-Met-NH_2 (II), and Z-Gln(Dmb)-Gly-Leu-Val-NH_2 (III). The protected peptides were released from the resin by 50% (v/v) trifluoroacetic acid in methylene chloride after 30 min and were purified by crystallization.

The products proved to be homogeneous by thin layer chromatography and gave the expected amino acid analysis after acid hydrolysis.

Experimental Section

Melting points are uncorrected. Infrared spectra were taken on a Perkin-Elmer IR-257 with KBr pellets. Amino acid analyses were carried out on a Beckman Model 120 B amino acid analyzer. Thin

Scheme I



layer chromatography was run on precoated silica gel plates (Merck, GF_{254}) using the following systems: A, benzene–ethyl acetate–acetic acid–water (10:10:2:1, v/v); B, 1-butanol–acetic acid–water (4:1:1, v/v); C, chloroform–methanol–acetic acid (85:10:31, v/v).

The Merrifield resin (IV) (chloromethylated copolystyrene, 1% divinylbenzene, 0.9 mequiv/g, 200–400 mesh) was purchased from Bio-Rad Laboratories.

***p*-Cyanophenyl Resin (V).** Merrifield resin (IV, 20 g, 18 mmol) in 200 ml of dry diglyme was treated with 14.28 g (120 mmol) of *p*-cyanophenol and 6.48 g (120 mmol) of $NaOCH_3$ at 60° for 2 hr. The resin was collected and washed with DMF, dioxane, CH_2Cl_2, and methanol to give 21.4 g of V. The resin absorbed strongly at 2250 cm^{-1}.

***p*-Alkoxybenzylamine Resin (VI).** A solution of 2.28 g (60 mmol) of $LiAlH_4$ in 60 ml of dry ether was placed in a three-necked flask. A suspension of the *p*-cyanophenyl resin (20 g) in 100 ml of dry ether was added from a dropping funnel. The mixture was then stirred for 6 hr under dry ammonia stream. The resin was then filtered and washed with ethyl acetate, methanol, and CH_2Cl_2 to give a grayish product. The colored matter was removed by stirring in 500 ml of a 1:1 mixture of acetic acid and 1 *N* HCl for 15 min. The product was washed with 10% (v/v) triethylamine in $CHCl_3$ to convert the hydrochloride to the free amine, $CHCl_3$, and CH_2Cl_2, and dried under vacuum at 30° to give 18.4 g of the *p*-alkoxybenzylamine resin (VI). The ir showed a broad absorption at 3500–3100 cm^{-1} and no cyano band. The capacity, determined by the Esko procedure,[7] was in the range of 0.6 mequiv of NH_2/g of polymer.

Ppoc-Glycyl-*p*-alkoxybenzylamine Resin (VII). The amino resin VI (10 g, 6 mmol) was washed several times with ethanol and methylene chloride and then treated with 2.84 g (12 mmol) of Ppoc-Gly and 2.48 g (12 mmol) of DCC for 120 min. After washings with CH_2Cl_2, $CHCl_3$–MeOH (1:1 v/v), and CH_2Cl_2, the resin was suspended in 100 ml of CH_2Cl_2 and then allowed to react with acetic anhydride (2 ml) for 30 min in the presence of a catalytic amount of 4-dimethylaminopyridine.[8] After washings with CH_2Cl_2, 11.2 g of resin was obtained; it contained no detectable amount of free amino group. Amino acid analysis indicated that there was 0.42 mmol of glycine/g of resin.

Ppoc-Met Resin (VIII) and Ppoc-Val Resin (IX). The amino resin VI was treated with Ppoc-Met or Ppoc-Val in the same manner as above yielding respectively Ppoc-Met resin (VIII) and Ppoc-Val resin (IX).

The resin VIII was found to have 0.47 mmol/g of methionine; the resin IX was found to have 0.39 mmol/g of valine.

Stability of the *p*-Alkoxybenzylamide Anchoring Bond. Several samples of resin VII (150 mg) were placed in test tubes and suspended in 1% TFA in CH_2Cl_2 (5 ml). The tubes were stoppered and the reaction was allowed to proceed for the desired time at 23°. Then the samples were taken, filtered, and washed with 2 ml of CH_2Cl_2. The liberated glycine amide was separated by thin layer chromatography on silica gel using the system B; the spots were detected with ninhydrin–cadmium acetate (0.2% v/v)[9] and evaluated by densitometry.[10]

Results of such experiments showed that there was 8% loss of the anchoring bond in 12 hr. In the case of polymers VIII and IX a loss of 7.7 and 7.2 was found in 12 hr.

Cleavage Experiments. Small samples of the resins VII, VIII, and IX were treated with 50% v/v TFA in methylene chloride for 30 min. The filtrates were concentrated and chromatographed. Gly-NH_2, Phe-NH_2, and Met-NH_2 were found in presence of traces of the free amino acids.

The results confirmed that the conversion of the amino resin VI into resins VII, VIII, and IX had proceeded satisfactorily.

Z-Pro-Leu-Gly-NH_2 (I). Solid phase synthesis was carried out on 5 g (2.1 mmol) of resin VII with a threefold excess of amino acid derivatives and DCC in each cycle. The tripeptide released (720 mg) was twice crystallized from methanol, yield 491 mg (56%), mp 161–162° (lit.[11] mp 162–163°).

Z-Ala-Phe-Gly-Leu-Met-NH_2 (II). Solid phase synthesis of this protected amide was carried out similarly starting from resin VIII, yield 32%, mp 222–223° from methanol, $[\alpha]^{25}D$ −29.54° (*c* 1, DMF). It gave corrected amino acid analysis upon acid hydrolysis: $Ala_{1.02}Gly_{1.00}Leu_{1.03}Met_{0.92}Phe_{1.06}$.

Anal. Calcd for $C_{33}H_{46}N_6O_7S$ (670.8): C, 59.03; H, 6.85; N, 16.69. Found: C, 59.51; H, 6.92; N, 16.58.

Z-Gln(Dmb)-Gly-Leu-Val-NH_2 (III). Resin IX (5 g, 1.95 mmol) was placed in the peptide synthesis flask and the synthesis was carried out with fourfold excess of amino acid derivatives and DCC in each cycle. Ppoc-Leu (2.28 g), Ppoc-Gly (1.84 g), and Z-Gln(Dmb) [*N*-benzyloxycarbonyl-N^{γ}-(2,4-dimethoxybenzyl)-L-glutamine] (4.76 g) were sequentially coupled to the resin to give 6.2 g of the protected tetrapeptide polymer. The peptide was then released from the polymer by stirring in 100 ml of 50% (v/v) trifluoroacetic acid in methylene chloride for 30 min. After filtration and evaporation, the residue was treated with ethyl acetate–petroleum ether. The solid obtained (0.920 g) was crystallized from ethyl acetate: yield 0.734 g (54%); mp 246–248°; $[\alpha]^{25}D$ +62.07° (*c* 1.5, DMF). On acid hydrolysis, the compound gave the correct amino acid analysis: $Gly_{1.04}Glu_{1.02}Leu_{1.02}Val_{0.97}$.

Anal. Calcd for $C_{35}H_{50}N_6O_9$ (698.6): C, 60.12; H, 7.22; N, 12.02. Found: C, 59.87; H, 7.35; N, 12.12.

Acknowledgment. We wish to thank Dr. U. Ragnarsson for supplying the Ppoc-amino acids.

Registry No.—I, 14485-80-4; II, 56195-91-6; III, 56195-92-7.

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Condensations of Phthalaldehydic and *o*-Acetylbenzoic Acids with Naphthalenes[1]

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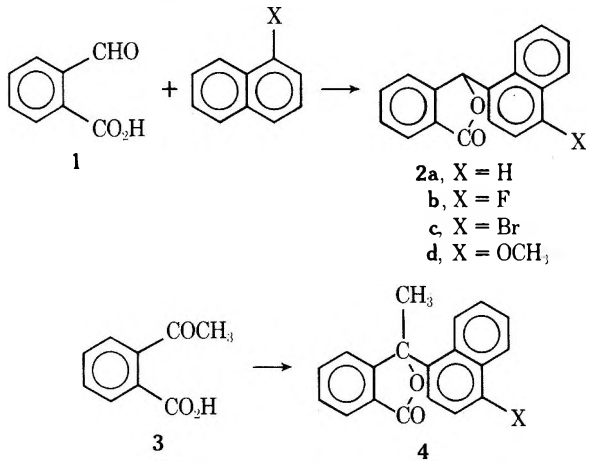
Received April 18, 1975

The acid-catalyzed condensation of phthaldehydic acid (**1**) with benzene and halogenated benzenes to produce 3-phenylphthalides[4] **2**, and of *o*-acetylbenzoic acid (**3**) with 1,2-dimethoxynaphthalene[5] have been reported. Because of the utility of this type of reaction in the synthesis of benz[*a*]anthracenes of interest in the field of cancer research we report herein on the condensations of phthaldehydic and *o*-acetylbenzoic acids with substituted naphthalenes.

In the condensation of **1** with benzene and halogenated benzenes, Floutz used concentrated sulfuric acid, or 20% oleum, at room temperature to obtain almost quantitative yields of 3-phenylphthalides,[4] **2**. However, we have found that such strong acid is not advisable for the condensation of **1** or **3** with naphthalene derivatives because sulfonation and/or oxidation occurs. In studies with naphthalenes and **1**, 90–100% methanesulfonic acid[6] proved superior as no sulfonation or oxidation occurred in 20–24 hr at room temperature and almost quantitative yields of 3-(4-X-1-naphthyl)phthalides, **2**, were attained. With the more reactive 1-methoxynaphthalene, the reaction was complete in 3 hr. In this case 90% methanesulfonic acid was preferable to 100% acid because the latter caused some demethylation.

When *o*-acetylbenzoic acid (**3**) (see Experimental Section for an improved synthesis of **3**) was used in place of **1** a different technique was required because of the tendence of **3**

to self condense in acidic media.[7] In these cases the best results were obtained when a solution of **3** in sulfolane[8] was slowly added to a stirred solution of the substrate in 100% methanesulfonic acid at room temperature. In this way a 94% yield of 3-methyl-3-(4-methoxy-1-naphthyl)phthalide (**4d**) was obtained. Lower yields, 55, 72, and 20%, of **4a, 4b,** and **4c,** respectively, were obtained.



1

2a, X = H
b, X = F
c, X = Br
d, X = OCH_3

3 4

The above route to the phthalides, **4,** is an attractive alternate to the route in which a 4-substituted naphthylmagnesium bromide is allowed to react with phthalic anhydride to yield a 2-(4-X-1-naphthoyl)benzoic acid[9] which is then treated with methylmagnesium halide to yield a substituted phthalide, **4.**[10] In the first place, 1-substituted naphthalenes are much easier to come by than 1-bromo-4-substituted naphthalenes. Secondly, the yields of **4** involving the acid-catalyzed route are superior to the yields obtained by the route involving two successive Grignard reactions. In spite of the only fair yields in the syntheses of **4a** and **4b,** this route is preferable to the double Grignard route[9,10] for **4a, 4b,** and **4d.** However, conditions for the attainment of acceptable yields for **4c** by this method have not been found.

The preparation of **3** has most often been carried out by heating a mixture of phthalic anhydride and malonic acid in pyridine on a steam bath for several hours,[11] although other methods for the synthesis of **3** have been described.[12] The best reported yield of **3** which we have found is 58%, obtained after a tedious and time-consuming work-up.[11b] By reaction of phthalic anhydride with malonic acid in triethylamine at 75–80° and isolation of **3** by continuous extraction we have obtained pure **3** in 89% yield.

Experimental Section[13]

o-Acetylbenzoic Acid (3). A stirred mixture of 148 g (1 mol) of finely powdered phthalic anhydride, 125 g (1.2 mol) of malonic acid (dried at 100° for 2 hr), and 200 ml of freshly distilled triethylamine (cooling at the start) in a 1-l. three-necked flask was warmed to 80°, at which temperature gas evolution was fairly rapid. After 2.5 hr (no more gas evolution) the cooled dark red solution was poured into 1 l. of water and 1 l. of 20% hydrochloric acid was stirred in. The organic acids were continuously extracted with ether for 2 days (no shorter time was tried). The ether solution (final volume about 700 ml) was washed with a small amount of saturated salt solution and then dried over anhydrous Na_2SO_4. Removal of ether from the dried solution yielded 161 g of solid which was extracted with 1 l. of hot benzene, the insoluble phthalic acid (6.8 g) being filtered. Concentration and crystallization afforded crude **3.** A second crystallization from benzene afforded 147 g (90%) of **3,** mp 110–112°, of off-white acid suitable for the condensations described below.

Condensations of Phthaldehydic Acid[14] (1) with Naphthalenes. A mixture of 4.5 g (0.03 mol) of **1,** 30 ml of 100% methanesulfonic acid,[6] and 7.3 g (0.05 mol) of 1-fluoronaphthalene[15] was stirred at room temperature until homogeneous. After 20 hr the brown solution was poured into 600 ml of ice water and the solid was collected by filtration and washed well with ice water. On trituration with cold ether (to remove excess fluoronaphthalene which was recovered in larger runs) 8.36 g (99%) of colorless 3-(4-fluoro-1-naphthyl)phthalide (**2b**), mp 151–153°, ir 5.7 μ, suitable for further use, was obtained. Recrystallization from benzene–petroleum ether yielded a purer sample, mp 153–154° (lit.[16] mp 154–154.5°). A similar result was obtained in a run ten times as large.

Pure 3-(1-naphthyl)phthalide (**2a**), mp 137–138°, was prepared similarly in almost quantitative yield when naphthalene was used in place of fluoronaphthalene.

Anal. Calcd for $C_{18}H_{12}O_2$: C, 83.1; H, 4.6. Found: C, 82.9; H, 4.8.

In a similar way, a nearly quantitative yield of colorless 3-(4-bromo-1-naphthyl)phthalide (**2c**), mp 207–209°, ir 5.7 μ, was obtained using 1-bromonaphthalene.

Anal. Calcd for $C_{18}H_{11}BrO_2$: C, 63.7; H, 3.3; Br, 23.4. Found: C, 64.1; H, 3.2; Br, 23.5.

In a reaction involving 0.30 mol of **1,** 0.50 mol of 1-methoxynaphthalene, and 300 ml of 90% methanesulfonic acid for 3 hr at room temperature there was obtained an almost quantitative yield of **2d.** Recrystallization from benzene–petroleum ether afforded pure 3-(4-methoxy-1-naphthyl)phthalide (**2d**), mp 199–200°, ir 5.7 μ, in 98% yield.

Anal. Calcd for $C_{19}H_{14}O_3$: C, 78.7; H, 4.9. Found: C, 78.3; H, 5.0.

Condensations of *o*-Acetylbenzoic Acid (3) with Naphthalenes. A solution of 65.6 g (0.40 mol) of **3** in 400 ml of sulfolane was added dropwise during 24 hr to a stirred solution at room temperature of 104 g (0.66 mol) of methyl 1-naphthyl ether in 400 ml of 100% methanesulfonic acid[6] in a 2-l. three-necked flask protected from moisture. After 6 hr more the dark red solution was poured into 3 l. of ice water. After the dark oil which separated was washed with several portions of ice water and triturated with ether, filtration afforded 114.5 g (94%) of 3-methyl-3-(4-methoxyl-1-naphthyl)phthalide (**4d**), mp 138–140°, suitable for further work. A pure sample of **4d,** mp 142–143° (lit.[17] mp 139–140°), was obtained with little loss by recrystallization from benzene.

In similar reactions 1-fluoronaphthalene was converted into 3-methyl-3-(4- fluoro-1-naphthyl)phthalide (**4b**), mp 142–143° (lit.[18] a, mp 140°; b, 143–144°), in 72% yield and naphthalene into 3-methyl-3-(1-naphthyl)phthalide (**4a**), mp 149–151° (lit.[19] mp 154.5–155.0°), in 55% yield.[20] No pure product was isolated when similar, or other, reactions were tried on bromonaphthalene.

Registry No.—**1,** 119-67-5; **2a,** 56282-14-5; **2b,** 27525-72-0; **2c,** 56282-15-6; **2d,** 40893-29-6; **3,** 577-56-0; **4a,** 56282-16-7; **4b,** 2968-71-0; **4d,** 56282-17-8; phthalic anhydride, 85-44-9; malonic acid, 141-82-2; 1-fluoronaphthalene, 321-38-0; naphthalene, 91-20-3; 1-bromonaphthalene, 90-11-9; 1-methoxynaphthalene, 2216-69-5.

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On the Mechanism of the Oxidation of Tropan-3α-ol with Benzoyl Chloride

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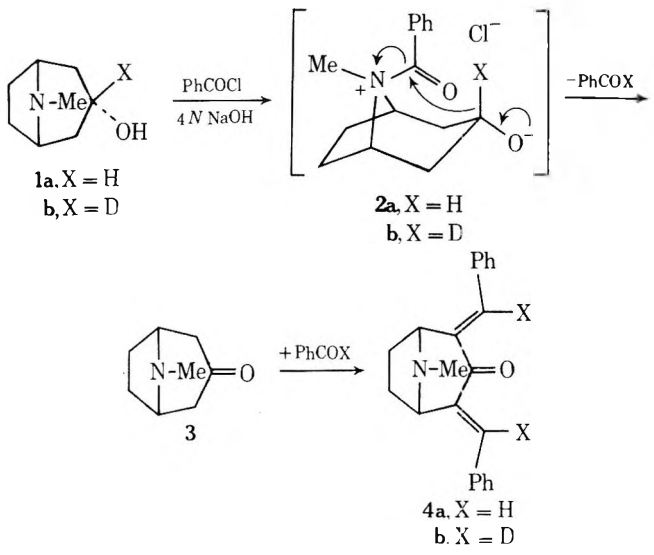
Received May 14, 1975

Polycyclic molecules having sterically proximate alcohol and keto functions have been occasionally observed to undergo base-catalyzed redox reactions under mild conditions.[1] However, postulated hydride transfer mechanisms have seldom been verified by isotopic labeling experiments. A case in point is the reaction of tropan-3α-ol[2] (**1a**) with benzoyl chloride under Schotten–Baumann conditions to give *trans,trans*-dibenzylidenetropinone (**4a**), for which Calvert and Hobson[3] proposed the mechanism abbreviated in Scheme I. Although circumstantial evidence is in accord with the proposed mechanism, we have reinvestigated this reaction employing deuterium-labeled precursors and the results of this study fully corroborate the mechanism of Calvert and Hobson.

Scheme I



Reduction of tropinone with $LiAlD_4$ in ether[4] afforded an 89% yield of a 1:1 mixture of the deuterated 3α- and 3β-tropanols which can be separated by fractional crystallization of the picrates.[5] Reaction of a well-stirred solution of 3β-deuteriotropan-3α-ol (**1b**) in 4 *N* NaOH with excess benzoyl chloride at ambient temperature for 15 hr gave the dideuterated dienone **4b** in ca. 80% yield. The presence of the label was readily determined by comparison of the mass spectra of **4b** and its undeuterated counterpart **4a**, which revealed that the molecular ion at *m/e* 315 and the major peaks at *m/e* 287 and 259 in **4a** were shifted two mass units higher in **4b**. Furthermore, the 100-MHz NMR spectra of **4a** and **4b** were superimposable except for the absence of the sharp singlet at δ 7.81 in **4b** corresponding to the benzylidene hydrogens.

These experimental results provide additional conclusive evidence in support of the proposed mechanism the key feature of which is the intramolecular transfer of a 3β-hydride to the strongly electrophilic carbonyl of the *N*-benzoylammonium ion **2** to afford tropinone and benzaldehyde.[6,7] The subsequent stereospecific aldol condensation of **3** with benzaldehyde is well precedented.[8] The fact that cyclohexanol, *N*-benzoylnortropine, and 3α-deuteriotropan-3β-ol are all recovered unchanged under the reaction conditions further implies the intermediacy of **2**.

Experimental Section[9]

Reaction of Tropan-3α-ol with Benzoyl Chloride. To a rapidly stirred solution of 0.426 g (3.38 mmol) of 3β-deuteriotropan-3α-ol in 65 ml of 4 *N* NaOH was added dropwise over a 30-min period 7.10 g (50.7 mmol) of freshly distilled benzoyl chloride. After addition was complete, the mixture was allowed to stir under nitrogen at ambient temperature for 15 hr. The pale yellow precipitate was collected by suction filtration, washed with 25 ml of water, and recrystallized from 10 ml of boiling methanol to afford 0.427 g (1.35 mmol, 80% yield) of the dideuterated *trans*-dibenzylidenetropinone as pale yellow needles: mp 151–153° (lit.[7] mp of undeuterated compound 153°); ir ($CHCl_3$) 1666, 1605, 1495, 1445, 1090, and 1070 cm^{-1}; 100-MHz NMR ($CDCl_3$) δ 7.36 (s, 10 H), 4.40 (m 2 H), 2.60 (m, 2 H), 2.26 (s, 3 H), 2.00 (m, 2 H); MS *m/e* (rel intensity) 317 (M^+, 41), 289 (100), and 261 (29).

Acknowledgment. The authors thank Mr. Jon Stickles for obtaining NMR and mass spectra and the SUNY Research Foundation for partial support.

Registry No.—**1b,** 56292-47-8; **4b,** 56290-48-9; benzoyl chloride, 98-88-4.

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(7) The *N*-benzoyl group must be situated syn relative to the 3β-hydride in order for the intramolecular transfer of hydride to occur as shown in structure **2**. However, Fodor has recently reviewed a body of evidence which indicates that irreversible N-quaternization and N-oxidation reactions of tropines occur preferentially anti. These data suggest that formation of the *N*-benzoylammonium ion is reversible, leading to both the syn and anti isomers, but only the syn isomer is reduced. See G. Fodor in "The Alkaloids", Vol. XIII, R. H. F. Manske, Ed., Academic Press, New York, N.Y., 1971, pp 359–365, for a discussion of the configuration of quaternary tropanium salts.

(8) R. Willstätter, *Ber.*, **30**, 731, 2679 (1897).

(9) The tropan-3α-ol, tropinone, and lithium aluminum deuteride were obtained from Sigma Chemical Co., Aldrich Chemical Co., and Merck Sharp and Dohme, Inc., respectively. The NMR spectra were recorded on a Varian HA-100 spectrometer, the ir spectra on a Perkin-Elmer 457 spectrometer, and mass spectra on a Du Pont 21-497B spectrometer.

Low-Melting Nematic Phenyl 4-Benzoyloxybenzoate Liquid Crystals[1]

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Received April 30, 1975

The preparation of nematic liquid crystals with specific physical properties for use in electrooptical applications has been the subject of many recent investigations.[2-5] The initial work on materials for use in these applications emphasized the preparation of liquid crystals that were either

Table I
Transition Temperatures[a] for Some Phenyl 4-Benzoyloxybenzoate Liquid Crystals (2)

R[b]	R' 3	4	5	6	7	8
5, X = Y = H	K78N188I	K75N179I	K78N180I	K74S78N169I	K76S104N169I	K79S117N161I
5, X = Cl; Y = H	K57N130I	K41N118I	K40N122I	K40N113I	K46N114I	K42N109I
5, X = H; Y = Cl	K75N133I	K76N123I	K67N130I	K58N119I	K58N119I	K63N112I
6, X = Cl; Y = H	K48N120I	K48N110I	K35N114I	K40N106I	K47N107I	K41S45N102I
7, X = Cl; Y = H	K46N119I	K45N109I	K34N115I	K40N107I	K46N109I	K41N104I
8, X = Cl; Y = H	K45N108I	K51N102I	K40N109I	K55N101I	K41N104I	K43S49N100I
8, X = H; Y = Cl	K60N117I	K64N109I	K65N112I	K34N105I	K72N106I	K73N101I

[a] Reference 25. [b] *R* equals number of carbon atoms in *n*-alkyl chain.

mesomorphic at room temperature or were sufficiently low melting to provide room temperature materials when two or more components were mixed. The preparation of compounds to meet the room temperature requirement has not been easy. The number of single-component room temperature nematic materials is fairly limited and these materials have relatively narrow nematic ranges. More success has been obtained by preparing low-melting materials that can be mixed to provide room temperature nematic compositions.[6,7] However, some of the currently available materials are unstable. For example, the commonly used Schiff base materials are readily hydrolyzed to the starting aldehyde and amine.[8] Mixtures of Schiff bases undergo exchange reactions under various conditions to give additional liquid crystals, which results in a new liquid crystal mixture with different physical properties.[9] Other examples are the α-chloro-*trans*-stilbenes prepared by Young,[3] which were found to be photochemically unstable, and thus not so generally useful.[6]

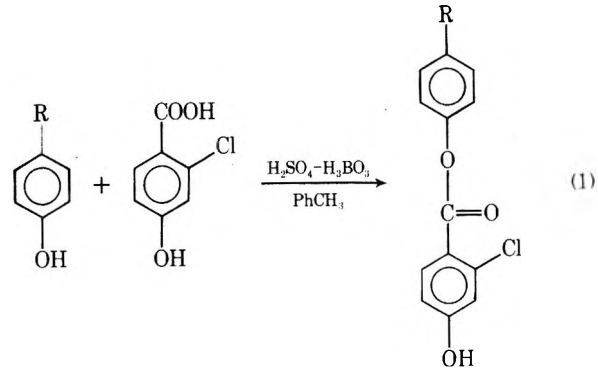
In addition to the mesomorphic transition temperatures, the dielectric anisotropy of the liquid crystal is of critical importance in that it governs the specific type of electrooptical effects for which a given material is suitable and also determines the type of molecular reorientations the liquid crystal molecules make with respect to the direction of an applied electric field.[10] Recent studies in relating the dielectric anisotropy to molecular structure have increased our understanding of this characteristic.[11-13] Although we now know the type of molecular modifications necessary to change the dielectric anisotropy, we are still confronted with the problem of preparing compounds that are both low melting and also have the desired dielectric properties. Thus there remains a considerable synthetic challenge to balance these physical properties into usable materials with high stability.

The recent work on the preparation of liquid crystalline aromatic esters may provide materials that are useful in electrooptical as well as other applications.[2,14] Additional research is required to ascertain the relative merits of the various classes of liquid crystals in the multitude of electrooptical applications that are now known.

In earlier work in this laboratory,[14] it was demonstrated that liquid crystals derived from phenyl 4-benzoyloxybenzoate melt at a significantly lower temperature than the corresponding isomeric liquid crystals derived from hydroquinone or terephthalic acid. It was also shown that the combination of terminal dialkyl substituents along with a chlorine atom ortho to the carbonyl of the ester linkage resulted in very low-melting compounds in the phenyl 4-benzoyloxybenzoate series. This paper describes the preparation of several homologous series of low-melting phenyl 4-benzoyloxybenzoate liquid crystals. Some of these compounds afforded room temperature compositions upon mixing.

Results and Discussion

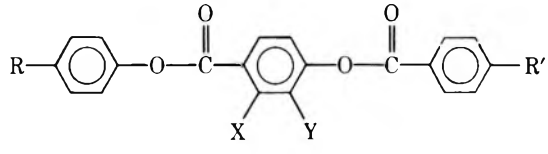
The phenyl 4-benzoyloxybenzoates were conveniently prepared in two steps. The first involved an acid-catalyzed esterification of a 4-alkylphenol with 4-hydroxybenzoic acid or one of its chlorinated derivatives to give a substituted phenyl 4-hydroxybenzoate (eq 1). The catalyst used in



(1)

1

this reaction was a combination of sulfuric acid and boric acid as described by Lowrance.[15] This catalyst was found to be remarkably specific in that only the hydroxyl group of the 4-alkylphenol was involved in ester formation. No esters or polymers resulting from the participation of the hydroxyl group of the 4-hydroxybenzoic acid were formed in the reaction. The reaction of 1 with a 4-alkylbenzoyl chloride gave the desired liquid crystal (2). In contrast to this



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procedure, Young and Green[16] have prepared some low-melting nematic derivatives of phenyl 3-methyl-4-benzoyloxybenzoate by a six-step method.

The compounds prepared in this study along with their mesomorphic transition temperatures are recorded in Table I. The effect of changing molecular structure on the transition temperatures for these compounds is consistent with well-known observations and can be briefly summarized as follows. A small, laterally placed substituent can be very effective in reducing the crystal-to-mesophase transition temperature.[17] The chlorine substituent reduced the nematic-to-isotropic transition temperature approximately 50–60° as a result of the increase in the width of the molecule. The even–odd effect in the nematic-to-isotropic transition temperatures was observed. The nematic-to-isotropic transition temperatures for these homologous series decrease with increasing carbon chain length, which is in

agreement with de Jeu,[18] who has shown that this trend is usually observed for series with relatively high transition temperatures.

The transition temperatures for the phenyl 3-methyl-4-benzoyloxybenzoates prepared by Young[16] and the 3-chloro derivatives in Table I are very similar, with most of the nematic-to-isotropic transitions as close as 1–2° for a chloro vs. methyl comparison. This again demonstrates the lack of influence permanent dipole moments have on the nematic-to-isotropic transition temperature.[19]

The optimum location for the chlorine substituent in obtaining low-melting phenyl 4-benzoyloxybenzoates is in a position ortho to the carbonyl of the ester linkage. In the comparisons in this study, the 2-chloro derivatives provided the lowest melting compounds compared to the 3-chloro and nonchlorinated analogs. The laterally placed chlorine atom coupled with terminal dialkyl substitution has resulted in some phenyl 4-benzoyloxybenzoates with nematic ranges extending from below 40° to above 100°. Room temperature compositions can be obtained easily by mixing two or more of these materials; for example, a 1:1 by weight mixture of 4-pentylphenyl 2-chloro-4-(4-pentylbenzoyloxy)-benzoate and 4-octylphenyl 2-chloro-4-(4-heptylbenzoyloxy)benzoate is nematic from 5° to 111°.

The effect of structural changes on the dielectric anisotropy of liquid crystals derived from phenyl 4-benzoyloxybenzoate has been discussed in a separate paper.[12] These compounds are also of special interest in that the dielectric anisotropy changes sign at relatively low frequencies,[13,20,21] which offers an additional means of modifying the operational characteristics of liquid crystal devices.[22]

Experimental Section

The 4-alkylphenols,[23] 4-alkylbenzoic acids,[24] and 2-chloro-4-hydroxybenzoic acid were prepared by known methods or were obtained from Eastman Organic Chemicals. 3-Chloro-4-hydroxybenzoic acid was obtained from Aldrich Chemical Co. The transition temperatures were determined in an open capillary tube and are uncorrected. Satisfactory elemental analyses were obtained for all new compounds. A representative procedure for the preparation of these liquid crystals is given below.

4-*n*-Hexylphenyl 2-Chloro-4-hydroxybenzoate. A mixture of 4-*n*-hexylphenol (40.0 g, 0.22 mol) and 2-chloro-4-hydroxybenzoic acid (34.5 g, 0.20 mol) in toluene (1 l.) containing concentrated sulfuric acid (1.0 g, 10 mmol) and boric acid (0.6 g, 10 mmol) was refluxed for 65 hr, a Dean-Stark trap being used to remove the water formed in the reaction. The solution was cooled and the solvent was removed under reduced pressure. The resulting solid was recrystallized twice from ethanol–water to give 53.9 g (81%) of 4-*n*-hexylphenyl 2-chloro-4-hydroxybenzoate: mp 141–143°; ir (KBr) 3320, 2900, 1700, 1590, 1560 cm^{-1}. The analytical sample melted at the same temperature.

4-*n*-Hexylphenyl 2-Chloro-4-(4-*n*-hexylbenzoyloxy)benzoate. To a solution of 4-*n*-hexylphenyl 2-chloro-4-hydroxybenzoate (1.15 g, 4.7 mmol) in dry pyridine (25 ml) was added 4-*n*-hexylbenzoyl chloride (1.13 g, 5.0 mmol). After standing at room temperature for 18 hr, the reaction mixture was poured into an ice–water mixture and the product was isolated by filtration. Recrystallization from ethanol gave 1.9 g (77%) of 4-*n*-hexylphenyl 2-chloro-4-(4-*n*-hexylbenzoyloxy) benzoate: K39N105I;[25] ir (KBr) 2900, 1740, 1600 cm^{-1}. The analytical sample was obtained from ethanol: K40N106I.

Registry No.—4-*n*-Hexylphenyl 2-chloro-4-hydroxybenzoate, 56363-83-8; 4-hexylphenol, 2446-69-7; 2-chloro-4-hydroxybenzoic acid, 56363-84-9; 4-*n*-hexylphenyl 2-chloro-4-(4-*n*-hexylbenzoyloxy)benzoate, 56363-85-0; 4-hexylbenzoyl chloride, 5060C-95-6.

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Synthetic Photochemistry with Heterocyclic Anilides. Stereochemistry of the Intramolecular 1,5-Hydrogen Shifts in Nonoxidative Photocyclization of Benzo[*b*]thiophene-2-carboxanilides[1,2]

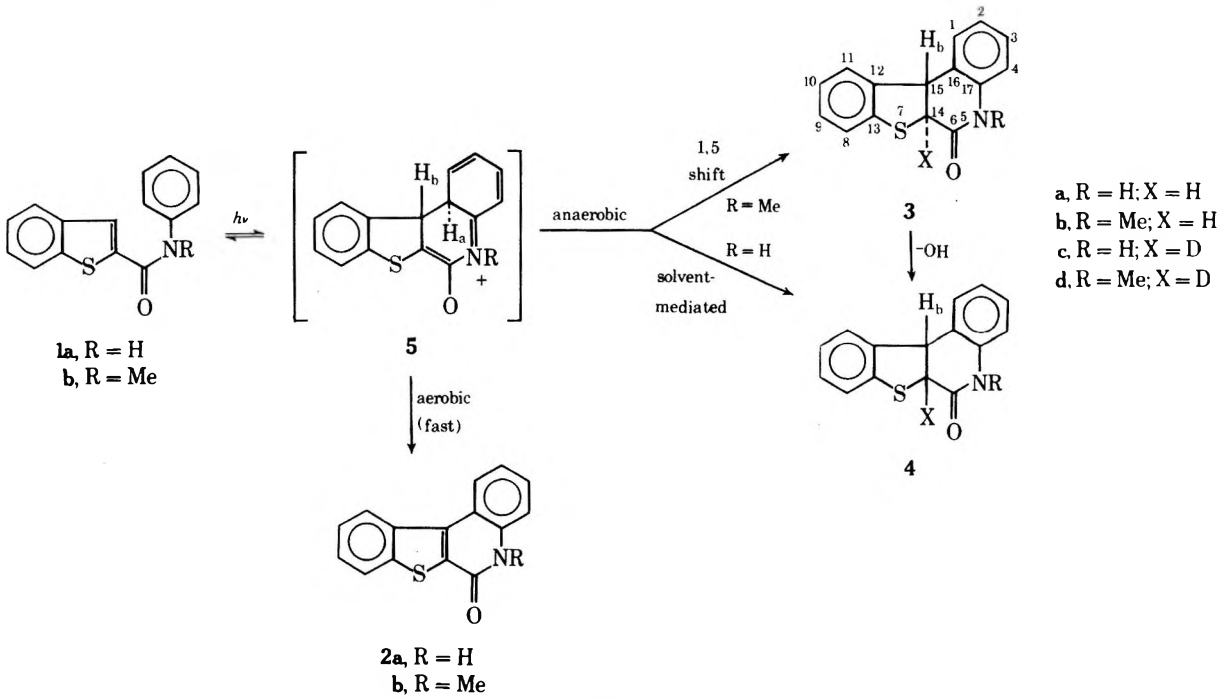
Summary. Photocyclization of benzo[*b*]thiophene-2-carboxy-*N*-methylanilide yielded 1-benzothiophene[2,3-*c*]-*trans*-14,15-dihydro-5-methylquinolin-6-one, while the lower homologous anilide gave 1-benzothiophene[2,3-*c*]-*cis*-14,15-dihydroquinolin-6-one by two distinct mechanisms. The structures were determined by single-crystal Roentgen-ray analysis.

Sir: Heterocyclic anilides, such as benzo[*b*]thiophene-2- (**1a**) and indole-2-carboxanilide, undergo photocyclization in the presence of dissolved oxygen to afford the heterocyclic-condensed quinolones (**2a**, etc.).[3] Whereas *oxidative* cyclizations of anilide systems[1,3,4] are closely related to the well-known photoreactions in the stilbene series,[5] Chapman et al. observed nonoxidative photocyclization of *N*-arylenamines.[6] Recently Ninomiya et al. have also studied similar nonoxidative reactions of enamides.[7] This report focuses on the stereochemical aspects involving the trans adduct intermediate **5** in the photocyclization of certain anilides as well as on the synthesis of novel heterocycles based on variations of the experimental conditions.

On irradiation[8] in a mixture of benzene and ethanol (10:1 v/v, 200 mg/20 ml) for 2 hr, **1a** cyclized oxidatively to **2a** (mp >310°, 45% yield), which was accompanied by a crystalline product **4a** (mp 250–251°, 15%) with the same composition as the starting material **1a** [*m/e* 253 (M^+)]. When the reaction was performed under a stream of nitrogen in a solvent free of oxygen, **4a** was obtained as the major product (50%) along with a trace of **2a.** Under the anaerobic conditions,[8] its *N*-methyl derivative **1b** also afforded the nonoxidative product **3b** (mp 168–169°, 52%). The relative stereochemistry of H_b and 14 H in **3b** and **4a** was not immediately apparent since the NMR of **4a** had only a singlet (2 H, 4.78 ppm) for the two hydrogens, although that of **3b** had an AB-type coupling. However, when **3b** was reduced to the deuterated amine [*O*-d_2, mp 102–103°, *m/e* 255 (M^+)] the NMR spectrum showed characteristic peaks for H_a at 4.16 ppm (1 H, d, J = 13 Hz) and H_b at 3.60 (1 H, d, J = 13 Hz) suggestive of trans ring fusion.[6] The complete structure of **3b** was directly established by X-ray analysis.[9] In a similar manner the structure of **4a** was determined using the sulfone derivative (mp >320°) prepared by oxi-

Table I
Physical Data

	3b	4a
Molecular formula	$C_{16}H_{13}NSO$	$C_{15}H_{11}NSO_3$
Crystal size	~(0.55 × 0.58 × 0.19) mm	~(0.13 × 0.38 × 0.68) mm
Space group	$P2_1/a$	$P\bar{1}$
a	10.258 (6) Å	8.300 (4) Å
b	14.518 (9) Å	10.768 (8) Å
c	8.898 (5) Å	7.957 (4) Å
α		110.2 (1)°
β	104.9 (2)°	73.7 (1)°
γ		100.8 (1)°
Z	4	2
d_{calcd}	1.39 gm/cc	1.49 gm/cc
Max U.R	5.7	8.2
Mounting axis	$\bar{1}20$	$\bar{1}12$
Data collection	Automatic diffractometer θ–2θ scan technique Cu Kα (λ = 1.54178 Å)	
Number of independent reflections	2074	1574



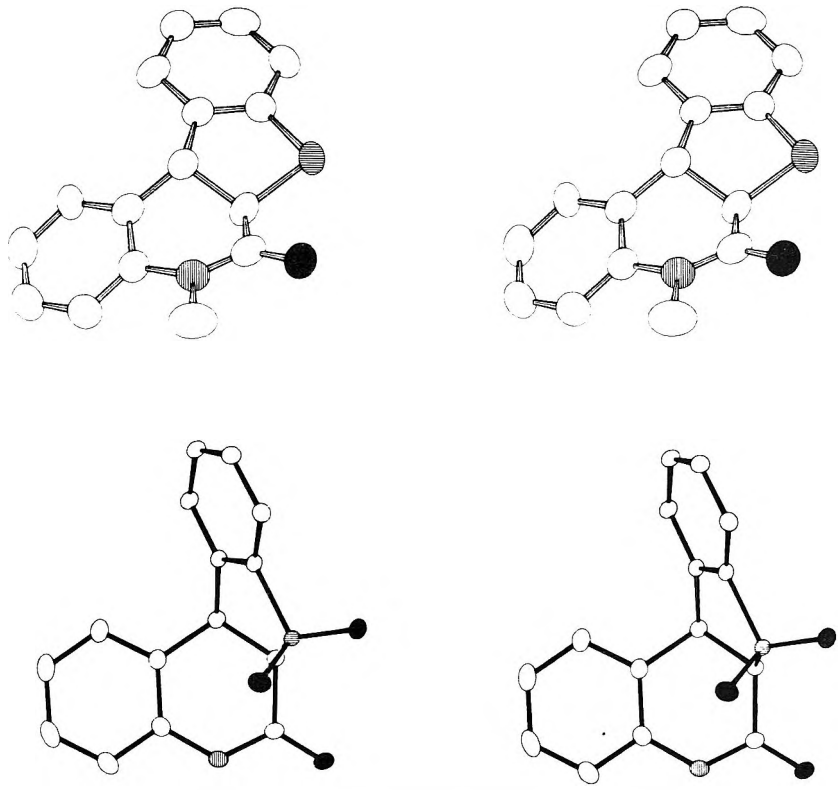


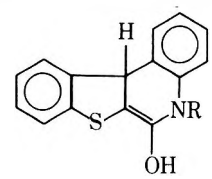
Figure 1. Top: Stereodiagram of 1-benzothiophene[2,3-*c*]-*trans*-14,15-dihydro-5-methylquinolin-6-one (**3b**). Bottom: Stereodiagram of 1-benzothiophene[2,3-*c*]-*cis*-14,15-dihydroquinolin-6-one (**4a**) sulfone. In both cases the sulfur is labeled ○, the nitrogen is labeled ○, and the oxygens are labeled ●. The figures were drawn by computer using program ORTEP written by C. K. Johnson of Oak Ridge National Laboratory, Oak Ridge, Tenn (1965).

dation (0.3% H_2O_2 in formic acid) of **4a** (see Table I and Figure 1). Careful product analysis showed that **3b** was accompanied by a small amount of **4b** (mp 168–169°), but **3a** was not detected in the reaction mixture from **1a.** The cis structure of **4b** was confirmed by methylation of **4a** with methyl iodide and sodium hydride. It is noteworthy that the *N*-H anilide **1a** produces the cis product **4a,** while the *N*-methyl anilide **1b** mainly gives the trans isomer **3b.** Although **4a** was converted into **2a** by oxidation with iodine, it is unlikely to be the true intermediate in the phototransformation (**1a** → **2a**), because on irradiation under aerobic conditions **4a** and **3b** afforded **2a** and **2b,** respectively, but at a lower rate than by the direct transformation (**1b** → **2b**). Thus **3b** and **4a** must be the products arising from a plausible intermediate, such as **5,** as a result of a process that competes with the direct oxidation to **2.**

Regardless of the details of the hydrogen shift, the trans junction in **3b**[9] requires the trans configuration for **5** in the initial bond formation process from **1b** consistent with simple HMO calculation, *i.e.,* the conrotatory course for the photochemical electrocyclic reaction and the subsequent thermally allowed sigmatropic suprafacial 1,5-hydrogen shift.[10] Anaerobic irradiation of anilide-*2,3,4,5,6-d*$_5$ **1b** gave **3d** (*1,2,3,4-d*$_4$, mp 165–166°) in which X (trans) contained >90% of deuterium in support of the intramolecular 1,5 shift of H_a subsequent to cycloaddition, at least in aprotic media, as the major pathway for the overall formation of **3b.** This example illustrates the principle of conservation of orbital symmetry for an arylanilide 6-π-electron system undergoing photocyclization.

In the course of the hydrogen shift from **1a,** rapid hydrogen exchange of N–H occurs and significant interaction between the medium, involving the imide carbonyl, must be considered. Indeed, irradiation of **1a** under anaerobic conditions in acetonitrile containing 10% D_2O afforded **4c** in 76% yield, demonstrating that the cis-14-H comes almost exclusively from the protons of the medium. The same treatment of **1b** gave a mixture of **3b** (28%) and **4d** (34%). These results confirm that the trans-14-H originates definitely from the internal source, and the cis-14-H is incorporated from the medium. Neither irradiation nor refluxing of **4a** and **4b** in the above solvents formed **4c** and **4d,** respectively, indicating that the cis-14-H (D) of **4a,b** is primarily established during and not after the process of the H shift. The cis structures are more stable than the trans. For example, when a solution of **3b** in 10% NaOH–tetrahydrofuran was allowed to stand at room temperature for 12 hr, nearly 80% **4b** was isolated. The analogous reaction with 10% NaOD formed **4d** showing that enolization favors the formation of the cis isomer.

A plausible mechanism for the formation of **4a** from **1a** may involve a "solvent-mediated" pathway in which the amide carbonyl participates, presumably, resulting in the intervention of an "enol" **6** (R = H). Such an enol would



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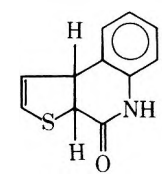

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lead preferably to the cis isomer **4.** Irradiation of **1b** (benzene, 10^{-3} *M*) in the presence of 1,2-cyclohexadiene quenched the formation of **3b** with a linear Stern–Volmer plot up to 0.1 *M* of the quencher, suggestive of a triplet-state intermediate for the cyclization.

In the stilbene series[5] *trans*-dihydrophenanthrene intermediates, analogous to **5,** have been postulated but proven only in a few cases.[11] The five-membered heteroaromatic anilide system is novel and useful in that it permits the separation of oxidative and nonoxidative pathways. In ad-

dition, on a preparative scale a variety of heterocyclic condensed dihydroquinolone systems have now become accessible; for example, 7 (mp 197–199.5°) was obtained by the nonoxidative photocyclization of thiophen-2-carboxanilide in 56% yield. Synthetic applications of the method to other heterocyclic systems including furan, pyrrole, and their benzo derivatives are in progress.

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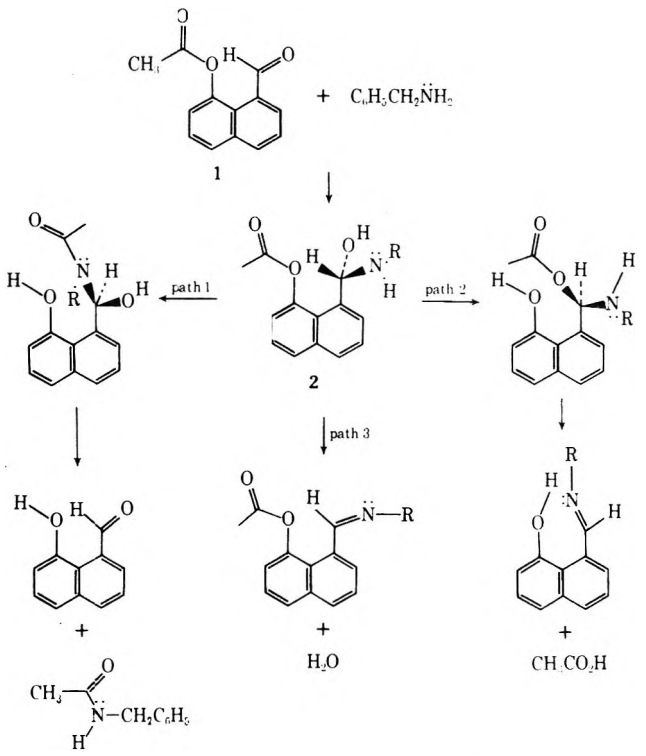
Received June 23, 1975

Rapid Intramolecular Acyl Transfer from Phenol to Carbinolamine—Progress toward a New Class of Peptide Coupling Reagent

Summary: Benzylamine and amino acid esters react with 8-acetoxy-1-naphthaldehyde, 2-acetoxybenzaldehyde, and 2-acetoxytrifluoroacetophenone with formation of carbinolamines, followed rapidly by solvent dependent *O*- or *N*-acyl transfer or dehydration.

Sir: We wish to report unusual, rapid intramolecular acyl transfer reactions via seven-ring intermediates, which represent the first step toward the development of a new class of peptide coupling reagent, as well as progress toward mimicking biochemical acyl transfer processes.

When 8-acetoxy-1-naphthaldehyde[1] (1) is treated with benzylamine (3 equiv, 1.2 *M*) in DMSO[2] a 70% yield of *N*-benzylacetamide is formed, together with 30% acetate ion; at 25° the half time is <1 min. We interpret this reaction as occurring via rapid formation of a carbinolamine, 2,[3] followed by seven-ring intramolecular *N*- (path 1, amide formation) or *O*- (path 2, acetate ion formation) acyl transfer.



The product composition is strikingly solvent dependent, although in no instance could a single product be obtained. DMSO or DMF give 60–70% amide (path 1) and ~30% acetate (path 2); in 1:1 DMSO–water the ratio is 3:7, while in 1:4 acetonitrile–water, the ratio is 1:9. In other solvents dehydration of 2 to an acetoxy Schiff base (path 3) was observed. Thus in acetonitrile the ratio of products from paths 1 and 3 is 1:1; in benzene, carbon tetrachloride, or chloroform no amide is formed, and paths 2 and 3 contribute in respective ratios of 7:3, 7:3, and 1:4. Variation of the equilibrium between 2 and its zwitterion and chloroform catalysis of dehydration of 2 are presumably responsible for these results. Rate constants for the combined acyl transfer processes in acetonitrile, DMF, and 1:4 acetonitrile–water at 30° are 0.1, 0.2, and 15 M^{-1} sec^{-1}, respectively. The latter is one of the faster intramolecular acyl transfers reported for a model system.[4]

Though exact models are problematic, an estimate of the rate of intermolecular attack of amine on the acyl site of 1 is 1×10^{-3} M^{-1} sec^{-1}, observed for reaction of benzylamine and 8-acetoxy-1-nitronaphthalene[5] in acetonitrile at 30°. We note that the rapid formation of acetic acid and the Schiff base of 8-hydroxy-1-naphthaldehyde in anhydrous solvents is only consistent with intermediacy of 2 and its decomposition by path 2.

Marked changes in product composition also result with change of amine. Reaction of 1 with methyl alaninate or other substituted peptide amines yields only the product of path 3. This result excludes exploitation of derivatives of 1 in peptide synthesis.

It was hoped that the formyl group of an 8-acyloxy-1-naphthaldehyde could be protected as an acetal, and the resulting functionality employed in peptide synthesis as a C-terminal protective group[6] capable of activation under midly acidic conditions. Along with the virtues of latent activation, amide formation by amine capture and intramolecular acylation offers several intrinsic advantages over intermolecular acylation. (1) The ester function can hopefully be of a low degree of activation, minimizing side reactions.[7] (2) The amide forming step must follow first- rather than second-order kinetics. (3) Provided that the amine capture step is rate determining, the rate of amide forma-

tion should not be reduced by steric bulk at the acyl site.[8] (4) Intermediates such as oxazolones which are formed by fragmentation at the acyl site should compete ineffectively with intramolecular acylation.

Two other attempts to exploit carbinolamine intermediates further defined the scope of this principle.[9] Aminolysis of 2-acetoxybenzaldehyde (3)[10] with benzylamine in any of the above solvents gives benzylacetamide in quantitative yield. Most strikingly, rate constants nearly identical with those of 1 were observed in DMF, acetonitrile, and acetonitrile–water. Since the ester functions of 1 and 3 must differ in intrinsic activation[11] as aldehydes, but not when converted to carbinolamines, we argue from this result that 3 also must react with benzylamine via a carbinolamine intermediate. In acetonitrile, benzylamine reacts 150 times as rapidly with 3 as with 4-acetoxybenzaldehyde.[12]

Although a 90% conversion of ethyl glycinate to amide results from reaction with 1 equiv of 3 in benzene (75% in acetonitrile), with the more hindered methyl esters of alanine, phenylalanine, and valine, the sole products detected are the Schiff bases of 3.

A third carbonyl derivative, 2-acetoxytrifluoroacetophenone (4),[13] was investigated in the hope that this species would form a less dehydration-prone carbinolamine. In fact, 4 reacts in benzene with any of the above amines with exclusive *O*-acyl migration, leading to quantitative formation of acetic acid. Half times were <1 min.

A noncovalent binding of an amine which maintains it in reactive proximity to a relatively unactivated aliphatic ester is the characteristic feature of biochemical peptide coupling.[14] The systems we have described can be regarded as models for this process in which noncovalent affinity is replaced by a covalent bond of the carbinolamine function.

The results achieved thus far for these systems are (1) a demonstration of at least a hundredfold catalysis over direct aminolysis, (2) a demonstration that with favorable geometry a seven-ring intermediate can achieve the catalytic advantage for acyl transfer of the more familiar six-ring cases, and (3) a demonstration that very great sensitivity of product ratio to amine bulk and solvent attends these reactions. This latter point has led us to seek systems which can trap amines at electrophilic sites to yield intermediates with less versatility than carbinolamines, and results of these studies will be reported subsequently.

Acknowledgment. Financial support from the National Institutes of Health (GM 13543) is gratefully acknowledged.

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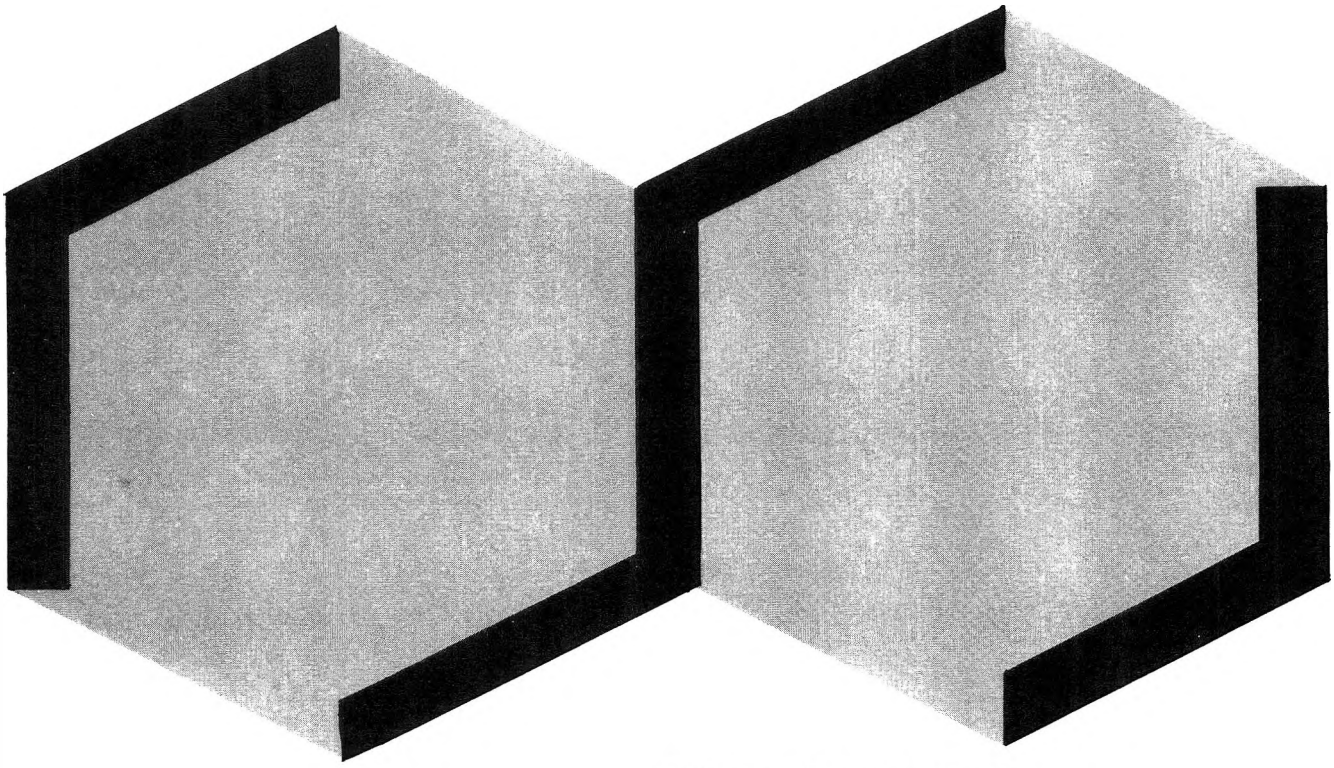

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Crown Ethers

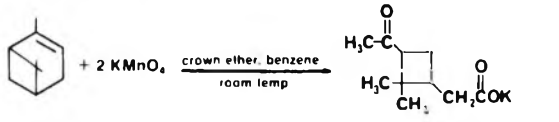
- 15-Crown-5: specific for Na^+
- 18-Crown-6: specific for K^+
- Dibenzo-18-crown-6
- Dicyclohexyl-18-crown-6

Since the discovery of their remarkable ability to dissolve alkali metal salts in non-polar solvents, crown ethers,[1a,b] a class of macrocyclic polyethers, have found novel application in synthesis. **18-Crown-6** promises even greater synthetic utility by virtue of its increased complexing ability.[2] For example, in acetonitrile or benzene effective solvation of the potassium ion of potassium fluoride by **18-crown-6** results in a highly reactive fluoride ion ("naked" fluoride).[2] "Naked" fluoride is a potent base and nucleophile,[2] being capable of converting a variety of alkyl, acyl, or activated aryl halides to their respective fluorides in good yields.

$$CH_3(CH_2)_6CH_2Br \xrightarrow[CH_3CN]{KF,\ 18\text{-crown-6}} \begin{matrix} CH_3(CH_2)_6CH_2F\ (92\%) \\ CH_3(CH_2)_5CH{=}CH_2\ (8\%) \end{matrix}$$

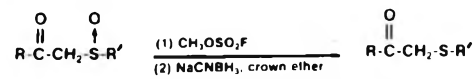
Acetate[3], cyanide[4] and nitrite[4] also display markedly enhanced nucleophilicity in the presence of **18-crown-6**.

In the presence of **dicyclohexyl-18-crown-6,** potassium permanganate readily dissolves in benzene to form a purple solution ("Purple Benzene")[5] which oxidizes alcohols, olefins, aldehydes and aralkyl hydrocarbons in excellent yield under neutral conditions.

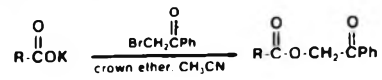


90%, *cis*
(40-60% with no crown ether in an aqueous system)

Alkoxysulfonium salts, formed by alkylation of sulfoxides with Magic Methyl® (methyl fluorosulfonate), are readily reduced with sodium cyanoborohydride in the presence of crown ethers[6] to give sulfides in excellent yield. Similarly, β-ketosulfoxides are reduced to β-ketosulfides,[6] whereas extensive decomposition occurs in the absence of the crown ether.



Phenacyl esters which are difficult to obtain in good yield using classical procedures are formed easily in a refluxing benzene or acetonitrile suspension of acyl salt, crown ether and α-bromoacetophenone.[6]



90% yield

The alkylation of acetoacetic ester enolates gives more *O*-alkylated product in the presence of a crown ether,[7] especially in weakly polar solvents. **Dicyclohexyl-18-crown-6** markedly changes the rates and stereochemical course[8] of alkoxide-catalyzed carbanion-generating reactions; *e.g.*, the reaction of 5-decyl tosylate with potassium alkoxides[9] produces more *trans* olefin in the presence of **dicyclohexyl-18-crown-6.** Crown ethers also find application in the resolution of α-amino acids[10] and show promise for the preparation of organometallics[11] by catalyzing the reaction between metals and C-halogen or acidic C-H compounds. The potassium hydroxide complex of **dicyclohexyl-18-crown-6** reacts with *o*-dichlorobenzene[12] to give *o*-chloroanisole in 40-50% through a non-benzyne mechanism. Finally, crown ethers may be contrasted with our **α- and β-cyclodextrins.** While the cyclodextrins have a lipophilic cavity and hydrophilic shell the reverse is true of the crown ethers.[13]

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