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## NOTES



## COMMUNICATIONS

## AUTHOR INDEX



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THE JOURNAL OF Organic Chemistry®

VOLUME 37, NUMBER 18

SEPTEMBER 8, 1972

# Base-Catalyzed Reactions. XLIII.[1] Sodium- and Potassium-Catalyzed Side-Chain Alkenylation of γ-Alkylpyridines with Piperylenes

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*Received January 12, 1972*

The sodium- and potassium-catalyzed side-chain alkenylation of γ-picoline and γ-ethylpyridine with *cis*- and *trans*-piperylene was investigated. The alkenylation was carried out at 0 and 40°, and it was initiated by the anions produced from the reaction of 1 g-atom of the alkali metals with the alkylpyridines. The pentenylation occurred exclusively on the alkyl carbon atom α to the pyridine ring. The monopentenylated product from the reaction with *trans*-piperylene consisted mainly of branched-chain isomers and was the result of the addition of the picolyl anion to carbon atom 4 of the piperylene. The monopentenylated product from the reaction with the cis isomer at 0 and at 40° consisted mainly of straight-chain isomers, and the ratio of straight- to branched-chain isomers with potassium was lower than with sodium and was lower when the reactions occurred at the higher temperature. The dipentenylated pyridines were formed almost exclusively from the straight-chain monoadducts. The relative rate constants of monopentenylated isomer formation were calculated. The structures of the alkenylpyridines and of the products of their selective hydrogenations were determined by ir and nmr spectroscopy. The mechanism of the alkenylation reaction is discussed.

It has been previously established in our laboratory that alkylpyridines undergo carbanion-catalyzed side-chain alkylation and alkenylation reactions[2-8] similar to those of alkylbenzenes.[9-14] The reaction proceeds through the addition of 1-pyridylalkyl (picolyl)[15] anion to the double bond of the olefins. The alkenylation with butadiene[5] and isoprene[8] has been reported. The purpose of the present study was to obtain a better understanding of the alkenylation reaction by investigating the selectivity of the addition reaction of γ-alkylpyridines to *cis*- and *trans*-piperylene.

The alkenylation of γ-picoline and γ-ethylpyridine with an equivalent molar amount of either *cis*- or *trans*-piperylene was made at 0° in the presence of catalysts prepared from 1 g-atom of either sodium or potassium. The experiments of γ-picoline with *cis*-piperylene were also made at 40°. The course of the reaction was followed by means of vpc. For quantitative determination of the product, 5 mol % of *n*-butylcyclohexane was added to the alkylpyridines as internal standard for vpc. The separation of the individual compounds was accomplished by preparative gas chromatography. The structures of the pure compounds were determined by nmr and ir, and the structures of the selectively hydrogenated compounds were confirmed by nmr. The structures of the latter were compared with the corresponding synthetically prepared alkylpyridines by the method of Brown and Murphey.[16]

The mechanism of pentanylation of alkylpyridines with piperylene is similar to that proposed for butadiene[5] and isoprene[8] and is presented in Scheme I.

## Results and Discussion

**Products Formed.**—The product obtained from the reaction of piperylenes with γ-picoline is given in Scheme II and that with 4-ethylpyridine in Scheme III. The relative rates of formation of the individual monoadduct isomers and the total yield of the diadducts are given in Tables I, II, and III.

Products of chain lengthening similar to those observed in the alkenylation of toluene[12] were not observed and neither were found products containing terminal double bonds or those having a double bond in conjuga-

(1) (a) For paper XLII, see H. Pines, S. V. Kannan, and J. Simonik, *J. Org. Chem.*, **36**, 2311 (1971). (b) Paper XIII of the series Alkylation of Heteroaromatics. For paper XII, see H. Pines, S. V. Kannan, and W. M. Stalick, *ibid.*, **36**, 2308 (1971).

(2) For general review see H. Pines and L. Schaap, *Advan. Catal.*, **12**, 117 (1960).

(3) H. Pines and B. Notari, *J. Amer. Chem. Soc.*, **82**, 2209 (1960).

(4) B. Notari and H. Pines, *ibid.*, **82**, 2945 (1960).

(5) H. Pines and J. Oszczapowicz, *J. Org. Chem.*, **32**, 3183 (1967).

(6) H. Pines and N. E. Sartoris, *ibid.*, **34**, 2113 (1969).

(7) N. E. Sartoris and H. Pines, *ibid.*, **34**, 2119 (1969).

(8) (a) W. M. Stalick and H. Pines, *ibid.*, **35**, 415 (1970); (b) *ibid.*, **35**, 422 (1970).

(9) S. V. Kannan and H. Pines, *ibid.*, **36**, 2304 (1971).

(10) H. Pines and J. Shabtai, *ibid.*, **26**, 4220 (1961).

(11) J. Shabtai and H. Pines, *ibid.*, **26**, 4225 (1961).

(12) H. Pines and N. C. Sih, *ibid.*, **30**, 280 (1965).

(13) B. Stipanović and H. Pines, *ibid.*, **34**, 2106 (1969).

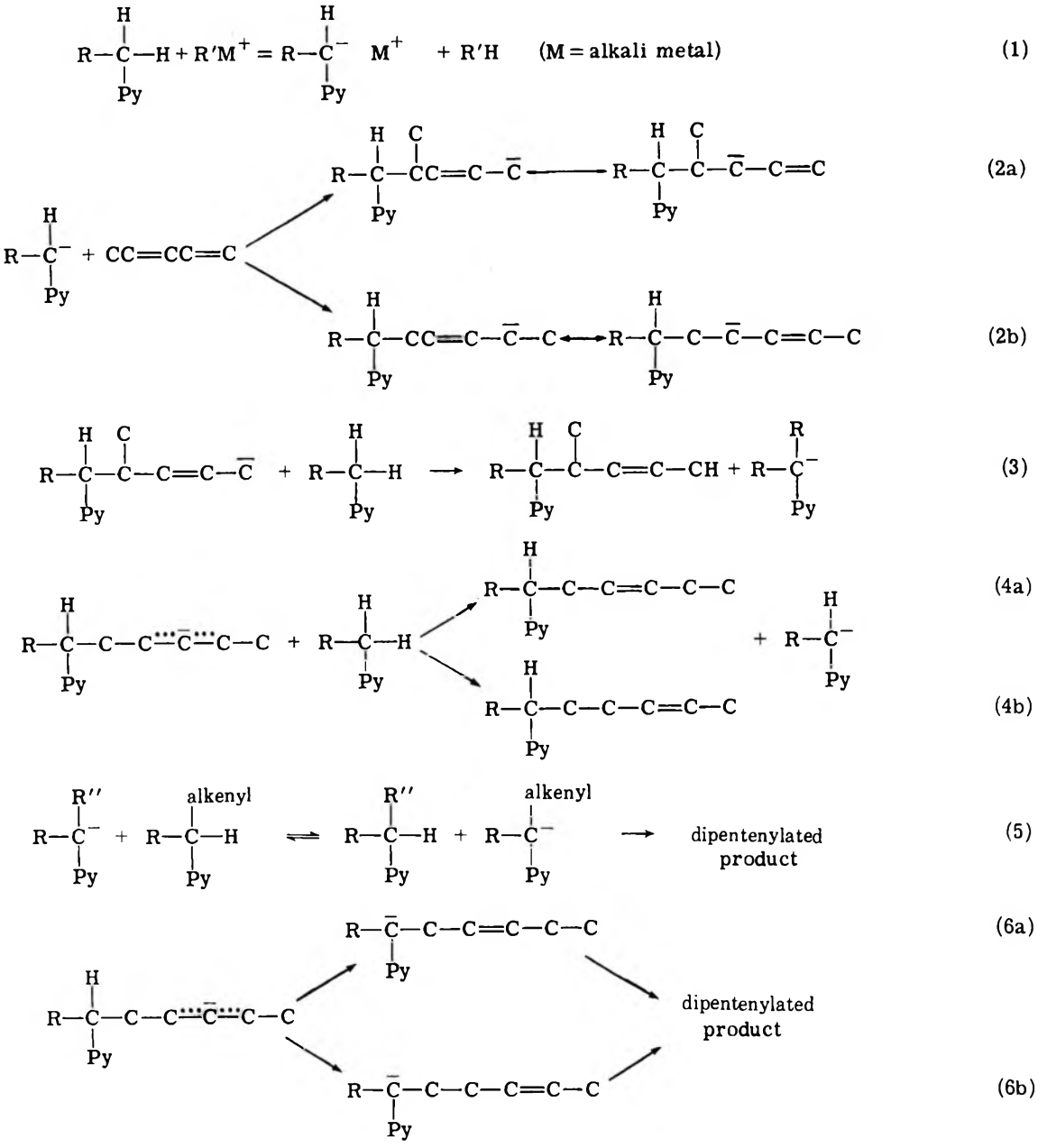
(14) B. Stipanović and H. Pines, *Chem. Commun.*, 1362 (1969).

(15) Picolyl anion throughout the paper is defined as an anion on the α-carbon atom of the alkyl group of the pyridine ring.

(16) H. C. Brown and W. A. Murphey, *J. Amer. Chem. Soc.*, **73**, 3308 (1951).

SCHEME I

MECHANISTIC PRESENTATION OF PENTENYLATION OF ALKYLPYRIDINES




(1) (2a) (2b) (3) (4a) (4b) (5) (6a) (6b)

tion with the pyridine ring, and this is in agreement with previous results from the alkenylation of alkylpyridines.[5,8] The isomeric piperylenes did not undergo reversible isomerization during the reaction.

The skeletal structures of the alkenylated γ-picoline obtained at 0° in the presence of either sodium or potassium depended primarily on the piperylene isomer used in the reaction. With the *cis*-piperylene the monoalkenylated product consisted of over 85% of straight-chain compounds, while with the trans isomer about 80% of branched-chain monoaddition products were formed (Table I, expt 1–4). Potassium was slightly less selective than sodium and this was especially true when the reaction was carried out at 40° instead of 0° (Table I, expt 5 and 6). At the higher temperature the rate of reaction was about 50% greater. The selectivity of addition of 4-ethylpyridine to the isomeric piperylenes was of the same type but of higher magnitude than that of picoline.

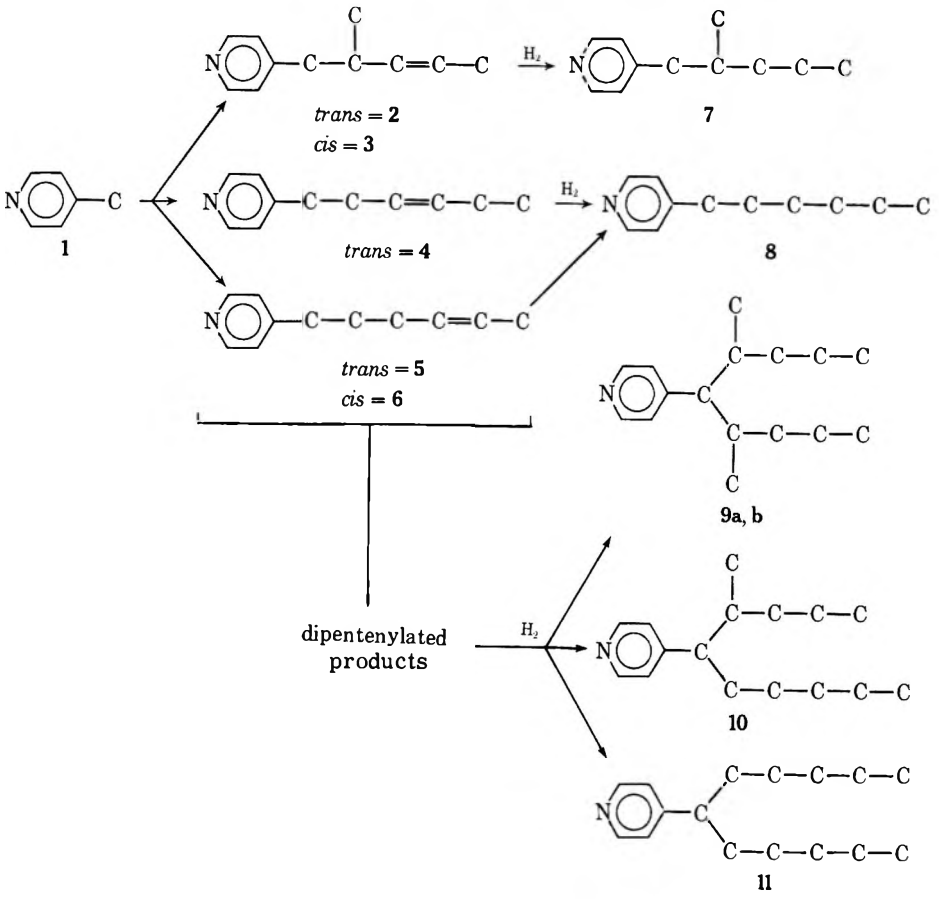
The pentenylation of γ-picoline with *trans*-piperylene produced a mixture of *trans*- and *cis*-4-methyl-5-(4-pyridyl)-2-pentene (**2** and **3**), *trans*-6-(4-pyridyl)-3-hexene (**4**), *trans*-6-(4-pyridyl)-2-hexene (**5**), and several dipentylated compounds. The latter, after selective hydrogenation, formed 4,6-dimethyl-5-(4-pyridyl)-nonane (**9**), 4-methyl-5-(4-pyridyl)decane (**10**), and 5-(4-pyridyl)undecane, the main product being **10**.

Pentenylation of γ-picoline with *cis*-piperylene gave also isomers **2**, **3**, and **4**, but, instead of **5**, *cis*-6-(4-pyridyl)-2-hexene (**6**) was formed. The dipentylated product after selective hydrogenation yielded almost exclusively **11**.

Pentenylation of 4-ethylpyridine with *trans*-piperylene formed four monoadducts: *trans*- and *cis*-4-methyl-5-(4-pyridyl)-2-hexene (**13** and **14**), *trans*-6-(4-pyridyl)-3-heptene (**15**), and *cis*-6-(4-pyridyl)-2-heptene (**16**) (Scheme III). With *cis*-piperylene only three monoadducts were obtained, **13**, **15**, and **16**.

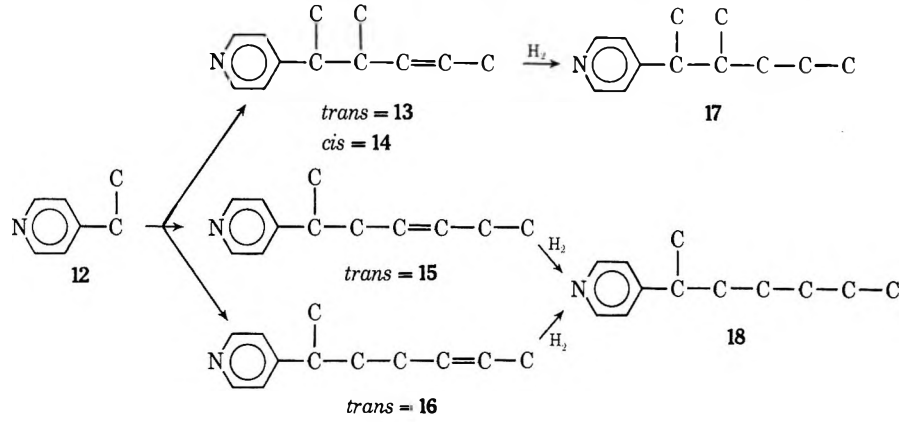
SCHEME II

PRODUCTS FORMED FROM REACTION OF γ-PICOLINE WITH PIPERYLENES




SCHEME III

PRODUCTS FORMED FROM REACTION OF 4-ETHYLPYRIDINE WITH PIPERYLENES




Isomer **14** was not detected even when 40% of the 4-ethylpyridine reacted. The yield of diadducts, with both *cis*- and *trans*-piperylene, was very low, less than 1%.

**Distribution of Products.**—The ratio of straight-chain to branched-chain alkenylpyridines depends greatly on the piperylenes and alkylpyridines used in the reactions, and to a smaller extent on the catalysts and temperatures. This ratio indicates the relative susceptibility of the isomeric piperylenes to undergo an attack on the 1- or 4-carbon atom by the picolyl anion. This ratio was constant during pentenylation of 4-ethylpyridine and was changing in the case of γ-picoline.

The rate of formation of isomeric monopentenylated alkylpyridines depends on several factors, such as the catalyst used in the reaction, configuration of piperylene, the structure of alkylpyridine employed, and the temperature of the reaction.

The monopentenylated pyridines can be produced either by reaction 2a and 3 or by 2b and 4 (Scheme I). The dipentenylated pyridines can be formed as a result of a parallel reaction 2b and 6, or a consecutive reaction 2b, 4, and 5. Since the rate of the consecutive

TABLE I

PENTENYLATION OF γ-PICOLINE WITH *cis*- AND *trans*-PIPERYLENE[a]

| Expt no. | Piperylene, catalyst, temp, °C | Sample no. | Time, hr | Conversion, %[b] | Yield of isomers, %[b,c] Monopentenylated: Branched chain, 2 + 3 | Monopentenylated: Straight chain, 4 | 5 | 6 | Dipentenylated, total | Isomers distribution: 4 + 5 + 6 / 2 + 3 | 5 or 6 / 4 | Di / mono |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 1.0 | 1.49 | 0.88 | 0.14 | 0.24 | 0 | 0.228 | 0.43 | 1.79 | 0.18 |
| | | 2 | 2.0 | 3.92 | 2.62 | 0.20 | 0.61 | 0 | 0.490 | 0.31 | 2.97 | 0.14 |
| | *trans*-, | 3 | 3.5 | 8.18 | 5.40 | 0.41 | 1.23 | 0 | 1.142 | 0.30 | 2.97 | 0.16 |
| 1 | Na, | 4 | 5.0 | 9.19 | 6.12 | 0.43 | 1.37 | 0 | 1.271 | 0.29 | 3.23 | 0.16 |
| | 0 | 5 | 7.0 | 13.23 | 8.63 | 0.57 | 1.95 | 0 | 2.09 | 0.29 | 3.44 | 0.18 |
| | | 6 | 10.0 | 19.85 | 13.14 | 0.78 | 2.72 | 0 | 3.21[d] | 0.27 | 3.49 | 0.19 |
| | | 1 | 1.0 | 0.84 | 0.52 | 0.10 | 0.14 | 0 | 0.084 | 0.45 | 1.38 | 0.11 |
| | | 2 | 2.0 | 1.93 | 1.29 | 0.20 | 0.24 | 0 | 0.202 | 0.34 | 1.20 | 0.12 |
| | *trans*-, | 3 | 3.5 | 2.65 | 1.74 | 0.24 | 0.41 | 0 | 0.259 | 0.37 | 1.76 | 0.11 |
| 2 | K, | 4 | 5.0 | 3.72 | 2.49 | 0.28 | 0.61 | 0 | 0.340 | 0.36 | 2.16 | 0.10 |
| | 0 | 5 | 7.0 | 5.51 | 3.62 | 0.36 | 0.79 | 0 | 0.730 | 0.32 | 2.18 | 0.15 |
| | | 6 | 10.0 | 7.12 | 4.24 | 0.42 | 1.02 | 0 | 1.44[d] | 0.34 | 2.43 | 0.25 |
| | | 1 | 1.0 | 2.66 | 0.16 | 0.66 | 0 | 0.98 | 0.86 | 10.4 | 1.47 | 0.48 |
| | | 2 | 2.0 | 5.08 | 0.30 | 0.96 | 0 | 1.60 | 2.22 | 8.47 | 1.67 | 0.78 |
| | *cis*-, | 3 | 3.5 | 8.10 | 0.50 | 1.22 | 0 | 2.48 | 3.90 | 7.44 | 2.03 | 0.94 |
| 3 | Na, | 4 | 5.0 | 10.16 | 0.60 | 1.28 | 0 | 2.95 | 5.33 | 7.04 | 2.30 | 1.10 |
| | 0 | 5 | 7.0 | 12.67 | 0.73 | 1.50 | 0 | 3.48 | 6.96 | 6.82 | 2.33 | 1.22 |
| | | 6 | 10.0 | 15.88 | 0.82 | 1.62 | 0 | 4.03 | 9.41[e] | 6.87 | 2.48 | 1.46 |
| | | 1 | 1.0 | 3.40 | 0.295 | 0.900 | 0 | 1.36 | 0.845 | 7.66 | 1.51 | 0.33 |
| | | 2 | 2.0 | 5.65 | 0.498 | 1.36 | 0 | 2.12 | 1.67 | 6.99 | 1.56 | 0.42 |
| | *cis*-, | 3 | 3.5 | 8.12 | 0.653 | 1.64 | 0 | 2.85 | 2.98 | 6.87 | 1.73 | 0.58 |
| 4 | K, | 4 | 5.0 | 9.63 | 0.837 | 1.88 | 0 | 3.24 | 3.67 | 6.12 | 1.72 | 0.62 |
| | 0 | 5 | 7.0 | 10.25 | 0.862 | 1.92 | 0 | 3.43 | 4.04 | 7.20 | 1.78 | 0.65 |
| | | 6 | 10.0 | 11.32 | 0.904 | 2.07 | 0 | 3.67 | 4.68[e] | 6.35 | 1.77 | 0.70 |
| | | 1 | 1.0 | 4.28 | 0.343 | 1.28 | 0 | 1.86 | 0.80 | 9.13 | 1.45 | 0.23 |
| | | 2 | 2.0 | 8.17 | 0.591 | 2.08 | 0 | 3.28 | 2.22 | 9.07 | 1.58 | 0.37 |
| | *cis*-, | 3 | 3.5 | 13.32 | 0.919 | 2.86 | 0 | 4.93 | 4.51 | 8.47 | 1.76 | 0.51 |
| 5 | Na, | 4 | 5.0 | 17.20 | 1.11 | 3.32 | 0 | 5.61 | 7.16 | 8.05 | 1.69 | 0.71 |
| | 40 | 5 | 7.0 | 21.14 | 1.33 | 3.62 | 0 | 6.26 | 9.93 | 7.43 | 1.73 | 0.89 |
| | | 6 | 10.0 | 23.99 | 1.44 | 3.85 | 0 | 6.60 | 12.1[e] | 7.26 | 1.72 | 1.02 |
| | | 1 | 1.0 | 5.28 | 0.789 | 1.38 | 0 | 2.04 | 1.07 | 4.34 | 1.47 | 0.25 |
| | | 2 | 2.0 | 9.07 | 1.32 | 1.98 | 0 | 3.33 | 2.44 | 4.02 | 1.68 | 0.37 |
| | *cis*-, | 3 | 3.5 | 12.04 | 1.79 | 2.38 | 0 | 4.23 | 3.64 | 3.69 | 1.77 | 0.43 |
| 6 | K, | 4 | 5.0 | 13.42 | 1.94 | 2.56 | 0 | 4.52 | 4.40 | 3.64 | 1.77 | 0.49 |
| | 40 | 5 | 7.0 | 14.59 | 2.13 | 2.61 | 0 | 4.75 | 5.10 | 3.46 | 1.82 | 0.54 |
| | | 6 | 10.0 | 14.86 | 2.14 | 2.64 | 0 | 4.81 | 5.27[e] | 3.48 | 1.82 | 0.54 |

[a] The following mole equivalents of active reagents were used: picoline, 1.0; piperylene, 1.0; alkali metal, 0.01 g-atom. For details see Experimental Section, General Procedure. [b] Based on γ-picoline used in the reaction. [c] The boldface numbers refer to compounds given in the text. [d] Selective hydrogenation gave mainly **10**. [e] Selective hydrogenation gave **11** with a small amount of **10**.

reaction can be ignored at very low conversions, the consumption of alkylpyridines in an overall reaction can be expressed by

$$-\frac{d[PyCR]}{dt} = \frac{dx}{dt} = k_{\Sigma}q[p - x][a - x] \qquad (I)$$

where [PyCR] = actual concentration of starting alkylpyridine, $p$ = initial concentration of starting alkylpyridine, $a$ = initial concentration of piperylene, $q$ = concentration of the catalyst, $x$ = total concentration of pentylated pyridines, and $k_{\Sigma}$ = rate constant for overall reaction.

The rates of formation of the individual pentenylated compounds can be expressed by a similar equation

$$\frac{dx_n}{dt} = k_n q[p - x][a - x] \qquad (II)$$

where $x_n$ = concentration of pentenylated product n and $k_n$ = rate constant of formation of compound n.

Dividing eq I by eq II and integrating between the limits of concentration from 0 to $x$ and $x_n$, respectively, eq III is obtained.

$$x_n/x = k_n/k_{\Sigma} \qquad (IIIa)$$

$$k_n = [x_n/x]k_{\Sigma} \qquad (IIIb)$$

The relative rate constants $k_n' = k_n/k_{\Sigma}$ for the formation of the various pentenylated products derived from eq III are given in Table III.

Equation III shows that mole per cent of isomer n formed can be plotted as a function of the amount of alkylpyridine reacted and that the plot should give a straight line. This would be true only if product n is formed as a result of the parallel reaction only and it it does not undergo any further reaction.

Figure 1 shows that branched-chain monopentenylated pyridines do not take part in the formation of dipentenylated products, inasmuch as the plot follows a straight line. Compound **4**, containing a double bond at the γ–δ position with respect to the pyridine ring, undergoes further pentenylation (reaction 5,

TABLE II

PENTENYLATION OF 4-ETHYLPYRIDINE WITH *cis*- AND *trans*-PIPERYLENE[a]

| Expt no. | Piperylene, catalyst, temp, °C | Sample no. | Time, hr | Conversion, %[b] | Yield of isomers, %[b,c] Branched chain 13 | Branched chain 14 | Straight chain 15 | Straight chain 16 | Isomer distribution (15 + 16)/(13 + 14) | Isomer distribution 16/15 |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 1.0 | 2.75 | 0.83 | 0.89 | 0.37 | 0.67 | 0.60 | 1.80 |
| | | 2 | 2.0 | 6.18 | 1.78 | 1.51 | 0.97 | 1.92 | 0.88 | 1.97 |
| | *trans*-, | 3 | 3.5 | 11.38 | 3.54 | 2.89 | 1.58 | 3.37 | 0.77 | 2.12 |
| 1 | Na, | 4 | 5.0 | 14.64 | 4.65 | 4.03 | 1.92 | 4.04 | 0.69 | 2.11 |
| | 0 | 5 | 7.0 | 22.95 | 7.12 | 5.47 | 3.22 | 7.14 | 0.82 | 2.22 |
| | | 6 | 10.0 | 32.48 | 11.8 | 6.32 | 4.46 | 9.90 | 0.79 | 2.22 |
| | | 1 | 1.0 | 1.89 | 0.56 | 0.40 | 0.40 | 0.54 | 0.97 | 1.34 |
| | | 2 | 2.0 | 4.78 | 1.38 | 1.15 | 0.88 | 1.36 | 0.89 | 1.55 |
| | *trans*-, | 3 | 3.5 | 8.76 | 2.54 | 2.12 | 1.67 | 2.43 | 0.88 | 1.46 |
| 2 | K, | 4 | 5.0 | 11.52 | 3.41 | 2.73 | 2.16 | 3.22 | 0.89 | 1.51 |
| | 0 | 5 | 7.0 | 15.64 | 4.55 | 3.67 | 2.96 | 4.46 | 0.90 | 1.51 |
| | | 6 | 10.0 | 19.44 | 6.09 | 3.79 | 3.69 | 5.87 | 0.97 | 1.59 |
| | | 1 | 1.0 | 3.23 | 0.09 | 0 | 1.45 | 1.68 | | 1.15 |
| | | 2 | 2.0 | 8.02 | 0.255 | 0 | 3.59 | 4.17 | 30.4 | 1.16 |
| | *cis*-, | 3 | 3.5 | 11.78 | 0.359 | 0 | 5.19 | 6.23 | 31.8 | 1.20 |
| 3 | Na, | 4 | 5.0 | 21.92 | 0.612 | 0 | 9.37 | 11.94 | 34.8 | 1.27 |
| | 0 | 5 | 7.0 | 27.88 | 0.883 | 0 | 12.2 | 14.8 | 30.6 | 1.21 |
| | | 6 | 10.0 | 40.9 | 1.30 | 0 | 17.9 | 21.7 | 30.5 | 1.21 |
| | | 1 | 1.0 | 4.81 | 0.22 | 0 | 1.84 | 2.75 | 20.9 | |
| | | 2 | 2.0 | 11.4 | 0.48 | 0 | 5.61 | 5.39 | 24.4 | 0.96 |
| | *cis*-, | 3 | 3.5 | 22.4 | 1.01 | 0 | 10.6 | 10.8 | 21.2 | 1.01 |
| 4 | K, | 4 | 5.0 | 28.9 | 1.18 | 0 | 13.8 | 13.9 | 24.8 | 1.01 |
| | 0 | 5 | 7.0 | 34.9 | 1.54 | 0 | 16.1 | 17.3 | 21.6 | 1.08 |
| | | 6 | 10.0 | 37.4 | 1.72 | 0 | 17.6 | 18.1 | 20.6 | 1.03 |

[a] See Table I, footnote *a*. [b] Based on 4-ethylpyridine used in the reaction. [c] The boldface numbers refer to compounds given in the text.

TABLE III

RELATIVE RATE CONSTANTS OF PENTENYLATION OF γ-PICOLINE[a]

| Expt no. | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Piperylene | *trans*- | | *cis*- | | | |
| Catalyst | Na | K | Na | K | Na | K |
| Temp, °C | 0 | 0 | 0 | 0 | 40 | 40 |
| Picoline consumption, $k_\Sigma$[a] | 1.6 | 1.0 | 2.0 | 2.8 | 3.8 | 5.0 |
| Pentenylated product | | | | | | |
| $k_2 + k_3/k_\Sigma$ | 0.65 | 0.65 | 0.05 | 0.08 | 0.08 | 0.14 |
| $k_4/k_\Sigma$ | 0.04 | 0.11 | 0.23 | 0.30 | 0.29 | 0.30 |
| $k_5/k_\Sigma$ | 0.14 | 0.14 | | | | |
| $k_6/k_\Sigma$ | | | 0.45 | 0.38 | 0.44 | 0.38 |
| $k_{di}/k_\Sigma$ | 0.15 | 0.15 | 0.26 | 0.22 | 0.18 | 0.17 |
| $\frac{k_4 + k_5 + k_6}{k_2 + k_3}$ = S/B[b] | 0.28 | 0.38 | 13.5 | 8.5 | 9.1 | 4.8 |
| $k_{di}/k_{mono}$[c] | 0.18 | 0.18 | 0.36 | 0.29 | 0.22 | 0.21 |

[a] Based on data given in Table I. [b] S/B = straight chain/branched chain monopentenylated product. [c] Di-/monopentenylated product.

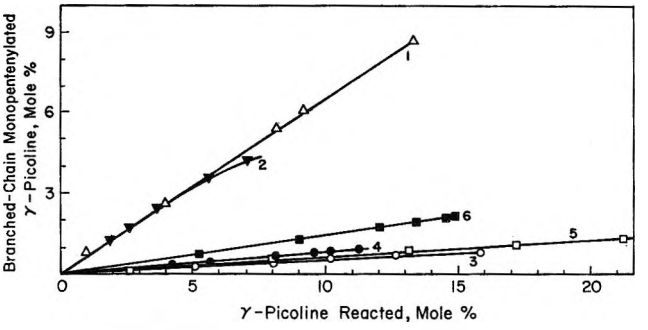
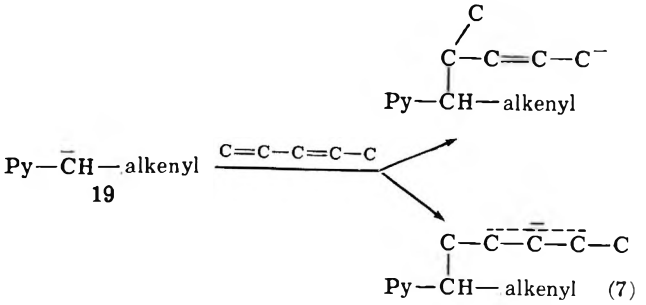



Figure 1.—Mole per cent of branched chain of monopentenylated products obtained from γ-picoline as a function of γ-picoline reacted. (The numbers refer to experiments listed in Table I.)

Scheme I) at a higher rate than those of the other straight-chain isomers **5** and **6**. For that reason the ratios of **5** to **4** and of **6** to **4** change during the reaction (Table I). The difference in the rate of further pentenylation of monopentenylpyridines can be explained by increased acidity of picolyl protons in compounds having double bonds at the γ–δ positions, as was reported previously.[2,6,8]

Dipentenylated products are formed as a result of the reaction of anion **19** with piperylene (eq 7).

The anion **19** can be generated in two ways. (1) It can be formed as a result of intermolecular transprotonation (reaction 5, Scheme I), and the rate of its formation would depend on the concentration of the monopentenylated isomers taking part in the consecutive reaction. In this case the ratio of dipentenylated to the monopentenylated isomers, di/mono, would be equal to zero at zero conversion and would increase with time, giving a plot with an upward curve. (2) The anion **19** may also be formed as a result of intramolecular transprotonation (reaction 6), and the rate of its formation would depend on the probability of such a process. The dipentenylated products would




(7)

thus be formed in a parallel reaction, and the kinetics would be described by eq II and IIIa. The ratio $k_{di}/k_{mono} = x_{di}/x_{mono}$ would be equal to the ratio of the number of those undergoing intermolecular protonation, $N_{intra}$, to the number of those undergoing intermolecular protonation, $N_{bi}$. Actually the formation of anion **19** occurs by both ways simultaneously, and the ratio of intra- to intermolecular protonation was estimated by the extrapolation of the ratio of $x_{di}/x_{mono}$ to zero conversion, or from the ratio

$$\frac{N_{intra}}{N_{bi}} = \frac{k_{di}}{k_2 + k_3 + k_4 + k_5 + k_6} = \frac{K_{di}}{k_{mono}}$$

The calculated data (Table III) show that at 0° considerable intramolecular transprotonation occurs. The ratio of rate constants of formation straight-chain to branched-chain pentenylpyridines is a measure of the susceptibility of the piperylene isomer to an attack by a picolyl anion in position 1 over position 4 (Table III).

The relative rate constant of overall reaction, $k_\Sigma$, was obtained by taking the slowest reaction as a unit. The rates were calculated from the initial slope of a total yield *vs.* time curve, based on the data given in Tables I and II. Since the same amount of gram-atoms of alkali metal was used in each experiment, it was assumed that the same concentration of catalyst was also present. In the pentenylation of γ-ethylpyridine the ratio of the isomeric products formed was constant within the experimental error (Table II). The relative rate constant of the isomers produced is listed in Table IV. The very low formation of di-

TABLE IV

RELATIVE RATE CONSTANTS OF PENTENYLATION OF γ-ETHYLPYRIDINE[a]

| Expt no. | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Piperylene | *trans* | | *cis* | |
| Catalyst | Na | K | Na | K |
| Temp, °C | 0 | 0 | 0 | 0 |
| Ethylpyridine consumption, $k^1_\Sigma$[b] | 2.5 | 1.7 | 3.2 | 4.5 |
| Pentenylated product | | | | |
| $k_{13}/k_\Sigma$ | 0.30 | 0.30 | 0.03 | 0.04 |
| $k_{14}/k_\Sigma$ | 0.26 | 0.23 | | |
| $k_{15}/k_\Sigma$ | 0.13 | 0.20 | 0.43 | 0.47 |
| $k_{16}/k_\Sigma$ | 0.29 | 0.27 | 0.52 | 0.48 |
| $\frac{k_{15} + k_{16}}{k_{13} + k_{14}}$ | 0.75 | 0.89 | 0.32 | 0.21 |

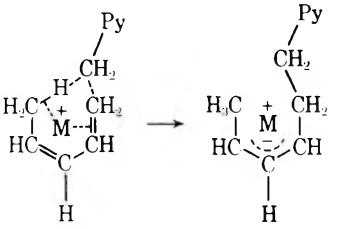
[a] Based on data given in Table II. [b] Relative to picoline consumption, Tables I and III.

pentenylated compounds in the case of ethylpyridine is most likely due to steric hindrance caused by the methyl and alkenyl groups situated at the picolyl carbon atom, and it is similar to the observation made in the case of 4-*sec*-butylpyridine.[8a]

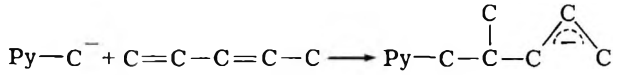
The relative rate of pentenylation of ethylpyridine with piperylene is about 1.5 times that of γ-picoline, which is in accordance with the results obtained previously with isoprene.[8]

**Reactivity of *cis*- and *trans*-Piperylene.**—γ-Picoline was treated with technical grade piperylene containing a mixture of cis and trans isomer. From the rate of the disappearance of the two isomers it was found that the cis isomer reacts about nine times faster than the trans isomer. The greater reactivity of *cis*-piperylene could by attributed to its polarization caused by the approaching picolyl anion. It is known that the protons of the methyl group in piperylene could be readily replaced by sodium during transmetalation with alkylsodium.[17] In the presence, however, of a relatively strong acid, such as γ-picoline, metalation of piperylene does not occur, as indicated by the absence of cis–trans isomerization of the dienes during the alkenylation reaction. It is, however, very plausible that the methyl group of piperylene can form strong hydrogen bonding with a picolyl anion and thus cause a change in polarization of the cis and trans diene. In the cis isomer only there is a possibility for an approach of the C-1 atom by a free rotation around the C-2–C-3 bond to the hydrogen-bonded picolyl anion. The reaction between the anion and the diene could then occur while the polarization of the molecule is still maintained, and as a result of this interaction an addition of a picolyl anion to the terminal double bond may occur to give a straight-chain adduct.

The transition state of the reaction can be presented as follows.



The stabilization of a not fully developed anion in position 5 relative to the double bond is suggested by previous alkenylation studies.[5,7] Since *trans*-piperylene cannot have such a configuration, the addition occurs in the carbon 4, because the resulting primary–secondary anion is more stable than the secondary–secondary as in the case of the addition of picolyl anion to the terminal double bond.



The temperature increase diminishes the probability of a required conformation, and thus the ratio of straight-chain to branched-chain isomers is lower (expt 5 and 6).

**Structure Determination.**—The product from the alkenylation of the alkylpyridines with piperylene was submitted to a distillation and frequent fraction were taken. The various fractions were then separated into pure compound by vpc. A portion of the fractions containing mostly one isomer was selectively hydrogenated to the corresponding alkylpyridines. The hydrogenation was made at atmospheric pressure using palladium as catalyst, and from the amount of hydrogen absorbed it was possible to determine the number of double bonds per molecule. The nmr and ir spectra of the individual alkyl- and alkenylpyridines are given in Tables III and IV.

The various groups of protons were determined from the position, intensity, and multiplicity of the resonance bands. Characteristic protons are listed in Table V. The total number of aliphatic protons and the number

(17) A. A. Morton, F. D. Marsh, R. D. Coombs, A. L. Lyons, S. E. Penner, H. E. Ramsden, V. B. Baker, E. L. Little, and R. L. Letsinger, *J. Amer. Chem. Soc.*, **72**, 3785 (1950).

TABLE V

CHARACTERIZATION AND NMR SPECTRA OF γ-ALKYL- AND γ-ALKENYLPYRIDINES DERIVED FROM PENTENYLATION OF γ-PICOLINE

| | | | Spectra of pyridines[a-c] Chemical shift, δ, ppm | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Compd | Bp, °C (mm) | $n^{21}D$ | $CH_3CCPy$ | $CH_3CCC$ | $C_n$ $CH_3CPy$ | $CH_3C{=}C$ | $CH_2C{=}C$ | Picolyl protons | Olefinic protons |
| 2 | | 1.5068 | 0.96 d | | | 1.59 d | | 2.51 | 5.37 |
| | 78 (3.5) | | | | | | | | |
| 3 | | | 0.96 d | | | 1.41 d | | 2.51 | 5.37 |
| 4 | 90 (2) | 1.5081 | | 0.94 t | | | 1.90[d] | 2.69 t | 5.47 |
| | | | | | | | ~2.3[e] | | |
| 5 | 101 (2) | 1.5085 | | | | 1.67 d | 2.08 | 2.60 | 5.47 |
| 6 | | 1.5108 | | | | 1.60 d | ~2.1 | 2.62 t | 5.46 |
| 7 | 90 (4) | 1.4907 | 0.84 d | 0.89 t | | | | 2.49 | |
| 8 | 79 (1, 5) | 1.4890 | | 0.90 t | | | | 2.59 t | |
| 9a | | 1.489 | 0.75 d | 0.89 t | | | | 2.16 | |
| 9b | | 1.4896 | 0.74 d | 0.93 t | | | | 2.34 | |
| | | | 0.82 d | | | | | | |
| 10 | | 1.487 | 0.71 d | 0.91 t | | | | 2.42 | |
| | | | 0.81 d | | | | | | |
| 11 | | 1.4865 | | 0.85 t | | | | 2.48 | |
| 13 | | 1.5067 | 0.94 d | | 1.20 d | 1.59 d | | ~2.6 | 5.37 |
| | | | | | 1.24 d | | | | |
| | 119 (9.5) | | | | | | | | |
| 14 | | 1.5078 | 0.95 d | | 1.26 d | 1.49 d | | ~2.6 | 5.35 |
| 15 | | 1.5041 | | 0.93 t | 1.25 d | | ~1.90[d] | 2.74 | 5.42 |
| | | | | | | | ~2.3[e] | | |
| | 126 (10) | | | | | | | | |
| 16 | | 1.509 | | | 1.26 d | 1.61 d | 2.05 | 2.73 | 5.43 |
| 17 | | 1.4196 | 0.74 d | 0.90 t | 1.19 d | | | 2.58 | |
| | | | 0.84 d | | 1.24 d | | | | |
| 18 | | 1.4867 | | 0.87 t | 1.24 d | | | 2.67 | |

[a] In the nmr spectra of all the compounds listed the bands of the two β pyridine protons at δ 7.05–7.21 ppm and the two α-pyridine protons at δ 8.50–8.60 ppm were present. [b] d = doublet; t = triplet. [c] Tetramethylsilicon (TMS) was used as a reference. [d] $CH_2$ between $CH_3$ and C=C. [e] $CH_2$ β to pyridine ring.

of protons causing multiplets were determined from an integration curve. The α- and β-pyridine protons were taken as internal standards for integration. In all the compounds the absorption bands of the two α-pyridine protons at δ 8.50–8.60 ppm and the two β-pyridine protons at δ 7.05–7.21 ppm were present, indicating that the substitution occurred only at the γ-pyridine side chain. The most significant resonance bands were those of $CH_3$ groups and bands of substituents at the C=C group. A doublet of the $CH_3$ group at the C atom β to the pyridine ring, $CH_3CCPy$, at δ 0.74–0.96 ppm indicated the branched-chain isomer. In the cases of dipentenylated products of picoline, **9b** and **10**, and monopentenylated ethylpyridine, **17**, two doublets were due to erythro and threo isomers.

The position of the C=C bond was indicated by the number of $CH_2C{=}C$ protons absorbing at δ 1.98–2.08 ppm and confirmed by the presence or absence of the $CH_3C{=}C$ band at δ 1.41–1.67 ppm. The protons at the picoline carbon atom connected to the pyridine ring absorbed in the range δ 2.16–2.74 ppm; from the number of protons the substitution at this atom was determined. The $-CH_2-$ groups linked with a saturated carbon atom gave broad bands with the maximum located in the region δ 1.12–1.42 ppm.

Cis and trans isomers of the alkenylpyridines were differentiated by the presence and absence of the specific bands in the infrared spectra before and after selective hydrogenation. The bands were at 970–960 $cm^{-1}$ for trans and 1310–1295 and about 690 $cm^{-1}$ for cis. The differentiation between the cis and trans isomers containing methyl group adjacent to the double bond, $CH_3C{=}C-$, was confirmed by the nmr spectra. The resonance band of the $CH_3$ group in the cis isomer shifted about 0.10–0.18 ppm upfield with reference to the corresponding band of the trans isomer.[18]

## Experimental Section

**Reagents.**—γ-Picoline and 4-ethylpyridine were purchased from Reilly Tar Co. The material was dried over barium oxide and distilled in a nitrogen atmosphere on a Podbielniak Heligrid column, 1.5 m long. The alkylpyridines used in the reaction were over 99.5% pure as adjudged by gas chromatography. *n*-Butylcyclohexane used as an internal standard was obtained by catalytic hydrogenation of *n*-butylbenzene.[5]

*cis*-Piperylene was isolated from commercial piperylene by the method of Frank, *et al.*,[19] and the piperylene prepared in this manner contained 66.7% *cis*-piperylene and 33.3% cyclopentene and was free from *trans*-piperylene. *trans*-Piperylene, which was purchased from Chemical Samples Co., Columbus, Ohio, contained 94.6% of trans and 1.2% of cis isomer; the remaining 4.2% consisted of cyclopentene, which was inert in this reaction.

**General Procedure.**—The preparation of the catalysts and the alkenylation reactions were performed according to the procedure described previously.[5]

For preparative purposes, in order to obtain larger amounts of isomers for the establishment of structures, 1.5 mol of alkylpyridines was pentenylated with 1.7 mol of technical grade piperylene and in the presence of 0.05 g-atom of sodium. After the piperylene had reacted, the catalyst was decomposed with methanol until the solution became colorless or pale yellow. The product was then distilled on a Podbielniak Heligrid column, and

(18) L. M. Jackman and R. H. Wiley, *J. Chem. Soc.*, 2881 (1960).

(19) R. L. Frank, R. D. Emmick, and R. S. Johnson, *J. Amer. Chem. Soc.*, **69**, 2313 (1947).

TABLE VI
DESCRIPTION OF THE VAPOR PHASE CHROMATOGRAPHIC COLUMNS

| Column | Packing: Liquid phase | Wt % | Solid support | Mesh size | Column: Length, m | O.d., in. |
|---|---|---|---|---|---|---|
| A | Gum rubber phenyl Methyl GE-SE-552 | 15 | GAS-Pack WAB | 60–80 | 1.5 | 1/4 |
| B | Versamid 900 | 10 | GAS-Pack WAB | 60–80 | 1.5 | 1/4 |
| C | Dimethyl sulfolane | 33 | Firebrick | 100–120 | 3.0 | 1/4 |
| D | Reoplex 400 | 15 | GAS-Pack WAB | 60–80 | 2.3 | 3/8 |
| E | Versamid 900 | 15 | GAS-Pack WAB | 60–80 | 2.3 | 3/8 |

pure isomers were separated by vpc and analyzed spectroscopically.

**Analyses.**—The infrared spectra of the pyridines purified by gas chromatography were taken with a Baird infrared spectrophotometer, Model 4-55. Samples of 8-10 μl were placed between two sodium chloride plates using air as a reference.

Nmr spectra were obtained on a Varian A-60 spectrometer at room temperature. Samples varying from 20 to 50 μl in carbon tetrachloride, total volume 400 μl, with an addition of 1–2 drops of tetramethylsilicon (TMS) as reference were used (Table V).

Refractive indices were measured on a Zeiss Opton refractometer with a thermostat at 20 ± 0.1°. All samples used for analysis were of purity higher than 95%.

Analyses and separations were performed with an F & M Model 720 dual-column gas chromatograph with a thermal conductivity detector, using helium as a carrier gas. The columns used are listed in Table VI.

The yields of alkenylated pyridines were determined by calculating the peak areas in relation to the internal standard *n*-butylcyclohexane added in known amount before alkenylation. The peak areas were determined from their heights and standard deviations[20] using the Bartlett and Smith method[21] in case of overlapped peaks.

The composition, purity, and consumption of piperylene was analyzed on column C at a column temperature of 30° and an injection port temperature of 70°, helium flow 100 ml/min, inlet pressure 35 psi; 20-μl samples were injected.

The composition of the product obtained from the reaction of γ-picoline with either *cis*- or *trans*-piperylene was analyzed on column A at 170° with a helium flow of 100 ml/min and an inlet pressure of 35 psi. The composition of the reaction products of 4-ethylpyridine was analyzed on column B at 160° with the same helium flow and inlet pressure; 40-μl samples were injected.

For preparative separation and purification of the various alkenylpyridines, the following conditions were used (compound, column, temperature, helium flow in ml/min): **2**, **3**, **4**, **7**, and **8**, D, 160°, 100; **5** and **6**, D, 140°, 125; **9a**, **9b**, **10**, and **11**, E, 190–200°, 100; **13**, **14**, **15**, **16**, **17**, and **18**, E, 170°, 100. The product obtained from each separation was analyzed again on vpc and when necessary the compound was repurified. The relative retention times of the alkyl- and alkenylpyridines are described separately.[22]

**Registry No.**—**1**, 108-89-4; **2**, 34993-35-6; **3**, 34993-36-7; **4**, 34993-37-8; **5**, 34993-38-9; **6**, 34993-39-0; **7**, 34993-40-3; **8**, 27876-24-0; **9a**, 34993-42-5; **10**, 34993-43-6; **11**, 34993-44-7; **12**, 536-75-4; **13**, 34993-45-8; **14**, 34993-46-9; **15**, 34993-47-0; **16**, 34993-48-1; **17**, 34993-49-2; **18**, 34993-50-5; *cis*-piperylene, 1574-41-0; *trans*-piperylene, 2004-70-8.

(20) O. E. Schupp, "Gas Chromatography," Interscience, New York, N. Y., 1968.

(21) K. C. Bartlett and D. M. Smith, *Can. J. Chem.*, **38**, 2057 (1960).

(22) J. Oszczapowicz, J. Golab, and H. Pines, *J. Chromatogr.*, **64**, 1 (1972).

# Alkylation of Disodioacetylacetone with Halo Ketals

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The reaction of bromo and chloro ketals (II) with disodioacetylacetone (I) were investigated. For II, $n = 1$; X = Br or Cl; R = $CH_3$—no reaction occurred. For II, $n = 2$; X = Br; R = $CH_3$—alkylation occurred in low yield. For II, $n = 3$, 4, or 5; X = Br or Cl; R = $CH_3$ or $CH_3CH_2$—alkylation occurred in fair to good yields to form the terminal alkylation products. These ketal β-diketones were hydrolized to the corresponding triketones. Copper chelates of the triketones were prepared.

In an effort to extend the versatility and usefulness of alkylations of dicarbanions of β-diketones, we have observed that 2-(chloromethyl)-2-methyl-1,3-dioxolane or 2-(bromomethyl)-2-methyl-1,3-dioxolane did not alkylate disodioacetylacetone (I) under the conditions in which simple alkyl halides (methyl iodide, butyl bromide, etc.[2]) alkylate I (see eq 1). That this lack of reactivity is a characteristic of these two compounds

$$\underset{\text{I}}{CH_3COCHCOCH_2} + RX \xrightarrow{H^+} CH_3COCH_2COCH_2R \quad (1)$$

R = methyl, ethyl, etc.

rather than a characteristic of ketal halides in general is discussed in the present paper.

The procedure involved conversion of acetylacetone to I by means of 2 molar equiv of sodium amide in liquid ammonia and treatment of this with 1 equiv of ketal halide (Scheme I). The results are summarized in Table I. It can be seen from Table I that, for $n = 1$, alkylation does not occur, but for II, $n = 2$, X = Br, alkylation does occur in poor yield. For $n = 3$, 4, and 5, X = Cl or Br, the reaction proceeds in much better yield. This indicates that, if the carbon bonded to the halogen is bonded to or near the ketal group, little or no alkylation reaction occurs because of the steric hindrance (II, $n = 1$, X = Cl or Br, similar to neopentyl halides), but, when the carbon bonded to halogen is further away from the ketal group, the steric hindrance decreases and allows the alkylation to proceed

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(2) C. R. Hauser and T. M. Harris, *J. Amer. Chem. Soc.*, **80**, 6360 (1958); K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 61 (1965).

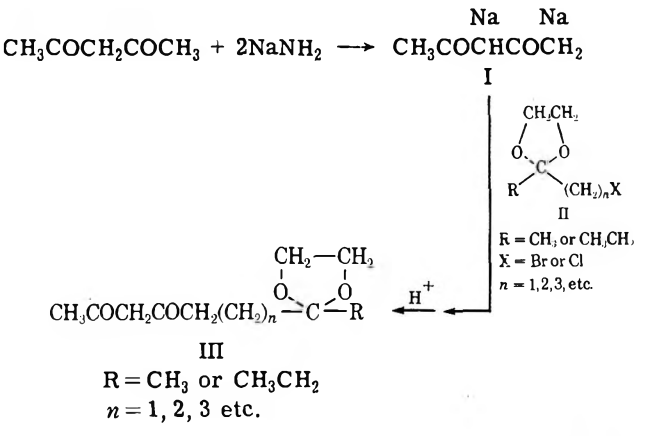
TABLE I

ALKYLATIONS OF DISODIOACETYLACETONE WITH HALO DIOXOLANES

| Reaction | Halo dioxolane | Product | Reaction time, hr | Bp, °C (mm) | Yield, % |
|---|---|---|---|---|---|
| 1 | 2-(Chloromethyl)-2-methyl-1,3-dioxolane | None | 0.5 | | 0 |
| 2 | 2-(Chloromethyl)-2-methyl-1,3-dioxolane | None | 4 | | 0 |
| 3 | 2-(Bromomethyl)-2-methyl-1,3-dioxolane | None | 2 | | 0 |
| 4 | 2-(2-Bromoethyl)-2-methyl-1,3-dioxolane | 8-Ethylenedioxy-2,4-nonanedione | 2 | 68–71 (0.10) | 19 |
| 5 | 2-(3-Chloropropyl)-2-methyl-1,3-dioxolane | 9-Ethylenedioxy-2,4-decanedione | 2 | 97–98 (0.05) | 47 |
| 6 | 2-(3-Chloropropyl)-2-methyl-1,3-dioxolane | 9-Ethylenedioxy-2,4-decanedione | 16 | 101–104 (0.15) | 68[a] |
| 7 | 2-(3-Chloropropyl)-2-methyl-1,3-dioxolane | 9-Ethylenedioxy-2,4-decanedione | 24 | 87–110 (0.09–0.10) | 35 |
| 8 | 2-(3-Bromopropyl)-2-methyl-1,3-dioxolane | 9-Ethylenedioxy-2,4-decanedione | 2 | 96–100 (0.01) | 54 |
| 9 | 2-(3 Chloropropyl)-2-ethyl-1,3-dioxolane | 9-Ethylenedioxy-2,4-undecanedione | 5 | 104–114 (0.15–0.25) | 12 |
| 10 | 2-(3-Chloropropyl)-2-ethyl-1,3-dioxolane | 9-Ethylenedioxy-2,4-undecanedione | 24 | 103–109 (0.05) | 45 |
| 11 | 2-(3-Chloropropyl)-2-ethyl-1,3-dioxolane | 9-Ethylenedioxy-2,4-undecanedione | 72 | 109–120 (0.15) | 58[b] |
| 12 | 2-(4-Bromobutyl)-2-methyl-1,3-dioxolane | 10-Ethylenedioxy-2,4-undecanedione | 24 | 119–123 (0.07–0.08) | 52 |
| 13 | 2-(4-Bromobutyl)-2-ethyl-1,3-dioxolane | 10-Ethylenedioxy-2,4-dodecanedione | 2 | 115–122 (0.08) | 64 |
| 14 | 2-(4-Bromobutyl)-2-ethyl-1,3-dioxolane | 10-Ethylenedioxy-2,4-dodecanedione | 24 | 111–121 (0.12) | 47 |
| 15 | 2-(5-Chloropentyl)-2-methyl-1,3-dioxolane | 11-Ethylenedioxy-2,4-dodecanedione | 2 | 132–138 (0.07) | 28 |
| 16 | 2-(5-Bromopentyl)-2-methyl-1,3-dioxolane | 11-Ethylenedioxy-2,4-dodecanedione | 24 | 115–121 (0.08–0.10) | 47 |
| 17 | 2-(5-Chloropentyl)-2-ethyl-1,3-dioxolane | 11-Ethylenedioxy-2,4-tridecanedione | 2 | 129–132 (0.08) | 30 |
| 18 | 2-(5-Bromopentyl)-2-ethyl-1,3-dioxolane | 11-Ethylenedioxy-2,4-tridecanedione | 2 | 127–132 (0.07) | 66 |
| 19 | 2-(5-Bromopentyl)-2-ethyl-1,3-dioxolane | 11-Ethylenedioxy-2,4-tridecanedione | 24 | 131–134 (0.10) | 55 |

[a] This reaction was run on a 0.25-mol scale; all others were run on a 0.05-mol scale. [b] 2,4,9-Undecanetrione (2.21 g) was filtered from this sample. The remaining 4.38 g was redistilled at 102–106° (0.10 mm) and was shown to be 9-ethylenedioxy-2,4-undecanedione. The combined yield of diketodioxolane and triketone was 58%.

SCHEME I




by an SN2 mechanism.[3] Except for $n = 1$ and $n = 2$ *vs.* the reactions $n = 3$, 4, and 5, there does not appear to be a definite trend in yields with changing $n$.

It was necessary to distill these liquid β-diketone dioxolanes at low pressures (Table I) to avoid decomposition, which could occur even below 140°. In general it was found that reactions stopped after 2 hr had a greater yield than those allowed to react for 24 hr. This may have been caused, in part, by a slow hydrolysis (see footnote *b*, Table I). In those cases where all the other variables were the same except for a different halogen, the yields were better when X = Br than when X = Cl. This does not mean that the bromo compound is always preferable to the chloro compound. Although 9-ethylenedioxy-2,4-decanedione was formed in better yield with a 2-hr reaction time when X = Br rather than Cl, the ease and yield in preparation of 5-chloro-2-pentanone was much better than that of 5-bromo-2-pentanone and, therefore, more than compensates for the difference in yield of the dianion reaction. The difference in yield of 11-ethylenedioxy-2,4-tridecanedione when X = Cl *vs.* X = Br would indicate that in this case the bromo compound is preferable. Comparison of reactions 7 *vs.* 10, 12 *vs.* 14, 15 *vs.* 17, and 16 *vs.* 19 shows no consistent trend when changing R from methyl to ethyl, although in three of the four

(3) The low yield when $n = 2$ may not only be caused by steric hindrance but also may be caused by a competing elimination reaction.

comparisons the yield of R = ethyl is 2 to 10% better than when R = methyl.

The structures of the diketodioxolanes were supported by analogy with previous alkylations of dianions of β-diketones,[2] by elemental analysis (see Table II), by conversion into derivatives which will be discussed below, and by infrared and nmr spectra. For example, the $^1H$ nmr spectrum of 9-ethylenedioxy-2,4-decanedione shows sharp singlets at $\tau$ 8.75, 7.96, 6.25, and 4.34 with relative areas of 3:3:4:1. Similarly, the $^1H$ nmr spectrum of 9-ethylenedioxy-2,4-undecanedione shows sharp singlets at $\tau$ 8.03, 6.20, and 4.50 with relative areas of 3:4:1. In addition there is a triplet (relative area 3) at $\tau$ 9.03. The spectra also show the hydroxylic absorption of the enol forms of these β-diketones at very low field (−6 to −5$\tau$). It is apparent from the ir and nmr data that the carbonyl groups and the dioxolane are both present in the products. In addition it should be noted that the sharp singlet being used as a reference ($\tau$ 7.86) has a relative area of three in each of the spectra. This indicates that alkylation has taken place at the methyl group of acetylacetone rather than at the more acidic methylene group. For the latter to be true it would be necessary for this singlet to have a relative area of six, indicating the presence of two equivalent methyl groups adjacent to the β-diketone.

Table II

Analyses of β-Diketone Dioxolanes

| Registry no. | Compd | | C, % | H, % |
|---|---|---|---|---|
| 34956-71-3 | 8-Ethylenedioxy-2,4-nonanedione ($C_{11}H_{18}O_4$) | Calcd | 61.68 | 8.41 |
| | | Found | 61.92 | 8.46 |
| 34956-72-4 | 9-Ethylenedioxy-2,4-decanedione ($C_{12}H_{20}O_4$) | Calcd | 63.13 | 8.83 |
| | | Found | 63.36 | 9.08 |
| 34956-73-5 | 9-Ethylenedioxy-2,4-undecanedione ($C_{13}H_{22}O_4$) | Calcd | 64.44 | 9.15 |
| | | Found | 64.68 | 9.15 |
| 34956-74-6 | 10-Ethylenedioxy-2,4-undecanedione ($C_{13}H_{22}O_4$) | Calcd | 64.44 | 9.15 |
| | | Found | 64.25 | 9.11 |
| 34956-75-7 | 10-Ethylenedioxy-2,4-dodecanedione ($C_{14}H_{24}O_4$) | Calcd | 65.60 | 9.44 |
| | | Found | 65.38 | 9.53 |
| 34982-06-4 | 11-Ethylenedioxy-2,4-dodecanedione ($C_{14}H_{24}O_4$) | Calcd | 65.60 | 9.44 |
| | | Found | 65.71 | 9.53 |
| 34956-76-8 | 11-Ethylenedioxy-2,4-tridecanedione ($C_{15}H_{26}O_4$) | Calcd | 66.64 | 9.69 |
| | | Found | 66.49 | 9.78 |

Another procedure which is generally used in showing where alkylation occurred on a β-diketone is the formation of copper chelates of the β-diketone.[2] The β-diketone dioxolanes formed a solid copper chelate very slowly if at all. Of the several attempts that were made only two chelated β-diketone dioxolanes (8-ethylenedioxy-2,4-nonanedione and 9-ethylenedioxy-2,4-undecanedione) were isolated. The structure of these was supported by elemental analysis and infrared spectra (see Experimental Section).

Each of the β-diketone dioxolanes was hydrolzyed to its corresponding triketone in an ethanol–water mixture using a drop of concentrated hydrochloric acid to catalyze the reaction. These triketones are low-melting solids with the exception of 2,4,8-nonanetrione, which was observed to freeze slightly below room temperature. This compound was extremely difficult to isolate, since it appears to be much more soluble in ethanol than the other triketones listed in Table III. The structure of each of these triketones was supported by analysis (Table III) and conversion to copper chelates. Unlike the β-diketone dioxolanes the triketones readily formed copper chelates. The melting point, elemental analysis, and infrared spectra data of these are given in Table IV. The two absorption bands in the 6.10–6.60 μ region are consistent with the unsubstituted methylene group of the β-diketone.[4] It should also be noted that there is an absorption band in the 5.8–5.9 μ region, an absorption band attributed to a free carbonyl group. This is what one would expect from such triketones, since only the β-diketone portion of each molecule should be involved in the formation of the copper chelate, thus leaving two free carbonyl groups in each of the chelates. A further study of the chemistry of these β-diketone dioxolanes and triketones is in progress as well as a study of the reactions of acetal halides with dicarbanions of β-diketones.

## Experimental Section[5]

**Halo Ketones and Halo Ketals.**—2-(Chloromethyl)-2-methyl-1,3-dioxolane was formed from chloracetone and ethylene glycol by the procedure of Salmi.[6] 2-(Bromomethyl)-2-methyl-1,3-dioxolane was formed from 2,2-dimethyl-1,3-dioxolane[7] and bromine by the procedure of Field.[8]

2-(2-Hydroxyethyl)-2-methyl-1,3-dioxolane was produced by a modification of the Bouveault–Blanc reaction to the reduction of ethyl acetoacetate ethylene acetal[9] and by the method of Willimann and Schninz.[10] 2-(2 Bromoethyl)-2-methyl-1,3-dioxolane was prepared from 2-(2-hydroxyethyl)-2-methyl-1,3-dioxolane (29 g, 0.22 mol) and phosphorus tribromide (20.8 g, 0.075 mol) in 55% yield, bp 76–77° (11 mm) [lit.[10] bp 76° (11 mm)].

Purchased 5-chloro-2-pentanone decomposed after a short period of time even after being freshly distilled. 5-Chloro-2-pentanone was prepared in 65% yield[11] and 5-bromo-2-pentanone was prepared in 25% yield[11] from 2-acetyl-γ-butyrolactone. 2-(3-Chloropropyl)-2-methyl-1,3-dioxolane and 2-(3-bromopropyl)-2-methyl-1,3-dioxolane were prepared from the corresponding halo ketone by the procedure of Salmi.[6]

II ($n$ = 4 or 5; X = Br or Cl; R = $CH_3$ or $CH_3CH_2$) was prepared by the same procedure starting with cyclopentanone or cyclohexanone. A typical sequence of reactions is given. A 1-l. three-necked flask was equipped with an inlet tube and a pressure-compensating addition funnel. In this flask 24 g (1.0 mol) of magnesium turnings, 111.2 g (1.02 mol) of ethyl bromide, a small crystal of iodine, and 400 ml of anhydrous ether were cooled to −40° in a Dry Ice–acetone bath. Cyclohexanone (98 g, 0.98 mol) was allowed to drip in slowly over a period of about 24 hr while the temperature was maintained between −40 and −20°.[12] When the addition of ketone was complete the reaction mixture

(4) R. P. Dryden and A. Winston, *J. Phys. Chem.*, **62**, 635 (1958).

(5) Melting points were taken on a Thomas-Hoover melting point apparatus in open capillary tubes. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and Chemalytics, Inc., Tempe, Ariz. The infrared spectra were recorded on a Beckman infrared spectrophotometer Model IR-8 and Perkin-Elmer grating infrared spectrophotometer Model 237B using potassium bromide pellets for solids and sodium chloride plates for liquids. The $^1H$ nmr spectra were obtained on a Varian Model A-60 spectrometer. The samples were either neat or dissolved in carbon tetrachloride with tetramethylsilane as the standard.

(6) E. J. Salmi, *Ber.*, **71B**, 1803 (1938).

(7) A. F. Isbell and D. W. Hodd, *J. Chem. Eng. Data*, **7**, 575 (1962).

(8) N. D. Field, *J. Amer. Chem. Soc.*, **83**, 3504 (1961).

(9) L. Palfray and P. Angluret, *C. R. Acad. Sci.*, **244**, 404 (1947).

(10) L. Willimann and H. Schninz, *Helv. Chim. Acta*, **32**, 2152 (1949).

(11) G. W. Cannon, R. C. Ellis, and J. R. Leal, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 597.

(12) D. G. M. Diaper, *Can. J. Chem.*, **33**, 1720 (1955).

TABLE III

TRIKETONES FROM HYDROLYSIS OF β-DIKETONE DIOXOLANES

| Registry no. | Hydrolysis Product | Mp, °C | | C, % | H, % |
|---|---|---|---|---|---|
| 34956-77-9 | 2,4,8-Nonanetrione ($C_9H_{14}O_3$) | *a* | | | |
| 34956-78-0 | 2,4,9-Decanetrione ($C_{10}H_{16}O_3$) | 35–36 | Calcd | 65.19 | 8.75 |
| | | | Found | 65.13 | 8.90 |
| 34956-79-1 | 2,4,9-Undecanetrione ($C_{11}H_{18}O_3$) | 45–46 | Calcd | 66.64 | 9.15 |
| | | | Found | 66.85 | 9.34 |
| 34956-80-4 | 2,4,10-Undecanetrione ($C_{11}H_{18}O_3$) | 42–43.5 | Calcd | 66.64 | 9.15 |
| | | | Found | 66.46 | 9.36 |
| 34956-81-5 | 2,4,10-Dodecanetrione ($C_{12}H_{20}O_3$) | 51–52 | Calcd | 67.89 | 9.50 |
| | | | Found | 67.62 | 9.49 |
| 34956-82-6 | 2,4,11-Dodecanetrione ($C_{12}H_{20}O_3$) | 48–49 | Calcd | 67.89 | 9.50 |
| | | | Found | 67.88 | 9.74 |
| 34956-83-7 | 2,4,11-Tridecanetrione ($C_{13}H_{22}O_3$) | 57–58 | Calcd | 68.99 | 9.80 |
| | | | Found | 68.79 | 9.87 |

[a] The compound was liquid at room temperature. No boiling point or melting point was recorded for this compound, nor was an analysis received.

TABLE IV

COPPER CHELATES OF TRIKETONES. MELTING POINT, ANALYSES, AND INFRARED DATA

| Registry no. | Copper chelate of | Mp, °C | | C, % | H, % | Cu, % | Absorption bands (microns) | | |
|---|---|---|---|---|---|---|---|---|---|
| 34952-73-3 | 2,4,8-Nonanetrione ($C_{18}H_{26}CuO_6$) | 141–142 | *a* | | | | 5.86 | 6.34 | 6.56 |
| 34952-74-4 | 2,4,9-Decanetrione ($C_{20}H_{30}CuO_6$) | 143.5–144 dec | Calcd | 55.86 | 7.03 | 14.78 | 5.86 | 6.35 | 6.56 |
| | | | Found | 55.64 | 6.96 | 14.52 | | | |
| 34952-75-5 | 2,4,9-Undecanetrione ($C_{22}H_{34}CuO_6$) | 146.5–148 dec | Calcd | 57.69 | 7.48 | 13.87 | 5.85 | 6.37 | 6.59 |
| | | | Found | 58.01 | 7.49 | 13.70 | | | |
| 34952-76-6 | 2,4,10-Undecanetrione ($C_{22}H_{34}CuO_6$) | 128.5–129 dec | Calcd | 57.69 | 7.48 | 13.87 | 5.86 | 6.40 | 6.55 |
| | | | Found | 57.77 | 7.71 | 13.88 | | | |
| 34952-77-7 | 2,4,10-Dodecanetrione ($C_{24}H_{38}CuO_6$) | 139.5–140.5 dec | Calcd | 59.30 | 7.88 | 13.07 | 5.84 | 6.40 | 6.56 |
| | | | Found | 58.99 | 7.98 | 13.19 | 5.90 | | |
| 34952-78-8 | 2,4,11-Dodecanetrione ($C_{24}H_{38}CuO_6$) | 139–140 dec | Calcd | 59.30 | 7.88 | 13.07 | 5.86 | 6.36 | 6.56 |
| | | | Found | 59.39 | 7.94 | 13.15 | | | |
| 34952-79-9 | 2,4,11-Tridecanetrione ($C_{26}H_{42}CuO_6$) | 141.5–142 dec | Calcd | 60.74 | 8.23 | 12.36 | 5.86 | 6.36 | 6.57 |
| | | | Found | 60.78 | 8.23 | 12.20 | | | |

[a] No analysis. Copper chelate of diketodioxolane was also prepared. See Experimental Section.

was allowed to warm to room temperature and stirring was continued for an additional 8 hr. The grey slurry of the magnesium salt in ether was slowly poured into a mixture of 300 g of ice and 130 ml of concentrated HCl in an ice bath. The flask was rinsed with water and ether. The aqueous layer was separated from the ether layer and extracted once with 40 ml of ether. The combined ethereal solutions were extracted with 40 ml of water once, 40 ml of saturated sodium bisulfite solution three times, and 40 ml of saturated potassium carbonate solution once. The ether solution was dried over anhydrous $Na_2SO_4$ and filtered, and the ether was removed under vacuum. The residue was distilled to afford 82.4 g (66%), bp 60–61° (7 mm) [lit.[13] bp 61–63° (7 mm)].

To a 1-l. three-necked flask equipped with a sealed stirrer, addition funnel, and condenser were added 700 ml of water, 30 g (0.75 mol) of sodium hydroxide pellets, and 48 g (0.375 mol) of 1-ethylcyclohexanol. The two layers were stirred vigorously for about 5 min before the mixture was cooled in an ice bath. Bromine (80 g) was added to the cold reaction mixture over a 2-hr period. The ice bath was removed and 75 ml of methylene chloride was added to the flask. The two layers were separated and the aqueous layer was extracted twice with 75 ml of methylene chloride. The methylene chloride solution was extracted with 75 ml of saturated $NaHCO_3$ and 75 ml of water. The methylene chloride solution was dried in the dark over anhydrous $MgSO_4$. The solution was filtered and the methylene chloride was removed under reduced pressure. The remaining liquid was allowed to stand at 50–60° for 2 hr in the sunlight. The solution was distilled at reduced pressure. It was necessary to collect the product in a flask which was submerged in a Dry Ice–acetone bath in order to prevent the halo ketone from turning black before it could be used in the next step. This is a modification of the procedure of Englund.[14] This reaction gave 27.4–32.3 g (35–42%) of 8-bromo-3 octanone, bp 74–80° (0.22 mm).

By a modification of the method of Salmi[6] the halo ketal was formed. The halo ketone was removed from the Dry Ice–acetone bath and was allowed to melt directly into dry benzene. The reaction flask was wrapped in order to keep out light. The reaction afforded a 76–89% yield of 2-(5-bromopentyl)-2-ethyl-1,3-dioxolane, bp 78–82° (0.07 mm). This appears to be a new compound.

*Anal.* Calcd for $C_{10}H_{19}BrO_2$: C, 47.82; H, 7.62; Br, 31.82. Found: C, 47.74; H, 7.72; Br, 31.60.

2-(4-Bromobutyl)-2-ethyl-1,3-dioxolane, which was made by the same procedure, appears to be a new compound.

*Anal.* Calcd for $C_9H_{17}BrO_2$: C, 45.58; H, 7.22; Br, 33.70. Found: C, 45.26; H, 7.43; Br, 33.82.

The other compounds prepared by this procedure have been made before. The physical properties we observed are consistent with those published earlier.

**Alkylation of I with Halo Ketals.**—To a solution of I prepared as described previously[2] was added 1 equiv of ketal halide II (see Table I for quantities) in 20 ml of ether over 5 min. After the reaction mixture was allowed to stir (see Table I for reaction times), anhydrous ether was added and the ammonia was allowed to evaporate by warming the reaction mixture with a warm water bath. The ethereal suspension was cooled in ice and a mixture of 50 g of ice and 10 ml of hydrochloric acid was added and stirred for about 0.5 min. Immediately, the two layers were separated and the aqueous layer was extracted with three 25-ml portions of ether. The water layer was checked prior to extraction to be sure that it was slightly acidic. The combined ethereal solution was dried over anhydrous $MgSO_4$ for several hours and filtered. The ether was removed at reduced pressure. The residue was

(13) F. K. Signaigo and P. L. Cramer, *J. Amer. Chem. Soc.*, **55**, 3326 (1933).

(14) B. E. Englund, U. S. Patent 2,675,402 (1954); T. L. Cairns and B. E. Englund, *J. Org. Chem.*, **21**, 140 (1956).

distilled under vacuum. See Table I for boiling points and yields.

**Hydrolysis of Diketodioxolanes. Preparation of Triketones.**—A solution of 5 ml of ethanol and 3 ml of water was used to dissolve approximately 1 g of the desired diketodioxolane. One drop of concentrated hydrochloric acid was added to this solution. The acidic solution was heated to near reflux temperature for 2 hr. At the end of this time the acidic solution was cooled in an ice bath and scratched occasionally with a stirring rod. The solid triketone precipitated within a few minutes in most cases. A few cases required a greater period of scratching. In a few cases it was necessary to remove some of the solvent at reduced pressure and then repeat the above precedure. The solid, flaky white triketone was filtered and then recrystallized from a small amount of ethanol. The resulting triketones were dried overnight at room temperature at about 0.1–0.2 mm.

**Preparation of Copper Chelates.**—A small amount of the β-diketodioxolane was dissolved in a small amount of methanol. A saturated solution of cupric acetate was then added two drops at a time. The glass container was scratched with a stirring rod after each addition of cupric acetate. Once the solid chelate was observed the cupric acetate was added more rapidly with continuous stirring. The chelate was filtered and recrystallized from methanol. It was then dried overnight under vacuum at about 0.1–0.2 mm. In the event that the dry blue chelate contained green spots on the surface, it was shaken vigorously with water for several minutes, filtered, and then redried in the vacuum. In only two cases was a solid precipitate formed from a β-diketodioxolane, and then only after a long period of scratching. The others that were attempted gave oils.

The copper chelate of 9-ethylenedioxy-2,4-undecanedione showed the following results.

*Anal.* Calcd for $C_{26}H_{42}CuO_8$: C, 57.18; H, 7.75 Cu, 11.63. Found: C, 56.99; H, 7.66 Cu, 11.89.

Elemental analysis of the copper chelate of 8-ethylenedioxy-2,4-nonanedione showed the following results.

*Anal.* Calcd for $C_{22}H_{34}CuO_8$: C, 53.92; H, 6.99; Cu, 12.97. Found: C, 53.71; H, 6.94; Cu, 12.80.

The above procedure was repeated for the triketones which readily formed the copper chelates. See Table IV.

**Registry No.**—I, 34956-84-8; II (R = Et, X = Br, $n$ = 5), 34956-85-9; II (R = Et, X = Br, $n$ = 4), 34956-86-0; 8-bromo-3-octanone, 2146-62-5; 9-ethylenedioxy-2,4-undecanedione copper chelate, 34952-80-2; 8-ethylenedioxy-2,4-nonanedione copper chelate, 34952-81-3.

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# Nitration Studies. XVIII. Conversion of Lower Nitroalkanes to Higher Members of the Series

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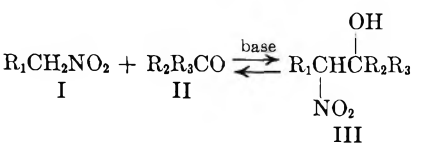
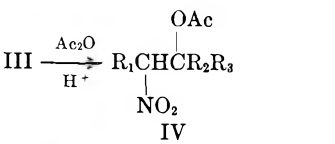
The lower primary nitroalkanes may be converted to higher nitroalkanes by a one pot synthesis involving successive reactions with aldehydes, acylating agents, and sodium borohydride. Overall conversions are in the 75–80% range. Lower aldehydes also give dialkylated products, *e.g.*, 3-nitropentane from nitromethane and acetaldehyde. With ketones isolation of the intermediate nitro alcohol is desirable. The mechanism of the reduction step in particular is discussed.

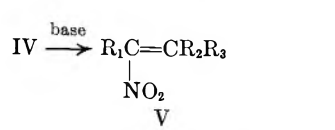
An attractive route for the preparation of higher primary and secondary nitroalkanes involves the condensation of an aldehyde or a ketone with a lower primary nitroalkane followed by acylation, elimination, and reduction of the product (eq 1–4). This process has not proved to be very useful, since published procedures[3] involve isolation of intermediates (III, IV, V), are time consuming (4–5 days) and lead to poor overall yields (14–33%). The low yields result in part from isolation steps and in part from the occurrence of side reactions (eq 5) in the reduction of V leading to 1,3-dinitroalkanes (VII).



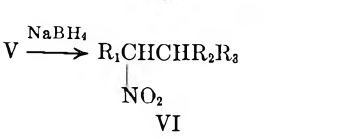
(1)



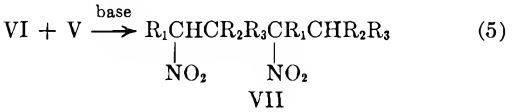
(2)



(3)



(4)



(5)

We wish to report an improved procedure for the processes shown in eq 1–4 which involves no isolation of intermediates. The synthesis is generally performed in one reaction vessel over a 24-hr period and provides VI in high yields (*cf.* Table I) based on I or II. In some cases (ketones) much better results are obtained if the intermediate nitro alcohol is isolated.

Various methods[4a] for the preparation of the higher

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(3) (a) H. Schechter, D. E. Ley, and E. B. Roberson, *J. Amer. Chem. Soc.*, **78**, 4984 (1956); (b) A. I. Meyers and J. C. Sircar, *J. Org. Chem.*, **32**, 4134 (1967).

(4) (a) N. Kornblum, *Org. React.*, **12**, 101 (1962); (b) N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto, and G. E. Graham, *J. Amer. Chem. Soc.*, **78**, 1497 (1956); (c) N. Kornblum and J. W. Powers, *J. Org. Chem.*, **22**, 455 (1957); (d) G. B. Bachman and N. W. Connon, *ibid.*, **34**, 4121 (1969); (e) G. B. Bachman and K. G. Strawn, *ibid.*, **33**, 313 (1968); (f) W. D. Emmons and A. S. Pagano, *J. Amer. Chem. Soc.*, **77**, 4557 (1955); (g) G. B. Bachman and T. F. Biermann, *J. Org. Chem.*, **35**, 4229 (1970).

TABLE I

PREPARATION OF HIGHER NITROALKANES FROM LOWER NITROALKANES AND CARBONYL COMPOUNDS

| Nitroalkane (mol) | Carbonyl compound (mol) | Ratio[a] | Product | % Convn[b,d] A | % Convn[b,d] B | % Convn[b,d] C | % Yield[b] A | % Yield[b] B | % Convn[c] B | % Convn[c] C |
|---|---|---|---|---|---|---|---|---|---|---|
| **A. One-Pot Syntheses from Aldehydes** | | | | | | | | | | |
| Nitromethane | Acetaldehyde | | | | | | | | | |
| (1) | (1) | 0.75 | 1-Nitropropane | 24 | 24 | | 24 | 24 | | |
| | | | 3-Nitropentane | 13 | 26 | | 13 | 26 | | |
| (2) | (1) | 0.75 | 1-Nitropropane | 33 | 66 | | 44 | 66 | | |
| Nitromethane | Propanal | | | | | | | | | |
| (1) | (1) | 0.75 | 1-Nitrobutane | 69 | 69 | | 78 | 69 | | |
| | | | 4-Nitroheptane | 1 | 2 | | 1 | 2 | | |
| (2) | (1) | 0.75 | 1-Nitrobutane | 40 | 80 | | 84 | 80 | | |
| Nitromethane | Pentanal | | | | | | | | | |
| (1) | (1) | 0.55 | 1-Nitrohexane | 78 | 78 | | 87 | 78 | 63 | |
| (2) | (1) | | 1-Nitrohexane | 43 | 85 | | 79 | 85 | 69 | |
| Nitroethane | Pentanal | | | | | | | | | |
| (1) | (1) | 0.55 | 2-Nitroheptane | 57 | 57 | | 63 | 57 | | |
| | | | 2-Nitro-2-heptene | 18 | 18 | | 20 | 18 | | |
| (1) | (1) | 0.70[e] | 2-Nitroheptane | 70 | 70 | | 75 | 70 | 60 | |
| (3) | (2) | 0.70 | 2-Nitroheptane | 48 | 71 | | 68 | 71 | 66 | |
| 1-Nitropropane | Pentanal | | | | | | | | | |
| (1) | (1) | 0.70[e] | 3-Nitrooctane | 70 | 70 | | 79 | 70 | 62 | |
| (2) | (1) | 0.70[e] | 3-Nitrooctane | 34 | 68 | | 75 | 68 | | |
| Nitromethane | 2-Ethylhexanal | | | | | | | | | |
| (1) | (1) | 0.70[e] | 3-Ethyl-1-nitroheptane[f] | 66 | 66 | | 73 | 66 | 53 | |
| (2) | (1) | 0.70[e] | 3-Ethyl-1-nitroheptane[f] | 39 | 78 | | 76 | 78 | 71 | |
| **B. Nitroalkanes from Isolated Nitro Alcohols** | | | | | | | | | | |
| Nitromethane | Propanal | | | | | | | | | |
| (1) | (1) | 0.55 | 1-Nitrobutane | 67 | 67 | 86 | 67 | 67 | | 78 |
| 1-Nitrobutane | Pentanal | | | | | | | | | |
| (1) | (1) | 0.71 | 4-Nitrononane[f] | 52 | 52 | 71 | 52 | 52 | | 61 |
| Nitromethane | Acetone | | | | | | | | | |
| (1) | (4) | 0.75 | 2-Methyl-1-nitropropane | 21 | 5 | 85 | 41 | 5 | | 72 |
| Nitroethane | 2-Ethylhexanal | | | | | | | | | |
| (1) | (1) | 0.81 | 4-Ethyl-2-nitrooctane[f] | 50 | 50 | 78 | 50 | 50 | | 72 |
| Nitromethane | Cyclohexanone | | | | | | | | | |
| (1) | (6) | 0.70 | Cyclohexylnitromethane | 59 | 9 | 88 | 59 | 49 | | 77 |
| Nitromethane | Benzaldehyde | | | | | | | | | |
| (1) | (1) | 0.70 | 2-Phenyl-1-nitroethane | 69 | 69 | 79 | 69 | 69 | | 64 |
| Nitroethane | Benzaldehyde | | | | | | | | | |
| (1) | (1) | 0.70 | 1-Phenyl-2-nitropropane | 40 | 43 | 74 | 40 | 43 | | 61 |

[a] Sodium borohydride–nitroalkyl acetate molar ratio. A 100% conversion to the acetate was assumed. [b] Determined by vpc analysis. [c] Determined by distillation. [d] A, based on starting nitroalkane; B, based on carbonyl compound; C, based on isolated nitroalcohol. [e] Products were contaminated with the aldehyde diacetate and had to be distilled from granular zinc. [f] A new compound. See Experimental Section for physical properties and analytical data.

primary and secondary nitroalkanes have been reported, among which are the reaction of metal nitrites with alkyl halides[4b,c] or nitrates,[4d] the oxidation of amines[4e] and oximes,[4f] and the thermal decomposition of acyl nitrates.[4g] The high conversions observed here along with the simple experimental procedure make this process a valuable addition to these known methods, especially when the starting materials for these other procedures are less readily available.

A key step in the new procedure involves the reduction of nitroalkyl acetates to the corresponding nitroalkane by the action of sodium borohydride in DMSO at 20–25°. Thus addition of 2-nitro-1-butyl acetate (VIII) to sodium borohydride dissolved in DMSO results in an optimum conversion to 2-nitrobutane of 75%. Use of other solvents (ethanol, sulfolane, and DMF) or higher reaction temperatures (40–45°) markedly decreases the conversions.

$$\underset{\underset{NO_2}{|}}{CH_3CH_2CHCH_2OAc} \xrightarrow[DMSO]{NaBH_4} \underset{\underset{NO_2}{|}}{CH_3CH_2CHCH_3} \qquad (6)$$

VIII

In order to avoid isolation steps in this synthesis it was first necessary to find one set of conditions adaptable to all three steps. Since the first step required basic conditions, the second step acidic conditions, and the third step a specific solvent (DMSO), a study of various combinations of reactants, catalysts, and solvents was necessary. Eventually it was found that

nitroalkanes will condense with aldehydes in the presence of about 5 mol % of powdered sodium hydroxide and in the absence of solvent in high yields. This new process avoids the problem of finding a solvent which will dissolve these reactants but which will not react in the next step with the acylating agent. Other bases, such as potassium hydroxide, calcium hydroxide, or tertiary amines, gave no better and usually considerably poorer results. With ketones the corresponding nitro alcohol had to be made and isolated according to published procedures[5] for best results.

Acylation with acetic anhydride is readily accomplished in the second step after addition of a slight excess of sulfuric acid, and is accompanied by the production of 1 equiv of acetic acid. However, addition of a solution of sodium borohydride and DMSO to the crude nitroalkyl acetate–acetic acid solution provides optimum conversions to the corresponding nitroalkane. The reduction is fast (0.5–1 hr), is accompanied by only moderate gas evolution, and provides product nitroalkane in 66–85% conversion based on starting aldehyde.

In the acylation step any unreacted aldehyde from the first step may be converted to aldehyde diacetate, which remains as an impurity in the final product. In some cases, *e.g.*, in the preparation of 3-nitrooctane and 3-ethyl-1-nitroheptane, this impurity is not readily removed by fractional distillation. When this is the case the addition of a small amount of metallic powdered zinc at the beginning of the distillation has been found to remove the impurity.

Table I lists the nitroalkanes prepared by methods A and B along with the yields and conversions based on the various species involved and also the amount of sodium borohydride necessary for optimum conversions. Use of nitromethane and lower aldehydes (*e.g.*, acetaldehyde, propanal) leads to the formation of significant quantities of symmetric dialkylated nitromethanes, probably as a result of the reduction of the diacetates IX, resulting from bis condensation (eq 7).

$$2R_1CHO + CH_3NO_2 \overset{\text{base}}{\rightleftharpoons} (R_1CH)_2CHNO_2 \quad (7)$$

(OH)

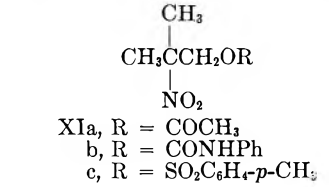
X

$$X \xrightarrow[2.\ NaBH_4,\ DMSO]{1.\ H^+,\ Ac_2O} (R_1CH_2)_2CHNO_2 \quad (8)$$

Since the condensation step is reversible, conversions and yields of product nitroalkane can often be significantly increased by the use of excess starting nitroalkane. Excess aldehyde, however, must be avoided due to the formation of the aldehyde diacetate impurity mentioned above.

Other derivatives of the alcohol group besides the acetate may be employed with no diminution in overall conversion. Thus the *p*-toluenesulfonate or the *N*-phenylcarbamate may be prepared instead of the acetate and reduced satisfactorily to the nitroalkane, but with no apparent advantage in either conversion or convenience.

**Mechanism of the Reduction.**—The reduction of nitroalkyl acetates to nitroalkanes with sodium borohydride apparently requires the presence of a proton on the nitro-bearing carbon atom, since all attempts to reduce nitroacetates without this structural feature failed. Thus the acetate (XIa), *N*-phenylcarbamate (XIb), and *p*-toluenesulfonate (XIc) of 2-methyl-2-nitro-1-propanol were recovered unchanged after prolonged treatment with sodium borohydride. This suggests but does not prove that elimination of acetic acid and formation and subsequent reduction of the



XIa, R = $COCH_3$
b, R = CONHPh
c, R = $SO_2C_6H_4$-*p*-$CH_3$

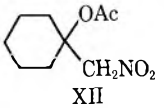
corresponding nitro olefin is the only mechanistic path for this reduction. It is also conceivable that a direct displacement of the acetate group by hydrogen may occur. Consideration of this possibility is suggested by the fact that reductions of nitro acetates IV give considerably better yields of nitroalkanes than reductions of the corresponding nitroalkenes V under identical conditions. This implies either that the nitroalkene is not an intermediate in the reduction or that its rate of reduction is considerably faster than its rate of conversion to other products (eq 5).

We favor the nitro olefin mechanism for three additional reasons.

(1) Inverse addition of the borohydride to the nitro acetate gives poorer yields of nitroalkane than normal addition unless the mixture is buffered with acetic acid. Inverse addition provides higher concentrations of nitronate anion and promotes more Michael addition (eq 5) unless acetic acid is added to buffer the solution.

(2) Nitro olefin intermediates have been isolated from reduction of nitro acetates in which insufficient amounts of sodium borohydride have been used.

(3) The acetate of 1-(nitromethyl)-1-cyclohexanol (XII) is reduced in excellent yield in a short period of time to cyclohexylnitromethane. The acetate group in this case is attached to a tertiary carbon atom and the steric factors involved in the transitions state for an SN2 process replacing this group by hydrogen make



XII

such a process highly unlikely. Carbonium ion formation seems equally unlikely due to the adjacent charge rule and it seems most likely that these reductions are proceeding primarily if not entirely by a nitro olefin mechanism.

## Experimental Section

**General.**—Nmr spectra were obtained with a Varian A-60 spectrometer using tetramethylsilane as internal standard. Ir spectra were recorded on a Perkin-Elmer 137 spectrometer.

Many of the conversions and yields reported in this work were calculated from vpc analysis using the common thermal conductivity correction factor method. An F & M Model 720 dual column temperature programmed gas chromatograph was employed. A 6 ft × 0.25 in. column containing 10% diisodecyl phthalate liquid phase on Chromosorb W DMCS A/W was used

(5) (a) A. Lambert and A. Lowe, *J. Chem. Soc.*, 1517 (1947); (b) L. M. Kozlov, E. E. Fink, and G. B. Liorber, *Tr. Kazan Khim.-Tekhnol. Inst.*, **23**, 148 (1958).

to analyze 1-nitrobutane and 1-nitropropane product solutions. All other products were analyzed on either as 12 ft or a 6 ft × 0.25 in. column containing 10% FFAP liquid phase on Chromosorb W DMCS A/W.

**Materials.**—All solvents and reagents were either of reagent grade or were purified by standard procedures.[6] Sodium borohydride was obtained from Metal Hydrides Co., and assayed according to a published procedure.[7] The method of Sprang and Degering[8] was used to prepare 1-nitro-2-butanol in 75% conversion. Crude 1-nitro-2-phenyl-2-ethanol and crude 1-phenyl-2-nitro-2-propanol were prepared in 88 and 58% conversions, respectively, by the method of Hass.[9] The method of Vanderbilt and Hass[10] was used to prepare 4-ethyl-2-nitro-3-octanol in 64% conversion. 2-Methyl-1-nitro-2-propanol was prepared according to the procedure of Lambert and Lowe[5a] in 48% yield, and the method of Kozlov[5b] was employed to prepare 1-(nitromethyl)-1-cyclohexanol in 67% yield. 2-Nitro-1-butene was prepared according to a published procedure.[11]

**4-Nitro-5-nonanol.**—This new nitro alcohol was prepared by the method of Vanderbilt and Hass[10] in 74% conversion: bp 86–87° (0.3 mm); $n^{20}D$ 1.4472; ir (neat) 2.98 (–CH) and 6.48 μ (–$NO_2$).

*Anal.* Calcd for $C_9H_{19}NO_3$: C, 57.10; H, 10.13; N, 7.41. Found: C, 57.23; H, 9.99; N, 7.60.

**2-Nitro-1-butyl *p*-toluenesulfonate** was prepared by a modification of Riebsomer's procedure.[12] Exactly 11.7 ml (0.1 mol) of 2,6-lutidine was added over 0.5 hr to a solution of 11.91 g (0.1 mol) of 2-nitro-1-butanol (obtained from Commercial Solvents Corp.), 19.0 g (0.1 mol) of *p*-toluenesulfonyl chloride, and 50 ml of diethyl ether cooled to 0–5° by means of an ice bath. The mixture was kept at 0–5° for 3 hr and was allowed to warm to room temperature overnight. The lutidine salt was filtered and washed with ether, and the filtrate was evaporated under reduced pressure to give a yellow solid which was recrystallized three times from isopropyl alcohol to provide 16.02 g (59% conversion) of the tosylate: mp 52–53° (lit.[12] mp 52.5–53°); ir (Nujol) 6.48, 7.38 (–$NO_2$), 8.39 μ (–$SO_3$–); nmr ($CCl_4$) δ 7.50 (m, 4, ArH), 4.30–4.80 (m, 3, –$CHNO_2$ and –$CH_2O_3S$–), 2.47 (s, 3, $ArCH_3$), 1.82 (m, 2, $CH_3CH_2$–), and 0.92 (t, 3, $CH_3CH_2$–).

**Reduction of 2-Nitro-1-butyl *p*-Toluenesulfonate.**—Exactly 1.365 g (0.005 mol) of the above tosylate dissolved in 8 ml of acetonitrile was added over 0.5 hr to a solution of 0.60 g (0.152 mol) of sodium borohydride and 20 ml of ethanol cooled to 0–5° by means of an ice bath. The solution was stirred overnight and was poured into 50 ml of ice and water. The resulting mixture was extracted with four 25-ml portions of ether and the ether solution were combined, dried ($MgSO_4$), and analyzed by vpc. A 68.5% conversion to 2-nitrobutane was observed. The product was identified by its vpc retention time and by comparison of its ir spectrum with that of an authentic sample.

**Reduction of 2-Nitro-1-butyl Acetate.**—Exactly 1.61 g (0.01 mol) of the acetate was added over a 5-min period to a rapidly stirred solution of 0.14 g (0.0035 mol) of sodium borohydride and 20 ml of DMSO. A water bath was used to control the temperature at 20–25° during the addition. Moderate gas evolution was accompanied by a change in the solution from colorless to light yellow. Stirring was continued 1 hr after the addition had been completed and the solution was worked up for vpc analysis exactly as above. A 75% conversion to 2-nitrobutane was observed. The product was identified exactly as above.

**Reverse Addition.**—The above experimental procedure was repeated except that the sodium borohydride solution was added to the acetate. After 1 hr a 52% conversion to 2-nitrobutane was observed.

**Effect of Acetic Acid.**—A solution of 3.22 g (0.02 mol) of 2-nitro-1-butyl acetate and 1.2 g (0.02 mol) of acetic acid was added at 20–25° to 0.55 g (0.014 mol, 97%) of sodium borohydride dissolved in 20 ml of DMSO. The temperature was maintained by means of an ice bath. The reaction was stirred for 1 hr and worked up for vpc analysis as above. The conversion to 2-nitrobutane was 76%. The above procedure was repeated except that a reverse addition of borohydride to acetate was employed. A 77% conversion to 2-nitrobutane was observed.

**Reduction of 2-Nitro-1-butene.**—Exactly 1.01 g (0.01 mol) of 2-nitro-1-butene was added at 20–25° to 0.140 g (0.035 mol, 97%) of sodium borohydride dissolved in 20 ml of DMSO. An ice bath was used to control the temperature. The solution was stirred for 1 hr and worked up for vpc analysis as above. A 10% conversion to 2-nitrobutane was observed. Removal of the ether under reduced pressure left 0.78 g of a heavy, brown oil whose ir spectrum indicated the presence of a nitro group. The nmr ($CDCl_3$) spectrum of the oil was very complex, but again a broad signal at δ 4.48 indicated protons bound to a carbon atom bearing a nitro group. The rest of the spectrum consisted of a broad, unresolved region at δ 3.2–0.9. The oil was probably polymerized nitroolefin.

**Preparation and Reduction of 2-Nitro-1-butyl *N*-Phenylcarbamate in DMSO.**—Phenyl isocyanate (13.09 g, 0.11 mol) was added over 0.75 hr to 11.90 g (0.1 mol) of 2-nitro-1-butanol and 76 ml of DMSO at 18–20°. A change from colorless to green to amber was observed during the addition. Stirring was continued overnight at room temperature and at the end of 20 hr the solution was divided.

**Isolation of the Urethane.**—Exactly one-half of the above solution was poured into 300 ml of ice and water. The yellow solid was collected on a filter, washed thoroughly with water, dried in a desiccator, and recrystallized twice from benzene–pentane to give 8.1 g (71% conversion) of the new urethane: mp 73–74°; ir (Nujol) 3.01 (NH), 5.73 (amide I), 6.19 (amide II), 6.43 μ (–$NO_2$); nmr ($CDCl_3$) δ 7.38 (m, 5, ArH), 7.01 (m, 1, –NH), 4.52 (m, 3, $CH_2O_2C$– and –$CHNO_2$), 1.80 (m, 2, $CH_3CH_2$–), and 0.99 (t, 3, $CH_3CH_2$–).

*Anal.* Calcd for $C_{11}H_{14}N_2O_4$: C, 55.38; H, 5.92; N, 11.76. Found: C, 55.65; H, 5.93; N, 11.67.

**Reduction of the Urethane.**—The other half of the solution was used for the reduction. Aliquots containing theoretically 0.01 mol of the urethan were added at 20–25° to the prescribed amount of sodium borohydride dissolved in 20 ml of DMSO. Work-up, vpc analysis, and product identification were all performed as described earlier for 2-nitrobutane. An optimum conversion of about 50% (based on the nitro alcohol) may be realized using a sodium borohydride:urethane ratio of 0.76:1.50 and a duration of reaction of 0.5–24 hr.

**Preparation of Higher Nitroalkanes from Lower Nitroalkanes and Aldehydes.**—The following general procedure (A) was used. Exactly 0.2 mol of starting nitroalkane and 0.01 mol of catalyst (triethylamine or powdered sodium hydroxide, the latter added slowly and in small portions to the cold nitroalkane) were cooled to 0–5° in an ice bath and 0.2 mole of aldehyde was added with stirring over 0.25 hr at the above temperature. The bath and contents were allowed to warm to room temperature overnight, during which time a change from colorless to light yellow was generally observed. The solution or mixture was cooled again to 0–5° and concentrated sulfuric acid (0.012 mol) was added carefully and in very small portions. The contents of the flask were allowed to warm to room temperature and acylated with 20.4 g (0.2 mol) of acetic anhydride at 30–40°. The temperature was regulated by means of an ice bath. The yellow solution was allowed to stand for 0.5 hr at room temperature and 100 ml of a DMSO solution containing the appropriate amount (see Table I) of sodium borohydride (95–97% purity) was added over 20–30 min at 20–25° with vigorous stirring to control foaming. After 1 hr an aliquot containing theoretically 0.01 mol of product was taken and poured into 75 ml of ice and water. The resulting mixture was extracted with 75 ml of ether and the ether solutions were combined, dried ($MgSO_4$), and analyzed by vpc.

The rest of the solution was poured in small portions into 300 ml of ice and water layered over with 40 ml of ether. The product was extracted with four 40-ml portions of ether and was recovered by distillation after back washing the ether solutions with four 50-ml portions of water and drying ($MgSO_4$).

Physical properties of the nitroalkanes prepared by this method are presented in Table II. Analytical data for the new nitroalkane, 3-ethyl-1-nitrohaptane, will be found in Table III.

**Isolation of a Nitroalkene Intermediate.**—Use of an insufficient amount of sodium borohydride in the preparation of 2-nitro-

(6) D. D. Perrin, W. L. Armarego, and D. R. Perrin, "Purification of Laboratory Chemicals," Pergamon Press, New York, N. Y., 1966, pp 54–285.

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(8) A. Sprang and F. Degering, *J. Amer. Chem. Soc.*, **64**, 1063 (1942).

(9) H. B. Hass, M. B. Neher, and R. T. Blickenstaff, *Ind. Eng. Chem.*, **43**, 2875 (1951).

(10) B. M. Vanderbilt and H. B. Hass, *ibid.*, **44**, 1388 (1952).

(11) H. B. Hass, A. G. Susie, and R. L. Heider, *J. Org. Chem.*, **15**, 8 (1950).

(12) J. L. Riebsomer, *J. Org. Chem.*, **11**, 182 (1946).

TABLE II
PHYSICAL PROPERTIES OF NITROALKANES

| Nitroalkane[a] | Method | Bp, °C (mm) | $n^{20}D$ | Lit. bp, °C (mm) | Lit. $n^{20}D$ | Ref |
|---|---|---|---|---|---|---|
| 4-Nitrononane[b] | B | 55–57 (0.2) | 1.4266 | | | |
| 4-Ethyl-2-nitrooctane[b] | B | 62–64 (0.1) | 1.4336 | | | |
| 2-Methyl-1-nitropropane | B | 63–65 (52) | 1.4050 | 140 (760) | 1.4050 | *c* |
| Cyclohexylnitromethane | B | 48 (1.5) | 1.4632 | 63–64 (3) | 1.4635 | *d* |
| 2-Phenyl-1-nitroethane | B | 74–75 (0.1) | 1.5261 | 126 (14) | 1.5270 | *e* |
| 1-Phenyl-2-nitropropane | B | 67–69 (0.2) | 1.5167 | 96 (2) | 1.5159 | *f* |
| 1-Nitrohexane | A | 80–81 (14) | 1.4212 | 81 (15) | 1.4225 | *g* |
| 2-Nitroheptane | A | 67–70 (1.5) | 1.4236 | 194 (760) | | *h* |
| 3-Nitrooctane | A | 64–65 (0.2) | 1.4240 | 101 (20) | 1.4253 | *i* |
| 3-Ethyl-1-nitroheptane[b] | A | 66–67 (0.1) | 1.4359 | | | |

[a] The ir spectra of all compounds contained strong absorption in the 6.45–6.50 and 7.4–7.5 regions; nmr spectra of all compounds were consistent with their structures. [b] A new nitroalkane. [c] H. B. Hass, E. B. Hodge, and B. M. Vanderbilt, *Ind. Eng. Chem.*, **28**, 341 (1936). [d] R. W. Rimmer, Ph.D. Thesis, Purdue University, 1953. [e] S. Kaneo, *J. Pharm. Soc. Jap.*, **58**, 256 (1938). [f] N. Kornblum, J. E. Ungnade, A. M. White, B. Taub, and S. A. Herbert, *J. Amer. Chem. Soc.*, **77**, 5528 (1951). [g] A. I. Vogel, *J. Chem. Soc.*, 1847 (1948). [h] F. Beilstein, *Ber.*, **13**, 2028 (1880). [i] F. Asinger, G. Geiseler, and M. Hoppe, *ibid.*, **90**, 115 (1954).

TABLE III
ANALYSES OF NEW NITROALKANES

| | Calcd, % | | | Found, % | | |
|---|---|---|---|---|---|---|
| Nitroalkane | C | H | N | C | H | N |
| 4-Nitrononane | 62.34 | 11.08 | 8.09 | 62.55 | 11.10 | 7.95 |
| 3-Ethyl-1-nitroheptane | 62.34 | 11.08 | 8.09 | 62.29 | 11.00 | 8.21 |
| 4-Ethyl-2-nitrooctane | 64.13 | 11.30 | 7.48 | 64.33 | 11.34 | 7.55 |

heptane led to an 18% conversion to 2-nitro-2-heptene: ir (neat) 6.01 (C=C), 6.59, 7.47 $\mu$ ($-NO_2$); nmr ($CDCl_3$) $\delta$ 7.19 (t, 1, $-CH=CNO_2$), 2.5–2.0 (s and m, 5, $CH_3CNO_2=$ and $-CH_2-CH=$), 1.40 [m, 4, $-(CH_2)_2-$], and 0.90 (m, 3, $CH_3CH_2-$).

**Isolation of an Aldehyde Diacetate.**—In the preparation of 3-nitrooctane, pentanal diacetate was isolated as an impurity from the distilled product: ir (neat) 5.69 (C=O), 8.04 $\mu$ (CO); nmr ($CDCl_3$) $\delta$ 6.78 [t, 1, $-CH(OAc)_2$], 2.08 (s, 6, $CH_3-CO-$), and 1.8–0.9 (m, 9, aliphatic protons).

**Preparation of Nitroalkanes from Isolated Nitro Alcohols.**—The following general procedure (B) was used. Exactly 20.4 g (0.2 mol) of acetic anhydride was added to a solution of 0.2 mol of the nitro alcohol and 5 drops of concentrated sulfuric acid contained in a 300-ml Morton flask equipped with an overhead stirrer. The temperature was regulated at 30–40° by means of an ice bath. The solution was allowed to stand for 0.5 hr at room temperature and 100 ml of a DMSO solution containing the appropriate amount of sodium borohydride (95–67% purity) was added over a 0.5-hr period at 20–25° with vigorous stirring. After 1 hr an aliquot containing theoretically 0.01 mol of product was taken and worked up for vpc analysis as in A.

The rest of the solution was worked up and distilled as reported in A. The new nitroalkanes prepared by this procedure are 4-nitrononane and 4-ethyl-2-nitrooctane, and the analytical data for these compounds are to be found in Table III. Physical properties of these compounds are presented in Table II.

**Registry No.**—3-Ethyl-1-nitroheptane, 34566-10-4; 4-nitrononane, 34566-11-5; 4-ethyl-2-nitrooctane, 34566-12-6; 4-nitro-5-nonanol, 34566-13-7; 2-nitro-1-butyl *N*-phenylcarbamate, 6526-60-9.

# The Conformational Effect of the Spiro Linkage between Three- and Six-Membered Rings

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The conformational properties of a six-membered ring linked in a spiro fashion to a three-membered ring are examined in spiro[2.5]octane (**1**), dispiro[2.2.2.2]decane (**2**), and 6-methylenespiro[2.5]octane (**3**). In contrast to the *exo*-methylene group, the spirocyclopropyl substituent has little effect on the barrier to ring reversal, and brings about only a slight flattening of the ring. It is concluded that the spiro linkage alters the hybridization of the orbitals of the quaternary carbon in comparison to those in unsubstituted cyclopropane. The free energies of activation to ring reversal were found to be 10.5 kcal/mol for **1**, 10.9 for **2**, and 8.7 for **3**. A complete line-shape analysis for the spectral changes of **2** gave $E_a$ = 12.1 kcal/mol and log $A$ = 13.8. The $R$ values for **2** and **3** were measured to be 2.01 and 1.73, respectively.

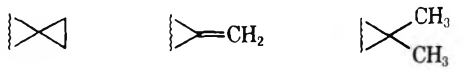
Both the static and the dynamic conformational properties of a six-membered ring are considerably altered by the introduction of an *exo*-methylene or oxo grouping. The substituted carbon atom becomes nearly $sp^2$ hybridized, so that the valence angle within the ring is expanded over that in cyclohexane. A structural alteration of this type gives rise to a flattening distortion in the ring[2] and a diminished barrier to ring reversal.[3] The magnitude of the directly bonded $^{13}C-H$ coupling constant indicates that the hybridization of orbitals emanating from a cyclopropyl ring is similar to that from an ethylenic source. We therefore wished to investigate the effect of a spiro linkage between a six- and a three-membered ring on the shape

(1) (a) This work was supported by the National Science Foundation (Grant GP-22942) and by the Petroleum Research Fund, administered by the American Chemical Society (Grant 2970-AC4,5). (b) NDEA Fellow, 1966–1969; National Science Foundation Trainee, 1969–1970.

(2) J. B. Lambert, *J. Amer. Chem. Soc.*, **89**, 1836 (1967); J. B. Lambert, *Accounts Chem. Res.*, **4**, 87 (1971).

(3) J. T. Gerig and R. A. Rimerman, *J. Amer. Chem. Soc.*, **92**, 1219 (1970); F. R. Jensen and B. H. Beck, *ibid.*, **90**, 1066 (1968).

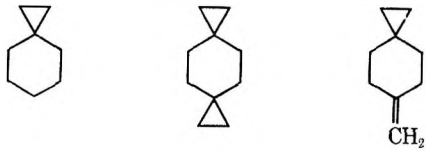
and the barrier to reversal of the larger ring. Three possible results could be imagined. (1) The spirocyclopropyl linkage (A) could give rise to a flattened



A B C

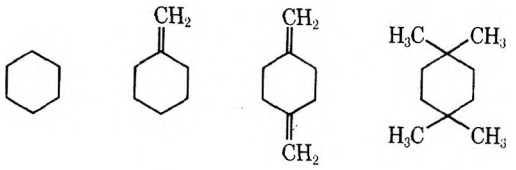
ring and a lower barrier, by analogy with the *exo*-methylene group (B). (2) The spirocyclopropyl linkage could more closely resemble a simple dialkyl substituent (C) and cause almost no observable effect on either. (3) An intermediate situation could transpire.

We selected the series **1–3** in order to examine these



**1** **2** **3**

effects. For comparison with unsubstituted,[4] *gem*-dimethyl-substituted,[2,5] and *exo*-methylene-substituted[2,3,6] systems, we include for discussion literature data on **4–7**. We conclude that the spirocyclopropyl



**4** **5** **6** **7**

group is conformationally more closely related to the *gem*-dimethyl group than to the *exo*-methylene group (case 2 above) and that the hybridization of the quaternary carbon in **1–3** is quite different from that in cyclopropane. The spiro linkage between three- and six-membered rings has previously been considered in a conformational context for certain 1,3-dioxanes,[7] for spiro[2.5]octan-6-ol,[8] and by us for dispiro[2.2.2.2]-decane.[9]

## Results

Spiro[2.5]octane (**1**) is a conformationally unbiased system in which ring reversal occurs rapidly on the nmr time scale at room temperature. The 60-MHz spectrum (Figure 1) consists of a broad singlet (δ 1.6) from the cyclohexyl protons not adjacent to the cyclopropyl group, a broad singlet (δ 1.4) from the protons on the adjacent carbons, and a sharp singlet (δ 0.38, not shown) from the cyclopropyl protons. As the temperature is lowered, the δ 1.4 peak broadens, passes through coalescence at −49°, and emerges as a well-

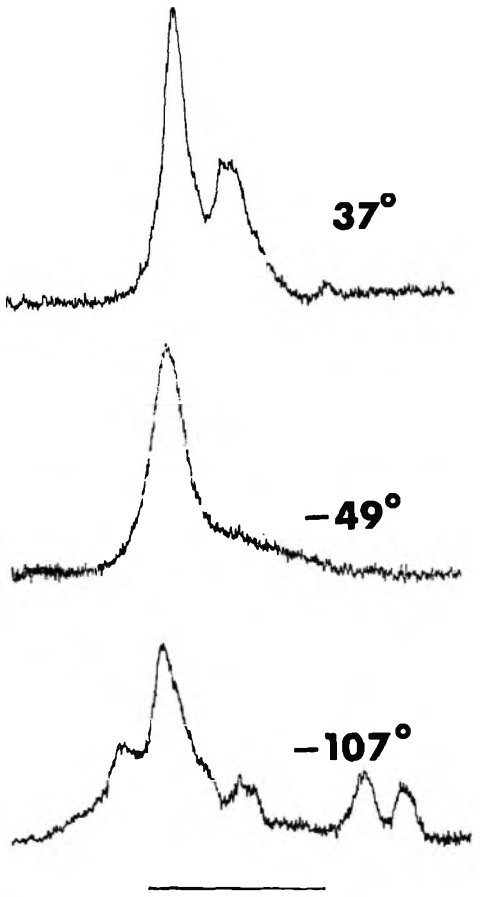



Figure 1.—The 60-MHz proton spectrum of spiro[2.5]octane (**1**) in 1:1 toluene-$d_8$/$CH_2Cl_2$ as a function of temperature. Only the cyclohexyl resonances are shown. The index bar represents 40 Hz.

resolved multiplet at −107°. This multiplet consists of a doublet at high field due to the equatorial protons and further resonances at low field due to the axial protons but obscured by other peaks. The assignment of the high-field resonance is determined from its doublet structure. The equatorial protons next to the spiro linkage, with only one major (geminal) coupling, are expected to give a doublet, whereas the axial protons, with two major couplings (geminal and axial–axial vicinal), should be a triplet. The peak at δ 1.6 also changes with temperature, although less drastically. The cyclopropyl peak broadens only slightly. The spectral changes for the δ 1.4 protons can be treated as a coupled $A_2$-to-AB system, and the free energy of activation for ring reversal is calculated from eq 1 and 2. The chemical-shift difference, determined by dou-

$$k_c = \frac{\pi}{\sqrt{2}}(\Delta\nu_{AB}^2 + 6J_{AB}^2)^{1/2} \quad (1)$$

$$\Delta G_c^{\ddagger} = 2.3RT_c(10.32 + \log T_c/k_c) \quad (2)$$

bling the distance between the room-temperature δ 1.4 peak and the mean of the −107° upfield doublet, was found to be 0.97 ppm, and the coupling constant 11 Hz. Insertion of these figures into eq 1 and 2 gives $\Delta G^{\ddagger}$ = 10.6 kcal/mol at −49°.

The spectrum of dispiro[2.2.2.2]decane (**2**) is composed of two equal-area singlets (δ 0.1 and 1.2). The cyclohexyl resonance (Figure 2) passes through coalescence at about −45° to give an AA′BB′ spectrum

(4) F. A. L. Anet, M. Ahmad, and L. D. Hall, *Proc. Chem. Soc.*, 145 (1964); F. A. Bovey, F. P. Hood, III, E. W. Anderson, and R. L. Kornegay, *J. Chem. Phys.*, **41**, 2041 (1964); E. W. Garbisch, Jr., and M. G. Griffith, *J. Amer. Chem. Soc.*, **90**, 6543 (1968).

(5) H. Friebolin, W. Faisst, H. G. Schmid, and S. Kabuss, *Tetrahedron Lett.*, 1317 (1966).

(6) M. St.-Jacques and M. Bernard, *Can. J. Chem.*, **47**, 2911 (1969).

(7) (a) J. E. Anderson, *Chem. Commun.*, 669 (1969); 417 (1970); (b) J. E. Anderson, *Org. Magn. Resonance*, **3**, 475 (1971).

(8) A. S. Orahovats, V. S. Dimitrov, and S. L. Spassov, *J. Mol. Struct.*, **6**, 405 (1970); R. D. Stolow, T. Groom, and P. D. McMaster, *Tetrahedron Lett.*, 5781 (1968).

(9) J. B. Lambert, J. L. Gosnell, Jr., D. S. Bailey, and L. G. Greifenstein, *Chem. Commun.*, 1004 (1970).

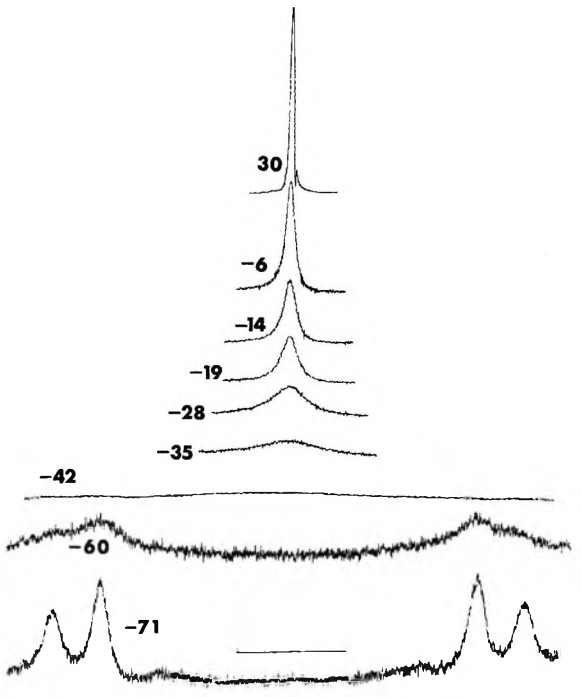



Figure 2.—The 60-MHz proton spectrum of dispiro[2.2.2.2]-decane (2) in toluene-$d_8$ as a function of temperature. Only the cyclohexyl resonances are shown. The index bar represents 20 Hz.

below −70°. The form of the spectral pattern closely resembles an AB quartet ($\Delta\nu$ = 1.21 ppm) because of the particular magnitudes of the coupling constants. Below −100° the cyclopropyl resonance broadens to a poorly resolved multiplet. We have performed a complete line-shape analysis on the spectral changes of the cyclohexyl resonance for each of 25 temperatures (Experimental Section). The following activation parameters were obtained from the Arrhenius plot (correlation coefficient = 0.998): $E_a$ = 12.1 kcal/mol; log $A$ = 13.8; $\Delta H^{\pm}$ = 11.5 kcal/mol; $\Delta S^{\pm}$ = 2.5 eu; $\Delta G^{\pm}$ (−45°) = 10.9 kcal/mol. An identical free energy of activation was calculated at the coalescence temperature by eq 1 and 2. The downfield carbon-13 side band of the cyclohexyl resonances was examined at room temperature for both 60- and 90-MHz spectra. Analysis of the side-band spectrum by usual techniques[2] gave $J_{trans}$ = 7.75 Hz and $J_{cis}$ = 3.85 Hz, for a ratio $R$ of 2.01.

The spectrum of 6-methylenespiro[2.5]octane (**3**) contains a broad singlet at δ 4.7 from the alkenic protons, and AA′BB′ spectrum at δ 2.25 and 1.45 from the cyclohexyl protons, and a sharp singlet at δ 0.4 from the cyclopropyl protons. The lower field half of the AA′BB′ spectrum is attributed to the protons next to the *exo*-methylenic substituent, because of the presence of a long-range coupling. Irradiation of the alkenic protons produces an AA′BB′ spectrum with the required mirror symmetry. Analysis of this pattern gave $J_{trans}$ = 8.04 and $J_{cis}$ = 4.61 Hz for a ratio $R$ of 1.74. As the temperature is lowered, the spectrum of **3** undergoes several changes. The upfield portion of the AA′BB′ spectrum (the methylene protons next to the spiro linkage) coalesces at −93° (60 MHz) and gives a slow-exchange spectrum at −111° that is very similar to the pattern produced by the δ 1.4 peak of **1**: a high-field doublet and a low-field multiplet, separated by 0.98 ppm. Application of eq 1 and 2 to these specific changes gives a free energy of activation at $T_c$ (−93°) of 8.7 kcal/mol.

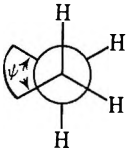
## Discussion

The conformational effects of the spirocyclopropyl group may be discussed in terms of the static property of ring deformation and the dynamic property of barrier size to ring reversal. Table I collects the available

TABLE I
FREE ENERGIES OF ACTIVATION AND DISTORTION PARAMETERS

| Compd | $\Delta G_c^{\pm}$, kcal/mol | $T_c$, °C | $R$ | Ψ, deg | Ref |
|---|---|---|---|---|---|
| 1 | 10.5 | −43 | | | This work |
| 2 | 10.9 | −45 | 2.01 | 57 | This work |
| 3 | 8.7 | −93 | 1.74 | 54 | This work |
| 4 | 10.2 | −67 | 2.16 | 58 | 4 |
| 5 | 8.4 | −100 | 1.83 | 55 | 3 |
| 6 | 7.5 | −118 | 1.42 | 51 | 2, 6 |
| 7 | 11.5 | −53 | 2.05 | 57 | 2, 5 |

data on these subjects for compounds **1**–**7**, *i.e.*, free energies of activation calculated at the coalescence temperature and torsional angles for the $-CH_2CH_2-$ fragment (**8**) calculated from the $R$ values.[2]




**8**

The spirocyclopropyl group, like the *gem*-dimethyl group, conveys almost no distortion to the cyclohexane ring, at most a flattening of about a degree. In contrast, the *exo*-methylene group gives rise to a considerable flattening. Comparison of **2** with **6**, in which the six-membered ring bears either two *exo*-methylene or two spirocyclopropyl groups, reveals a torsional difference of 6°. The compound that contains both the methylene and the spirocyclopropyl groups (**3**) exhibits a flattening ($\psi$ ~54–55°) similar to that in molecules with only the methylene group (**5**). Analogy between the double bond and the cyclopropane ring therefore does not hold up in the conformational sense.

A similar conclusion is reached from consideration of barriers to ring reversal. The barriers for compounds with zero (**4**), one (**1**), and two (**2**) spirocyclopropyl substitutents are 10.2, 10.5, and 10.9 kcal/mol. The corresponding series for molecules possessing exocyclic double bonds (**4**, **5**, **6**) is 10.2, 8.4, and 7.5 kcal/mol. The contrast between the double-bond and the cyclopropyl systems is particularly evident in a comparison of the dimethylene compound with the dispiro compound (**6** and **2**), in which the barriers differ by about 3.4 kcal/mol.

The conclusion from both the ring-deformation and the ring-reversal data is that the spirocyclopropyl group has little conformational effect on the six-membered ring. The spiro linkage must actually change the hybridization of the cyclopropyl orbitals at the quaternary carbon in comparison with those in unsubstituted cyclopropane. The central carbon in spiro[2.2]pentane is $sp^3$ by symmetry, despite its location

in three-membered rings.[10] Although lacking the precise symmetry constraints of spiropentane, the spiro carbon of **1–3** apparently has four orbitals that are all close to $sp^3$, in contrast to those in cyclopropane itself, which contains two $sp^2$ C–H orbitals and two $sp^5$ C–C orbitals.

It is interesting that the barrier to reversal is not an additive function of substitution or of ring deformation. Addition of the first double bond (**4** → **5**) reduces the barrier by about 1.8 kcal/mol, but the second double bond (**5** → **6**) provides an additional decrease of only 0.9 kcal/mol. For the same reason, the barrier for the functionally mixed compound **3** is not midway between those for **2** and **6**. The barrier to ring reversal is primarily a function of the ease of rotation about the bonds within the ring. Steric hindrance and ring deformations, unless extreme, have a less important role. The presence of one exocyclic double bond provides a fragment of the six-membered ring that has a lower torsional barrier than any in cyclohexane. Reversal therefore probably begins with deformation of this portion of the ring. Introduction of the second exocyclic double bond provides an additional site for the same process, rather than for any new torsional operation. The fact that exocyclic double bonds flatten the ring probably does not bear directly on the question of the magnitude of the reversal barrier. Thus, **5** is flattened by about 3° with respect to cyclohexane and has a barrier 1.8 kcal/mol lower, whereas **6** is flattened an additional 4° but has a barrier only another 0.9 kcal/mol lower. Analogously, ring puckering does not raise the barrier to reversal. In the series tetrahydropyran, thiane, selenane, tellurane (**9**, X = O, S,


**9**

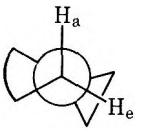
Se, Te) puckering increases significantly but the barrier decreases monotonically.[2,11]

One further aspect of the nmr spectra of **1–3** deserves comment. The chemical-shift difference between the axial and equatorial protons on the carbons adjacent to the spirocyclopropyl group is 0.97, 1.21, and 0.98 ppm, respectively for **1**, **2**, and **3**, greatly enhanced from 0.48 ppm observed for cyclohexane.[4] The doublet pattern observed in each of the spiro cases for the upfield resonance is attributed to the equatorial proton, with only one major coupling, rather than to the axial proton, with two major couplings, as noted already. Because the reverse situation occurs in the spectrum of cyclohexane (axial resonance upfield), the net relative shift must be the sum of the chemical-shift differences observed in **1–3** and that in cyclohexane, or a total of 1.5–1.7 ppm.

(10) R. D. Bertrand, D. M. Grant, E. L. Allred, J. C. Hinshaw, and A. B. Strong, *J. Amer. Chem. Soc.*, **94**, 997 (1972).

(11) J. B. Lambert, R. G. Keske, and D. K. Weary, *ibid.*, **89**, 5921 (1967); unpublished results with D. H. Johnson and C. E. Mixan.

The higher shielding of the axial proton in cyclohexane has been attributed to its location in the shielding region of the anisotropic single bonds elsewhere in the molecule. The reversed and enhanced effect for these spirocyclopropyl systems can be understood by examination of the Newman projection **10**. The equa-




**10**

torial proton is located directly over the shielding region of the highly anisotropic cylopropane ring, and the axial proton is located in the neutral or deshielding zone. The net result is a strong shift of the equatorial protons to higher field. Effects along these lines have been observed previously in related systems.[7b,9,12]

## Experimental Section

Nmr spectra were recorded on Varian Associates T-60 and A-60 spectrometers and the Bruker HFX-90 spectrometer. Line-shape analyses were carried out on the Control Data Corp. 6400 computer equipped with a CalComp plotting accessory. Vapor phase chromatography was performed on the F & M Model 700.

**Spiro[2.5]octane** (**1**) was purchased from Chemical Samples Co., Columbus, Ohio, and used without further purification.

**6-Methylenespiro[2.5]octane** (**3**) **and Dispiro[2.2.2.2]decane** (**2**).—To 7.5 g (0.13 mol based on zinc) of Zn/Cu couple stirred in 300 ml of dry ether was added a mixture of 26 g (0.095 mol) of $CH_2I_2$ in 100 ml of dry ether. After the mixture had refluxed for 1 hr, 5.0 g (0.045 mol) of 1,4-bis-*exo*-methylenecyclohexane (**6**, Chemical Samples Co.) in 200 ml of dry ether was added, and the stirred mixture was refluxed overnight. The cooled mixture was filtered under vacuum and the filtrate was washed with 3 × 50 ml of saturated aqueous $NH_4Cl$, 3 × 50 ml of saturated aqueous $NaHCO_3$, and 3 × 50 ml of saturated aqueous NaCl. A flocculent white precipitate was observed in the combined aqueous washings. The ether solution was dried ($MgSO_4$), filtered, and reduced by distillation to a small volume. Separation of the two products was afforded by preparative vapor phase chromatography utilizing a 6 ft × 0.25 in. column (15% THEED, 3% KOH, Chromosorb W 60/80) at 120° or a 14 ft × 2 in. column (Dow-Corning 550 on Chromosorb P) at 150°. Retention times on the former column were 12, 15, and 18 min for **6**, **3**, and **2**. On the latter column the times were 35, 45, and 55 min, respectively. At the ice–water collection temperature **3** was a liquid and **2** a solid. The collected materials were chromatographically pure. The structures were confirmed by their nmr spectra.

Complete line-shape analysis of the temperature-dependent spectra of **2** (Figure 2) gave the following values for the mean lifetime ($\tau = k^{-1}$): 28.3° (0.000010), 14.3 (0.000032), 9.8 (0.000045), 5.8 (0.000063), −1.0 (0.000081), −4.2 (0.000095), −6.5 (0.000120), −9.3 (0.000140), −12.1 (0.000160), −14.4 (0.00020), −16.7 (0.00032), −19.6 (0.00040), −22.9 (0.00055), −25.7 (0.00073), −28.1 (0.00100), −31.5 (0.00160), −35.8 (0.0023), −43.6 (0.0060), −44.1 (0.0060), −46.5 (0.0065), −47.5 (0.0100), −50.5 (0.0120), −53.5 (0.020), −58.4 (0.026), −61.4 (0.056).

**Registry No.**—**1**, 185-65-9; **2**, 24518-94-3; **3**, 34959-75-6.

(12) J. Tadanier and W. Cole, *J. Org. Chem.*, **27**, 4610 (1962); J. B. Uebel and J. C. Martin, *J. Amer. Chem. Soc.*, **86**, 4618 (1964).

# Protolytic Cleavage of Cyclopropanes. The Two Mechanisms for the Acid-Catalyzed Cleavage of 1-Phenylcyclopropylmethyl Ether[1]

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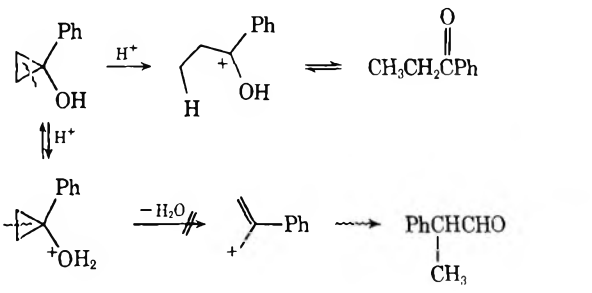
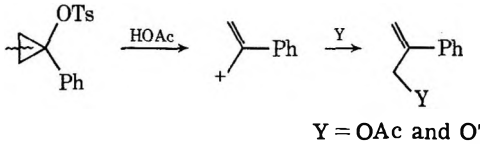
The kinetics of cleavage of 1-phenylcyclopropylmethyl ether (1) in acid solution has been measured as a function of sulfuric acid concentration in 64–75 wt % acid. The ether was found to cleave by two mechanisms: a normal rate-determining protonation of the carbon–carbon bent bond of the cyclopropyl ring leading to propiophenone (2) and a reversible protonation of the ether oxygen followed by the loss of methanol leading to 2-phenylpropionaldehyde (5). It was shown that 2-phenylallyl alcohol (4) is a reasonable intermediate in the reaction which produces 5. The percentages of 2 and 5 formed were a function of acid concentration. A kinetic scheme has been outlined to allow calculation of the rates of formation of 2 and 5 over the acid range studied. The "p$K_a$" of protonated 1 is estimated from the data to be −5.06. The reactivity of 1 is compared to those of other 1-substituted phenylcyclopropanes and the reactivities are discussed in terms of initial-state inductive effects.

Recently there has been a good deal of interest in the chemistry of cyclopropanols both in terms of mechanism of reaction[2] and as intermediates in organochemical synthesis.[3] Cyclopropanols are cleaved in acid solution by a rate-determining protonation at carbon with retention of configuration.[4] The sole product of cleavage of 1-phenylcyclopropanol in acid solution is propiophenone.[4] Thus, proton attack occurs at $C_2$ or $C_3$ and the carbon–carbon bond adjacent to the hydroxyl group is cleaved. Proton attack at oxygen followed by loss of water leading to cleavage of the $C_2$–$C_3$ bond is not observed. Cyclopropyl tosylates[5,6]




undergo solvolytic ring cleavage in acetic acid, producing allyl acetates. The bond cleaved in this case is across the ring from the leaving tosylate group.




Y = OAc and OTs

Although the acid cleavage of cyclopropyl methyl ethers has been used synthetically to prepare quaternary α-methyl compounds,[3] the mechanism of cyclopropyl ether cleavages in general has not been extensively studied. The only mechanistic study reported involves the cleavage of cyclopropyl methyl ethers with mercuric acetate.[7] The cleavage was found by DePuy to be a bimolecular process with the mercury(II) attacking the least substituted ring carbon. The reaction proceeds with inversion of configuration at the site of electrophilic attack.

We have examined the acid-catalyzed cleavage of 1-phenylcyclopropyl methyl ether (1) and we find, in marked contrast to the cleavage of 1-phenylcyclopropanol,[4] that the cyclopropyl ether cleaves by way of two competitive pathways. The first is that operative in the acid-catalyzed ring opening of cyclopropanols[4] and arylcyclopropanes,[8] namely, a rate-determining protonation on carbon. The second involves reversible protonation on oxygen followed by loss of methanol. The acidity of the medium determines which mechanistic pathway predominates.

## Experimental Section[9]

**Preparation of Materials. 1-Phenylcyclopropylmethyl Ether (1).**—This ether was synthesized through Simmons–Smith[10] methylene addition to α-methoxystyrene, which was prepared by elimination of hydrogen iodide from 2-methoxy-2-phenylethyl iodide.[11] Distillation at reduced pressure gave 1: bp 75–77° (12 mm) [lit.[7] bp 50° (2 mm)]; nmr ($CCl_4$) δ 0.92 (m, 2, cyclopropyl), 1.12 (m, 2, cyclopropyl), 3.25 (s, 3, $-OCH_3$), and 7.5 (s, 5, $-C_6H_5$). *Anal.* Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.54; H, 8.30.

**2-Phenyl Allyl Alcohol (4).**—This alcohol was prepared by the oxidation of α-methylstyrene with selenium dioxide[12] in acetic acid–acetic anhydride. The acetate ester obtained was reduced with lithium aluminum hydride and the crude product was distilled, bp 73° (0.25 mm) [lit.[12] bp 116–118° (11 mm)].

**2-Phenylpropionaldehyde (5) and propiophenone (2)** were purchased from Aldrich Chemical Co., Milwaukee, Wis. Both were distilled at reduced pressure before use.

**Product Study.**—To determine the products obtained from the reaction of 1 or 4 with aqueous sulfuric acid, 100–200 mg of the substrate was dissolved in 5 ml of absolute ethanol and the solu-

(1) (a) This work was supported by Grant No. 1259-G1 of the Petroleum Research Fund, administered by the American Chemical Society. (b) Presented in part at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 1971, Abstract ORGN-45.

(2) For a recent review, see C. H. DePuy, *Accounts Chem. Res.*, **1**, 33 (1968).

(3) (a) E. Wenkert, R. A. Mueller, E. J. Reardon, Jr., S. S. Sathe, D. J. Scharf, and G. Tosi, *J. Amer. Chem. Soc.*, **92**, 7428 (1970); (b) E. Wenkert and D. A. Berges, *ibid.*, **89**, 2507 (1967); (c) R. E. Ireland, D. R. Marshall, and J. W. Tilley, *ibid.*, **92**, 4754 (1970).

(4) C. H. DePuy, F. W. Breitbeil, and K. R. DeBruin, *ibid.*, **88**, 3347 (1966).

(5) C. H. DePuy, L. G. Schnack, J. W. Hausser, and W. Wiedemann, *ibid.*, **87**, 4006 (1965).

(6) C. H. DePuy, L. G. Schnack, and J. W. Hausser, *ibid.*, **88**, 3343 (1966).

(7) A. DeBoer and C. H. DePuy, *ibid.*, **92**, 4008 (1970).

(8) M. A. McKinney, S. H. Smith, S. Hempelman, M. M. Gearen, B. V. M., and L. Pearson, *Tetrahedron Lett.*, 3657 (1971).

(9) Boiling points are uncorrected. Microanalyses were performed by Micro-Tech Laboratory, Skokie, Ill. The nuclear magnetic resonance spectra were recorded at 60 Mc with a Varian A-60A spectrometer.

(10) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **81**, 4256 (1959).

(11) S. Winstein and L. L. Ingraham, *ibid.*, **77**, 1738 (1955).

(12) L. Hatch and T. Patton, *ibid.*, **76**, 2705 (1954).

tion was injected by means of a syringe into 1 l. of sulfuric acid of known concentration. The reaction mixture was stirred for 5–7 half-lives reaction and poured into 2 l. of ice–water, and the resulting solution was extracted with three portions of ether. The combined ether extracts were washed with saturated sodium bicarbonate solution to neutrality, dried over sodium sulfate, and concentrated. The concentrated product mixture was analyzed by glc.[13] The concentrated reaction mixture obtained from 1 in sulfuric acid showed two peaks in the chromatogram. These were identified as 2 and 5 by comparison of the retention time and nmr spectra of collected samples with those of authentic samples.

Only a single product was obtained in the analysis of the concentrated reaction mixture from 4 in sulfuric acid. It was identified as 5 by comparison of retention time and nmr spectra with those of an authentic sample.

**Kinetic Procedure.**—For the ring opening of 1 in sulfuric acid, the rates of the reaction were determined by observing the increase in optical density at the absorption maximum of 2 or protonated 2 at 255 or 285 nm, respectively. The ultraviolet spectrophotometer[14] was set at a fixed wavelength and optical density *vs.* time curves were recorded. For the rearrangement of 4 in sulfuric acid, the disappearance of 4 was followed at 238 nm.

The kinetic runs were initiated by injecting 50 $\mu$l of a stock solution (*ca.* $1 \times 10^{-3}$ *M*) of substrate in absolute ethanol into 30 ml of acid solution contained in a 10-cm spectrophotometric cell. Prior to injection, the acid solution was allowed to equilibrate to the constant temperature maintained in the cell compartment. The rate of increase or decrease in optical density was recorded for at least ten half-lives reaction, after which a product spectrum was taken from 400 to 210 nm. From the product spectrum at different acid concentrations, the extent of reaction was calculated. Pseudo-first-order rate constants were obtained as the slope of a plot of $\ln (A_\infty - A)$ *vs.* time.

The acid solutions used were prepared from reagent grade concentrated sulfuric acid and distilled water. The weight per cent sulfuric acid was determined by titration of a weighed sample of acid solution with standard sodium hydroxide solution.

## Results

In terms of acid catalysis there are two mechanisms by which a cyclopropyl ether can react. The first is the mechanism by which cyclopropanols cleave,[2] namely, a rate-determining protonation of the carbon–carbon bent bond of the cyclopropane ring. Such a mechanism of cleavage for 1-phenylcyclopropylmethyl ether is shown below (eq 1–4).

The second mechanism involves the reversible protonation of the ether oxygen followed by a rate determining loss of methanol leading to products (eq 5–9).

The two mechanistic pathways are distinguishable because each leads to a different product.

The cyclopropyl ether 1 was found to cleave in 65–75 wt % sulfuric acid, yielding propiophenone (2) and 2-phenylpropionaldehyde (5). The rate of appearance of 2 was followed spectrophotometrically and the relative composition of the product mixtures was determined from the relation

$$\frac{[2]}{[5]} = \frac{\epsilon_{\text{mixture}} - \epsilon_5}{\epsilon_2 - \epsilon_{\text{mixture}}}$$

where $\epsilon_{\text{mixture}}$ is the molar extinction coefficient of the product mixture, and $\epsilon_2$ and $\epsilon_5$ are the molar extinction coefficients for the pure compounds in the appropriate acid at a fixed wavelength. The reaction product composition was also determined by glc analysis of the product mixtures isolated from the appropriate acid. The product compositions and the observed pseudo-first-order rate constants for the appearance of 2, as a function of acid concentration, are given in Table I.

The proposed intermediate in the formation of 5, 2-phenylallyl alcohol (4), was found to be converted to 5 at a conveniently measurable rate in 37–50 wt % sulfuric acid. The rate of disappearance of 4 as a func-

(13) Vapor phase analyses were made with a Hewlett-Packard F & M Scientific 700 laboratory chromatograph equipped with a thermal conductivity detector and a Leeds and Northrup nonintegrating recorder. A 6 ft × 0.25 in. aluminum column packed with 20% SE-30 on 80–100 mesh Chromosorb W was used.

(14) Ultraviolet spectra were recorded on a Cary Model 14 recording spectrophotometer equipped with a constant-temperature cell compartment regulated by a Precision Scientific Co. constant temperature and circulating bath with a Philadelphia microset thermoregulator.

Table I

Product Composition and Observed Rate of Cleavage of 1-Phenylcyclopropylmethyl Ether (1) in Sulfuric Acid at 25°

| Wt % $H_2SO_4$ | $-H_0$ | Ketone Uv[a] | Ketone Glc[a] | $10^4 k_{obsd}$, $sec^{-1}$ [b] |
|---|---|---|---|---|
| 64.19 | 4.96 | 92.0 | 96.5 | 1.31 |
| 67.16 | 5.37 | 89.0 | | 2.11 |
| 70.86 | 5.93 | 87.0 | 90.0 | 3.83 |
| 73.45 | 6.32 | 75.4 | 79.0 | 6.86 |
| 74.00 | 6.40 | 72.0 | 73.0 | 8.31 |
| 75.95 | 6.70 | 60.0 | 63.0 | 11.3 |

[a] The percentage listed is for propiophenone. The balance of product is 2-phenylpropionaldehyde. [b] The rate constants given are the average of at least two determinations; the initial concentration of 1 in all the kinetic runs was $8.5 \times 10^{-6}$ M.

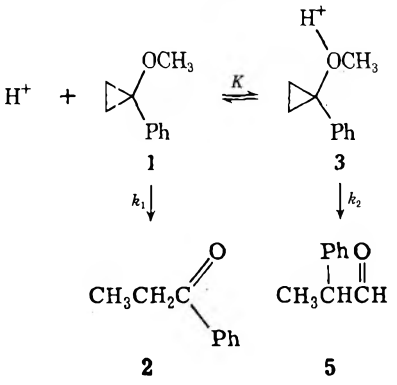
tion of acid concentration was measured spectrophotometrically and the data are given in Table II. Extrapolation of the linear log $k$ *vs.* $-H_0$ plot[15] for reaction of **4** to higher acid concentrations allows a calculation of the expected half-life for reaction of **4** in 64.19% sulfuric acid. At this acid concentration, the weakest acid used in the cleavage of **1**, the half-life for the rearrangement of **4** to **5** would be $8.4 \times 10^{-4}$ sec. Thus, **4** is a reasonable intermediate in the formation of **5** from **3**.

Table II

Rates of Rearrangement of 2-Phenylallyl Alcohol (4) in Sulfuric Acid at 25°

| Wt % $H_2SO_4$ | $-H_0$ | $10^3 k_{obsd}$, $sec^{-1}$ |
|---|---|---|
| 36.97 | 2.21 | 0.383 |
| 38.50 | 2.32 | 0.472 |
| 41.90 | 2.56 | 1.00 |
| 45.28 | 2.88 | 1.94 |
| 47.81 | 3.14 | 3.48 |
| 48.74 | 3.24 | 4.10 |
| 50.46 | 3.42 | 6.29 |

The acid cleavage of 1-phenylcyclopropylmethyl ether (1) therefore proceeds according to the scheme shown in eq 10.




(10)

Here $k_1$ is the pseudo-first-order rate constant for Se2 cleavage of **1**, $k_2$ is the first-order rate constant for the solvolytic cleavage of **3**, and $K$ is the ratio of **3**:**1** at a given acid concentration. The three differential equations which can be written for the scheme with their solutions are given in ref 16. Using the data of Table I and the equations given below,[16] the following relationships must hold for the cleavage of **1** in 64.19% sulfuric acid. The independent knowledge of $k_1$ or $K$

$$\frac{k_1}{k_2K} = \frac{[2]_\infty}{[5]_\infty} = 16.3 \qquad \frac{k_1}{K+1} = k_{obsd}[2]_\infty = 1.23 \times 10^{-4}\ sec^{-1}$$

would allow calculation of the other two variables. Although $k_1$ and $K$ cannot be measured independently, $k_1$ can be estimated. The lower limit for $k_1$ is $1.2 \times 10^{-4}$ $sec^{-1}$. A value smaller than this would make $K$ negative. It has been observed by DePuy[7] that cyclopropanols are cleaved by mercuric acetate 10–20 times faster than their methyl ether derivatives when an Se2 mechanism of cleavage is operative. If a rate ratio of 10 is assumed for the relative rate of cleavage of 1-phenylcyclopropanol[17] to **1** in 64.19% sulfuric acid, a value of $2.3 \times 10^{-4}$ $sec^{-1}$ is obtained for $k_1$. At this acid concentration the cyclopropyl ether is cleaved in an Se2 fashion to the extent of 94% (see Table I). The values of $K$ and $k_2$ thus obtained are 0.84 and $1.64 \times 10^{-5}$ $sec^{-1}$, respectively. If the acidity dependence of protonation of **1** is assumed to be similar to the methyl ethers studied by Arnett,[18] a value of −5.06 is obtained for the "p$K_a$" of **3**. The p$K_a$'s of the methyl ethers studied by Arnett correlated with Taft's substituent parameters,[19] $\sigma^*$, indicating that inductive effects are of major importance in determining the acidity of these oxonium ions. If the correlation is used to calculate the "p$K_a$" of **3**, a value of −5.89 is obtained.[20] The knowledge of the "p$K_a$" of **3** allows a calculation of $k_1$, $k_2$, and $K$ for all the acid concentrations studied. These values are compiled in Table III.

Table III

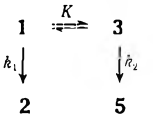
Calculated Values of $k_1$, $k_2$, and $K$

| Wt % $H_2SO_4$ | $K$[a] | $10^4 k_1$, $sec^{-1}$ | $10^4 k_2$, $sec^{-1}$ |
|---|---|---|---|
| 64.19 | 0.84 | 2.26 | 0.164 |
| 67.16 | 1.80 | 5.26 | 0.340 |
| 70.86 | 5.20 | 20.9 | 0.525 |
| 73.45 | 10.76 | 62.1 | 1.71 |
| 74.00 | 12.6 | 82.2 | 2.89 |
| 75.95 | 21.9 | 152.0 | 4.35 |

[a] A plot of log $K$ *vs.* $-H_0$ was used to calculate $K$. A slope of 0.83 was assumed. This slope is the average of the slopes observed for the seven methyl ethers studied by Arnett, ref 18.

(15) The rate data fit the relation $\log k = -1.00H_0 - 5.62$.

(16) The three differential equations which can be written for the scheme




are $d[2]/dt = k_1[1]$, $d[5]/dt = k_2[3]$, and $-d[E]/dt = d[2]/dt + d[5]/dt$, where $[E] = [1] + [3]$. These equations may be solved to give $[2]_\infty = \frac{k_1[E]_0}{k_1 + Kk_2}$, $[5]_\infty = \frac{Kk_2[E]_0}{k_1 + Kk_2}$, and $k_{obsd} = \frac{k_1 + k_2K}{K+1}$, where $[2]_\infty$ and $[5]_\infty$ are the concentrations of **2** and **5**, respectively, after 10 half-lives reaction, $[E]_0$ is the initial concentration of **1** (assuming that there is no **3** present at $t = 0$), and $k_{obsd}$ is the pseudo-first-order rate constant for the appearance of **2**.

(17) M. A. McKinney, Ph.D. Thesis, Illinois Institute of Technology, 1967.

(18) E. M. Arnett and C. Y. Wu, *J. Amer. Chem. Soc.*, **84**, 1680 (1962).

(19) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 619.

(20) The correlation equation for the methyl ethers is "p$K_a$" $= -3.90 - 3.33\Sigma\sigma^*$. A $\sigma^*$ of 0.60 was used for Ph and a $\sigma^*$ of 0.0 for cyclopropyl.

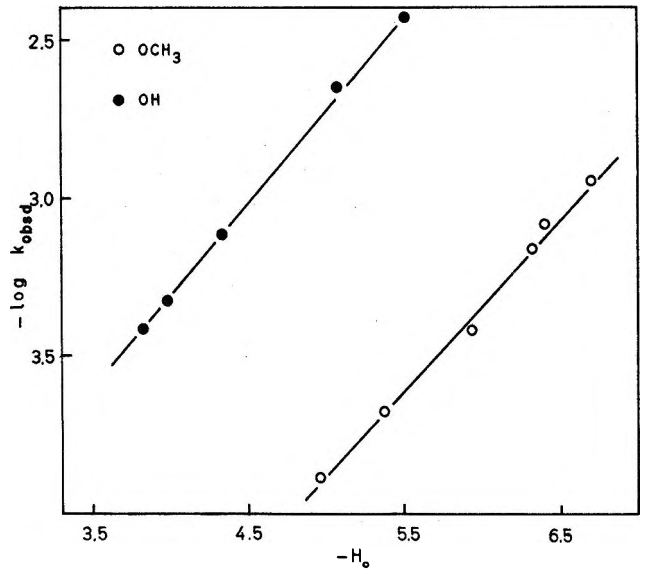
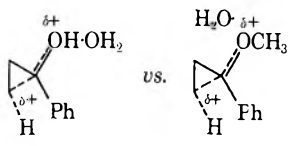



Figure 1.—The relationship between $H_0$ and log $k_{obsd}$ for 1-phenylcyclopropylmethyl ether and 1-phenylcyclopropanol.

## Discussion

**Acidity Dependence.**—The data of Tables II and III allow a comparison of the kinetic acidity dependence of the cleavage rates of 1-phenylcyclopropylmethyl ether (**1**) and 1-phenylcyclopropanol (**6**)[17] in sulfuric acid solution. The comparisons are shown graphically in Figures 1 and 2. The observed rate of cleavage of **1** shows a linear relationship between log $k_{obsd}$ and $-H_0$ with a slope of 0.58 and the rates of cleavage of **6** exhibit a similar linear relationship with a slope of 0.59 (Figure 1). However, when account is made of the two distinct paths of cleavage of **1**, and the relationship between log $k_1$ and $-H_0$ is determined, a linear relationship with a slope of 1.11 is obtained (Figure 2).

This diverse acidity dependence behavior is nevertheless consistent with a single reaction mechanism when account is made of the solvation interactions present in the transition states for the two reactions. The transition state for cleavage of **6** can form a hydrogen bond with the solvent, whereas the corresponding transition state for the normal cleavage of **1** can only interact with the solvent electrostatically. These interactions are shown below.




As the water activity of sulfuric acid solutions decreases with increasing acid concentration, the water available for solvation is decreased. The transition state for the cleavage of **6** is destabilized to a greater extent than the transition state for cleavage of **1** by the water loss and, thus, the cleavage rates for **6** show a less steep acidity dependence than those of **1**. These effects are similar to those proposed to account for differences in protonation behavior between primary, secondary, and tertiary anilines[21] as well as the protonation behavior of phenols and phenol ethers.[22]

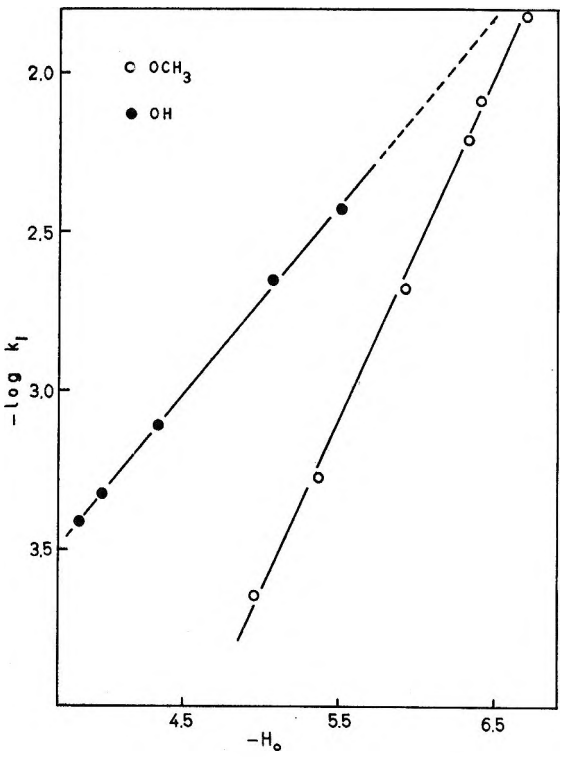



Figure 2.—The relationsnship between $H_0$ and log $k_1$ for 1-phenylcyclopropylmethyl ether and 1-phenylcyclopropanol.

**Structure–Reactivity.**—The data of Table III shows that the normal $C_1$–$C_2$ bond cleavage of **1** proceeds 14 to 40 times faster than the solvolytic $C_2$–$C_3$ bond cleavage of **3**, its protonated form. The solvolysis reaction can effectively compete with the normal cleavage, however, because the protonation equilibrium is shifted toward the oxonium ion in the acid range studied. The proposed dual mechanism of cleavage of **1** is not observed for 1-phenylcyclopropanol, owing to the greater $C_1$–$C_2$ bond cleavage reactivity of the cyclopropanol as well as to its lower basicity.

The cyclopropanol is more reactive than the cyclopropyl ether at relatively dilute sulfuric acid concentrations because of the hydroxyl group's ability to stabilize a carbonium ion center relative to a methoxyl group. Thus, phenol is brominated in acetic acid 90 times faster than anisole.[23] As seen in Figure 2, the reactivity order is reversed in more concentrated acid owing to the solvation effects noted above.

The kinetic data reported herein, and the data for cyclopropane[24] and the substituted phenylcyclopropanes reported previously,[8] allow a quantitative evaluation of the effect of substituents on the rate of ring cleavage. The pertinent data are summarized in Table IV. The data show that substitution of phenyl on a cyclopropane ring results in an almost eightfold rate *deceleration*. This is in contrast to the analogous hydration of olefins, where the substitution of phenyl at the 2 position of propene leads to a rate acceleration of 5000.[25] It therefore appears that the electron-with-

(21) R. W. Taft Jr., *J. Amer. Chem. Soc.*, **82**, 2965 (1960); E. M. Arnett and G. W. Mack, *ibid.*, **86**, 2671 (1964); **88**, 1177 (1966).

(22) A. J. Kresge, H. J. Chen, L. E. Hakka, and J. E. Kouba, *ibid.*, **93**, 6174 (1971), and references cited therein.

(23) P. B. D. de la Mare, *Tetrahedron*, **5**, 112 (1959).

(24) R. L. Baird and A. A. Aboderin, *J. Amer. Chem. Soc.*, **86**, 252 (1964).

(25) P. B. D. de la Mare and R. Bolton, "Electrophilic Additions to Unsaturated Systems," Elsevier, New York, N. Y., 1965, p 26.

TABLE IV

RATE CONSTANTS FOR THE REACTION OF CYCLOPROPANE AND ITS DERIVATIVES IN SULFURIC ACID ($-H_0$ = 4.1) AT 25°

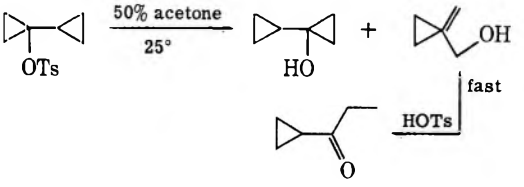
| | $10^3 k_1$, sec$^{-1}$ | $k_{rel}$ | $-d \log k/dH_0$ |
|---|---|---|---|
|  7 | 5.07[a] | 113[d] | ~1.0 |
|  8 | 5.95[b] | 133 | 1.18 |
|  9 | 0.645[b] | 14.5 | 1.25 |
|  6 | 0.551[c] | 12.3 | 0.59 |
|  1 | 0.0447 | 1 | 1.11 |

[a] Calculated from the data in ref 24. [b] See ref 8. [c] This value is taken from ref 17. [d] Corrected for three equivalent sites of cleavage.

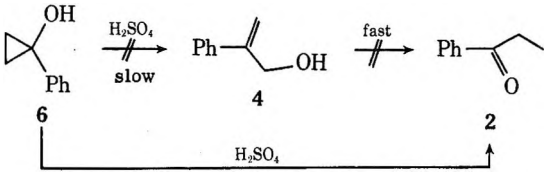
drawing inductive effect of the phenyl group is stabilizing the initial state to a greater extent than the resonance stabilization of the transition state. In the series of phenylcyclopropanes which have a 1 substituent, initial state inductive effects again play a predominant role in controlling reactivity. Thus, 1-methylphenylcyclopropane (**8**) is cleaved 9.2 times faster than phenylcyclopropane (**9**). The introduction of a hydroxyl group or a methoxyl group at C-1 of **9** caused a rate retardation relative to **9** of 0.85 and 0.07, respectively. The effect of substitution on the rate of ring cleavage is relatively independent of acid concentration except for **6**. At a sulfuric acid concentration of 20 wt % ($-H_0$ = 1.0), **6** is $10^3$ times more reactive than **9**. This rate acceleration is similar to the $10^4$ effect observed by DePuy[7] in the mercury(II) acetate cleavage of **6** relative to the similar cleavage of **9** studied by Ouellette.[26] However, 1-phenylcyclopropyl methyl ether does not exhibit such a reversal of reactivity relative to **9** and, thus, remains less reactive than **9** over a wide acid concentration range.

On the basis of the substituent effects discussed above on the reactivity of 1-substituted phenylcyclopropanes and the results reported earlier[8] on the reactivity and site of cleavage of C-1 and C-2 methyl-substituted phenylcyclopropanes, it appears that both initial- and transition-state electronic effects are important in controlling these reactions. The reactivity of the cyclopropane bent bonds toward a proton is determined by initial-state inductive effects of the substituents on the cyclopropane ring. Thus, phenyl, hydroxyl (in relatively concentrated acid), and methoxyl substitution cause a rate retardation while methyl substitution produces a modest rate acceleration. However, the site of cleavage appears to be controlled, at least in part, by the ability of the substituents to stabilize the carbon-bridged intermediates and/or transition states which are produced in these cleavages.[8]

Finally, it was recently found by Jewett[27] that 1-cyclopropylcyclopropyl tosylate hydrolyzes in aqueous acetone to unrearranged alcohol and ethyl cyclopropyl ketone. The latter product was found to arise from a rearrangement of 2-cyclopropylallyl alcohol and not a normal acid-catalyzed cleavage of 1-cyclopropylcyclopropanol as outlined below.




These results suggested that in other homoketonizations of cyclopropanols allylic alcohols may have been undetected intermediates which gave rise to the ketone products observed. Thus, 1-phenylcyclopropanol (**6**)




may cleave, in part, in acid solution by a solvolytic pathway giving 2-phenylallyl alcohol (**4**) as an initial product which then, in a fast step, rearranges to propiophenone (**2**).

That this is not the case if borne out by our results, which show that **4** rearranges to 2-phenylpropionaldehyde (**5**) in the acid range where **6** is cleaved to give **2**. It would therefore appear that the results of Jewett only pertain to the system he was studying and they do not necessitate a revision of the generally accepted mechanism for the homoketonization of cyclopropanols.[2]

**Registry No.**—**1**, 29526-97-4; **4**, 6006-81-1; **6**, 29526-96-3.

(26) R. J. Ouellette, R. D. Robins, and A. South, Jr., *J. Amer. Chem. Soc.*, **90**, 1619 (1968).

(27) B. A. Howell and J. G. Jewett, *ibid.*, **93**, 798 (1971).

# Ring Opening Reactions of Triphenylcyclopropyl Anions. II. An Apparent Disrotatory Opening of a Cyclopropyl Anion[1]

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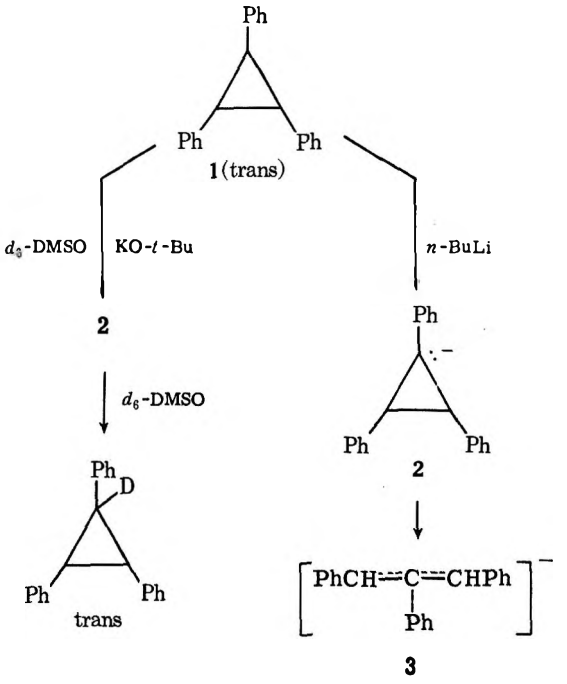
*Received February 16, 1972*

2,3,4-Triphenyl-*endo*-tricyclo[3.2.1.0$^{2,4}$]octane (6) and 2,3,4-triphenyl-*endo*-tricyclo[3.2.1.0$^{2,4}$]-6-octene (7) rearrange to 2,3,4-triphenylbicyclo[3.2.1]-2-octene (8a) and 2,3,4-triphenyltricyclo[3.2.1.0$^{2,7}$]-3-octene (9), respectively, upon treatment with potassium *tert*-butoxide in dimethyl sulfoxide. Although the reactions require the orbital symmetry forbidden disrotatory transformation of a cyclopropyl anion to an allylic anion, it is likely that the opening does not occur in a concerted manner. Evidence is presented that the conjugate base of 7 consists of one or more discrete ions rather than a delocalized bishomocyclopentadienyl anion.

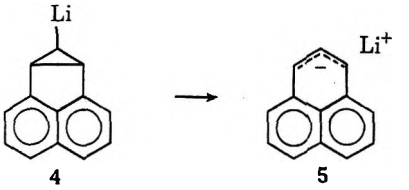
In a preceding paper it was shown that *trans*-1,2,3-triphenylcyclopropane (1) undergoes ring opening upon treatment with organolithium compounds to give the 1,2,3-triphenylallyl carbanion (3). However, when 1



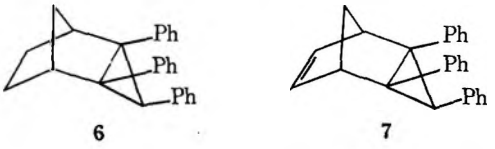

is treated with potassium *tert*-butoxide in $d_6$-dimethyl sulfoxide ($d_6$-DMSO), the cyclopropyl carbanion is intercepted by the solvent before the ring opening occurs.[3]

Because there are stereoisomers of 2 and because 3 undergoes rotational isomerization under the reaction conditions,[3] it was not possible to determine whether the conversion of the cyclopropyl anion 2 to the allylic ion 3 occurs by an orbital symmetry allowed conrotatory process or by the forbidden disrotatory opening.[4]

To our knowledge there are only three examples of the ring opening of a cyclopropyl anion or anionlike intermediate. Huisgen has observed the allowed thermal conrotatory–photochemical disrotatory opening of the isoelectronic aziridine to the azomethine ylide.[5] Boche, Martens, and Danzer have observed a conrotatory thermal opening of a cyclopropyl anion to a cyclononatetraenyl anion;[6] Wittig, Rautenstranch, and Wingler[7] observed the transformation 4 → 5, an apparent disrotatory opening, but this reaction required a temperature of 100° for 24 hr, and the mechanism of the ring opening is not necessarily apparent and could invoke homolytic bond scission.[8]




To determine the stereochemistry of the opening of a triphenylcyclopropyl anion, 2,3,4-triphenyl-*endo*-tricyclo[3.2.1.0$^{2,4}$]octane (6) and 2,3,4-triphenyl-*endo*-tricyclo[3.2.1.0$^{2,4}$]-6-octene (7) were treated with base.




Using potassium *tert*-butoxide in $d_6$-DMSO at room temperature, conditions under which both *cis*- and *trans*-1,2,3-triphenylcyclopropane exchanged cyclo-

(1) Work supported by the National Science Foundation from The University of Arizona Science Development Program.

(2) Recipient of an NSF Traineeship, 1968–1972.

(3) J. E. Mulvaney and D. J. Savage, *J. Org. Chem.*, **36**, 2592 (1971).

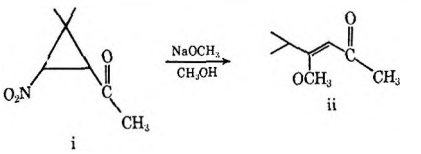
(4) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie, Weinheim, 1970.

(5) R. Huisgen, W. Scheer, and H. Huber, *J. Amer. Chem. Soc.*, **89**, 1753 (1967).

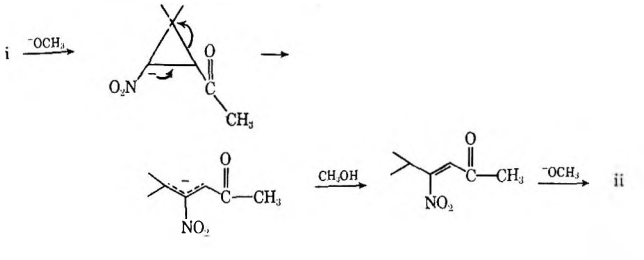
(6) G. Boche, D. Martens, and W. Danzer, *Angew Chem., Int. Ed. Engl.*, **8**, 984 (1969).

(7) G. Wittig, V. Rautenstranch, and F. Wingler, *Tetrahedron, Suppl. No. 7*, 189 (1966).

(8) Another reaction which may involve the opening of a cyclopropyl anion is the conversion of i to ii. Evidence was presented to indicate that

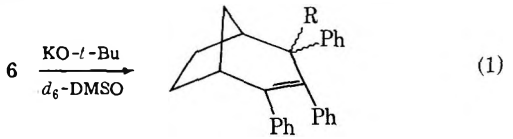



the mechanism was the following.[9]



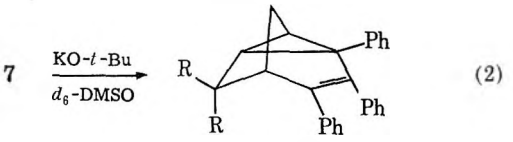

(9) L. I. Smith and V. A. Engelhardt, *J. Amer. Chem. Soc.*, **71**, 2676 (1949).

propyl hydrogens, but did not undergo ring opening,[3] compounds **6** and **7** were recovered with no ring opening or hydrogen exchange. The lack of exchange may be due to a steric effect. However, at 70° after 20 hr both **6** and **7** were essentially completely converted to new compounds, **8** and **9**, respectively.




(1)

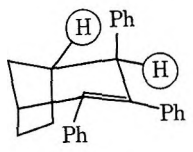
**8a**, R = H
**b**, R = D




(2)

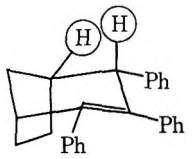
**9a**, R = H
**b**, R = D

Compound **8a**, mp 151–153° was isolated pure in 85% yield and had the expected composition. Although the highly hindered double bond does not react with $Br_2$–$CCl_4$ or $KMnO_4$ *cis*-stilbenyl unsaturation manifested itself in the uv spectrum $\epsilon_{258\ nm}$ 9680. The most significant aspect of the nmr spectrum of **8** is the lowest field signal at $\tau$ 6.25 ($J$ = 2 Hz). This doublet must be due to the proton at C-4, and the low value of the coupling constant is consistent with equatorial–equatorial or equatorial–axial coupling[10] between the proton at C-4 and C-5 (see **8c** and **8d**). The product




**8c**

e–e coupling

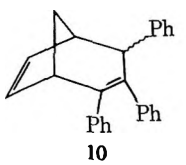



**8d**

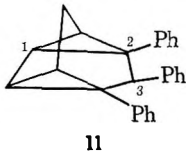
e–a coupling

**8b** obtained when the **6** → **8** conversion was carried out in $d_6$-DMSO contained 0.98 D/molecule and the low field signal at $\tau$ 6.25 was absent.

The nmr of **9** obtained from reaction 2 (mp 157–158°, 75% isolated) shows no olefinic hydrogens in the $\tau$ 4–5 region. Just as in the case of **8** the highly hindered stilbenyl double bond of **9** does not react with permanganate, but in contrast a positive $Br_2$–$CCl_4$ test was obtained. We consider this a manifestation of the vinyl and phenyl conjugated cyclopropyl ring in **9**. These observations rule out the possibility of **10** as the product. Furthermore, the quadricyclane **11** was pre-




**10**

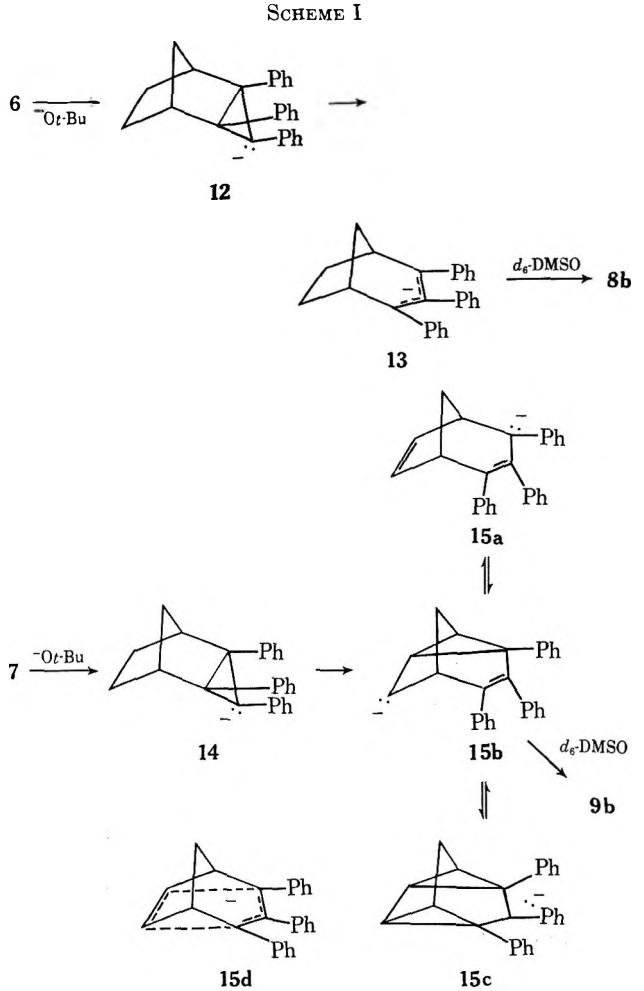



**11**

pared[11] and comparison of physical and spectroscopic properties definitely rules this compound out as the product of reaction 2. Particularly noteworthy is the absence of a low field signal in **9** in the region $\tau$ 5.69 assigned to the benzylic proton at C-3 in **11**. The uv of compound **11** has $\epsilon_{275,224\ nm}$ 750, 21,000, whereas product **9** has $\epsilon_{277\ nm}$ 11,300. A high field multiplet at $\tau$ 8.1 in **9** is consistent with the cyclopropyl hydrogens.[12] When reaction 2 is carried out in $d_6$-DMSO, the product, **9b**, contains 1.50 D/molecule.

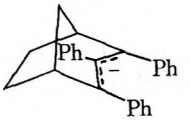
It appears that both products **8** and **9** arise by abstraction of a benzylic cyclopropyl proton from **6** and **7**, respectively, followed by an apparent disrotatory ring opening as shown in Scheme I.

SCHEME I

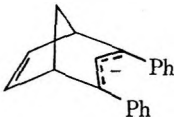



It should be noted that, when reactions 1 and 2 are carried out in the absence of KO-*t*-Bu, the starting materials are recovered unchanged.

A conrotatory opening of anion **12** or **14** would result in the formation of the highly strained *trans*-allylic anions **13a** or **15e** which could rapidly isomerize to **13**




**13a**




**15e**

and **15**, respectively. Although *trans*-cycloheptenone is known[14] as a reactive intermediate, there are no

(10) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967, p 132.

(11) H. Prinzbach and H. D. Martin, *Helv. Chim. Acta*, **51**, 438 (1968).

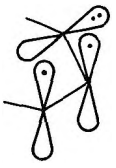
(12) A footnote in a recent paper[13] mentions that Li–$NH_2CH_2CH_2NH_2$-catalyzed conversion of **7** to **9a** at 100°. Details are not given.

(13) W. Eberbach and H. Prinzbach, *Chem. Ber.*, **102**, 4164 (1969).

(14) E. J. Corey, M. Tada R. La Mahieu, and L. Libit, *J. Amer. Chem. Soc.*, **87**, 2051 (1965).

examples of trans olefinic bonds in six-, or less, membered rings and, although **13a** and **15e** cannot be dismissed as possible intermediates, they would be quite extraordinary.

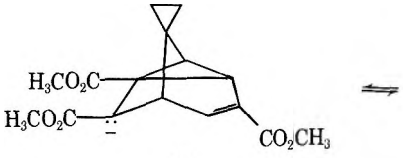
If anion **12** or **14** is opened in a disrotatory mode, this would be an apparent violation of the Woodward–Hoffmann rules.[4] However the concerted nature of the ring opening has not been proven. For example, ring opening could occur to give a nonplanar undelocalized carbanion (but still phenyl delocalized) as indicated in **16**.



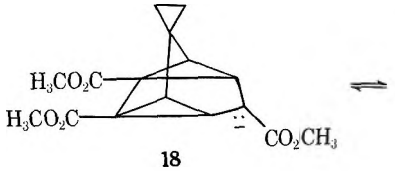
**16**

Anions **15a, b, c** are written as an equilibrium mixture, rather than as a single delocalized bishomocyclopentadienyl anion (**15d**). Although the unphenylated anion corresponding to **15d** has clearly been shown to be delocalized,[15] we observe that, when quadricyclane **11** is treated with KO-*t*-Bu–$d_6$-DMSO, the only product recovered is the monodeuterated (at the 3 position) quadricyclane. If **11** and **7** were to yield a common intermediate, **15d**, the same products would be expected after the prolonged equilibration times in these experiments.

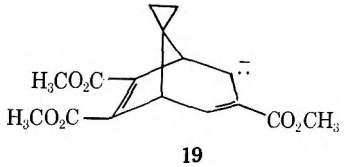
It should be noted that a tricarbomethoxylated derivative of anion **15** has been proposed to exist as an equilibrium mixture of discrete ions **17**–**19**.[13]



**17**



**18**



**19**

The isolation of compound **9** after 20-hr reaction time may indicate that **9** is the most thermodynamically stable of the isomers **9**, **10**, and **11**. There is precedent for this in the case of the unphenylated ion[16] as well as in the case of a tricarbomethoxylated derivative of the anion.[13,17]

(15) (a) J. M. Brown and J. L. Occolowitz, *Chem. Commun.*, 376 (1965); J. M. Brown, *ibid.*, 639 (1967); J. M. Brown and J. L. Occolowitz, *J. Chem. Soc. B*, 411 (1968). (b) S. Winstein, M. Ogharuso M. Sakai and J. M. Nicholson, *J. Amer. Chem. Soc.*, **89**, 3656 (1967).

(16) S. Winstein, *Chem. Soc. Spec. Publ.*, No. 21, 5 (1967).

(17) H. Prinzbach, W. Eberbach, M. Klaus, and G. Veh, *Chem. Ber.*, **101**, 4066 (1968).

A comparison of the rate of reaction of **6** and **7** with KO-*t*-Bu in $d_6$-DMSO is expected to help clarify the nature of the anions derived from these materials.

## Experimental Section

Carbon and hydrogen microanalyses were performed by the Micro-Tech Laboratories, Skokie, Ill., or Huffman Laboratories, Inc., Wheatridge, Colo. Deuterium analyses reported as "deuterium atom per molecule" were calculated from mass spectral data. Deuterium analyses reported in this manner and all other molecular weight data were obtained using a Hitachi Perkin-Elmer RHU-6E mass spectrometer. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Reagent grade dimethyl sulfoxide was refluxed over calcium hydride 1 hr prior to final distillation.

Matheson Coleman and Bell practical grade potassium *tert*-butoxide was used without further purification.

Dimethyl sulfoxide (99.5 atom % deuterium) was obtained from Stohler Isotope Chemicals.

Potassium *tert*-butoxide reactions were run under a nitrogen atmosphere in flame-dried apparatus protected by calcium chloride drying tubes.

**Preparation of 2,3,4-Triphenyl-*endo*-tricyclo[3.2.1.$0^{2,4}$]-6-octene (7).**—The procedure was adopted from a communication by Battiste.[18] A solution of 1,2,3-triphenylcyclopropene (1.0 g, 0.0037 mol) and freshly distilled cyclopentadiene (8.0 g, 0.12 mol) was stirred at room temperature for 16 hr. At the end of this time, the excess diene had evaporated and the remaining white solid was recrystallized twice from 95% ethanol to give 0.80 g (65%) at 2,3,4-triphenyl-*endo*-tricyclo[3.2.1.$0^{2,4}$]-6-octene (**7**) as small white needles, mp 162–164° (lit.[18] mp 160–162°). The nmr spectrum was in complete accord with the literature spectrum.

**Preparation of Dipotassium Diazocarboxylate.**—This compound was prepared in 81% yield by the procedure of Thiele.[19]

**Preparation of 2,3,4-Triphenyl-*endo*-tricyclo[3.2.1.$0^{2,4}$]octane (6).**—The procedure was adopted from a communication by Battiste.[18] To a solution of 2,3,4-triphenyl-*endo*-tricyclo-[3.2.1.$0^{2,4}$]-6-octene (**7**, 1.0 g, 0.0030 mol) in a mixed solvent of dimethoxyethane (30 ml) and methanol (10 ml) were added dipotassium diazocarboxylate (2.0 g, 0.010 mol) and several drops of glacial acetic acid. The solution was stirred at room temperature until all of the diazo compound had been consumed (3 hr). The reaction mixture was diluted with water and extracted with ether. The combined organic layers were dried over sodium sulfate. Removal of the solvent and recrystallization from 95% ethanol gave 0.95 g (95%) of 2,3,4-triphenyl-*endo*-tricyclo-[3.2.1.$0^{2,4}$]octane (**6**) as shiny white plates, mp 151–152° (lit.[18] mp 149–150.5°). The nmr spectrum was in complete accord with the literature spectrum.

**Reaction of 2,3,4-Triphenyl-*endo*-tricyclo[3.2.1.$0^{2,4}$]-6-octene (7) and Potassium *tert*-Butoxide in DMSO.**—Potassium *tert*-butoxide (1.02 g, 0.0092 mol) was added to a solution of 2,3,4-triphenyl-*endo*-tricyclo[3.2.1.$0^{2,4}$]-6 octene (**7**, 0.84 g, 0.0025 mol) in DMSO (12 ml) with stirring under nitrogen. The deep red reaction mixture was stirred at 70° for 20 hr, after which the solution was diluted with water and extracted with ether. The ether layer was dried over sodium sulfate. Removal of the solvent and recrystallization from 95% ethanol afforded 0.63 g (75%) of 2,3,4-triphenyltricyclo[3.2.1.$0^{2,7}$]-3-octene (**9a**), mp 157–158°. The uv spectrum in 95% EtOH had $\lambda_{max}$ 277 nm ($\epsilon$ 11,300). The nmr spectrum ($CDCl_3$) featured the following resonances (peak assignments tentative in some cases): aromatic multiplet centered at $\tau$ 3.1 (15 H); allylic bridgehead proton $C_5$ at 6.9, multiplet; equivalent methylenes at $C_6$ and $C_8$, multiplet centered at 8.1; cyclopropyl hydrogens centered at 8.6. The unsaturation test with bromine was positive while that with permanganate was negative. Vpc analysis (5-ft SE-30, 225°) of the crude reaction mixture and the ether extract showed only the tricyclic product **9a**. It should be noted that it was possible to separate an authentic mixture of 2,3,4-triphenyl-*endo*-tricyclo[3.2.1.$0^{2,4}$]-octene (**7**) and 2,3,4-triphenyltricyclo[3.2.1.$0^{2,7}$]-3-octene (**9**) on this column.

*Anal.* Calcd for $C_{26}H_{22}$: C, 93.42; H, 6.58; mol wt, 334. Found: C, 93.39; H, 6.67; mol wt (mass spectrum), 334.

(18) M. A. Battiste, *Tetrahedron Lett.*, **No. 50**, 3795 (1964).

(19) J. Thiele, *Ann.*, **271**, 127 (1892).

When this reaction was carried out under the same conditions in $d_6$-DMSO, the same product was obtained except that it contained 1.50 D/molecule.

**Reaction of 2,3,4-Triphenyl-*endo*-tricyclo[3.2.1.0$^{2,4}$]octane (6) with Potassium *tert*-Butoxide in DMSO at 70°.**—Potassium *tert*-butoxide (1.00 g, 0.009 mol) was added to a solution of 2,3,4-triphenyl-*endo*-tricyclo[3.2.1.0$^{2,4}$]octane (6, 0.79 g, 0.0023 mol) in DMSO (15 ml) with stirring under nitrogen. The reaction mixture became deep green after a few minutes and the solution was stirred at 70° for 20 hr. The solution was diluted with water and extracted with ether. The ether layer was dried over sodium sulfate. Removal of the solvent and recrystallization from 95% ethanol yielded 0.67 g (85%) of 2,3,4-triphenylbicyclo[3.2.1]-2-octene (**8a**), mp 151–154°. The uv spectrum (95% EtOH) had $\lambda_{max}$ 258 nm ($\epsilon$ 9680). The nmr spectrum ($CDCl_3$) featured the following resonances: aromatic multiplet centered at $\tau$ 3.00 (15 H); benzyl proton at 6.25 (1 H) as a doublet ($J$ = 2 Hz); stilbenyl bridgehead as a multiplet at 7.1 (1 H); the other bridgehead proton at 7.65 (1 H) as a multiplet; a multiplet centered at 8.15 (4 H) assigned to methylene proton anti to the double bond, the two protons of C-7 and the exo proton at C-6; a multiplet at 8.75 (2 H) assigned to the methylene proton syn to the double bond and the endo proton of C-6. Unsaturation tests (bromine and permanganate) were negative.

Glpc analysis (5-ft SE-30, 225°) of the crude reaction mixture and the ether extract showed only the bicyclic product (**8a**). It should be noted that it was possible to separate an authentic mixture of 2,3,4-triphenyl-*endo*-tricyclo[3.2.1.0$^{2,4}$]octane (**6**) and 2,3,4-triphenylbicyclo[3.2.1]-2-octene on this column.

*Anal.* Calcd for $C_{26}H_{24}$: C, 92 85; H, 7.15; mol wt, 336. Found: C, 92.61; H, 7.26; mol wt (mass spectrum), 336.

When the reaction was carried out under the same conditions in $d_6$-DMSO the same product was obtained except that it contained 0.98 D/molecule. The low field signal at $\tau$ 6.25 due to the allylic proton at C-4 was absent.

**Preparation of Triphenylbishomocyclopentadiene (11).**—The procedure was adopted from Prinzbach and Martin.[11] In a sealed tube under nitrogen, 2,3,4-triphenyl-*endo*-tricyclo-[3.2.1.0$^{2,4}$]-6-octene (**7**, 3.0 g, 0.00896 mol) was heated at 190° for 24 hr. The green-black solid was recrystallized three times from 95% ethanol to give 0.9 g (30%) the quadricyclane **11** as white crystals, mp 138–141°. The nmr and uv spectra were in complete accord with the literature spectra.

**Reaction of Triphenylbishomocyclopentadiene (11) with Potassium *tert*-Butoxide in $d_6$-DMSO.**—Potassium *tert*-butoxide (0.63 g, 0.0056 mol) was added to a solution of the quadricyclane **11**, 0.50 g, 0.00149 mol) in $d_6$-DMSO (15 ml) with stirring under nitrogen. The orange-red solution was stirred for 20 hr at 70° after which the solution was diluted with water and extracted with ether. The ether layer was dried over sodium sulfate. Removal of the solvent and recrystallization from 95% ethanol gave 0.45 g (90%) of the quadricyclane **11**, mp 138–141°. The nmr spectrum was identical with that of the starting compound except for the absence of the benzyl proton. A mixture melting point with an authentic sample was not depressed.

*Anal.* Calcd for $C_{26}H_{21}D$: C, 93.13; H, 6.87; mol wt, 335. Found: C, 93.40; H, 6.69; mol wt (mass spectrum), 335; 1.01 deuterium atom per molecule.

**Registry No.**—**6**, 906-84-3; **7**, 906-85-4; **8a**, 34934-84-4; **9a**, 34922-26-4; **11**, 34938-92-6.

# Linear Free-Energy Relationships among Reactions Occurring on the Cyclohexyl Ring. The Bromination of $C_4$-Substituted Cyclohexanones

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*Received June 8, 1970*

The rates and activation parameters in bromination of $C_4$-substituted cyclohexanones under various reaction conditions show very little change with large variation in the nature of the remote substituent. It is shown that these exceedingly small rate effects are to be reconciled with factors inherent in the enolization mechanism of bromination. The effort to apply these rate data in a linear free-energy relationship with corresponding data for ArSCl addition and $NaBH_4$ reduction reactions occurring at a ring atom in $C_4$-substituted cyclohexyl derivatives has afforded some understanding of the factors which vitiate correlations of this nature.

In earlier investigations[2,3] examples were cited which indicated that in some instances conformational influences of remote substituents as well as polar effects govern the reaction rates. In one such example[3] the conclusion was drawn that a given substituent may influence the competing rate processes differentially. Thus, in the reduction of 4-substituted cyclohexanones it was shown that the substituent may exert a different influence on the transition state for reduction to a cis alcohol than in the transition state for reduction to a trans. It is conceivable, however, that cases can exist in which a given 4 substituent regulates a (common) transition state *via* two different but simultaneously active influences, namely conformational and polar. These influences, furthermore, could be considered as separable and correlatable in a linear free-energy relationship. Equation 1 may be proposed as a

$$\log k_a = (m\sigma_c + n\sigma_p)\rho_a \quad (1)$$

possible expression for correlating such conformational and polar effects exercised simultaneously in a given transition state. Here $k_a$ is the rate constant for the reaction a under study, $\sigma_c$ and $\sigma_p$ are the substituent constants expressing, respectively, the conformational and polar effects of substituents, and $m$ and $n$ are weighing factors related to the nature of both the substituents and the reaction under study. The parameter $\rho_a$ has the usual significance of the reaction constant.

For the addition of ArSCl to 4-substituted cyclohexenes[2a] polar effects dominate, and it has been found that

$$(m\sigma_c + n\sigma_p) \cong n_2\sigma_p = \sigma_I \quad (2)$$

where $\sigma_I$ is the familiar inductive substituent constant,[4] reducing to the situation prevailing in rigid, bicyclic

(1) (a) Facultad De Quimica, Universidad Nacional Autonoma De Mexico 20, D. F.; (b) Department of Chemistry, University of Delaware, Newark, Del.

(2) (a) H. Kwart and L. J. Miller, *J. Amer. Chem. Soc.*, **83**, 4552 (1961). (b) H. Kwart and T. Takeshita, *ibid.*, **84**, 2833 (1962). (c) Much of the rate data for the ArSCl addition reactions and $NaBH_4$ reductions applied in various plots in this article have been taken from the Ph.D. dissertation of S. Hsia, University of Delaware, June 1967. A publication discussing this work is presently in preparation. (d) The results of A. A. Khan from these laboratories to be discussed in a future article.

(3) H. Kwart and T. Takeshita, *J. Amer. Chem. Soc.*, **86**, 1161 (1964).

(4) R. W. Taft and I. C. Lewis, *ibid.*, **80**, 2436 (1958).

TABLE I

RATES OF BROMINATION[a] OF C4-SUBSTITUTED CYCLOHEXANONES AND ACTIVATION PARAMETERS

| C4 substituent[b] | $k^c$ ($10^5$) sec$^{-1}$ 15° | 25° | 37.5° | 50° | $\Delta S^{\pm}$, eu | $\Delta H^{\pm}$, kcal/mol | $\Delta F^{\pm}$, kcal/mol 15° | 25° | 37.5° | 50° |
|---|---|---|---|---|---|---|---|---|---|---|
| $CO_2H$ | | 1.87 | 7.52 | 30.1 | −10.9 | 20.7 | 23.8 | 23.9 | 24.1 | 24.2 |
| CN | 0.373 | 1.20 | 4.38 | 16.9 | −15.9 | 19.4 | 24.0 | 24.2 | 24.4 | 24.6 |
| $CO_2Me$ | 0.588 | 1.92 | 7.58 | 26.1 | −14.9 | 19.5 | 23.7 | 23.9 | 24.1 | 24.3 |
| BzO | 0.610 | 1.17 | 7.46 | 23.9 | −16.9 | 18.9 | 23.7 | 23.9 | 24.1 | 24.3 |
| MeO | 0.721 | 1.62 | 8.33 | 30.9 | −15.5 | 19.2 | 23.6 | 23.8 | 24.0 | 24.2 |
| $SiMe_3$ | 0.892 | 3.03 | 11.4 | 38.7 | −14.6 | 19.3 | 23.5 | 23.6 | 23.8 | 24.0 |
| H | 0.987 | 1.92 | 9.70 | 35.3 | −18.3 | 18.2 | 23.5 | 23.7 | 23.9 | 24.1 |
| $C_6H_5$ | 1.07 | 3.29 | 12.0 | 38.6 | −17.5 | 18.4 | 23.4 | 23.6 | 23.8 | 24.0 |
| $CH_3$ | 1.10 | 2.06 | 12.4 | 43.7 | −15.8 | 18.8 | 23.4 | 23.6 | 23.8 | 24.0 |
| $C_6H_{11}$ | 1.21 | 3.29 | 14.6 | 53.2 | −13.8 | 19.3 | 23.3 | 23.4 | 23.6 | 23.7 |
| *t*-Bu | 1.46 | 3.13 | 16.4 | 56.7 | −15.7 | 18.7 | 23.2 | 23.4 | 23.6 | 23.8 |

[a] In 70% HOAc–$H_2O$–HCl; see Experimental Section for kinetic procedures. [b] Registry numbers are, respectively, 874-61-3, 34916-10-4, 6297-22-9, 23510-95-4, 13482-23-0, 7452-95-1, 108-94-1, 4894-75-1, 589-92-4, 92-68-2, 98-53-3. [c] Pseudo-first-order rate constant.

systems[5] in which a conformational effect cannot be a factor. On the other hand, the solvolysis of various 4-substituted cyclohexyl tosylates[3] has been found to involve both polar and conformational effects.

The bromination of ketones in acetic acid–HCl media is recognized as a first-order reaction,[6] the rate-determining step of which is formation of the enol. The basic objective of the current investigation was to gain deeper insight concerning the transition state of this particular reaction by means of kinetic studies of the characteristics of this reaction in ring systems with which we have dealt in the earlier investigations. The rates of bromination of eleven 4-substituted cyclohexanones were measured at four different temperatures within a range of 35°.

## Results and Discussion

The results obtained and the activation parameters computed from these rate data are compiled in Table I. The plot of log $k$ *vs.* the inductive substituent constant[4] $\sigma_I$ (see Figure 1 for a typical case) not only departs from linearity but also demonstrates clearly how little change of rate is experienced, despite the very large variation in the character of the substituents encompassed by the reaction series.

A second noteworthy feature is represented by the observation that the transition state is sensitive to medium effects to the point that the substituent effect, such that it is, can be made to change sign. The competing influences which result in the insensitivity to polar effects of substituents while simultaneously exhibiting a high degree of responsiveness to medium effects can be regarded as direct consequences of the nature of the transition state. This can be seen with the aid of the analysis given in Scheme I.

In acidic media the energy pinnacle on the reaction pathway is characterized by partial breaking of the $\alpha$ carbon–hydrogen bond of the conjugate acid of the ketone. The degree of double-bond character associated with the $\alpha$ carbon and the extent of charge residing on the enol system (both) tend to increase the energy of the transition state in the presence of an electron-withdrawing substituent. Contrary to this,

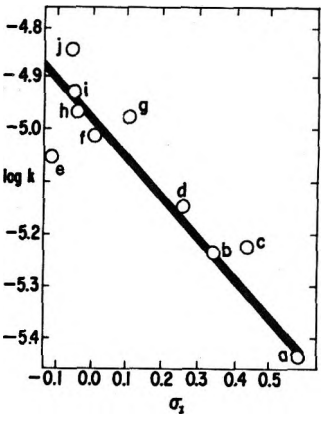
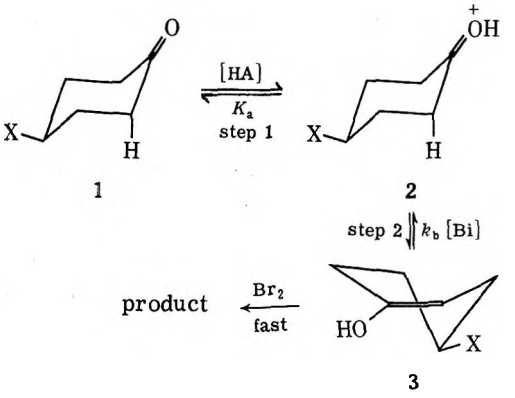



Figure 1.—Log $k$ of bromination of 4-substituted cyclohexanone at 15° in 70% AcOH–$H_2O$–HCl *vs.* Taft $\sigma_I$ values. Substituent legend in all figures: a, –CN; b, $-CO_2Me$; c, –BzO; d, –MeO; e, $-SiMe_3$; f, –H; g, $-C_6H_5$; h, –Me; i, $-C_6H_{11}$; j, –*t*-Bu.

SCHEME I




($k_{obsd} = K_a k_b$, and

$$\log k_{obsd} = \log K_a + \log k_b \cong \sigma(K_a + k_b) = \sigma\rho_{overall}$$

the electron-donor properties of the hydroxyl oxygen tend to offset the electron demand on the $\alpha$ carbon created by $sp^2$ hybridization. Similarly, the electron-donor properties of the oxygen aid in stabilizing the positive charge centers of the conjugate acid of the ketone. The latter, of course, is transferred to the solvent in the process of removing the proton from the $\alpha$ carbon. These features of the transition state structure allow for very considerable variation in charge distribution. Thus, there is a net increase in electron demand (as compared to the parent ketone) in highly

(5) J. D. Roberts and W. T. Moreland, *J. Amer. Chem. Soc.*, **75**, 2167 (1953).

(6) See H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, 1965, pp 145–147, for a discussion of the mechanistic course of this reaction; H. O. House, V. Paragamian, R. S. Ro, and D. J. Wluka, *J. Amer. Chem. Soc.*, **82**, 1457 (1960).

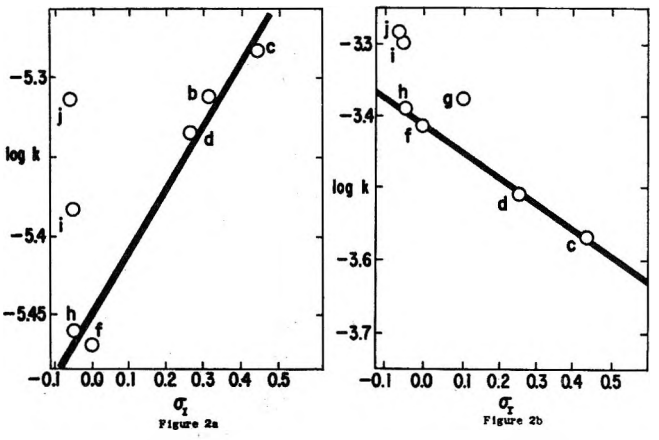



Figure 2.—(a) Log $k$ of bromination of 4-substituted cyclohexanones at 25° in 90% AcOH–$H_2O$–AcONa *vs.* Taft $\sigma_I$ values. (b) Log $k$ bromination of 4-substituted cyclohexanones at 25° in 90% AcOH–$H_2O$–HCl *vs.* Taft $\sigma_I$ values.

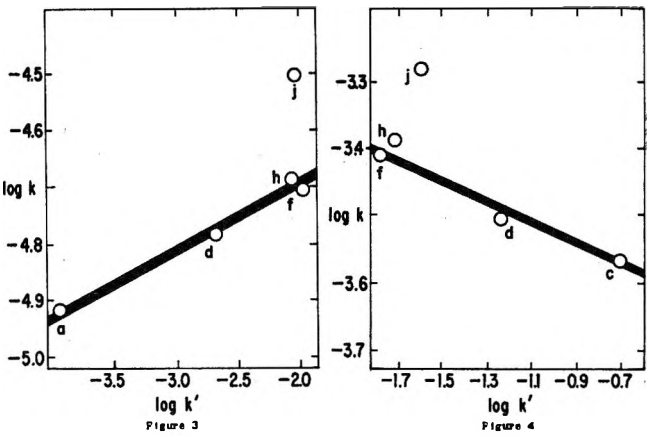



Figure 3.—Log $k$ of bromination of 4- substituted cyclohexanones at 25° in 70% AcOH–$H_2O$–HCl *vs.* log $k'$ of addition of ArSCl to 4-substituted cyclohexanones.

Figure 4.—Log $k$ of bromination of 4-substituted cyclohexanones at 25° in 90% AcOH–$H_2O$–HCl *vs.* log $k'$ of $NaBH_4$ reduction.

acidic media where the solvent itself must fulfill the role of the weak base. Conversely, when medium acidity is low and the concentration of a negatively charged base [$B^-$] is high, a decreased electron demand can be experienced in the enol region of the molecule to such an extent that the $\rho$ constant will be driven to the positive side.

The data, in general, bear out these expectations. Electron-withdrawing substituents retard the bromination reaction in strong acid media and increase the rate slightly compared to $H^+$ in weak acid media containing significant concentrations of acetate ion. However, in both cases the correlation of log $k_{obsd}$ *vs.* $\sigma_I$ is far from satisfactory, being only fair in the acid-catalyzed reaction and very poor in the acetate-catalyzed case. In both cases, the points at greatest departure from any kind of linearity are those which correspond to the substituents of very low polarity and large bulk such as *tert*-butyl and cyclohexyl. Thus, in the instance of ArSCl addition reactions previously mentioned,[2] where the polar effect of the substituent is of paramount influence, (*i.e.*, where either $m\sigma_c$ is a linear function of $n\sigma_p$, or $n\sigma_p \gg m\sigma_0$), it is clear that eq 2 can be applied as a useful approximation. It is equally apparent, now, that, in the bromination of cyclohexanones, the conformational effect of the substituent cannot be completely ignored and can vitiate the simplification of eq 2 (*i.e.*, $n_2\sigma_p = \sigma_I$). This must be particularly true in the acetate-catalyzed reaction where *tert*-butyl deviates most widely from the line in Figures 2a and 2b (see Table II data). It is consistent with the idea that an axial $\beta$ proton is removed by acetate in the transition state and the bulky substituents (of very low polarity) flatten the ring to the greatest extent. This distortion acts to promote attainment of the geometric requirement that the axial orbital develops at $C_2$ (through $H^+$ abstraction by acetate) in coplanarity with the p lobes of the trigonal carbon at $C_1$, but, since step 2 ($\rho_{-k_b}$), comprises only a part of the overall rate process which can be influenced by substitution at $C_4$, the true magnitude of this conformational effect on $\rho_{-overall}$ in terms of rate factors cannot be gauged because of compensation by $\rho_{-K_a}$.

**Correlation with Rates of ArSCl Addition to Cyclohexenes.**—Though the bromination of 4-substituted cyclohexanones does not conform to the simplification of eq 2, a plot of the log $k_{obsd}$ values *vs.* those of the respective ArSCl addition reactions (which do) affords what appears to be a reasonably good correlation with the one significant deviation from linearity, namely, the *tert*-butyl substituent (in Figure 3). The critical observation here is simply that, as opposed to the other substituents studied, *tert*-butyl is of such size and nature as to induce conformational irregularities which interfere with a linear relationship. The plots in Figures 1 and 3 tell the same story. It will be noticed that in Figure 1, for example, the deviations exist for phenyl, *tert*-butyl, and trimethylsilyl. In Figure 3, for which plot phenyl and trimethylsilyl data are lacking, the one group which would be anticipated for conformational reasons to depart from the linear relation clearly fulfills this expectation.

Table II
RATES OF BROMINATION OF $C_4$-SUBSTITUTED CYCLOHEXANONES COMPARED AT 25° IN VARIOUS MEDIA

| $C_4$ substituent | $k^a$ ($10^5$), sec$^{-1}$ More acidic medium[b] | $k^a$ ($10^5$), sec$^{-1}$ Less acidic medium[c] |
|---|---|---|
| $C_6H_5CO_2$ | 27.3 | 0.521 |
| MeO | 31.2 | 0.462 |
| H | 38.8 | 0.336 |
| $C_6H_5$ | 42.3 | 0.933 |
| $CH_3$ | 40.9 | 0.345 |
| $C_6H_{11}$ | 50.6 | 0.411 |
| *t*-Bu | 52.4 | 0.483 |

[a] Pseudo-first-order rate constant. [b] In 90% HOAc–$H_2O$–HCl; see Experimental Section for kinetic procedures. [c] In 90% HOAc–$H_2O$–NaOAc.

Further study of these data leads to the following simple conclusion. With the exception of cyclohexyl, phenyl, *tert*-butyl, and trimethylsilyl, the rate effects of all the other 4 substituents examined can be correlated quite well with polar substituent constants $\sigma_I$, and that for these substituents the rate can also be related to the substituent group dipole moment. The fact that the trimethylsilyl moment correlates reasonably well with the log of the bromination rate constant in Figure 6 (as will be seen in a subsequent section of this discussion) but shows no correlation with $\sigma_I$ reflects a lack of total correspondence between $\sigma_I$ and the dipole moments of this group. Since such groups,

which tend to produce departure from the linearity of the free-energy relationship, are neither strongly polar nor sufficiently bulky to effect complete control of the ring conformation,[2a] a constant relationship between their $\sigma_I$ and $\mu$ values could not in most cases have been anticipated.

**Correlations with Rates of Sodium Borohydride Reduction of Cyclohexanones.**—It has earlier[2b,c] been shown that both rate and the reduction product stereochemistry are strongly affected by the polarity of the $C_4$ substituent. Figures 4 and 5 demonstrate now that the rates of $NaBH_4$ reduction of $C_4$ substituted cyclohexanones also can be correlated with the respective bromination rates. Again we observe that *tert*-butyl stands above the line delineated by all the remaining substituents for which comparative data are available. This *tert*-butyl case represents still another instance where the conformational control exerted by the substituent is totally unrelated to its polar characteristic in the transition state. For most substituents the conformation of the ring in the transition state is strongly controlled by interaction of the permanent dipole of the $C_4$ substituent and the charge developed at the seat of reaction ($C_1$) extending into the low dielectric of the ring cavity.[2,3,5] Thus, we have at hand additional indication that a charge–dipole interaction of sufficient magnitude can be responsible for the simplification of eq 2; *i.e.*, under these circumstances $m\sigma_c$ is function of $n\sigma_p$. In general, circumstances which vitiate this simple correlation can be identified readily as points of departure in plots like Figures 4 and 5.

**Correlation of Bromination Rates with Substituent Dipole.**—Figure 6 represents a plot of the rates of bromination in the acid-catalyzed reaction *vs.* $\mu$ for all substituents for which the dipole moment value of the functionally substituted hydrocarbon $CH_3CH_2X$ has been recorded. The linearity of the correlation must be regarded as quite satisfactory. The only point which can be said to deviate significantly from the line comprising all of the other substituents is the phenyl case, where the ground-state interaction giving rise to a measurable dipole moment for ethylbenzene is still a matter of controversy. It is certainly not clear that the dipole of the phenyl ring in the activated state would be the same since it originates largely as a result of some polarizability phenomenon. Conversely, we can deduce that the permanent (ground state) dipoles of the remaining functional groups correlated in this series would interact in the same way with a charge developing at a remote ($C_1$) center in the reaction transition state. This correlation affords further support for the conclusions reached above. That is to say, when both the 4-substituent dipole and the charge developed at the reaction center in the transition state are of sufficient magnitude, a dominant influence on reaction rate will result from charge stabilization directly at $C_1$ (field effect), and indirectly through control of the ring conformation arising through exercise of the resulting coulombic restraint. One could scarcely have expected a linear relationship of log $k$ and $\mu$ were it not for the fact that the substituent dipole in the transition state constituted a degree of regulation on both of these factors comprising the total energy of the transition state, and the fact that the conformational effect of the substituent in the transition state is

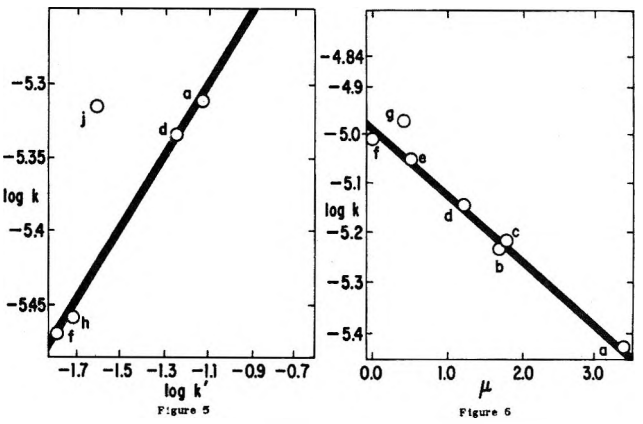



Figure 5 Figure 6

Figure 5.—Log $k$ of bromination of 4-substituted cyclohexanones at 25° in 90% AcOH–$H_2O$–AcONa *vs.* log $k'$ of $NaBH_4$ reduction.

Figure 6.—Log $k$ of bromination of 4-substituted cyclohexanones at 15° in 70% AcOH–$H_2O$–HCl *vs.* the dipole moment ($\mu$) $CH_3CH_2R$.

related to the degree of this charge–dipole interaction (*i.e.*, again, $m\sigma_c$ is a function of $n\sigma_p$).

## Experimental Section

**Kinetic Procedures.**—An exact amount of the $C_4$-substituted cyclohexanone was weighed into a 100-ml volumetric flask necessary to obtain a final concentration of substrate in the range of 0.01–0.02 *M*. To this was added about 85 ml of solution "A" (see below) and the flask was immersed in the constant-temperature bath. After sufficient time was allowed to reach temperature the flask was made up to volume with exactly 10 ml of solution "B" and additional solution "A," as required. Samples (10 ml) were withdrawn at time intervals suited to the bromine consumption rate in the reaction and titrated in the usual way with standard thiosulfate.[7]

Three rate determinations were performed for each of the various substrates at each of the temperatures and reaction conditions selected, and the results were averaged. The straight-line relationship of the usual psuedo-first-order plot held to at least 70% of completion in all cases. Beyond this point a slight deviation was often noted because of the incidence of polybromination and the catalytic effects of the hydrobromic acid formed by the reaction.[8]

Anhydrous acetic acid was prepared by treating 10 l. of 95% AR grade with 822 g of acetic anhydride and 200 g of AR chromic anhydride. The solution was refluxed for 30 min and distilled through a 25-cm glass bead column at 580 mm. The product boiling at 107–110° (collected for use) melted at 16–17°.

**Solution "A"** was prepared in three variations. $A_1$ consisted of 3.6 l. of anhydrous acetic and 0.4 l. of $H_2O$ (corresponding to 90% acetic acid; density = 1.0605 at 20°). A stream of HCl gas (dried by bubbling through a $H_2SO_4$ wash bottle) was passed into this acetic acid until a concentration of 0.082 *N* HCl was attained. $A_2$ consisted of 2.8 l. of acetic acid and 1.2 l. of $H_2O$ (corresponding to 70% acetic acid; density = 1.0690 at 20°). A stream of dry HCl gas was then passed into this solution until a concentration of 0.067 *M* HCl was reached. $A_3$ consisted of 3.6 l. of acetic acid and 0.4 l. of $H_2O$ to which was added 80 g of anhydrous sodium acetate, corresponding to a 2% concentration in the 90% acetic acid medium.

**Solution "B"** was prepared in three variations. $B_1$ consisted of 0.5 l. of solution A and 9.6 g of purified (AR) bromine. $B_2$ consisted of 0.5 l. of $A_2$ solution and 9.6 g of bromine. $B_3$ consisted of 0.45 l. of anhydrous acetic acid, 0.05 l. of $H_2O$, and 9.6 g of bromine. In each of the above cases, the exact concentration of bromine was determined by sodium thiosulfate titration before use.

**Preparation of the Cyclohexanone Substrates and Intermediates.**—The structues and purities of all of the cyclohexanones

(7) D. P. Evans, *J. Chem. Soc.*, 785 (1936).

(8) D. H. R. Barton, J. F. McGhie, M. K. Pradham, and S. A. Knight, *ibid.*, 876 (1955).

used for the kinetic measurements were established in all cases by means of ir, nmr, and glpc criteria.

**4-Carboxycyclohexanone** was prepared by oxidation of the precursor alcohol with Jones reagent[9] at 15°. The product recrystallized from benzene–hexane melted at 67–68°.[10]

**4-Carbomethoxycyclohexanone** was prepared in analogous fashion starting from 4-carbomethoxycyclohexanol. The product was distilled under reduced pressure and the fraction used for kinetic study had bp 74–75° (0.3 mm).

**4-Benzoxycyclohexanone** was prepared by the method of Jones and Sondheimer:[11] after recrystallization from ether–hexane, mp 58–59°; dinitrophenyl hydrazone mp 159–160°.

**4-Methoxycyclohexanone** was prepared according to directions of Helfer[12] by chromate oxidation of 4-methoxycyclohexanol. The latter was obtained by reduction of hydroquinone monomethyl ether with Raney nickel and hydrogen following familiar procedures.[13]

**Cyclohexanone** was purified *via* the Girard T reagent.[14]

**4-Phenylcyclohexanone** was synthesized by a two-step procedure starting from *p*-phenylphenol reduction[15] to a cis–trans mixture of 4-phenylcyclohexanol. The mixture was oxidized to the ketone using the Jones reagent.[9] The product[15] used for kinetic studies had mp 73–74°.

**4-Methylcyclohexanone** was purified (as a commercial sample) by distillation, $n^{20}D$ 1.4448.[16]

**4-Cyclohexylcyclohexanone** was obtained in a two-step procedure[15] beginning with reduction of *p*-phenylphenol with palladium/charcoal and hydrogen at 1500 psi and 150°. The reduction product mixture was oxidized with Jones reagent[9] in the usual way to ketone product which was isolated and purified by means of the Girard T reagent according to the method described by Büchi and Pappas,[17] mp 27–28°.

**4-*tert*-Butylcyclohexanone** was prepared according to directions of Winstein and Holness,[18] mp 45–46°.

**4-Cyanocyclohexanone and 4-trimethylsilylcyclohexanone** were provided by Dr. A. A. Khan[19] who prepared them according to methods in the literature. Their structures and purities were confirmed in the usual ways before use in kinetic procedures.

(9) E. R. H. Jones and K. Bowden, *J. Chem. Soc.*, 39 (1946).
(10) W. H. Perkin, Jr., *J. Amer. Chem. Soc.*, **85**, 416 (1904).
(11) E. R. H. Jones and F. Sondheimer, *J. Chem. Soc.*, 616 (1949).
(12) L. Helfer, *Helv. Chim. Acta*, **7**, 950 (1924).
(13) R. B. Thompson, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p. 278.
(14) A. E. Osterberg and E. C. Kendall, *J. Amer. Chem. Soc.*, **42**, 2612 (1920).
(15) H. E. Ungnade, *J. Org. Chem.*, **13**, 361 (1948).
(16) H. E. Ungnade and A. D. MacLaren, *ibid.*, **10**, 29 (1945).
(17) G. Büchi and J. J. Pappas, *J. Amer. Chem. Soc.*, **76**, 2963 (1954).
(18) S. Winstein and J. J. Holness, *ibid.*, **77**, 5562 (1955).
(19) Detailed directions for the preparation of these compounds will appear in a forthcoming publication by A. A. Khan.

# Structural Constraints on Electrocyclic Reactions of Unsaturated Ketenes. Synthesis and Irradiation of 2,4,4,5-Tetramethylbicyclo[4.2.0]octa-1,5-dien-3-one

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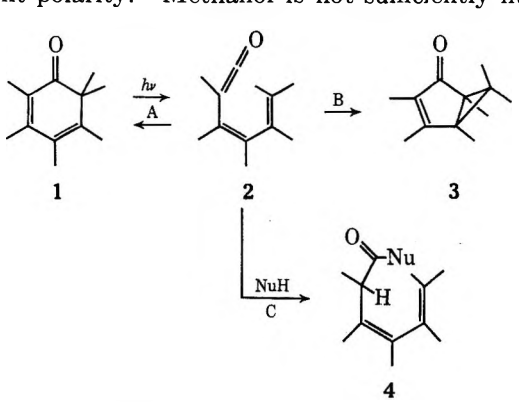
Oxidation of tetramethylbenzocyclobutene (**7**) with peroxytrifluoracetic acid–boron fluoride gave as the sole volatile cyclohexadienone (34% yield) 2,4,4,5-tetramethylbicyclo[4.2.0]octa-1,5-dien-3-one (**5**). The oxidation provides a striking illustration of the preference for β- (over α-) benzenonium ions in reactions of electrophiles with benzocyclobutenes, since both steps (electrophilic attack and methyl migration) are regiospecific. Irradiation of **5** in methanol (Pyrex) gave five methyl esters, **13** (55%) and the four stereoisomers of **14** (nearly equal amounts of each). This result contrasts with the irradiation of hexamethyl-2,4-cyclohexadienone (**1**), which under identical conditions gave no methyl esters. Reasons for the difference are discussed.

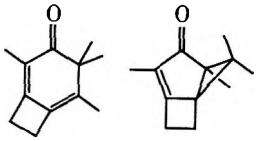
The unsaturated ketene **2**, produced by irradiation of the hexamethyldienone **1**, may react thermally in three different ways (A–C).[1,2] The particular reaction path depends on the nucleophile strength and on the solvent polarity. Methanol is not sufficiently nucleophilic to compete with the electrocyclic paths, but secondary amines divert the reaction completely along path C.[2] Of the two electrocyclic paths, B is favored by polar solvents and A by nonpolar solvents. For example, in ethanol virtually every ketene molecule produced by irradiation of **1** goes on to **3**, whereas in hexane approximately two-thirds of the ketene produced recyclizes to **1**.[2]




The reaction scheme shown for **1** is general, except that path B is only observed for heavily substituted ketenes.[1–5] This reaction path requires overlap of the ketene π-orbital lobes at C-4 with C-6, and C-1 with C-5, which can only be affected if the ketene twists appreciably from planarity and approaches the geometry of the bicyclo[3.1.0]hexenone product (*i.e.*, **3**).[4] To examine structural constraints on the electrocyclic reaction (B), we have studied the effect of incorporating two adjacent substituents into a ring. This would be expected to limit the conformations accessible to the ketene, and therefore affect the cyclization reaction. We report here on the synthesis and irradiation of the

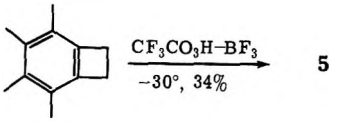
(1) H. Hart, P. M. Collins, and A. J. Waring, *J. Amer. Chem. Soc.*, **88**, 1005 (1966).
(2) J. Griffiths and H. Hart, *ibid.*, **90**, 3297 (1968).
(3) P. M. Collins and H. Hart, *J. Chem. Soc. C*, 895 (1967); H. Hart and R. K. Murray, Jr., *J. Org. Chem.*, **32**, 2448 (1967); H. Hart and D. C. Lankin, *ibid.*, **33**, 4398 (1968); J. Griffiths and H. Hart, *J. Amer. Chem. Soc.*, **90**, 5296 (1968); H. Perst and K. Dimroth, *Tetrahedron*, **24**, 5385 (1968); M. R. Morris and A. J. Waring, *Chem. Commun.*, 526 (1969); H. Hart and R. K. Murray, Jr., *J. Org. Chem.*, **35**, 1535 (1970); H. Perst and I. Weisemeier, *Tetrahedron Lett.*, 4189 (1970).
(4) M. R. Morris and A. J. Waring, *J. Chem. Soc. C*, 3266, 3269 (1971); A. J. Waring, M. R. Morris, and M. M. Islam, *ibid.*, 3274 (1971).
(5) However, not all heavily substituted cyclohexadienones react by path B; some, with electron-withdrawing substituents, react with nucleophiles (path C) in preference to cyclizing [*cf.* P. Vogel, B. Willhelm, and H. Prinzbach, *Helv. Chim. Acta*, **52**, 584 (1969)].

title dienone **5**,[6] which differs from **1** only in that the C-3 and C-4 substituents are joined in a small ring. If the ketene derived from **5** were to cyclize according to path B, it would lead to the highly strained bicyclo-[3.1.0]hexenone **6**.



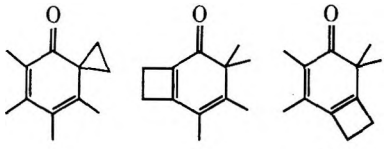
**5** **6**

**Synthesis of 5.**—Oxidation of tetramethylbenzocyclobutene (**7**)[7] with peroxytrifluoracetic acid–boron fluoride[8] was not clean, even at −30°, possibly due to the fact that benzocyclobutenes can suffer ring opening and polymerization under electrophilic substitution conditions.[9] Nevertheless, a 34% yield of a single volatile product was obtained, to which we assign structure **5**. The ir and uv spectra were consistent with the conjugated cyclohexadienone structure.




**7**

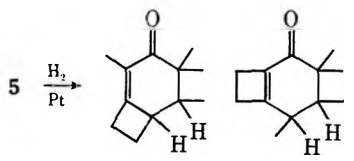
Three other cyclohexadienones which could conceivably arise from the electrophilic oxidation of **7** are **8**–**10**. The nmr spectrum showed a singlet at $\tau$ 8.90 (6 H) for the aliphatic *gem*-dimethyl group, ruling out



**8** **9** **10**

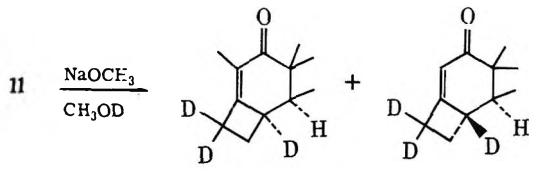
structure **8**. To distinguish **10** from **5** and **9**, advantage was taken of the fact[1] that base-catalyzed hydrogen–deuterium exchange in alkyl 2,4-cyclohexadienones occurs much more rapidly at C-3 than at C-5. The oxidation product was treated with $NaOCH_3$–$CH_3OD$ at room temperature; mass spectral and nmr analysis showed that only two deuterium atoms were introduced, thus eliminating structure **10**, which should readily exchange three hydrogen atoms.

The distinction between structures **5** and **9** was made by partial hydrogenation of the dienone over platinum. A conjugated enone ($\nu_{C=O}$ 1655 $cm^{-1}$, $\lambda_{max}^{MeOH}$ 247 nm) with two additional mass units was obtained. The nmr spectrum of this enone still showed one allylic methyl group ($\tau$ 8.45), as well as an aliphatic methyl doublet ($\tau$ 9.14, $J$ = 7 Hz). This compound must have structure **11**, since structure **12**, which would have been obtained if the original dienone were **9**, is inconsistent with the nmr results. The hydrogenation prod-




**11** **12**

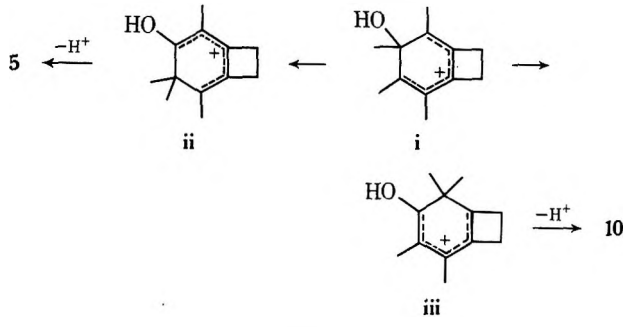
uct **11** is thought to have the hydrogens cis. When **11** was treated with $NaOCH_3$–$CH_3OD$, two enones were obtained, each of which contained three deuterium atoms. One had an nmr spectrum with bands for the four distinctive methyl groups at identical shifts as in **11**, whereas the other had the same overall band pattern, but with different chemical shifts. Presumably base caused epimerization as well as exchange; the products are formulated as shown.




*cis*-**11**-$d_3$ *trans*-**11**-$d_3$

These data are consistent only with structure **5** for the oxidation product of **7**.

**The Oxidation Mechanism.**—Electrophilic attack on benzocyclobutenes generally occurs at the $\beta$ aromatic position.[10] The two expected oxidation products of **7** are therefore **5** and **10**, which could arise from the intermediate benzenonium ion i by methyl migration




in either of the two possible directions. Rearrangement to ii (and, after proton loss, **5**) gives another $\beta$-type benzenonium ion, whereas rearrangement to iii gives an $\alpha$-type benzenonium ion. Since **5** was the only observed product, it is clear that whatever factors direct the initial electrophilic attack to the $\beta$ position also control the direction of methyl migration. Several plausible explanations for the greater reactivity of the $\beta$ position toward electrophiles have been offered.[11] The present case provides a rather striking example of the preference for $\beta$- (over $\alpha$-) benzenonium ions in reactions of electrophiles with benzocyclobutenes, since both steps are regiospecific.

**Irradiation of Dienone 5.**—Irradiation of a methanol solution of **5** through Pyrex, or in a Rayonet reactor with a 300-nm light source, rapidly gave a mixture of methyl esters. The major product (55%) was the

(6) For a preliminary account, see R. J. Bastiani, D. J. Hart, and H. Hart, *Tetrahedron Lett.*, 4841 (1969).

(7) This hydrocarbon is readily available in three steps (overall yield 70%) from pentamethylbenzene: H. Hart, J. A. Hartlage, R. W. Fish, and R. R. Rafos, *J. Org. Chem.*, **31**, 2244 (1966); D. J. Hart and H. Hart, *Org. Prep. Proced.*, **2**, 89 (1970).

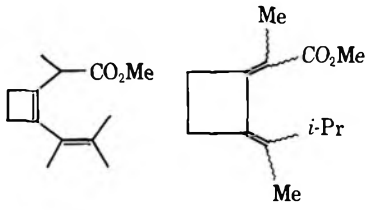
(8) For a review, see H. Hart, *Accounts Chem. Res.*, **4**, 337 (1971).

(9) J. B. F. Lloyd and P. A. Ongley, *Tetrahedron*, **20**, 2185 (1964); **21**, 245 (1965).

(10) I. L. Klundt, *Chem. Rev.*, **70**, 471 (1970).

(11) A. Streitwieser, Jr., G. R. Ziegler, P. C. Mowery, A. Lewis, and R. G. Lawler, *J. Amer. Chem. Soc.*, **90**, 1357 (1968); R. Taylor, G. J. Wright, and A. J. Homes, *J. Chem. Soc. B*, 780 (1967).

nonconjugated ester **13**; the remainder (45%) consisted of nearly equal amounts of the four geometric isomers of the completely conjugated ester **14**.

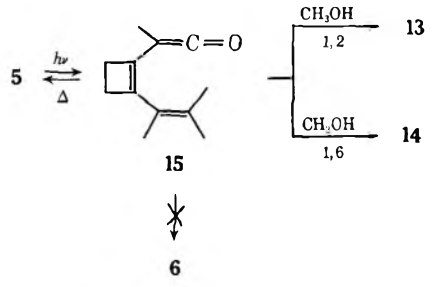



**13** **14**

The structures were assigned on the basis of spectral properties. Whereas **13** had a $\lambda_{max}^{MeOH}$ at 239 nm and a $\nu_{C=O}$ at 1715 $cm^{-1}$, all isomers of **14** had a $\lambda_{max}^{MeOH}$ at 288–290 nm and a $\nu_{C=O}$ at 1700 $cm^{-1}$. These data show that in **13** the carbon–carbon double bonds are not conjugated with the ester function, whereas in **14** they are fully conjugated.[12]

The nmr spectrum of **13** showed a doublet at $\tau$ 8.80 (3 H) and a quartet at $\tau$ 6.73 (1 H), $J$ = 7.0 Hz, for the $\alpha$-methyl group and hydrogen atom, clearly eliminating any alternative structure. In contrast with the spectrum of **13**, which had a peak corresponding to three allylic methyl groups, the spectrum of each isomer of **14** had two singlets in the expected region for the two allylic methyl groups as well as peaks due to the isopropyl group.[13]

The photolysis of **5** therefore follows the path shown.

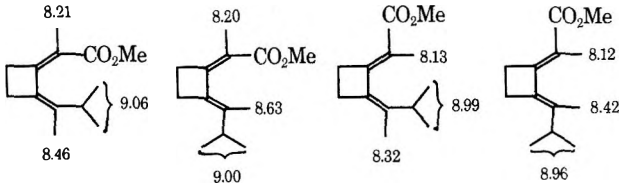



Irradiation of a methylene chloride solution of **5** containing no added nucleophile resulted only in recovered, unchanged starting material. Since the ketene **15** was almost certainly formed under these conditions (irradiation was carried out for a much longer time than is needed to convert **5** completely to esters on irradiation in methanol), it must recyclize entirely to **5**, since no product corresponding to **6** was detected. Presumably steric strain prevents the C-1–C-5 and C-4–C-6 overlap essential to the formation of **6**.

In contrast with ketene **2**, **15** reacts rapidly with methanol. Possibly the constraints of the cyclobutene ring enlarge the C-2,3,4 and C-3,4,5 angles over what they would be in the acyclic ketene. This has the effect of decreasing steric hindrance, and makes the ketene more susceptible to nucleophilic attack than it would otherwise be. The formation of **14** represents, we believe, the first authentic example of 1,6 addition to dieneketenes.[13a]

In a subsequent paper, the effect of incorporating the C-3 and C-4 dienone substituents in a ring larger than cyclobutyl will be described.

**Assignment of Geometry to Esters 14.**—The four stereoisomers of **14** were readily separated from **13** and from one another by preparative vpc. Though a definitive assignment of the geometry of each ester was not attempted, careful analysis of the uv and nmr spectrum of each isomer permits a reasonable assignment to be made. The structures are believed to be as shown.




| *Z,Z*-14 | *Z,E*-14 | *E,Z*-14 | *E,E*-14 |
|---|---|---|---|
| 6700[a] | 8100[a] | 14,000[a] | 17,000[a] |

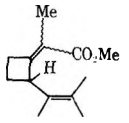
[a] $\epsilon_{max}^{280-290}$

Although the $\lambda_{max}$ values were nearly identical for all four isomers, the extinction coefficients varied considerably and fell into two distinct groups. The two isomers with the lower extinction coefficients are thought to have the carbomethoxy group in the most hindered position (*Z,Z* and *Z,E* isomers), whereas those with the larger extinction coefficients have the carbomethoxy group in a position where the carbon–oxygen and carbon–carbon double bonds can interact more strongly (*E,Z* and *E,E* isomers). Within each of these pairs, the isomer with the lower extinction coefficient is assigned the structure in which the isopropyl group (attached to the $\gamma,\delta$ double bond) is in the most obstructive position to coplanarity of the chromophore (*Z,Z* and *E,Z* isomers).

The nmr spectra provide several lines of support for certain of these assignments. For example, the cyclobutyl protons in the *Z,Z* and *Z,E* isomers appear as a fairly sharp peak at $\tau$ 7.50–7.55, whereas in the *E,Z* and *E,E* isomers, where two of these protons are close to the carbomethoxy group, a broad and complex pattern is seen between $\tau$ 6.9–7.8. The $\alpha$-methyls appear at $\tau$ 8.20–8.21 in the *Z,Z* and *Z,E* isomers, where they are located "away" from the remainder of the molecule, but at somewhat lower field ($\tau$ 8.12–8.13) when directed toward the $\gamma,\delta$ double bond. Finally, in one isomer the allylic methyl on the $\gamma$ carbon appears at unusually high field ($\tau$ 8.63); this is clearly the *Z,E* isomer, in which that methyl must be shielded by the nearby carbomethoxy group. Thus the assignments of the *Z,Z* and *Z,E* structures seem fairly certain; since the nmr and uv spectra of the *E,Z* and *E,E* isomers

(12) The calculated values of $\lambda_{max}$ for **13** and **14** are 247 and 316 nm, respectively; if only one double bond were conjugated with the ester function, the calculated value would be 234 nm (R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967, pp 157 and 161). Some expected twisting due to steric crowding apparently lowers the observed values from those calculated.

(13) The nmr data clearly rule out the alternative conjugated structure




(13a) NOTE ADDED IN PROOF.—Professor G. Quinkert reported, at the 4th IUPAC International Symposium on Photochemistry, Baden-Baden, Germany, July 1972, that 6-acetoxy-2,4,6-trimethyl-2,4-cyclohexadienone gave 5% of a 1,6-ketene adduct.

are very similar, it is possible that these two assignments may be reversed.[14]

## Experimental Section

Melting points are uncorrected. Ir spectra were calibrated against polystyrene film, and tetramethylsilane was an internal reference for all nmr spectra. The ir and nmr solvent was carbon tetrachloride; the uv solvent was methanol. All elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

**Oxidation of Tetramethylbenzocyclobutene (7).**—A solution of peroxytrifluoroacetic acid was prepared from 2.28 ml (83 mmol) of 90% hydrogen peroxide and 17.7 g (83 mmol) of trifluoroacetic anhydride in 24 ml of methylene chloride. The solution was maintained at 0° as it was added with stirring (45 min) to a solution of 9.0 g (57 mmol) of **7**[7] in 400 ml of methylene chloride which had previously been cooled to −30°. Boron fluoride etherate (27 ml of 48% $BF_3 \cdot Et_2O$) was added concurrently with the peracid. The temperature was maintained at −30° during the addition and for 2 hr of stirring thereafter. The mixture was hydrolyzed (100 ml of water), and the organic layer was washed with water (2 × 100 ml), saturated sodium bicarbonate (3 × 100 ml), 5% aqueous sodium hydroxide (3 × 100 ml), and again with water (3 × 100 ml). The dried ($MgSO_4$) organic layer was concentrated to a deep red, viscous oil which on distillation gave 3.41 g (34%) of 2,4,4,5-tetramethylbicyclo[4.2.0]octa-1,5-dien-3-one (**5**): bp 80–90° (0.2 Torr); $\lambda_{max}$ 320 nm ($\epsilon$ 4800); $\nu_{C=O}$ 1685 cm$^{-1}$, $\nu_{C=C}$ 1630 cm$^{-1}$; nmr $\tau$ 8.90 (s, 6 H, *gem*-dimethyl), 8.31, 8.36 (br s, 6 H, allylic methyls), 7.14 (br s, 4 H, cyclobutyl); mass spectrum *m/e* 176.

*Anal.* Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.89; H, 9.26.

A solution containing 100 mg of **5** in 0.5 ml of 1 *M* sodium methoxide in methanol-*d*, after standing for 1.5 hr at room temperature, was diluted with 2 ml of carbon tetrachloride, then washed with water (3 × 5 ml). The dried organic layer ($MgSO_4$) gave, on concentration, a quantitative yield of **5**-$d_2$: $\nu_{CD}$ 2200 cm$^{-1}$; nmr identical with that of **5**, except for the cyclobutyl protons, $\tau$ 7.18 (br s, 2 H); mass spectrum *m/e* 178.

**Hydrogenation of 5.**—To 50 mg of prereduced platinum oxide suspended in 13 ml of absolute ethanol was added 100 mg (0.57 mmol) of **5** in 1 ml of absolute ethanol. The mixture was stirred under 1 atm of hydrogen. After 13 min, when 1 equiv of hydrogen had been absorbed, there was a sharp decrease in the rate of hydrogen absorption. After removal of the catalyst and solvent, a yellow oil remained which constituted a 95% yield of 2,4,4,5-tetramethylbicyclo[4.2.0]octa-1-en-3-one (**11**). The product, when purified by preparative vpc (10 ft × 0.25 in. SE-30 column, 180°, 80 ml/min He) was a colorless oil: $\lambda_{max}$ 247 nm ($\epsilon$ 4800); $\nu_{C=O}$ 1655 cm$^{-1}$; nmr $\tau$ 9.14 (d, 3 H, $J$ = 7 Hz, C-5 methyl), 9.0, 8.83 (s, 6 H, *gem*-dimethyls), 8.45 (br s, 3 H, allylic methyl), 7.8–8.3 (m, 3 H, C-7 and C-6 protons), 7.1–7.5 (m, 2 H, C-8 protons), 6.34 (q, 1 H, C-5 proton); mass spectrum *m/e* 178.

*Anal.* Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.91; H, 10.23.

A solution containing 100 mg of **11** in 0.5 ml of 1 *M* sodium methoxide in methanol-*d*, after standing for 1.5 hr at room temperature, was diluted with 2 ml of carbon tetrachloride, then washed with water (3 × 5 ml). The dried ($MgSO_4$) organic layer, after concentration, showed (vpc) the presence of two components, which were separated by preparative vpc (10 ft × 0.25 in. SE-30 column, 180°, 80 ml/min of He). One product, with an identical retention time with that of **11**, was *cis*-**11**-$d_3$, nmr identical with that of **11** except that the band at $\tau$ 8.45 became a sharp singlet, the area of the $\tau$ 7.8–8.3 multiplet decreased to 2 H, and the multiplet at $\tau$ 7.1–7.5 was absent. The second product, *trans*-**11**-$d_3$, had ir and uv spectra similar to those of **11**, but the following nmr: $\tau$ 9.10 (d, 3 H, $J$ = 6.5 Hz, C-5 methyl), 9.11, 8.98 (s, 6 H, *gem*-dimethyls), 8.45 (s, 3 H, allylic methyl), 8.0–8.6 (m, 3 H, C-5 and C-7 protons); mass spectrum *m/e* 181.

**Irradiation of 5 in Methanol.**—A solution of 200 mg of **5** in 18 ml of methanol was irradiated using a Rayonet photochemical reactor equipped with 3000-Å lamps. The photolysis, which was monitored by vpc, was complete in 22 hr. Using a 450-W Hanovia lamp with a Pyrex filter, reaction was complete in 2 hr. The five photoproducts were separated by preparative vpc (10 ft × 0.25 in. SE-30 column, 200°, 80 ml/min of He). Product ratios varied slightly with irradiation conditions and are given here for the Rayonet conditions.

The product with retention time of 10.5 min (55%) is methyl 2-(1,2-dimethylpropenyl)-$\alpha$-methyl-1-cyclobutene-1-acetate (**13**): $\lambda_{max}$ 239 nm ($\epsilon$ 8100); $\nu_{C=O}$ 1715 cm$^{-1}$, $\nu_{C=C}$ 1630 cm$^{-1}$; nmr $\tau$ 8.80 (d, 3 H, $J$ = 7 Hz, $\alpha$-methyl), 8.30 (br s, 9 H, allylic methyls), 7.61 (br d, 4 H, cyclobutyl), 6.73 (q, 1 H, $J$ = 7 Hz, $\alpha$ proton), 6.40 (s, 3 H, $OCH_3$); mass spectrum *m/e* 208.

*Anal.* Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.79; H, 9.67.

The product with retention time of 14.7 min (12%) is considered to be (*Z,Z*)-methyl 2-(1,2-dimethylpropylidene)-$\alpha$-methyl-$\Delta^{1,\alpha}$-cyclobutaneacetate (*Z,Z*-**14**): $\lambda_{max}$ 289 nm ($\epsilon$ 6700); $\nu_{C=O}$ 1700 cm$^{-1}$, $\nu_{C=C}$ 1650 cm$^{-1}$; nmr $\tau$ 9.07 (d, 6 H, $J$ = 7.0 Hz, isopropyl methyls), 8.46 (br s, 3 H, allylic methyl), 8.22 (s, 3 H, allylic methyl), 7.57 (br s, 4 H, cyclobutyl), 6.36 (s, 3 H, $OCH_3$); mass spectrum *m/e* 208.

*Anal.* Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.04; H, 9.78.

The product with retention time of 17.7 min (12%) is considered to be *Z,E*-**14**: $\lambda_{max}$ 289 nm ($\epsilon$ 8100) $\nu_{C=O}$ 1702 cm$^{-1}$, $\nu_{C=C}$ 1650 cm$^{-1}$; nmr $\tau$ 8.99 (d, 6 H, $J$ = 7.0 Hz, isopropyl methyls), 8.63 (s, 3 H, allylic methyl), 8.20 (s, 3 H, allylic methyl), 7.50 (br s, 4 H, cyclobutyl), 6.36 (s, 3 H, $OCH_3$); mass spectrum *m/e* 208.

*Anal.* Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.92; H, 9.63.

The product with retention time of 20.5 min (9%) is either *E,E*-**14** or *E,Z*-**14**: $\lambda_{max}$ 288 nm ($\epsilon$ 17,000); $\nu_{C=O}$ 1700 cm$^{-1}$, $\nu_{C=C}$ 1640 cm$^{-1}$; nmr $\tau$ 8.96 (d, 6 H, $J$ = 7.0 Hz, isopropyl methyls), 8.42 (s, 3 H, allylic methyl), 8.15 (s, 3 H, allylic methyl), 6.95–7.95 (br m, 5 H, cyclobutyl and isopropyl protons), 6.35 (s, 3 H, $OCH_3$); mass spectrum *m/e* 208.

*Anal.* Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.90; H, 9.65.

The product with retention time of 22.5 min (12%) is either *E,Z*-**14** or *E,E*-**14**: $\lambda_{max}$ 290 nm ($\epsilon$ 14,000); $\nu_{C=O}$ 1700 cm$^{-1}$, $\nu_{C=C}$ 1640 cm$^{-1}$; nmr $\tau$ 8.99 (d, 6 H, $J$ = 7.0 Hz, isopropyl methyls), 8.32 (s, 3 H, allylic methyl), 8.13 (s, 3 H, allylic methyl), 6.93–7.65 (br m, 5 H, cyclobutyl and isopropyl protons), 6.36 (s, 3 H, $OCH_3$); mass spectrum *m/e* 208.

*Anal.* Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.80; H, 9.65.

**Irradiation of 5 in Methylene Chloride.**—A solution of 200 mg of **5** in 18 ml of methylene chloride was irradiated for 8 hr using a 450-W Hanovia lamp with a Pyrex filter. The starting material was recovered unchanged.

**Registry No.**—**5**, 28124-15-4; **11**, 34922-01-5; **13**, 34922-02-6; *Z,Z*-**14**, 34922-03-7; *Z,E*-**14**, 34922-04-8; *E,Z*-**14**, 34922-05-9; *E,E*-**14**, 34922-06-0.

**Acknowledgment.**—We are indebted to the National Science Foundation and the National Institutes of Health for financial aid.

(14) If the assignment were reversed, the chemical shift of the δ-methyl ($\tau$ 8.42) would agree better with that of the similar methyl in the *Z,Z* isomer ($\tau$ 8.46).

# Acyl Rearrangements in Radical Reactions

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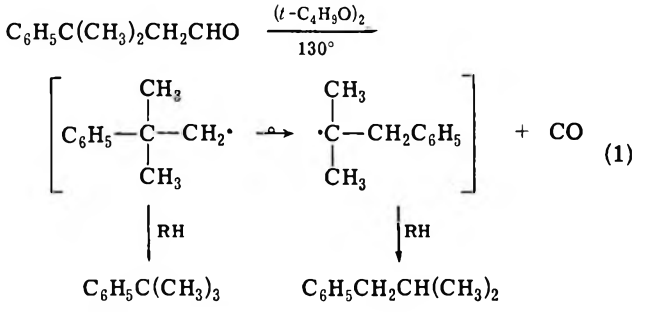
*Received March 21, 1972*

Solutions of the *tert*-butyl perlevulinate esters Ia,b,c undergo thermal decomposition (131°) *via* radical intermediates. The latter two peresters give some unrearranged *tert*-butyl ethers, but the remaining products are exclusively derived from acyl rearranged radicals (*e.g.*, methyl isobutyl ketone from Ib and 4-phenyl-2-pentanone, 4-phenyl-3-penten-2-one, and 4-phenyl-4-penten-2-one from Ic). No phenyl rearranged products (<1%) are found among the decomposition products from Ic, which also include rearranged dimeric diketones. Rearrangement during the decomposition of deuterium-labeled Ia was assessed at *ca.* 10%; thus substituents at the migration origin seem to provide a driving force for the 1,2-acyl shift. Reaction of 4-bromo-3,3-dimethyl-2-butanone (VIII) with triphenyltin hydride gave chiefly the unrearranged ketone pinacolone along with 3–5% of methyl isobutyl ketone. Slightly more rearrangement was observed with the corresponding chloride. The merits of a cyclopropoxy radical intermediate or transition state for these rearrangements are discussed.

Although examples of intramolecular 1,2 shifts of adjacent substituents to cationic sites are well documented,[1a–f] corresponding rearrangements to radical sites[2] are less common.[1g] In particular, no unambiguous cases of concerted hydrogen or alkyl shifts in 1,2-radical rearrangements have been observed,[3] in contrast with the facile rearrangement of these groups in carbonium ions.

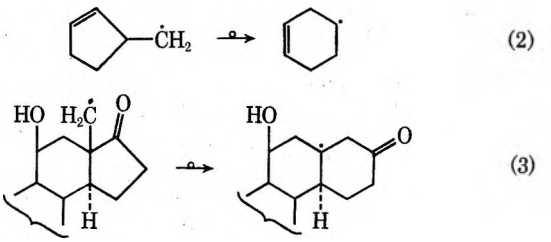
On the other hand, numerous examples of 1,2 shifts of aryl groups to radical sites have been reported,[4] beginning with Winstein and Seubold's study of the neophyl radical (eq 1).



(1)

Similar results were obtained when different methods of generating a given radical were employed. For example, the 2,2,2-triphenylethyl radical generated by aldehyde decarbonylation, thermal decomposition of azo compounds, the Hunsdiecker reaction, peroxide decomposition, or Kolbe electrolysis normally undergoes extensive rearrangement to the 1,1,2-triphenylethyl radical, but can be intercepted before rearrangement by hydrogen abstraction from triphenyl tin hydride.[5] These studies[4,5] suggest that the major factors influencing aryl rearrangements are the nature and number of substituents at the $\beta$-carbon atom (the migration origin) and the relative ease of competitive hydrogen abstraction from solvent or solute molecules.

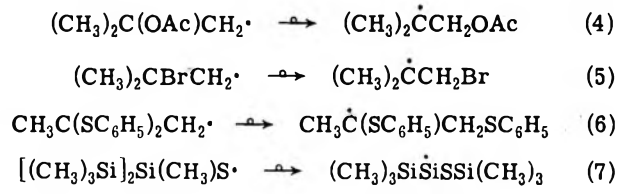
Rearrangements involving 1,2 shifts of olefin substitutents[6] (eq 2), acyl groups[7] (eq 3), acetate[8] (eq 4), halogen[9] (eq 5), sulfur substituents[10] (eq 6), and silicon substituents[11] (eq 7) have also been reported. The



(2)



(3)



(4)



(5)



(6)



(7)

mechanisms of most of these rearrangements have not been rigorously studied, and in some cases cleavage–recombination pathways have been shown to operate.[9c]

In this paper we report the results of our study of 1,2-acyl shifts to free-radical sites,[12] an area in which our interest was initially aroused by certain radical-initiated transformations of epoxy ketones.[7b]

(1) Chapters by (a) Y. Pocker, (b) J. Berson, (c) P. A. S. Smith, (d) J. King and P. de Mayo, (e) E. W. Warnhoff, (f) N. L. Wendler, and (g) C. Walling in "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1963.

(2) In this paper we restrict our attention to monoradicals. The exceptional behavior of diradicals is well illustrated by the work of F. D. Greene, W. Adam, and G. Knudsen, Jr., *J. Org. Chem.*, **31**, 2087 (1966).

(3) The exceptional rearrangement occurring to a small extent during thermal decomposition of 2,2'-bisazocamphane appears to proceed by a cleavage–recombination mechanism: J. A. Berson, C. J. Olsen, and J. S. Walia, *J. Amer. Chem. Soc.*, **84**, 3337 (1962).

(4) (a) S. Winstein and F. Seubold, *J. Amer. Chem. Soc.*, **69**, 2916 (1947); (b) D. Curtin and M. Hurwitz, *ibid.*, **74**, 5381 (1952); (c) F. Seubold, *ibid.*, **75**, 2532 (1953); (d) C. Overberger and H. Gainer, *ibid.*, **80**, 4561 (1958); (e) M. Kharasch, A. Poshkus, A. Fono, and W. Nudenberg, *J. Org. Chem.*, **16**, 1458 (1951); (f) J. Wilt and H. Philip, *ibid.*, **25**, 891 (1960); (g) C. Rüchardt, *Chem. Ber.*, **94**, 2609 (1961); (h) C. Rüchardt and R. Hecht, *ibid.*, **98**, 2460, 2471 (1965); (i) P. Cote and B. Vittimberga, *J. Amer. Chem. Soc.*, **93**, 276 (1971).

(5) L. Kaplan, *J. Amer. Chem. Soc.*, **88**, 4531 (1966).

(6) (a) L. H. Slaugh, *J. Amer. Chem. Soc.*, **87**, 1522 (1965); (b) L. K. Montgomery and J. Matt, *ibid.*, **89**, 6556 (1967); (c) T. Halgren, M. Howden, M. Medof, and J. D. Roberts, *ibid.*, **89**, 3051 (1967).

(7) (a) H. Reimann, A. Capomaggi, T. Strauss, E. Oliveto, and D. H. R. Barton, *ibid.*, **83**, 4481 (1961); (b) W. Reusch, C. Johnson, and J. Manner, *ibid.*, **88**, 2803 (1966).

(8) D. Tanner and F. Law, *ibid.*, **91**, 7535 (1969).

(9) (a) A. Nesmeyanov, R. Kh. Freidlina, and A. Belyavsky, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1028 (1959); (b) P. S. Skell, R. Allen, and N. Gilmore, *J. Amer. Chem. Soc.*, **83**, 504 (1961); (c) W. Haag and E. Heiba, *Tetrahedron Lett.*, 3683 (1965).

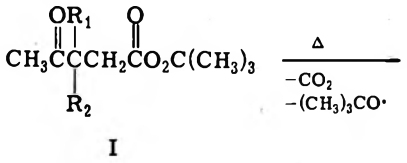
(10) R. Kh. Freidlina, A. Terentiev, and R. Petrova, *Dokl. Akad. Nauk SSSR*, **149**, 860 (1963); **151**, 866 (1963).

(11) (a) H. Sukurai, R. Koh, A. Hasomi, and M. Kumada, *Bull. Chem. Soc. Jap.*, **39**, 2050 (1966); (b) C. Pitt and M. Fowler, *J. Amer. Chem. Soc.*, **90**, 1928 (1968); *cf.* J. Wilt, O. Kolewe, and J. Kraemer, *ibid.*, **91**, 2624 (1969).

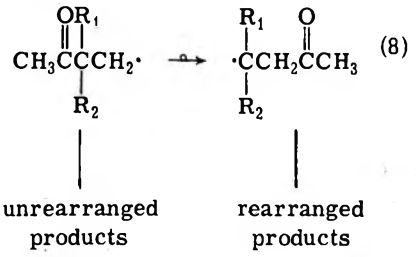
(12) A preliminary report of this work was presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., 1968, Abstracts P-79.

## Results

The radical intermediates necessary for this study were generated by thermal decomposition of appropriately substituted *tert*-butyl perlevulinate esters (eq 8). Substituents $R_1$ and $R_2$ provide a means for distinguishing rearranged from unrearranged products, and in most cases introduce a "driving force" for the rearrangement.

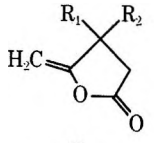


I

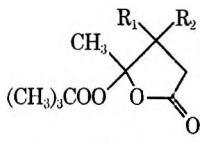



(8)

Efforts to prepare pure samples of *tert*-butyl perlevulinate esters were at first frustrated by the formation of enol lactones (II) or pseudoesters (III). Indeed,



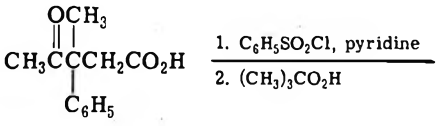
II



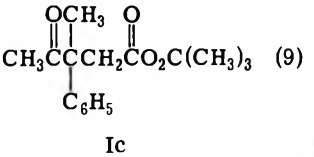
III

interconversion of I and III often occurs in the presence of acid or base catalysts. The presence of unreactive pseudoester contaminants was easily detected by a characteristic strong band at 901 $cm^{-1}$ in the infrared spectrum, as well as by thin layer chromatography.

These difficulties in perester synthesis were circumvented by the mixed sulfonic anhydride method of Brewster and Ciotti[13] and the *N,N'*-carbonyldiimidazole method of Hecht and Rüchardt,[14] as shown in eq 9 and 10.



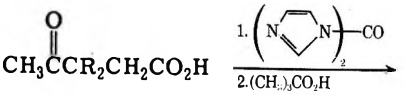
IV



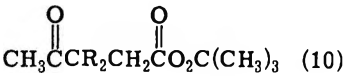
(9)

Ic

The thermal decomposition of peresters Ia–c was studied at 130–132° using 0.25 *M* solutions in diphenyl ether, triglyme, or *p*-cymene. These thermolyses were effected in such a way (Experimental Section) that the progress of the reactions could be followed by observing either the carbon dioxide evolution or the disappearance of perester. Although we did not attempt a careful kinetic analysis of the reactions, four facts did emerge from our initial examination.



Va, R = H
b, R = $CH_3$



(10)

Ia, R = H
b, R = $CH_3$

(1) The rate of carbon dioxide evolution tended to be uneven, and the total recovery in ascarite traps ranged from 65 to 90%.

(2) The rate of decomposition of all the peresters was essentially independent of the solvent being used.

(3) With the exception of Ia, the rate of decomposition during the first 40–60 min exceeded the roughly first-order rate observed for the later states of reaction. Induced decomposition is possible at the concentrations employed in these studies.

(4) The apparent first-order rate constants calculated from measurements made during the second and third hours of reaction (peresters Ia–c had essentially disappeared after ≤5 hr at 130°) are close to that reported for *tert*-butyl-3-phenylperpropanoate[15] under similar conditions.

Volatile reaction products were continuously swept from the reaction flask into a cold trap by a slow nitrogen stream. This trap contained most of the *tert*-butyl alcohol and acetone formed during the reaction, and the effect of a change in solvent on the ratio of these compounds confirmed the radical nature of these perester decompositions.[16] Thus, the alcohol to acetone ratio was large (10–200) in those solvents (triglyme and *p*-cymene) which offered the *tert*-butoxy radical a source of readily abstractable hydrogen atoms, and low (0.5–1.0) in diphenyl ether.

Abstraction of solvent hydrogen by the concurrently generated carboxy radical ($CH_3COCR_1R_2CH_2CO_2\cdot$) would produce the corresponding levulinic acids; however, the yield of such acids after complete perester decomposition seldom exceeded 1% in any of the solvents used.

The majority of the volatile perester decomposition products were divided between the cold traps and the final reaction solution. After unreacted perester was reduced and the resulting carboxylic acids were extracted, the crude reaction mixture was distilled at reduced pressure (spinning band column), thereby concentrating the volatile components in the first few fractions. Analysis of these fractions and the cold trap condensates by gas–liquid chromatography (with the aid of internal standards) yielded the results outlined in Table I. Product identification was accomplished by chromatographic and spectroscopic comparison of glc-trapped samples with authentic compounds (see the Experimental Section for the sources of these materials).

Dimeric reaction products were also observed in the pyrolysis of Ic. We presume that the initially ob-

(13) J. H. Brewster and C. J. Ciotti, *J. Amer. Chem. Soc.*, **77**, 6214 (1955).
(14) R. Hecht and C. Rüchardt, *Chem. Ber.*, **96**, 1281 (1963).
(15) M. M. Martin, *J. Amer. Chem. Soc.*, **84**, 1986 (1962).
(16) J. H. Raley, F. F. Rust, and W. E. Vaughan, *ibid.*, **70**, 1337 (1948).

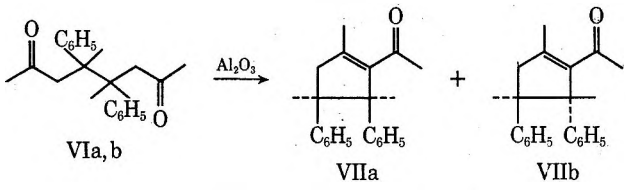
TABLE I

MONOMERIC VOLATILE PRODUCTS FROM β-ACETYL PERESTER DECOMPOSITION

| Perester | Solvents | Volatile products[a] | Average yields,[b] %[c] |
|---|---|---|---|
| Ia | Diphenyl ether or triglyme | $CH_3COC_2H_5$ | 44 |
| Ib | Diphenyl ether or triglyme | $CH_3COC(CH_3)_2CH_2OC(CH_3)_3$ (XI) | 11 |
| | | $CH_3COCH_2CH(CH_3)_2$ | 12[d] |
| | | $CH_3COC(CH_3)_3$ | 0.6[d] |
| Ic | Diphenyl ether or *p*-cymene | $CH_3COC(CH_3)C_6H_5CH_2OC(CH_3)_3$ (X) | 26 |
| | | $CH_3COCH_2CH(CH_3)C_6H_5$ | 15 |
| | | $CH_3COCH{=}C(CH_3)C_6H_5$ | 9 |
| | | $CH_3COCH_2C(C_6H_5){=}CH_2$ | 9 |

[a] Excluding *tert*-butyl alcohol and acetone. [b] With one exception (see following note) these yields did not vary by more than 1 or 2% on changing the solvent. [c] Corrected for unreacted perester. [d] These yields are from runs made in diphenyl ether. In triglyme the yields were doubled.

tained pyrolysate contains the stereoisomeric diketones VIa and b; however, these compounds were not




VIa, b VIIa VIIb

detected by our glc analysis procedure. Chromatography of the distillation pot residue on neutral alumina apparently transformed VIa and b into the isomeric acetylcyclopentenes VIIa and b, which were easily detected and purified (the configurational assignments are described in the Experimental Section). No corresponding dimeric products were found in the pyrolysates from Ia or Ib.

The distillation pot residue also contained a number of other compounds which we believe result from a combination of substrate radicals with solvent molecules. Aside from noting that these were high molecular weight substances having carbonyl absorption at *ca.* 1710 $cm^{-1}$, we made no effort to identify them. All the reactions in diphenyl ether yielded methylated phenyl ethers, and the *p*-cymene reaction produced up to 16% cymene dimers.

In order to determine the extent of acetyl rearrangement in the decomposition of *tert*-butyl perlevulinate, we attempted to introduce an isotopic label onto the perester. Since efforts to exchange the C-2 protons in the ethylene ketal of levulinic acid or its ethyl ester failed under moderate conditions and resulted in ketal cleavage when more vigorous methods were employed, we chose to effect direct exchange of the C-3 and C-5 protons of levulinic acid itself by saponification of the ethyl ester in heavy water (eq 11).

$$CH_3COCH_2CH_2CO_2C_2H_5 + D_2O \xrightarrow{NaOD} CD_3COCD_2CH_2CO_2Na \quad (11)$$

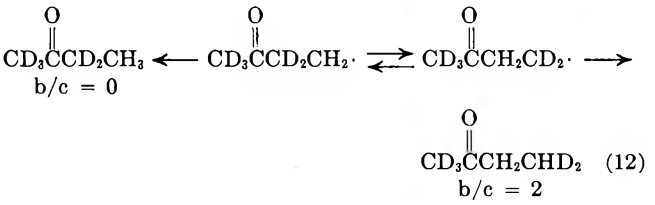
The acid obtained by careful neutralization of this saponification mixture was converted to the corresponding *tert*-butyl perester (eq 10), which was analyzed as a 2,4-dinitrophenylhydrazone (DNP) derivative. Unfortunately, the usefulness of this labeled perester was limited by the broad range of deuterium incorporation revealed by mass spectrometric analysis of the DNP: $d_0$ 0.7%, $d_1$ 1.3%, $d_2$ 2.8%, $d_3$ 7.5%, $d_4$ 26.5%, $d_5$ 44.5%, $d_6$ 12.8%, $d_7$ 3.9%. The isotopic composition of the 2-butanone obtained by pyrolysis of the deuterium-labeled perester in triglyme was also determined by mass spectrometry ($d_0$ and $d_1$ <1%, $d_2$ 1.6%, $d_3$ 7.4%, $d_4$ 24.3%, $d_5$ 46.3%, $d_6$ 16.7%, $d_7$ 3.4%) and the distribution of deuterium in this ketone was deduced from its nmr spectrum (Table II).

TABLE II

PROTON DISTRIBUTION IN DEUTERIUM-LABELED 2-BUTANONE

| Source of 2-butanone | Area of proton resonance signals (relative to c = 3.0) $CH_3$—CO—$CH_2$—$CH_3$ a | b | c |
|---|---|---|---|
| Perester pyrolysis in triglyme | 0.60 ± 0.08 | 0.22 ± 0.02 | 3.0 |
| Perester pyrolysis in diphenyl ether | 0.69 ± 0.06 | 0.25 ± 0.02 | 3.0 |

The relative areas of the three distinct proton resonance signals characterizing the labeled 2-butanone (a δ 2.06, b δ 2.39, c δ 1.02) will clearly change as rearrangement takes place (eq 12). If the perester could




(12)

have been cleanly and specifically labeled, the resulting 2-butanone would consist entirely of $d_5$ molecules with hydrogen located only at positions b and c. The ratio b/c would be zero in the absence of any rearrangement, and would rise to 2 in the event of a complete and directionally specific shift of the acetyl group. However, since it is likely that rearrangement proceeds through a symmetrical intermediate or at least is reversible, the greatest experimentally observed b/c ratio would in fact be 0.5. The expression relating this ratio to the mole fraction of rearrangement ($x$) is $b/c = 2x/(3 - 2x)$ for the hypothetical case of complete rearrangement and $b/c = 2x/(3 + x)$ for the expected methylene scrambling. Applying the latter expression to the experiments recorded in Table II fixes the per cent rearrangement at 13% in diphenyl ether and 11.5% in triglyme.

The assumption that all the labeled 2-butanone is $d_5$ is of course not correct and the major error in the previous argument is that hydrogen atoms remaining at b due to incomplete exchange are counted as hydrogen atoms from rearrangement. This leads to an exaggerated estimate for the extent of rearrangement, the true value probably being less than 11%.[17a]

Radical intermediates similar to those generated by perester decomposition presumably form during the reduction of β-halo ketones by trialkyltin hydrides.[17b] Reduction of roughly 1 *M* benzene solutions of 4-

(17) (a) A check of the internal consistency of this conclusion with the isotopic composition revealed by the mass spectrometric analysis is described in an Appendix following the Experimental Section. (b) H. G. Kuivila, *Accounts Chem. Res.*, **1**, 299 (1968).

bromo-3,3-dimethyl-2-butanone (VIII), containing from 1.1 to 2.4 molar equiv of triphenyltin hydride, at 130° proceeded with very little rearrangement (eq 13). Under similar conditions, the corresponding

$$\underset{\text{VIII}}{CH_3COC(CH_3)_2CH_2Br} + (C_6H_5)_3SnH \xrightarrow[130^\circ]{(C_4H_9O)_2} \underset{96\text{–}97\%}{CH_3COC(CH_3)_3} + \underset{4\text{–}3\%}{CH_3COCH_2CH(CH_3)_2} \quad (13)$$

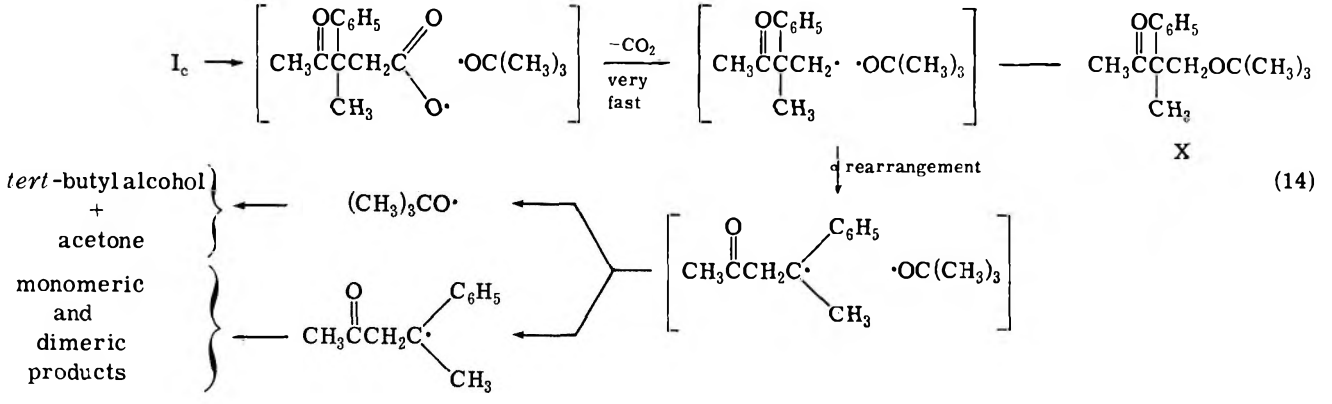
chloride (IX) gave slightly larger amounts of rearranged ketone (*ca.* 13%), and in one experiment using tri-*n*-butyltin hydride rearrangement accounted for 15% of the ketonic products.

## Discussion

The herein reported examples of intramolecular 1,2-acyl shifts to conventionally generated free radicals should remove any doubts regarding the possibility or plausibility[7] of these transformations. Indeed, a surprising similarity between these rearrangements and the well-established 1,2-aryl shifts[4] exists. In both cases rearrangement to a more stable radical dominates solvent hydrogen abstraction, but can be prevented by interception of the unrearranged radical by trialkyltin hydrides. However, in the absence of a driving force for the 1,2 shift, very little rearrangement (*ca.* 13%) is observed.

The initial peroxide bond homolysis of the perlevulinate esters must be closely followed by (or possibly concerted with[18]) carbon dioxide release, as witnessed by the very low yields of the corresponding levulinic acids in all solvents. Acyl rearrangement of the resulting primary radicals from Ib and Ic must also be rapid, since only traces of the products from direct hydrogen abstraction are found, even in *p*-cymene and triglyme solvents.

Substantial amounts of unrearranged *tert*-butyl ethers are found among the decomposition products of peresters Ib and Ic (eq 14), and these set an upper




(14)

limit for the "cage effect" or any alternative intramolecular decomposition mechanism. The absence of 6,6-dimethyl-5-oxa-2-heptanone (XII) among the products of *tert*-butyl perlevulinate (Ia) decomposition was confirmed by the addition of authentic XII to the product mixture, and may be due to a facile $\beta$ elimination of *tert*-butyl alcohol followed by polymerization of the resulting methyl vinyl ketone. A similar argument could be used to rationalize the absence of any rearranged *tert*-butyl ethers from Ib and Ic; however, it is more likely that the stability of the rearranged radicals enables them to escape the "cage," and subsequent recombination of the radicals would be improbable. In fact, the very stable tertiary benzylic radical (rearranged) from Ic survives long enough to produce significant amounts of dimers (15–40%).

The facility with which trialkyltin hydrides deliver a hydrogen atom to labile radical intermediates was noted earlier.[5,17] Recent work by Wenkert, *et al.*,[19] suggested that $\beta$-halo ketones could be reduced by these reagents without rearrangement, and our study of 4-bromo-3,3-dimethyl-2-butanone (and the corresponding chloride) confirmed this for a substrate known to rearrange in the absence of tin hydrides.

Further studies should be conducted to determine whether the increased rearrangement observed for reduction of the corresponding chloro ketone (IX) is a reflection of acyl participation in the radical-forming step. A similar halogen effect in the 1,4 and 1,5 rearrangement of phenyl from silicon to carbon was recently noted by Wilt and Dockus[20] in tin hydride reductions of $C_6H_5(CH_3)_2Si(CH_2)_nX$.

The preferential rearrangement of an acetyl group rather than a phenyl group[21a] in the primary radical derived from Ic (eq 4) is certainly one of the most interesting and unexpected results to emerge from our investigations. It seems unlikely that this specificity represents an inherent superiority in the migratory applitude of acyl groups, but probably reflects instead a tendency to form the most stable radical. This cannot be accomplished by an equilibrium, however, since the reverse of either rearrangement would be prohibitively endothermic.

In their review of intramolecular free-radical reactions Heusler and Kalvoda[21b] suggest that a 1,2-acyl shift proceeds *via* a cyclopropoxy radical intermediate (eq 15), a view which we accepted and adopted in an earlier paper.[7b] This attractive mechanism parallels currently accepted mechanisms for aryl[4] and vinyl[6] rearrangement, and is consistent with what is known about cyclopropoxy radical intermediates.[22] On the

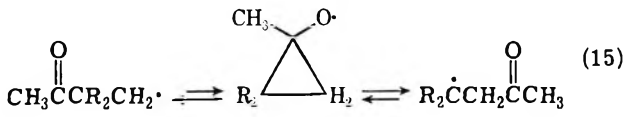
(18) P. D. Bartlett and R. Hiatt, *J. Amer. Chem. Soc.*, **80**, 1398 (1958).

(19) E. Wenkert, P. Bakuzis, J. Baumgarten, D. Doddrell, P. Jeffs, C. Leicht, R. Mueller, and A. Yoshikoshi, *ibid.*, **92**, 1617 (1970).

(20) J. Wilt and C. Dockus, Abstracts, 161st National Meeting of the American Chemical Society, Los Angeles, Calif., 1971, ORGN 163.

(21) (a) As little as 1% of the saturated and unsaturated ketones resulting from a phenyl shift (*i.e.*, 3-methyl-4-phenyl-2-butanone and 3-methyl-4-phenyl-3-buten-2-one) could have been detected by our glc and nmr analysis procedure. (b) K. Heusler and J. Kalvoda, *Angew. Chem., Int. Ed. Engl.*, **3**, 525 (1964).

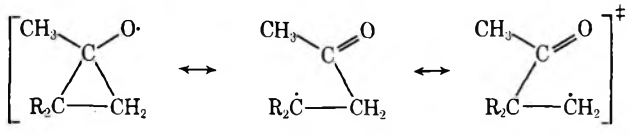
(22) C. H. DePuy, *Accounts Chem. Res.*, **1**, 33 (1968).



(15)

other hand, the influence of substituents (R) at the $\alpha$-methylene group is difficult to reconcile with the intermediacy of a discrete cyclopropoxy radical, since the relative stability of the rearranged radical should have a negligible effect on the rate-determining initial step (see eq 15). The driving force introduced by the $\alpha$ substituents may, of course, have nothing to do with the stability of the rearranged radical. Thus, a combination of nonbonded interactions in the initial radical, the "Thorpe–Ingold effect," and other undefined aspects of the "*gem*-dialkyl effect"[23] would be expected to increase the rate of cyclopropane formation, as bulky R groups are introduced. This interpretation of the substituent driving force does not, however, help to explain the selective acetyl shift in Ic.

An alternative rationalization of these facts is suggested by the extraordinary facility with which cyclopropoxy radicals rearrange on formation. For example, cyclopropanol nitrite esters undergo thermal homolysis and rearrangement at temperatures as low as $-80°$, the rates of these reactions being extremely sensitive to the nature of substituents at C-2.[24] The authors propose that O–NO bond homolysis and cyclopropane ring opening are concerted, and that relief of ring strain and radical delocalization in the transition state account for the accelerating effect. In a similar way, hydroxyl hydrogen abstraction by molecular oxygen is facilitated in cyclopropanols by concerted opening of the adjacent three-membered ring,[25] and is even further enhanced by the second hydroxyl substituent in vicinal cyclopropanediols.[26] We suggest, therefore, that a discrete cyclopropoxy radical (localized) is not an intermediate in the rearrangements discussed in this paper, but that a cyclic transition state having radical character at both the migration origin and terminus must be invoked. In this way the substituent driving force and the preferential acetyl migration in Ic can be explained.



Rüchardt[4h] and Vittimberga[4i] have drawn similar conclusions regarding aryl rearrangements. In both cases the ability of the migrating group (*i.e.*, acyl or aryl) to engage in a bonding interaction with the nearby unpaired electron must significantly lower the activation energy for its rearrangement relative to that for an alkyl group.[27]

An alternative fragmentation–recombination mechanism for these acyl shifts has not been ruled out, but we regard this as an unlikely possibility for the following reasons.

(1) The rearrangements described here take place under much milder conditions than those employed by Berson, *et al.*,[3] to effect the only documented example of alkyl rearrangement by this mechanism.

(2) The acyl radical fragments formed in this mechanism should suffer a facile decarbonylation, and yet no substantial products derived from such a process were observed (*e.g.*, $\alpha$-methylstyrene from Ic).

## Experimental Section

Melting points were obtained using a Hoover "Uni-Melt" apparatus or a Reichert hot-stage microscope and are uncorrected. A Perkin-Elmer 237B grating spectrophotometer was used to obtain infrared spectra; Varian A-60 and HA-100 high-resolution spectrometers were used to record nmr spectra; and mass spectra were obtained using a Hitachi RMU-6 spectrometer. Vapor phase chromatographic analyses and separations were performed with Varian Aerograph A-90P3 and 1200 instruments. All elemental analyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich.

**Preparation of Substituted Levulinic Acids. A. Levulinic Acid-$d_5$.**—A mixture of ethyl levulinate (28.8 g) and anhydrous potassium carbonate (30 g) in 100 ml of $D_2O$ was refluxed under a dry nitrogen atmosphere for 48 hr, concentrated under vacuum, and refluxed for an additional 12 hr with a fresh portion of $D_2O$. Careful neutralization of the chilled reaction mixture with concentrated hydrochloric acid followed immediately by several methylene chloride extractions gave, after drying and evaporating the combined extracts, 24.3 g of deuterium-labeled levulinic acid. Mass spectrometric analysis was conducted with the *tert*-butyl perester.

**B. 3,3-Dimethyllevulinic acid** was prepared by the method of Baumgarten and Gleason.[28]

**C. 3-Methyl-3-phenyllevulinic Acid.**—A solution of the conjugate base of 3-phenyl-2-butanone,[29] prepared by heating 4.45 g (0.03 mol) of the ketone in 100 ml of dry DMSO with 0.80 g of sodium hydride, was added dropwise (1 hr) under nitrogen to a rapidly stirred solution of ethyl bromoacetate in 100 ml of dry DMSO, the temperature being maintained at *ca.* 25°. After the pale yellow reaction mixture was stirred for an additional 30 min, it was poured into ice water and extracted with ether. The dried ether extracts yielded a yellow oil, which after fractional distillation at 0.5 Torr resulted in a 70% yield of ethyl 3-methyl-3-phenyllevulinate, nmr absorptions at $\delta$ 1.07 (3 H, triplet, $J \cong 7$ Hz), 1.70 (3 H, singlet), 1.90 (3 H, singlet), 2.90 (2 H, AB quartet center, $J \cong 16$ Hz), 3.98 (2 H, quartet, $J \cong 7$ Hz), 7.28 (5 H, singlet). Saponification of this ester by refluxing ethanolic KOH solution (24 hr) gave, after acidification with hydrochloric acid and extraction with ether, crude 3-methyl-3-phenyllevulinic acid, which on crystallization from hot water gave white needles, mp 96.5–97°, in 80% yield. Broad infrared absorptions at 3400 and 1710 $cm^{-1}$ and nmr absorptions ($CDCl_3$) at $\delta$ 1.72 (3 H, singlet), 1.88 (3 H, singlet), 2.93 (2 H, AB quartet center, $J \cong 16$ Hz), 7.28 (5 H, singlet), and 9.46 (1 H, singlet) support the structural sssignment.

*Anal.* Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.48; H, 6.80.

**Preparation of *tert*-Butyl Perlevulinate Esters. A. The Acylimidazole Method.**[14]—A solution of the levulinic acid in dry THF was added dropwise to a stirred solution of an equimolar quantity of 1,1′-carbonyldiimidazole in THF. An hour after the initial gas evolution had ceased (*ca.* 30 min) an equimolar amount of freshly distilled *tert*-butyl hydroperoxide was added dropwise, and the reaction mixture was stirred for 2 days at room temperature. Solvent evaporation under vacuum (temperature <50°) left a residue which was dissolved in ether and washed successively with cold 10% sulfuric acid, cold sodium carbonate, and water. The crude perester obtained from the dried ether extracts could be freed from traces of hydroperoxide by drying under vacuum. Yields ranged from 40 to 60%.

(23) E. Eliel, N. Allinger, S. Angyal, and G. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 191.

(24) C. H. DePuy, H. L. Jones, and D. H. Gibson, *J. Amer. Chem. Soc.*, **90**, 5306 (1968).

(25) D. H. Gibson and C. H. DePuy, *Tetrahedron Lett.*, 2203 (1969).

(26) D. B. Priddy and W. Reusch, *ibid.*, 2637 (1970).

(27) (a) H. E. Zimmerman and A. Zweig, *J. Amer. Chem. Soc.*, **83**, 1196 (1961); (b) N. F. Phelan, H. H. Jaffe, and M. Orchin, *J. Chem. Educ.*, **44**, 626 (1967).

(28) H. Baumgarten and D. Gleason, *J. Org. Chem.*, **16**, 1658 (1951).

(29) E. M. Schultz, J. B. Becking, S. Mickey, and F. Crossley, *J. Amer. Chem. Soc.*, **75**, 1072 (1953).

The perester from deuterium-labeled levulinic acid (Ia) was distilled, bp 84–85° (0.001 Torr), and characterized by infrared absorptions at 2985, 1775, 1705, 1370, 1105, and 850 $cm^{-1}$ and nmr absorptions at $\delta$ 1.24 (9 H, singlet) and 2.44 (1.95 H, multiplet). The 2,4-dinitrophenylhydrazone derivative of this perester, mp 134°, exhibited the following ions in the parent ion region of the mass spectrum: *m/e* (rel intensity) 368 (0.6), 369 (1.2), 370 (2.6), 371 (6.7), 372 (23.5), 373 (41.6), 374 (17.9), and 375 (5.9).

The perester from 3,3-dimethyllevulinic acid (Ib) was distilled, bp 93–94° ($2 \times 10^{-4}$ Torr), and characterized by infrared absorptions at 2980, 1770, 1700, 1355, 1080, and 850 $cm^{-1}$ and nmr absorptions at $\delta$ 1.21 (6 H, singlet), 1.27 (9 H, singlet), 2.12 (3 H, singlet), and 2.57 (2 H, singlet). A 2,4-dinitrophenylhydrazone derivative, mp 121–122°, was prepared.

*Anal.* Calcd for $C_{17}H_{24}N_4O_7$: C, 51.51; H, 6.10; N, 14.13. Found: C, 51.64; H, 6.13; N, 14.20.

**B. The Sulfonyl Anhydride Method.**[18]—To a solution of 3-methyl-3-phenyllevulinic acid (1.03 g, 5 mmol) in 45 ml of dry pyridine was added 19.91 g (10 mmol) of *p*-toluenesulfonyl chloride, and this mixture was stirred for 1 hr at room temperature before being cooled in an ice bath. Freshly distilled *tert*-butyl hydroperoxide (0.42 g, 4.8 mmol) was added to the cold reaction mixture, stirring was maintained for 2.5 hr at 0°, and the resulting solution was poured into ice water and extracted with ether. After being washed with cold aqueous acid, sodium carbonate solution, and water, the ether extracts were dried and evaporated under vacuum. Chromatography of the crude perester on a Florisil column removed traces of unreacted hydroperoxide. The resulting perester (Ic) was a viscous, colorless oil, giving a singlet spot on silica gel tlc, and characterized by infrared absorptions at 2930, 1775, 1710, 1377, 1361, and 850 $cm^{-1}$ and nmr absorptions at $\delta$ 1.10 (9 H, singlet), 1.77 (3 H, singlet), 1.90 (3 H, singlet), 2.84 (2 H, AB quartet center, $J \cong 15$ Hz), and 7.26 (5 H, singlet).

*Anal.* Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.78; H, 7.94.

**Perester Thermolysis. A. Solvent Purification. 1. Diphenyl ether** (>99% pure) was washed with a 10% potassium hydroxide solution, dried over anhydrous sodium sulfate, and distilled, bp 257–258°. When the purified ether was heated to 200° for 5 hr under a stream of dry nitrogen, no volatile substances were observed in a Dry Ice trap.

**2. *p*-Cymene** (reagent grade, "terpene-free") proved to be contaminated with sufficient volatile impurities to complicate our product analysis. Purification was effected by refluxing for 2 days over sulfur, extraction of the distilled *p*-cymene with concentrated sulfuric acid, subsequent washing with dilute sodium hydroxide followed by brine, and final fractionation on a spinning band column. The purified solvent showed no impurities on glc analysis.

**3. Triethylene glycol dimethyl ether** (triglyme) was refluxed over lithium aluminum hydride for 24 hr and then distilled, bp 220–221°. Earlier fractions contained glyme and diglyme. When the purified triglyme was heated to 150° in a nitrogen stream only a trace (*ca.* 2 mg) of volatile substances collected in a Dry Ice cooled trap after 4 hr.

**B. General Reaction Procedure.**—A three-necked reaction flask was equipped with a magnetic stirring bar, a rubber serum cap, and gas inlet and exit tubes. The inlet tube was connected to a source of dry, carbon dioxide free nitrogen. The exit tube was connected to two Dry Ice–isopropyl alcohol traps in series, and these in turn were connected to a pair of parallel, tared, ascarite-filled tubes equipped with stopcocks, and finally to a bubble counter.

All but 1–2 ml of the solvent to be used was added to the reaction flask, which was then lowered into a preheated oil bath (130°), purged with nitrogen, and connected to the traps and ascarite tubes, one of which was open to the exit gas stream. The perester was dissolved in the remaining solvent and rapidly introduced into the hot solvent by injection through the serum cap. The rate of carbon dioxide evolution was determined by weighing alternate ascarite traps at various time intervals, one trap remaining connected to the system at all times. Alternatively, aliquots were withdrawn from the reaction solution for analysis of unreacted perester.[30]

After 3 hr at 130°, the oil bath was removed and the reaction vessel was cooled by a Dry Ice bath for a brief period in order to quench the pyrolysis. Unreacted perester (negligible amounts remain) was decomposed by a little sodium iodide, ice water was added, and the pH was adjusted to *ca.* 6. After the phases were separated and the water layer was extracted with ether, the combined organic phases were washed with aqueous sodium hydroxide to remove acids, dried over anhydrous sodium sulfate, and carefully distilled through a spinning band column. The volatile products not found in the Dry Ice traps were in this manner concentrated in the first 3–4 ml of distillate. The distillation residue was examined by tlc and glc prior to chromatography on silica gel. Quantitative results were obtained by glc analysis of residue solutions containing *trans*-stilbene as an internal standard.

**Reaction Product Identification. A.**—A comparison of glc retention times, infrared spectra, and nmr spectra of products believed to be 2-butanone, 3,3-dimethyl-2-butanone, and 4-methyl-2-pentanone with the authentic compounds (Aldrich Chemical Co.) confirmed these assignments.

**B. 4-Phenyl-2-pentanone** was prepared by the reaction of methylmagnesium bromide with ethyl cinnamate, according to the procedure of Munch-Peterson,[31] semicarbazone mp 135–136°.

**C. 4-Phenyl-3-penten-2-one** was identified from its infrared spectrum ($\bar{\nu}_{max}$ 1680 and 1600 $cm^{-1}$) and nmr spectrum: $\delta$ 2.18 (3 H, singlet), 2.48 (3 H, singlet), 6.43 (1 H, singlet), and 7.34 (5 H, singlet).

**D. 4-Phenyl-4-penten-2-one** was identified from its infrared spectrum ($\bar{\nu}_{max}$ 1715 and 1600 $cm^{-1}$) and nmr spectrum: $\delta$ 2.03 (3 H, singlet), 3.47 (2 H, singlet), 5.20 and 5.50 (singlets in a poorly defined 2 H AB quartet), and 7.31 (5 H, singlet).

**E. 3-Methyl-4-phenyl-2-butanone** was prepared by catalytic hydrogenation of 3-methyl-4-phenyl-3-buten-2-one, synthesized by acid-catalyzed condensation of benzaldehyde with 2-butanone.[32]

**F. 3-Phenyl-2-pentanone** was prepared by alkylation of the enolate base from methyl benzyl ketone with ethyl iodide,[29] semicarbazone mp 187–190°.

**G. 3-Methyl-3-phenyl-2-butanone** was prepared by methylation of 3-phenyl-2-butanone, 2,4-dinitrophenylhydrazone derivative mp 151°.

**H. 6,6-Dimethyl-5-oxa-2-heptanone** (XII) was prepared from methyl vinyl ketone and *tert*-butyl alcohol according to the method of Milas, *et al.*[33] Nmr absorptions at $\delta$ 1.13 (9 H, singlet), 2.05 (3 H, singlet), 2.50 (2 H, triplet, $J = 7$ Hz), and 3.55 (2 H, triplet, $J = 7$ Hz) support the structural assignment.

**I. 3,3,6,6-Tetramethyl-5-oxa-2-heptanone** (XI) was isolated from the first spinning band distillation fraction during the work-up of perester Ib decomposition. This volatile keto ether was purified by preparative glc (20% SE-30 column), and exhibited infrared absorptions ($\bar{\nu}_{max}$ 2960, 1710, 1365, 1195, 1080, and 980 $cm^{-1}$) and nmr absorptions [$\delta$ 1.09 (6 H, singlet), 1.16 (9 H, singlet), 2.05 (3 H, singlet), and 3.25 (2 H, singlet)] consistent with its structure. A 2,4-dinitrophenylhydrazone derivative, mp 115–116°, was prepared.

*Anal.* Calcd for $C_{16}H_{24}N_4O_5$: C, 54.54; H, 6.90; N, 15.90. Found: C, 54.74; H, 6.97; N, 16.06.

**J. 3,6,6-Trimethyl-3-phenyl-5-oxa-2-heptanone** (X) was isolated from the decomposition products of perester Ic by chromatography on alumina. Final purification by glc gave a clear liquid with an nmr spectrum: $\delta$ 1.13 (9 H, singlet), 1.47 (3 H, singlet), 1.90 (3 H, singlet), 3.75 ( 2 H, AB quartet, $J \cong 9$ Hz), and 7.23 (5 H, singlet).

*Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.87; H, 9.42. Found: C, 77.14; H, 9.33.

**K. *cis*- and *trans*-1-Acetyl-2,4,5-trimethyl-4,5-diphenylcyclopentene (VIIa and b).**—Pure samples of these isomers were obtained by preparative glc of the distillation residue from perester Ic decomposition, after an initial chromatography on neutral alumina. Both isomers exhibited strong infrared absorption at 1670 and 1615 $cm^{-1}$ and a parent ion at *m/e* 304 in the mass spectrum. The nmr spectrum of the cis isomer consisted of signals at $\delta$ 1.48 (3 H, singlet), 1.67 (3 H, singlet), 1.78 (3 H, singlet), 2.16 (3 H, singlet), 2.74 (2 H, AB quartet, $J \cong 16$ Hz), and 6.84 (sharp multiplet, 10 H).

The trans isomer (VIIb) showed a relative upfield shift of the methyl resonances and a downfield shift of the aromatic protons: $\delta$ 1.02 (3 H, singlet), 1.18 (3 H, singlet), 1.70 (3 H, singlet), 2.10

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(3 H, singlet), 2.84 (2 H, AB quartet, $J \cong 18$ Hz), and 7.18 (10 H, multiplet).

**Preparation of 4-Halo-3,3-dimethyl-2-butanones (VIII and IX).** A.—Reduction of ethyl 3,3-ethylenedioxy-2,2-dimethylbutanoate (62.5 g), prepared from ethyl 3-keto-2,2-dimethylbutanoate[34] by reaction with ethylene glycol, by a solution of lithium aluminum hydride (6.5 g) in tetrahydrofuran (150 ml) gave, after the customary work-up and acid-catalyzed hydrolysis in aqueous acetone, 3,3-dimethyl-4-hydroxy-2-butanone, bp 78–79° (14 Torr), in 88% yield after distillation. The infrared spectrum of this ketol ($\bar{\nu}_{max}$ 3400, 2950, 1710, 1475, 1120, and 1035 $cm^{-1}$) and its nmr spectrum [$\delta$ 1.08 (6 H, singlet), 2.09 (3 H, singlet), 3.47 (2 H, singlet), and 4.18 (1 H, singlet)] support this structural assignment.

The tosylate prepared from this ketol by reaction with *p*-toluenesulfonyl chloride in pyridine, mp 56°, was converted to 4-bromo-3,3-dimethyl-2-butanone (VIII) by treatment with a sixfold excess of lithium bromide in refluxing 2-butanone for 48 hr. Distillation of crude VIII, bp 79° (18 Torr), gave the pure keto bromide: $\bar{\nu}_{max}$ 2980, 1705, 1470, 1350, 1248, and 1150 $cm^{-1}$; nmr $\delta$ 1.24 (6 H, singlet), 2.16 (3 H, singlet), and 3.52 (2 H, singlet); parent ions at *m/e* 178 and 180 in the mass spectrum.

B.—4-Chloro-3,3-dimethyl-2-butanone (IX) was prepared by the reaction of 1,2,2-trimethylcyclopropanol[35] with *tert*-butyl hypochlorite. Distillation of crude IX, bp 25° (0.5 mm), gave pure chloro ketone: $\bar{\nu}_{max}$ 2980, 1710, 1470, 1355, 1105, and 765 $cm^{-1}$; nmr $\delta$ 1.22 (6 H, singlet), 2.16 (3 H, singlet), and 3.63 (2 H, singlet); parent ions at *m/e* 134 and 136 in the mass spectrum.

The bromide can also be prepared from this cyclopropanol intermediate.

**Reaction of 4-Halo-2-butanones with Triphenyltin Hydride.**—A benzene solution containing 1.5 equiv of triphenyltin hydride, 1.0 equiv of 4-halo-3,3-dimethyl-2-butanone, and 3–5 mol % di-*tert*-butyl peroxide was placed in an ampoule and degassed as follows. (1) The ampoule was slowly inserted into a liquid nitrogen bath. (2) The cooled ampoule was evacuated. (3) The ampoule was allowed to warm to ambient temperature. This process was repeated three times, following which the ampoule was sealed while under vacuum. The sealed ampoule was suspended in an oil bath (130°) for 36–48 hr. At the end of this time the ampoule was removed and cooled, and the contents were analyzed by glc.

## Appendix

In order to check the internal consistency of our conclusions regarding acetyl rearrangement in the 3-ketobutyl radical, we have calculated the isotopic composition at each position in the labeled 2-butanone (Table III) from the mass spectral data and the following assumptions.

(1) If there is no rearrangement, all the deuterium in 2-butanone-$d_5$ is at positions a and b. The extra hydrogen in $d_2$-, $d_3$-, and $d_4$-labeled ketone is at positions a and b, while the extra deuterium in the $d_6$ and $d_7$ compounds must be at c.

(2) If 10% of the methylene units at c rearrange to b, a reasonable a/b hydrogen ratio (*ca.* 2.7 from Table II) is possible only if *all* the extra hydrogen in the sample (*i.e.*, the 0.44 fraction associated with the $d_2$-, $d_3$-, and $d_4$-labeled ketone) is located at a.

(3) The distribution of hydrogen and deuterium for a 5% rearrangement of methylene groups lies midway between the 0 and 10% values.

Since the total number of hydrogen and deuterium units remains unchanged for the cases in Table III, we can judge them by comparing the ratio of hydrogen atoms at positions a, b, and c with the experimental results given in Table II. In the absence of rearrangement the ratio is 0.35:0.13:3.0; at 5% rearrangement it is 0.43:0.15:3.0, changing to 0.51:0.21:3.0 for 10% methylene exchange. Although none of these examples fit the observed ratio (0.60:0.22:3.0) exactly, the best agreement is clearly for 10% exchange (20% rearrangement). The assumption that isotopic exchange in the levulinic ester precursor is complete at methylene group b but incomplete at the acetyl methyl group (a) is not entirely unreasonable, since the inductive effect of the carboxyl group should enhance the acidity of the methylene protons. We conclude, therefore, that a small but significant amount of rearrangement has occurred during decomposition of the per-levulinate ester.

TABLE III

CALCULATED HYDROGEN–DEUTERIUM DISTRIBUTIONS IN 2-BUTANONE

| Extent of methylene rearrangement,[a] % | Hydrogen and deuterium distribution | | |
|---|---|---|---|
| | a | b | c |
| 0 | 0.32 H, 2.68 D | 0.12 H, 1.88 D | 2.77 H, 0.23 D |
| 5 | 0.38 H, 2.62 D | 0.15 H, 1.85 D | 2.68 H, 0.32 D |
| 10 | 0.44 H, 2.56 D | 0.18 H, 1.82 D | 2.59 H, 0.41 D |

[a] The rearrangement values in this table must be multiplied by two before being compared with the per cent rearrangements discussed earlier.

**Registry No.**—Ia, 34965-32-7; Ia (DNP), 34965-33-8; Ib, 34965-34-9; Ib (DNP), 34965-35-0; Ic, 18854-62-1; VIIa, 34965-37-2; VIIb, 34965-38-3; VIII, 19961-40-1; IX, 13104-53-5; X, 34965-41-8; XI, 34965-42-9; XI (DNP), 34965-43-0; 2-butanone, 78-93-3; ethyl 3-methyl-3-phenyllevulinate, 34965-44-1; 3-methyl-3-phenyllevulinic acid, 34965-45-2; 3,3-dimethyl-4-hydroxy-2-butanone, 1823-90-1; 3,3-dimethyl-4-hydroxy-2-butanone (tosylate), 24706-89-6.

**Acknowledgment.**—This work was supported in part by National Science Foundation Grants GP 2807 and GP 02025.

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# The Chemistry of Carbanions. XXI. The Stereochemistry of Enolate Alkylation in the 1-Decalone System[1a]

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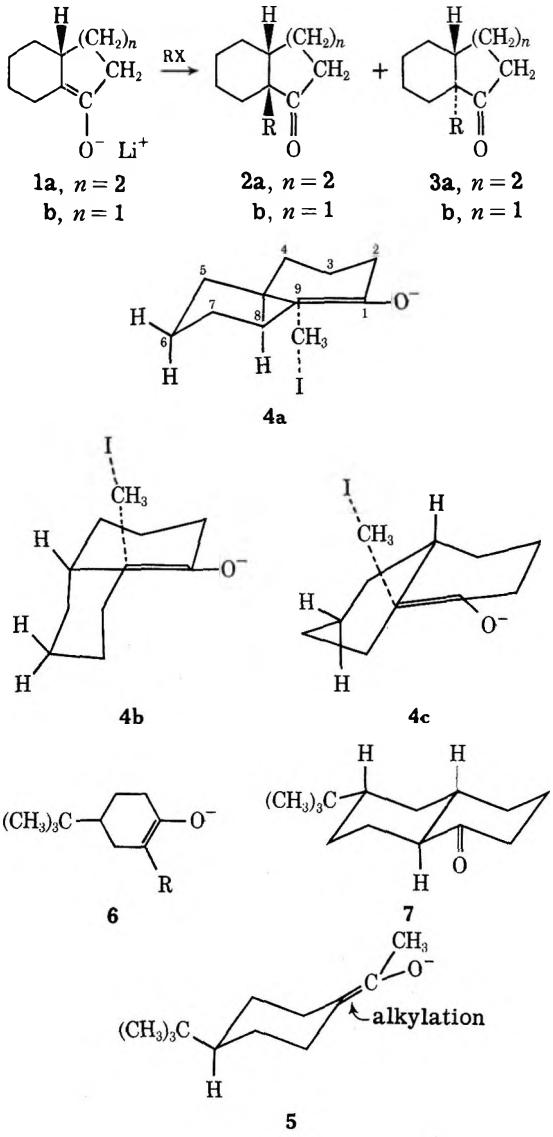
Reaction of the lithium $\Delta^{1,9}$-enolate of *syn*-6-*tert*-butyl-*trans*-1-decalone (**7**) with methyl iodide yielded the same proportion of cis (**13**, 80–86%) and trans (**14**, 14–20%) monoalkylated products as was found in the analogous reaction with the 1-decalone enolate **1a**. This result indicates that it is not necessary to postulate a transition state such as **4c** to account for the predominant formation of 9-alkyl-*cis*-1-decalones in alkylation reactions.

The bridgehead alkylation of enolate anions **1** derived from either 1-decalone or perhydro-1-indanone produces predominantly the cis-fused product **2** (Scheme I);[2] for example, the monoalkylated product

SCHEME I




obtained from the decalone lithium enolate **1a** and methyl iodide in 1,2-dimethoxyethane contained 78–83% of the cis product **2a** (R = $CH_3$) and 17–22% of the trans isomer **3a** (R = $CH_3$).[2a,b] The relationship of these results to those obtained with monocyclic enolates such as **5** (introduction of an equatorial alkyl group favored)[3] and **6** (substantial amounts of both epimers formed)[2d] are uncertain because both rings in the decalone enolate are conformationally mobile, so that three different enolate conformers **4** could be precursors of the cis- (**2a**) and trans- (**3a**) alkylated products. In the reactantlike transition states believed applicable[3,4] in all these alkylation reactions, reaction with conformers **4b** and **4c** would appear especially favorable to the formation of the cis product since attack by the alkylation agent from top side of these conformers (see **4b** and **4c**) is sterically less hindered than attack from the bottom. To overcome at least part of this ambiguity we have examined the corresponding methylation of the enolate **8** derived from the 6-*tert*-butyl-1-decalone **7** since the equatorial 6-*tert*-butyl substituent in this molecule precludes the existence of the corresponding enolate **8** in a conformation analogous to **4c**.

The reactions resulting in formation and alkylation of the enolate **8** are summarized in Scheme II. The stereochemistry of the alkylated products was established by the chemical correlations shown in Scheme III in which use was made of the known[5] stereoselective addition of methylcopper(I) derivatives to $\Delta^{1,9}$-octal-2-one systems (*e.g.*, **9a**) to form 9-methyl-*cis*-decalin derivatives (*e.g.*, **16** and **17**). The major monoalkylated product **13** and the major di- and trialkylated products **15** and **19** formed after relatively long reaction times were all derivatives of the 9-methyl-*cis*-1-decalone system **2a** (R = $CH_3$). In addition, small amounts of 9-methyl-*trans*-1-decalone **14** and other minor products were also formed. From alkylation reactions (see Table I) run for relatively short times to minimize dialkylation, the proportions of 9-methyl products were found to be 80–86% cis (**13**) and 14–20% trans (**14**), a product distribution essentially the same as that found for the methylation of the 1-decalone enolate **1a** under comparable conditions. Thus, we

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SCHEME II

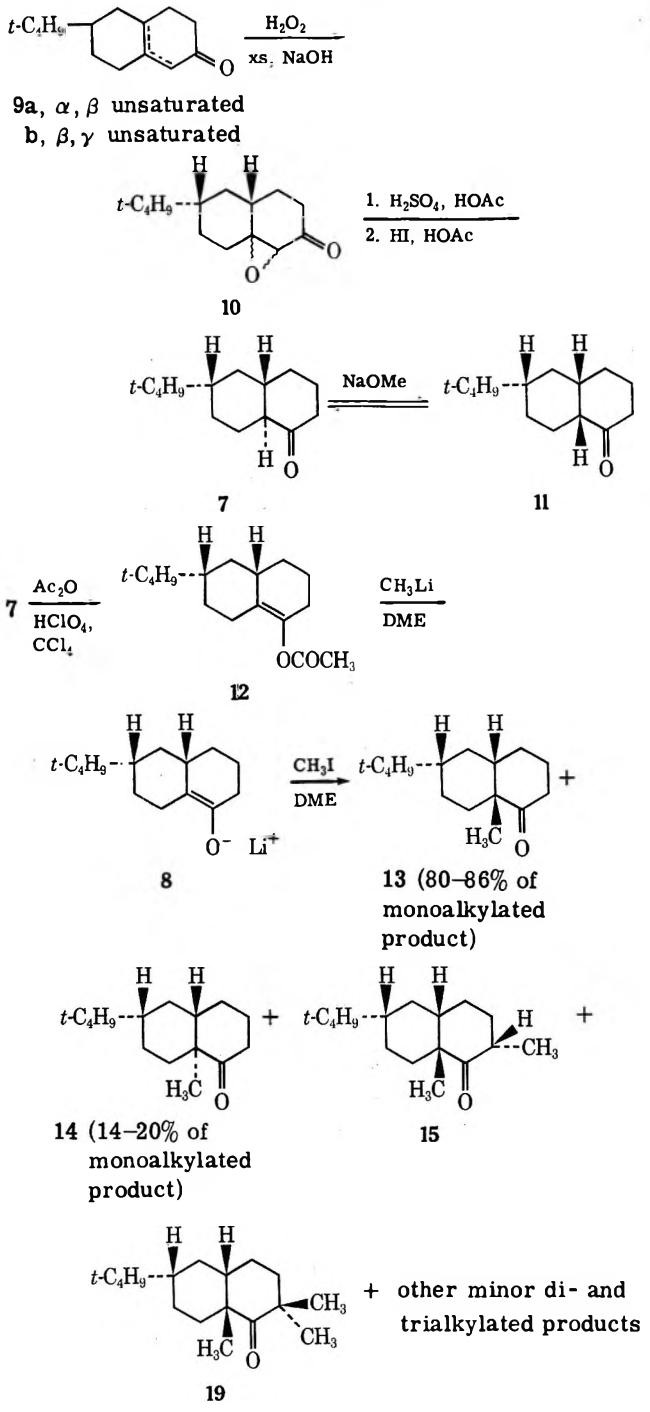



TABLE I

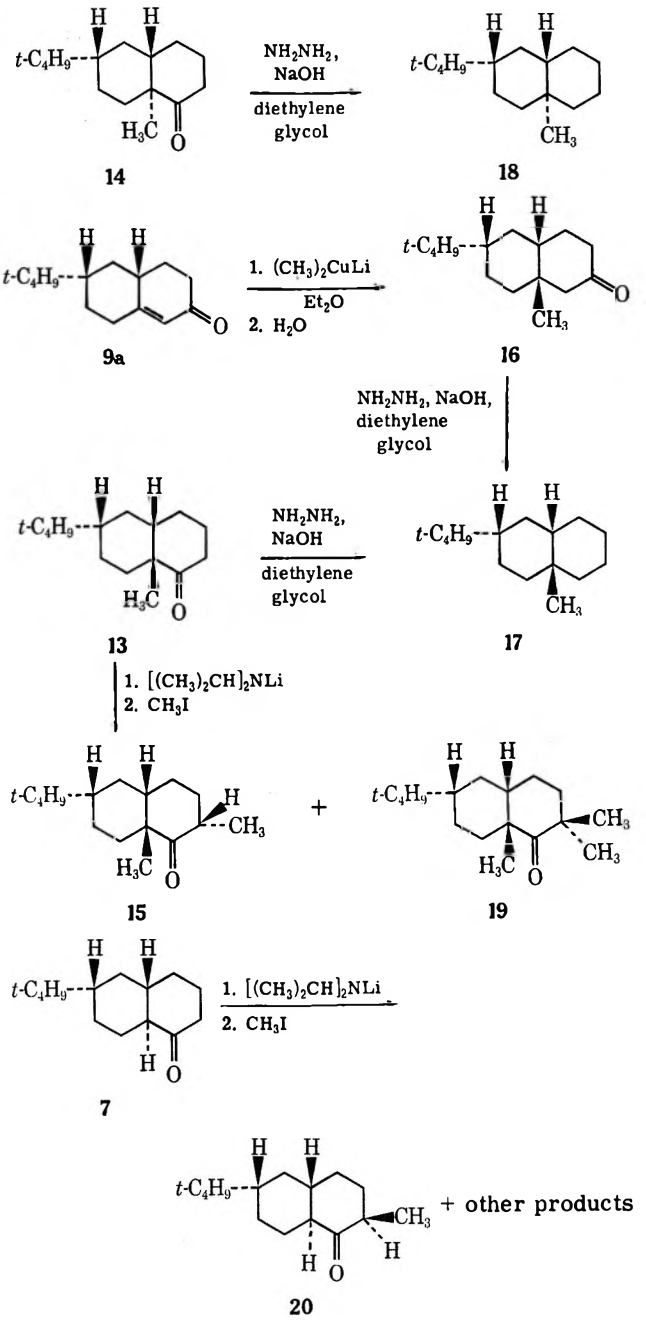
MONOALKYLATED PRODUCTS 13 AND 14 FROM REACTION OF THE ENOLATE 8 WITH MeI IN 1,2-DIMETHOXYETHANE

| Time, sec | Yield of 13 + 14, % | Monoalkylated product composition— 13, % | 14, % |
|---|---|---|---|
| 18 | 30 | 86 | 14 |
| 30 | 51 | 85 | 15 |
| 105 | 49[a] | 82 | 18 |
| 300 | 44[a] | 81 | 19 |
| 1800 | 38[a] | 80 | 20 |

[a] Substantial amounts of dialkylated ketone 15 and other polyalkylated products were present in these reaction mixtures.

conclude that alkylation of the 1-decalone enolate **1a** *via* transition states **4a** and **4b** is adequate to account for the proportion of 9-methyl-*cis*-1-decalone (**2a**, R = $CH_3$) formed. It is appropriate to note that both transition states **4a** and **4b** (but not **4c**) follow the same pattern as the model system **5** in that introduction of the alkyl group equatorial to the nonoxygenated cyclohexane ring is preferred by a factor of 4 or 5 to 1.

SCHEME III




## Experimental Section[6]

**Preparation of the Decalone 7.**—A mixture of the octalones **9**, bp 115–132° (0.08–0.1 mm), $n^{23.5}$D 1.5073 [lit.[7] bp 110–115° (0.05

(6) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated, magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer Model 237 or Model 257 infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Perkin-Elmer Model 202 recording spectrophotometer. The nmr spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60 or a Perkin-Elmer Model R-20B nmr spectrometer. The chemical shifts are expressed in δ values (parts per million) relative to a tetramethylsilane internal standard. The mass spectra were obtained with an Hitachi Perkin-Elmer mass spectrometer. All reactions involving strong bases or organometallic intermediates were performed under a nitrogen atmosphere.

mm), $n^{26.5}$D 1.5100], was prepared by previously described[7] procedures. To avoid separation[7] of the isomeric octalones **9**, the mixture was treated with $H_2O_2$ under sufficiently alkaline conditions that interconversion of the isomers **9a** and **9b** occurred and the conjugated isomer **9a** was epoxidized. Four 35.0-g (0.17 mol) portions of the octalones were each dissolved in 820 ml of MeOH and then treated with sufficient aqueous 1 *M* NaOH to give a solution of pH 10. After each solution had been stirred at 25° for 1.8 hr it was cooled to 0° and treated with 49.5 ml (0.528 mol) of aqueous 30% $H_2O_2$ and a sufficient amount of aqueous 1 *M* NaOH to bring the solution to pH 10. Each solution (which warmed to 10–12°) was stirred with ice-bath cooling for 11–12 min and then diluted with 1 l. of $H_2O$ and extracted with $Et_2O$. The combined ethereal extracts from the four reactions were washed with aqueous NaCl, dried, and concentrated. Recrystallization of the residual white solid from pentane afforded 97.8 g (65%) of the epoxy ketone **10** (presumably a mixture of stereoisomers) as white needles, mp 67.5–71.5°. A portion of this material was repeatedly recrystallized from pentane to separate one stereoisomer of **10**, mp 70.5–71.5° (lit.[7] mp 72–72.5°). Reaction of the epoxy ketone **10** with $H_2SO_4$ in HOAc as previously described[7] yielded the crude enolic $\alpha$-diketone that was reduced with aqueous 57% HI in HOAc as described[7] to form the crude decalone **7**, bp 106–116° (0.2–0.4 mm), mp 59–71°. Recrystallization from MeOH separated the pure decalone **7** as white prisms, mp 74–75.5°, identified with the sample described previously[7] by comparison of ir spectra and glpc retention times.

A solution of 215 mg (1.03 mmol) of the trans ketone **7** and 29.5 mg (0.55 mmol) of NaOMe in 5 ml of MeOH was refluxed for 14.8 hr and then partitioned between pentane and aqueous NaCl. After the pentane solution had been concentrated, analysis (glpc, Apiezon M on Chromosorb P) indicated the presence of the trans ketone **7** (retention time 14.1 min) accompanied by *ca.* 5% of a second component believed to be the cis ketone **11** (11.8 min).

**Preparation of the Enol Acetate 12.**—A solution of 19.0 g (91.3 mmol) of the decalone **7**, 102 g (1.0 mol) of $Ac_2O$, and 0.49 ml of aqueous 70% $HClO_4$ in 283 ml of $CCl_4$ was stirred at 23° for 1 hr and then mixed with 185 ml of cold (3–5°), saturated aqueous $NaHCO_3$ and 185 ml of pentane. Solid $NaHCO_3$ was added portionwise and with stirring until all the HOAc was neutralized. The pentane layer was separated, combined with the pentane extract of the aqueous phase, and then washed with $H_2O$, dried, and concentrated. Distillation separated 19.5 g (86%) of the crude product, bp 96–103.5° (0.1 mm), $n^{26.5}$D 1.4877–1.4878, which contained (glpc, Carbowax 20 M on Chromosorb P) the enol acetate **12** (retention time 26.0 min) accompanied by small amounts of the starting ketone **7** (19.8 min) and a second, unidentified component (29.8 min). Fractional distillation through a 60-cm spinning band column separated the pure enol acetate **12**: bp 101–103° (0.1 mm); $n^{25.5}$D 1.4878; ir ($CCl_4$) 1750 $cm^{-1}$ (enol ester C=O); uv (95% EtOH) end absorption ($\epsilon$ 5700 at 210 m$\mu$); nmr ($CCl_4$) $\delta$ 0.7–2.8 (14 H, m, aliphatic CH), 2.02 (3 H, s, $CH_3CO$), and 0.85 [9 H, s, $(CH_3)_3C$]; mass spectrum *m/e* (rel intensity) 250 (5, $M^+$), 208 (100), 151 (50), 133 (26), 123 (45), 110 (33), 57 (45), 55 (33), 43 (86), and 41 (61).

*Anal.* Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 77.00 H, 10.44.

**Preparation of the 9-Methyldecalin Derivatives 16 and 17.**—To a cold (−10°) solution of $LiMe_2Cu$, prepared from 5.25 g (27.6 mmol) of CuI and 66 mmol of MeLi, in 45 ml of $Et_2O$ was added, dropwise and with stirring, a solution of 5.05 g (24.5 mmol) of the octalone **9a** (purified by low-temperature crystallization[7]) in 5 ml of $Et_2O$. The resulting mixture was stirred for 10 min and then partitioned between $Et_2O$ and an aqueous solution of $NH_4Cl$ and $NH_3$. The organic layer was washed with aqueous $Na_2S_2O_3$, dried, and concentrated to leave a yellow liquid which was crystallized from pentane at Dry Ice temperatures. The ketone **16** separated as 3.77 g (69%) of white needles, mp 48–49°. Recrystallization gave the pure ketone **16**: mp 48.5–49.5°;[8] ir ($CCl_4$) 1710 $cm^{-1}$ (C=O); uv max (95% EtOH) 282 m$\mu$ ($\epsilon$ 20); nmr ($CCl_4$) $\delta$ 0.9–2.7 (14 H, m, aliphatic CH) and 0.89 [12 H, s, $CH_3$ and $(CH_3)_3C$]; mass spectrum *m/e* (rel intensity), 222 (24, $M^+$), 166 (65), 151 (42), 124 (38), 123 (61), 110 (41), 57 (100), 55 (33), and 41 (47).

*Anal.* Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.01; H, 11.91.

A solution of 717 mg (3.2 mmol) of the ketone **16** and 917 mg (15.6 mmol) of 85% $H_2NNH_2$ in 6.6 ml of diethylene glycol was refluxed for 1 hr, cooled, and treated with 390 mg (9.8 mmol) of NaOH. The solution was heated to boiling, the $H_2O$ and unchanged $H_2NNH_2$ were allowed to distil, and the remaining solution was refluxed for 3 hr. The reaction mixture was cooled and partitioned between $Et_2O$ and aqueous 10% HCl. After the ethereal layer had been washed with aqueous NaCl, dried, and concentrated, distillation of the residue (1.066 g of yellow liquid) in a short-path still (0.1 mm and 60–80° bath) separated 403 mg (60%) of the pure (glpc) hydrocarbon **17** as a colorless liquid: $n^{25}$D 1.4792; ir ($CCl_4$) no OH or CO absorption in the 3- or 6-$\mu$ regions; nmr ($CCl_4$) $\delta$ 0.8–2.0 (multiplet, aliphatic CH) with superimposed singlets at 0.97 ($CH_3$) and 0.87 [$(CH_3)_3C$]; mass spectrum *m/e* (rel intensity), 208 (5, $M^+$), 152 (28), 151 (35), 150 (24), 137 (57), 109 (43), 96 (30), 95 (100), 83 (33), 81 (53), 69 (32), 67 (38), 57 (65), 56 (28), 55 (55), and 41 (68).

*Anal.* Calcd for $C_{15}H_{28}$: C, 86.46 H, 13.54. Found: C, 86.65; H, 13.44.

**Methylation of the Lithium Enolate 8. A. Preparation of Alkylated Products.**—To a solution of 65 mmol of MeLi and several milligrams of 2,2-bipyridyl (an indicator) in 62 ml of 1,2-dimethoxyethane was added, dropwise and with stirring, 7.848 g (31.4 mmol) of the enol acetate **12**, during which time the temperature of the reaction solution rose to 60°. The resulting red (indicating excess MeLi) solution was cooled to 20–25° and then 22.2 g (156 mmol) of MeI was added. The resulting yellow reaction mixture was stirred for 1.5 min and then partitioned between pentane and aqueous $NaHCO_3$. After the pentane solution had been dried ($Na_2SO_4$), the volatile organic materials were fractionally distilled from the mixture and the residual liquid was distilled to separate 6.896 g of crude alkylated product, bp 80–86° (0.2 mm), $n^{25}$D 1.4837. Analysis (glpc, silicone fluid $QF_1$ on Chromosorb P) indicated the presence of the following components: **15** (*ca.* 30%, retention time 26.2 min); **19** (*ca.* 16%, 29.2 min); **13** (*ca.* 31%, 31.0 min); an unresolved mixture believed to contain **7**, **20**, and an unidentified dimethylated product (*ca.* 6%, 35.8 min); an unresolved mixture believed to contain an unidentified dimethylated and an unidentified trimethylated product (*ca.* 7%, 40.8 min); and **14** (*ca.* 9%, 43.2 min). On a second glpc column (ethylene glycol adipate on Chromosorb P), the same mixture was resolved into the following components: **15** and **19** (unresolved, *ca.* 45%, 16.6 min); **13** (*ca.* 31%, 17.7 min); **7** and other unidentified components (*ca.* 8%, 24.6 min); unidentified di- and/or trialkylated components (*ca.* 6%, 26.9 min); and **14** (*ca.* 9%, 29.1 min).

Partial separation of the mixture was accomplished by the selective formylation[9] of those materials with no substituents at C-2. To a cold (0–5°), stirred slurry of 1.402 g (25.9 mmol) of NaOMe in 40 ml of $Et_2O$ was added a mixture of 4.99 g of the crude alkylated product and 1.548 g (20.8 mmol) of $HCO_2Et$. After the mixture had been stirred in an ice bath for 15 min and then at room temperature for 17 hr, it was partitioned between $Et_2O$ and $H_2O$. The ethereal layer was washed with aqueous 1 *M* NaOH, dried ($Na_2SO_4$), concentrated, and distilled to separate 2.55 g of alkylated products, bp 70–75° (0.05 mm). This material contained (glpc) the following components: **15**, *ca.* 57%; **19**, *ca.* 20%; **20**, *ca.* 9%; a mixture of unidentified dimethylated and trimethylated isomers, *ca.* 23%.

The alkaline aqueous phase from the formylation procedure was mixed with 3.0 g of NaOH and refluxed for 4 hr, at which time an acidified aliquot of the mixture no longer gave a red-orange color with $FeCl_3$. After the reaction mixture had been neutralized with HCl, it was extracted with $Et_2O$ and the ethereal extract was washed with aqueous NaCl, dried ($Na_2SO_4$), and concentrated. A short-path distillation (0.3–0.4 mm and 80–100° bath) of the residue separated 1.699 g of alkylated products containing (glpc) **13**, *ca.* 71%; **7**, *ca.* 7%; and **14**, *ca.* 22%.

The components of these mixtures were collected (glpc) and ir and mass spectra of each collected peak were used for tentative identification. In cases where single substances could be obtained, sufficient amounts were collected (glpc) for characterization.

(7) H. O. House, R. W. Giese, K. Kronberger, J. P. Kaplan, and J. F. Simeone, *J. Amer. Chem. Soc.*, **92**, 2800 (1970).

(8) The position of the 9-methyl signal in the nmr spectrum of the ketone **16** has been described by M. J. T. Robinson, *Tetrahedron Lett.*, **No. 22**, 1685 (1965).

(9) (a) W. J. Bailey and M. Madoff, *J. Amer. Chem. Soc.*, **76**, 2707 (1954); (b) F. E. King, T. J. King and J. G. Topliss *J. Chem. Soc.* 919 (1957).

A collected sample of the *cis*-9-methyl ketone **13** was obtained as a colorless liquid: $n^{25}D$ 1.4871; ir ($CCl_4$) 1708 $cm^{-1}$ (C=O); uv max (95% EtOH) 296 mμ (ε 34); nmr ($CCl_4$) δ 0.7–2.5 (14 H, m, aliphatic CH), 1.19 (3 H, s, $CH_3$), and 0.82 [9 H, s, $(CH_3)_3C$]; in benzene-$d_6$ the two singlets are at δ 1.00 ($CH_3$) and 0.82 [$(CH_3)_3C$]; mass spectrum *m/e* (rel intensity) 222 (5, $M^+$), 124 (100), 111 (52), 84 (24), 67 (24), 57 (52), 55 (28), and 41 (55).

*Anal.* Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.85; H, 11.86.

A 306-mg (1.4 mmol) sample of this ketone **13** was subjected to the previously described Wolff–Kishner reduction procedure employing 471 mg (8.0 mmol) of 85% $H_2NNH_2$, 190 mg (4.8 mmol) of NaOH, and 3.1 ml of diethylene glycol. The crude product, 178 mg (62%) of yellow liquid, contained (glpc) one major component, the hydrocarbon **17**. A collected (glpc) sample of this hydrocarbon was identified with the previously described sample by comparison of glpc retention times and ir and mass spectra.

A collected (glpc) sample of the *trans*-9-methyl ketone **14** was obtained as a colorless liquid: $n^{25}D$ 1.4879; ir ($CCl_4$) 1705 $cm^{-1}$ (C=O); uv max (95% EtOH) 288 mμ (ε 34); nmr ($CCl_4$) δ 0.8–2.8 (14 H, m, aliphatic CH), 1.03 (3 H, s, $CH_3$), and 0.89 [9 H, s, $(CH_3)_3C$]; in benzene-$d_6$ the two singlets are superimposed at δ 0.80; mass spectrum *m/e* (rel intensity) 222 (17, $M^+$), 147 (34), 111 (29), 109 (21), 95 (30), 81 (47), 68 (21), 67 (40), 57 (100), 55 (51), 53 (21), 43 (23), 41 (96), and 39 (22).

*Anal.* Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.92; H, 11.61.

The previously described Wolff–Kishner reduction procedure was followed with 68.7 mg (0.309 mmol) of the trans ketone **14**, 110 mg (3.4 mmol) of 95% $H_2NNH_2$, 68.5 mg (1.7 mmol) of NaOH, and 0.7 ml of diethylene glycol. The crude neutral reaction product contained (glpc) a single major component, the hydrocarbon **18**. A collected (glpc) sample of the product **18** was obtained as a colorless liquid with ir ($CCl_4$), nmr, and mass spectra clearly different from those of the hydrocarbon **17**. The trans hydrocarbon **18** has an nmr ($CCl_4$) multiplet at δ 0.4–1.9 with superimposed singlets at δ 0.78 (*ca.* 3 H, $CH_3$) and 0.85 [*ca.* 9 H, $(CH_3)_3C$]; mass spectrum *m/e* (rel intensity) 208 (12, $M^+$), 152 (65), 151 (27), 137 (39), 109 (41), 96 (37), 95 (100), 83 (36), 81 (51), 69 (34), 67 (42), 57 (83), 55 (60), and 41 (77).

*Anal.* Calcd for $C_{15}H_{28}$: C, 86.46 H, 13.54. Found: C, 86.74; H, 13.29.

A collected (glpc) sample of the dimethylated ketone **15** was obtained as a colorless liquid: $n^{25}D$ 1.4800; ir ($CCl_4$) 1705 $cm^{-1}$ (C=O); uv max (95% EtOH) 297 mμ (ε 37); nmr ($CCl_4$) δ 0.7–2.8 (13 H, m, aliphatic CH), 1.20 (3 H, s, $CH_3$ at C-9), 0.93 (3 H, d, $J$ = 6.5 Hz, $CH_3$ at C-2), and 0.83 [9 H, s, $(CH_3)_3C$]; in benzene-$d_6$ the nmr peaks are found at δ 1.03 ($CH_3$ at C-9), 0.97 (doublet, $CH_3$ at C-2), and 0.80 [$(CH_3)_3C$]; mass spectrum *m/e* (rel intensity) 236 (9, $M^+$), 138 (24), 125 (44), 109 (35), 95 (37), 81 (40), 79 (20), 69 (22), 68 (23), 67 (41), 57 (63), 55 (48), 53 (20), 43 (35), 41 (100), and 39 (21).

*Anal.* Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.30; H, 11.97.

A collected (glpc) sample of the starting ketone **7** present among the alkylated products was identified with an authentic sample by comparison of glpc retention times and ir spectra. A collected (glpc) sample of the trimethylated ketone **19** exhibited the following spectral properties: ir ($CCl_4$) 1695 $cm^{-1}$ (C=O); nmr ($CCl_4$) δ 0.6–2.7 (12 H, m, aliphatic CH), 1.10 (6 H, s, two $CH_3$ groups), 0.98 (3 H, s, $CH_3$), and 0.78 [9 H, s, $(CH_3)_3C$]; in benzene-$d_6$ the nmr singlets are found at δ 1.11 (3 H, $CH_3$), 1.07 (6 H, two $CH_3$ groups), and 0.79 [9 H, $(CH_3)_3C$]; mass spectrum *m/e* (rel intensity) 250 (10, $M^+$), 193 (20), 152 (62), 110 (22), 109 (65), 95 (46), 81 (36), 69 (32), 68 (20), 67 (38), 57 (100), 55 (47), 43 (37), and 41 (75).

To establish the presence of a cis ring fusion in the major dimethylated product **15** and the major trimethylated product **19**, the cis monomethyl ketone **13** was alkylated by the following procedure.

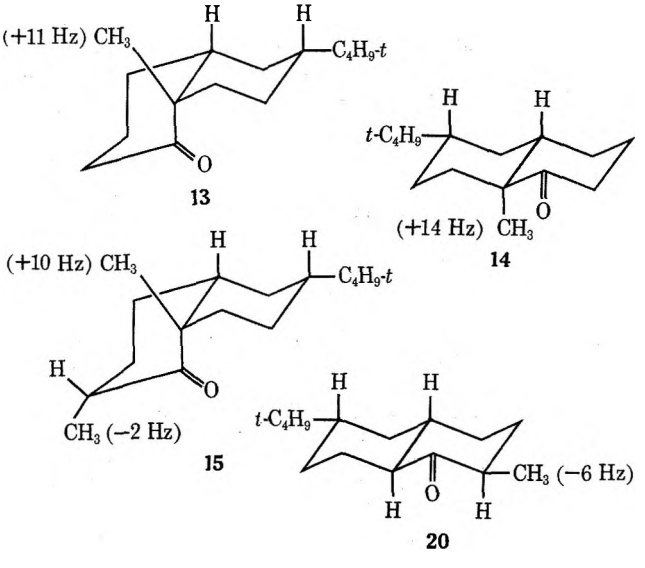
To a cold (0°) solution of $(Me_2CH)_2NLi$ [from 1.39 mmol of MeLi and 158 mg (1.56 mmol) of $(Me_2CH)_2NH$] in 3.7 ml of 1,2-dimethoxyethane containing several milligrams of 2,2-bipyridyl (as an indicator) was added 265.5 mg (1.20 mmol) of the ketone **13**. The resulting solution was warmed to 28°, treated with 744 mg (5.23 mmol) of MeI, stirred at 28–32° for 6.8 min, and then partitioned between pentane and aqueous $NaHCO_3$. The organic layer was washed successively with aqueous 1 *M* HCl and aqueous $NaHCO_3$ and then dried and concentrated to leave a liquid product containing (glpc) ketones **13**, **15**, and **19**. A collected (glpc) sample of the dimethyl ketone **15** was identified with the previously described sample by comparison of glpc retention times and ir spectra. A solution of the remaining reaction product mixture (106 mg) in 1 ml of 1,2-dimethoxyethane was added to 0.55 mmol of $(Me_2CH)_2NLi$ in 1 ml of 1,2-dimethoxyethane and then 191 mg (1.95 mmol) of MeI was added and the mixture was stirred at 25–35° for 23.5 hr. Use of the previously described isolation procedure afforded a crude liquid containing (glpc) primarily the trimethyl ketone **19**. A collected (glpc) sample of **19** was identified with the previously described sample by comparison of ir spectra and glpc retention times.

To obtain an authentic sample of the 2-methyl ketone **20**, the same alkylation procedure was followed with 5.96 mmol of $(Me_2CH)_2NLi$, 1.179 g (5.68 mmol) of the ketone **7**, and 1.77 g (12.5 mmol) of MeI in 13 ml of 1,2-dimethoxyethane. After a reaction period of 6.3 min at 30°, the usual isolation procedure followed by short-path distillation separated 992.4 mg (*ca.* 79%) of crude alkylated product. Reaction of this product with 406 mg (5.5 mmol) of $HCO_2Et$ and 251 mg (4.7 mmol) of NaOMe in 8.6 ml of $Et_2O$, as previously described, followed by separation of the unformylated material and short-path distillation, separated 423 mg of material containing (glpc, silicone fluid $QF_1$ on Chromosorb P) the 2-methyl ketone **20** (retention time 49.2 min) accompanied by at least three minor components (33.6, 39.9, and 54.5 min), some of which are believed to be the less stable stereoisomers of ketone **20**. A collected (glpc) sample of ketone **20** has the following properties: ir ($CCl_4$) 1715 $cm^{-1}$ (C=O); nmr ($CCl_4$) δ 0.86 [9 H, s, $(CH_3)_3C$], 0.90 (3 H, d, $J$ = 6 Hz, $CH_3$), and 0.8–2.5 (14 H, m, aliphatic CH); in benzene-$d_6$ the resolved peaks are at δ 0.82 [$(CH_3)_3C$] and 1.00 (d, $J$ = 5.7 Hz, $CH_3$); mass spectrum *m/e* (rel intensity) 222 ($M^+$, 32), 166 (41), 165 (24), 124 (28), 81 (24), 67 (25), 57 (100), 55 (24), and 41 (55).

*Anal.* Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.94; H, 11.68.

The stereochemical assignments made for ketones **13**, **14**, **15**, and **20** are all consistent with the generalization[10] that the nmr signal for α-methyl groups axial to a cyclohexanone ring will be shifted upfield significantly by changing the solvent from $CCl_4$ to $C_6D_6$ whereas the corresponding equatorial methyl groups will exhibit a slight downfield shift with the same solvent change. The solvent-shift values, $\delta_{CCl_4} - \delta_{C_6D_6}$, for these ketones are summarized in Scheme IV.

SCHEME IV




**B. Determination of the Proportions of Monoalkylated Ketones 13 and 14.**—Employing glpc equipment calibrated with known mixtures of the ketones **13** and **14** and an internal standard

(10) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 159–182.

($n$-$C_{16}H_{34}$), the yields of alkylated products obtained after various reaction times (see Table I) at 2–7° were determined. The reaction solutions contained the enolate **8** (from 1.030 g or 4.12 mmol of enol acetate **12** and 8.3 mmol of MeLi), and 2.676 g (18.8 mmol) of MeI in 7.8 ml of 1,2-dimethoxyethane.

**Registry No.**—**7**, 28435-46-3; **8**, 35096-20-9; **12**, 35096-21-0; **13**, 35096-22-1; **14**, 35096-23-2; **15**, 35096-24-3; **16**, 2530-19-0; **17**, 35096-26-5; **18**, 35096-27-6; **19**, 35096-28-7; **20**, 35096-29-8.

# Stereoselective Syntheses of Isoquinuclidones. I[1,2]

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*Received September 30, 1971*

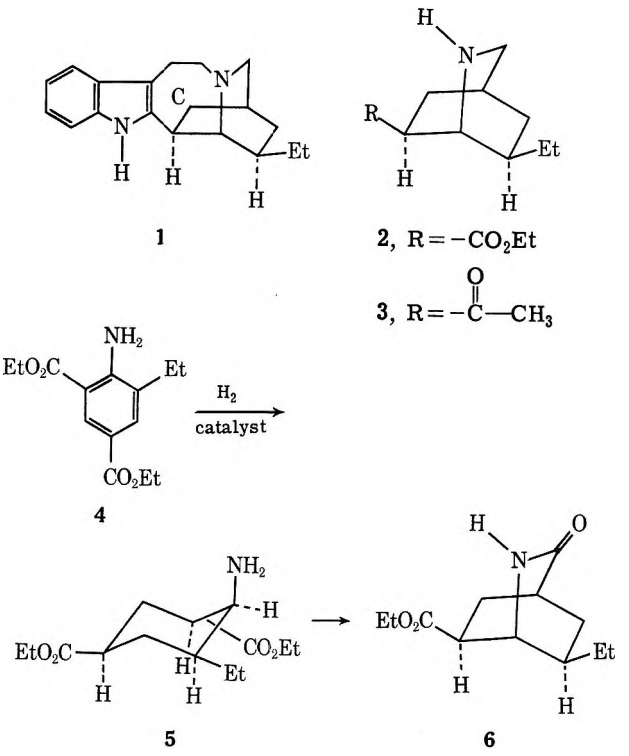
Catalytic hydrogenation of 2,4,6-trisubstituted anilines over a ruthenium catalyst occurs in all cis fashion with concomitant lactam formation to give the corresponding isoquinuclidone derivatives. The 6-acetyl-7-ethyl derivative **23** and the 6-carbethoxy-7-ethyl derivative **6**, prepared in this way, have interest as precursors for the synthesis of iboga and related alkaloids.

The first synthesis of ibogamine (**1**) was reported by Büchi, *et al.*, in 1965.[3] Since then, alternate and stereoselective syntheses of ibogamine have been reported by a number of different groups,[4] as well as partial syntheses[5,6] and alternate approaches.[7] Prior to the synthesis by Büchi, *et al.*,[3] we had undertaken an approach to the synthesis of ibogamine involving a stereoselective synthesis of the isoquinuclidine moiety of the molecule.[2] Since our work has not been duplicated in the intervening period[7] and since the methods employed may be useful to others, the present report and its companion paper[8] are presented to summarize our findings.

Through chemical studies and X-ray crystallographic analysis[9] the configuration of ibogamine has been shown to be as given by structure **1**. Thus, the isoquinuclidine moiety has both substituents cis to the nitrogen bridge. For an eventual synthesis of **1** it appeared desirable to synthesize an isoquinuclidine moiety where R is carbethoxy (**2**) or acetyl (**3**). The key to our approach was the expectation that catalytic hydrogenation of a 2,4,6-trisubstituted aniline such as **4** could be accomplished in an all cis fashion to give **5** which, either spontaneously or on heating, would cyclize to the corresponding isoquinuclidone **6**. To test this idea, then, it was necessary to develop convenient syntheses of 2,4,6-trisubstituted anilines.

As starting material, *o*-ethylaniline was converted to 7-ethylisatin (**7**) in good yield following the general procedure of Marvel and Hiers.[10] This was readily brominated in high yield to the 5-bromo derivative **8** which, on treatment with hydrogen peroxide and base, gave the anthranilic acid derivative **9** in quantitative yield. A von Braun reaction between cuprous cyanide and the corresponding ester **10** proceeded in 83% yield to the cyano derivative **11**. Treatment of **11** with ethanolic hydrogen chloride then gave the desired diester **4** in 83% yield. Although, as summarized in Scheme I, five steps are involved in the formation of **4**, they all proceed in high yield and are convenient to carry out.

Although a number of catalysts and different procedures were investigated for the reduction of **4**, the best conditions found were those using ruthenium oxide as catalyst in absolute ethanol under 2200 psi of hydrogen at 125.° Under these circumstances spontaneous cyclization occurred and the desired isoquinuclidone **6** was isolated in 41% yield, accompanied by the cor-




(1) We thank the Public Health Service, National Heart Institute Grant No. 5-ROI-HE 09813, for financial support of this investigation.

(2) Abstracted from the doctoral dissertation of V. A. Snieckus, University of Oregon, 1965.

(3) G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *J. Amer. Chem. Soc.*, **87**, 2073 (1965); *ibid.*, **88**, 3099 (1966).

(4) (a) Y. Ban, T. Wakamatsu, Y. Fujimoto, and T. Oishi, *Tetrahedron Lett.*, 3383 (1968); (b) W. Nagata, S. Hirai, T. Okumura, and K. Kawata, *J. Amer. Chem. Soc.* **90**, 1650 (1968); (C) S. Hirai, K. Kawata, and W. Nagata, *Chem. Commun.*, 1016 (1968); (d) S. Sallay, *J. Amer. Chem. Soc.*, **89**, 6762 (1967); (e) J. P. Kutney, W. J. Cretney, P. LeQueane, B. McKague, and E. Piers, *ibid.*, **88**, 4756 (1966); (f) J. Harley-Mason, Altaur-Rahman, and J. A. Beisler, *Chem. Commun.*, 743 (1966); *ibid.*, 208 (1967); (g) D. Khac Manh Duc and M. Fetizon, *Bull. Soc. Chim. Fr.*, 771 (1966); (h) *ibid.*, 4154 (1969).

(5) J. W. Huffman, C. B. S. Rao, and T. Kamiya, *J. Org. Chem.*, **32**, 697 (1967).

(6) R. L. Augustine and W. G. Pierson, *ibid.*, **34**, 1070 (1969).

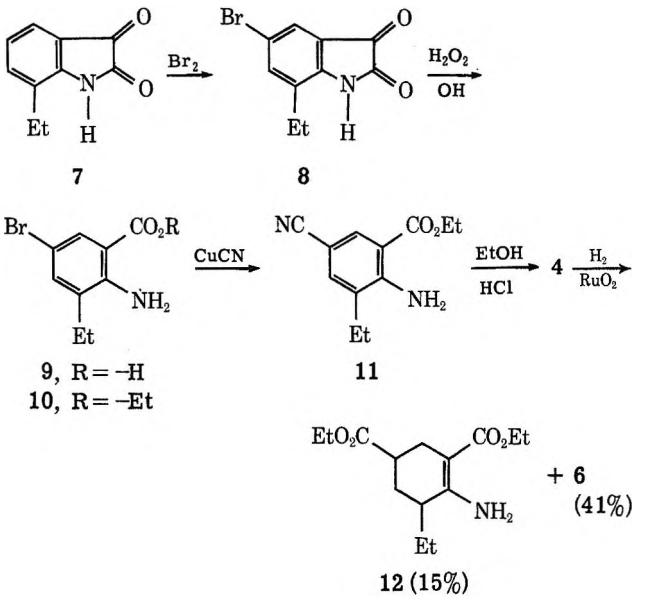
(7) R. L. Augustine and R. F. Bellina, *ibid.*, **34**, 2141 (1969). Although these authors have reported the synthesis of the methyl ester of **6**, their synthetic route is rather different from ours and apparently yielded a mixture of isomers.

(8) J. Witte, and V. Boekelheide, *J. Org. Chem.*, **37**, 2849 (1972).

(9) G. A. Jeffrey, G. Arai, and J. Coppola, *Acta Crystallogr.*, **13**, 553 (1960); J. P. Kutney, R. T. Brown, and E. Piers, *Can. J. Chem.*, **44**, 637 (1966).

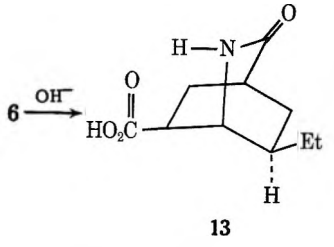
(10) C. S. Marvel and G. S. Hiers, "Organic Syntheses, Collect. Vol. I, Wiley, New York, N. Y., 1951, p 357.

SCHEME I



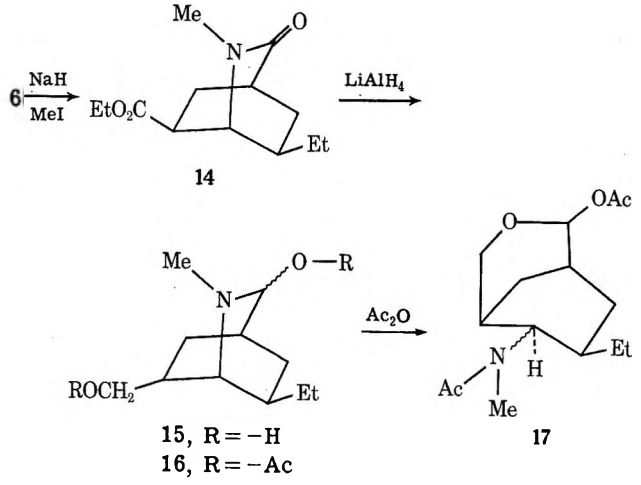
responding tetrahydroanthranilic ester derivative **12** in 15% yield.

Although **6** is a colorless oil, it gives a single spot on tlc and appears in all respects to be homogeneous as would be expected from formation of a single isomer through all cis addition of hydrogen to **4**. Furthermore, careful hydrolysis of **6** gave the corresponding acid **13**



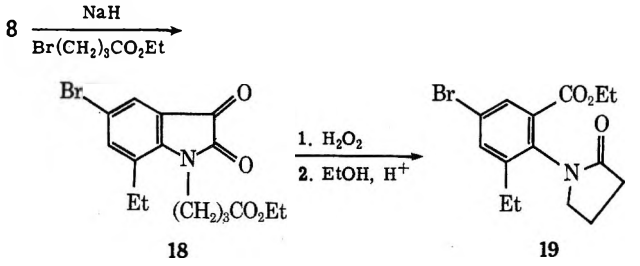
in high yield as a sharp-melting, crystalline compound. The nmr spectrum of **13** showed a single methyl triplet at $\tau$ 9.09, providing additional evidence for the absence of other stereoisomers.

Further evidence regarding the cis relationship of the carbethoxyl group and the nitrogen bridge was obtained in the following way. Methylation of **6** gave the *N*-methyl quinuclidone **14** and reduction of this with lithium aluminium hydride led to the carbinol



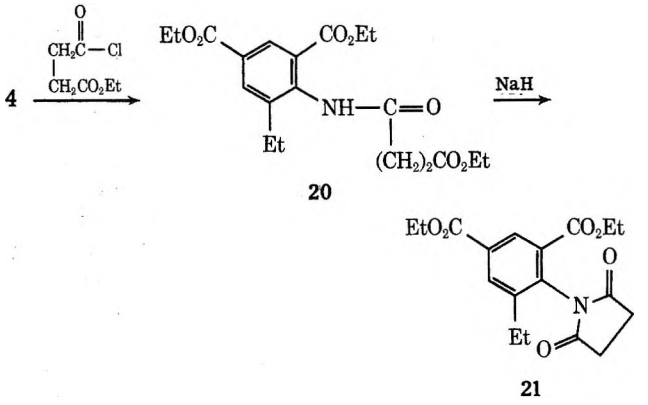
amine **15**. Interestingly enough, the carbinol amine, on acetylation, did not give the expected diacetate **16**, but rather the rearranged diacetate **17**, thus establishing the cis relationship of the carbethoxyl group and the nitrogen bridge in **6**.

With this evidence at hand attempts were then made to elaborate the synthesis to provide the seven-membered C ring of ibogamine. Although methylation of **6** had occurred smoothly, all attempts at its alkylation with ethyl $\gamma$-bromobutyrate were without success. We then attempted to introduce the carbethoxypropyl group at an earlier stage in the synthesis. However, alkylation of **10** with ethyl $\gamma$-bromobutyrate was also unsuccessful.[11] Alkylation of the isatin derivative **8** did occur in good yield to give **18**, but treatment of



**18** with hydrogen peroxide and base, in the usual fashion for cleaving isatin derivatives, gave directly the pyrrolidone derivative **19**, a product not amenable to further elaboration.

Treatment of **4** with $\beta$-carbethoxypropionyl chloride did give the acyl derivative **20**. However, again an

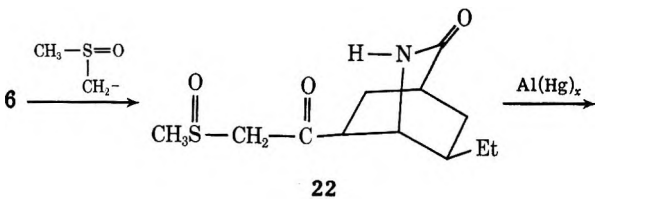


attempted Dieckmann cyclization led only to the corresponding succinimide derivative **21**. At this stage modifications of this synthesis to introduce the seven-membered ring were abandoned and a completely new approach, as described in the accompanying paper, was undertaken.[8]

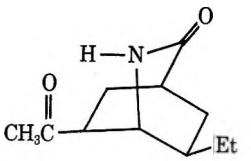
The conversion of the carbethoxy group to acetyl, as an entree for introducing the indole moiety, was also explored, though. Treatment of **6** with dimsyl anion, as described by Cory and Chaykovsky,[12] gave the corresponding $\beta$-keto sulfoxide **22** which, on reduction with aluminum amalgam, gave the acetyl derivative **23** as a colorless oil in 40% overall yield. The structure of the acetyl derivative **23** was further estab-

(11) H. B. MacPhillamy, R. L. Dziemian, R. A. Lueas, and M. E. Kuehne, *J. Amer. Chem. Soc.*, **80**, 2172 (1958), have likewise been unsuccessful in introducing the $\gamma$-carbethoxypropyl group by alkylation of anthranilate esters.

(12) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1345 (1965).




22




23

lished by showing that its properties were completely identical in all respects with those of a sample of **23** prepared *via* an independent synthesis.[8]

## Experimental Section[13]

**5-Bromo-7-ethylisatin (8).**—The conversion of *o*-ethylaniline to 7-ethylisatin occurred in 63% yield, following the procedure of Marvel and Hiers,[10] and gave orange needles: mp 194–195° (lit.[14] mp 193°). To a solution of 37.0 g of 7-ethylisatin in 1.0 l. of chloroform there was added dropwise with stirring over a period of 4.5 hr a solution of 13 ml of bromine in 350 ml of chloroform. The solution was then boiled under reflux for 11 hr, filtered hot to remove tarry impurities, and concentrated to one-quarter of its volume. From the cold solution there separated 41.9 g (78%) of orange crystals: mp 208–210°. An analytical sample, prepared by recrystallization from a methanol–water mixture, was obtained as orange-red needles: mp 209–210°; uv maxima (EtOH) 217 nm (log $\epsilon$ 3.72), 250 (3.73), 256 (sh, 3.69), 303 (2.98), and 443 (2.03); ir (KBr) 1745 cm$^{-1}$ (C=O); nmr ($F_3CCO_2H$) $\tau$ 0.32 (broad s, 1 H, -N-*H*-), 2.20 (q, 2 H, Ar*H*), 7.33 (q, 2 H, ArC*H*$_2$-), and 8.67 (t, 3 H, -$CH_2CH_3$).

*Anal.* Calcd for $C_{10}H_8NO_2Br$: C, 47.26; H, 3.17; N, 5.51; Br, 31.45. Found: C, 47.25; H, 3.25; N, 5.66; Br, 31.48.

**3-Ethyl-5-bromoanthranilic Acid (9).**—To a solution of 53.1 g of 5-bromo-7-ethylisatin (**8**) in 1.0 l. of water containing 52 g of sodium hydroxide there was added dropwise with stirring a solution of 52 ml of 30% hydrogen peroxide in 450 ml of water. The temperature was maintained at 25–30° during the addition and, afterward, the mixture was stirred at room temperature overnight. The precipitate, which separated on acidification, was collected and dried to give 50.5 g (99%) of a crystalline solid of satisfactory purity for use in the next step. A sample recrystallized from an ethanol–water mixture gave fine white needles: mp 198–200°; ir (KBr), 3510 and 3400 cm$^{-1}$ (-$NH_2$), 3000–2500 (-$CO_2H$, broad), and 1670 (C=O).

*Anal.* Calcd for $C_9H_{10}NO_2Br$: C, 44.28; H, 4.42; N, 5.74; Br, 32.73. Found: C, 44.26; H, 4.10; N, 5.98; Br, 33.00.

**Ethyl 3-Ethyl-5-bromoanthranilate (10).**—A stream of hydrogen chloride was bubbled through a boiling solution of 57.0 g of 3-ethyl-5-bromoanthranilic acid (**9**) in 1.5 l. of ethanol over a 48-hr period. Then the solution was poured into 8.0 l. of water containing 150 g of sodium carbonate. The precipitate, which separated, was collected, washed with water, and dried. On recrystallization from an ethanol–water mixture it gave 46.5 g (76%) of yellow needle: mp 37.5–38.0°; ir ($CCl_4$) 3509 and 3367 cm$^{-1}$ (-$NH_2$), 1686 (C=O); nmr ($CCl_4$) 2.20 (d, 1 H, Ar*H*), 2.83 (d, 1 H, Ar*H*), 4.10 (broad s, 2 H, -$NH_2$), 5.72 (q, 2 H, -$CH_2CH_3$), 7.63 (q, 2 H, -$CH_2CH_3$), 8.72 (m, 6 H, -$CH_2CH_3$).

*Anal.* Calcd for $C_{11}H_{14}NO_2Br$: C, 48.53; H, 5.18; N, 5.15; Br, 29.36. Found: C, 48.38; H, 5.33; N, 5.33; Br, 28.95.

The *N*-**acetyl derivative** of **10** was prepared by treating **10** with acetic anhydride in pyridine and was obtained, after recrystallization from petroleum ether, as colorless needles: mp 97.0–97.5°; ir (KBr) 3260 cm$^{-1}$ (-NH), 1720 (-C(O)-O-), and 1660 (-C(O)-NH).

*Anal.* Calcd for $C_{13}H_{16}NO_3Br$: C, 49.68; H, 5.13; N, 4.46; Br, 25.72. Found: C, 49.67; H, 5.09; N, 4.47; Br, 25.97.

**5-Cyano-7-ethylisatin.**—A mixture of 5.1 g of 5-bromo-7-ethylisatin (**8**) and 1.8 g of curpous cyanide in 15 ml of *N*-methyl-2-pyrrolidone was heated at 165° for 15 hr, cooled, and poured into 200 ml of ice water. The resulting precipitate was collected and washed with water. A clean suction flask was substituted and the precipitate was washed thoroughly with acetone. Concentration of the acetone filtrate gave orange crystals which, after recrystallization from chloroform, were obtained as thin orange needles: mp 246.0–247.5°; uv maxima (EtOH) 219 nm (log $\epsilon$ 4.19), 250 (4.30), 256 (4.03), 275 (3.85), 301 (3.53), and 4.06 (2.48); ir (KBr) 2245 cm$^{-1}$ (CN) and 1750 (C=O).

*Anal.* Calcd for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 65.52; H, 4.25; N, 13.36.

**Ethyl 3-Ethyl-5-cyanoanthranilate (11).**—The procedure employed followed the general directions of Friedman and Schechter.[15] Boiling a mixture of 29.0 g of ethyl 3-ethyl-5-bromoanthranilate (**10**) and 11.4 g of cuprous cyanide in 145 ml of *N*-methyl-2-pyrrolidone under reflux for 3 hr, followed by work-up as described,[15] gave, after recrystallization from petroleum ether (60–90°), 18.5 g (83%) of fine white needles: mp 97.5–98.0°; ir ($CHCl_3$) 3472 and 3333 cm$^{-1}$ ($NH_2$), 2222 (CN), and 1689 (C=O).

*Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; N, 6.47. Found: C, 65.96; H, 6.48.

**3-Ethyl-5-cyanoanthranilic Acid.**—The reaction of 3-ethyl-5-bromoanthranilic acid (**9**) with cuprous cyanide in *N*-methyl-2-pyrrolidone following the procedure of Friedman and Schechter gave 3-ethyl-5-cyanoanthranilic acid as white needles, mp 222–225°, in 62% yield after recrystallization from an ethanol–water mixture. The same product was obtained by basic hydrolysis of **11**.

*Anal.* Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30. Found: C, 63.18; H, 5.41.

**Ethyl 3-Ethyl-5-carbethoxyanthranilate (4).**—A solution of 18.5 g of ethyl 3-ethyl-5-cyanoanthranilate (**11**) in 500 ml of absolute ethanol saturated with dry hydrogen chloride was boiled under reflux for 3 hr. After concentration, 500 ml of water was added to the residual solid and the mixture was made basic. The resulting solid imino ester was collected and recrystallized from an ethanol–water mixture to give 21.5 g (100%) of tiny, colorless needles: mp 174.5–175.5°; ir (Nujol) 3497, 3401, and 3344 cm$^{-1}$ (NH, $NH_2$), 1667 (C=O), and 1634 (C=N). The amino ester was suspended in water and the mixture was shaken at room temperature for 60 hr. The resulting solid was collected and recrystallized from an ethanol–water mixture to give 18.0 g (83%) of white needles: mp 65–66°; ir ($CCl_4$) 3571 and 3401 cm$^{-1}$ ($NH_2$) and 1709 and 1689 (C=O); nmr ($CCl_4$) $\tau$ 1.60 (d, 1 H, Ar*H*), 2.21 (d, 1 H, Ar*H*), 3.60 (broad s, 1 H, N-H), 5.67 (q, 4 H, -$CH_2CH_3$), 7.48 (q, 2 H, -$CH_2CH_3$), and 8.63 (m, 9 H, -$CH_2CH_3$).

*Anal.* Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.54; H, 7.18; N, 5.42.

The *N*-**acetyl derivative** of **4** was prepared by reaction of **4** with acetic anhydride and pyridine and obtained, after recrystallization from petroleum ether (30–60°), as colorless needles: mp 85.5–86.5°; ir (Nujol) 3279 cm$^{-1}$ (NH), 1727 (C=O), and 1658 (-C(O)-NH); nmr ($CCl_4$) $\tau$ 0.75 (s, 1 H, N-*H*), 1.75 (d, 1 H, Ar*H*), 2.04 (d, 1 H, Ar*H*), 5.67 (q, 4 H, -$OCH_2$-), 7.47 (q, 2 H, -$CH_2CH_3$), 7.91 (s, 3 H, -C(O)-$CH_3$), and 8.67 (m, 9 H, -$CH_3$).

*Anal.* Calcd for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.88. Found: C, 62.46; H, 6.93.

**Reduction of Ethyl 3-Ethyl-5-carbethoxyanthranilate (4) to give 6 and 12.**—A mixture of 10.7 g of ethyl 3-ethyl-5-carbethoxyanthranilate (**4**) and 25 of ruthenium oxide in 85 ml of ethanol was subjected to hydrogenation at 125° and 2200 psi of hydrogen. After 27 hr, the catalyst was removed and the filtrate concentrated. The resulting pale yellow oil was chromatographed over Florisil using chloroform for elution. The first main eluate fraction gave 1.37 g (15%) of a colorless oil whose spectral properties (uv maxima (EtOH) 294 nm ($\epsilon$ 20,000) and 331 (1250); ir ($CCl_4$) 3460 and 3375 cm$^{-1}$ ($NH_2$), 1735 (C=O), 1690 (C=O), and 1630 (C=C); nmr ($CDCl_3$) $\tau$ 3.50 (broad t,

(13) Elemental analyses reported were determined by Micro-Tech Laboratories. Ultraviolet and visible spectra were taken using a Cary 15 spectrometer, infrared spectra using a Beckman IR-7 spectrometer, and nmr spectra using a Varian A-60. The mass spectral data are by courtesy of Professor D. F. Swinehart.

(14) N. P. Buu-Hoi and P. Jacquignon, *J. Chem. Soc.*, 3C95 (1959).

(15) L. Friedman and H. Schechter, *J. Org. Chem.*, **26**, 2525 (1961).

6 H, $-CH_2CH_3$), and 9.07 (t, 3 H, $-CH_2CH_3$)) and elemental analysis (*Anal.* Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.54; H, 8.57; N, 5.25.) are in agreement with structure **12**.

The second main eluate fraction gave 3.65 g (41%) of a colorless oil: uv (EtOH) only end absorption; ir ($CCl_4$) 3205 $cm^{-1}$ (N–H), 1740 (–C(O)–O–) and 1690 (–C(O)–NH); nmr ($CCl_4$) $\tau$ 2.68 (broad s, 1 H, N–*H*), 5.88 (q, 2 H, $-O-CH_2-$), 6.29 (m, 1 H), 8.75–9.05 (broad, multiplet with two overlapping triplets, 15 H). These properties and the elemental analysis are in agreement with structure **6**.

*Anal.* Calcd for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22. Found: C, 63.87; H, 8.75; N, 6.22.

**6-Carboxy-7-ethyl-2-azabicyclo[2.2.2]octan-3-one (13).**—A solution of 300 mg of **6** in 10 ml of a 5% methanolic potassium hydroxide solution was allowed to stand at room temperature for 3 hr. After concentration, the residue was dissolved in water and carefully neutralized. The precipitate was collected and recrystallized to give 240 mg (90%) of colorless plates: mp 206.5–207.5°; ir (KBr) 3279 $cm^{-1}$ (NH), 3000–2500 (broad, –OH), 1709 (–C(O)–OH), and 1634 (–C(O)–NH–). These crystals sublimed nicely under high vacuum.

*Anal.* Calcd for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.79; H, 7.75; N, 6.98.

**6-Hydroxymethyl-7-ethyl-2-methyl-2-azabicyclo[2.2.2]octan-3-ol (15).**—A solution of 850 mg of **6** and 197 mg of sodium hydride in 20 ml of toluene was boiled under reflux until gas evolution ceased and then a solution of 1.0 g of methyl iodide in 5 ml of toluene was added dropwise with stirring. The mixture was boiled under reflux for 11 hr, cooled, and poured into 50 ml of ice water. The organic layer was extracted with two 30-ml portions of benzene, dried, and concentrated. This gave **14** as 734 mg of a crude yellow oil: ir ($CCl_4$) 1730 $cm^{-1}$ (–C(O)–O–) and 1670 (–C(O)–N<). This was dissolved in 20 ml of tetrahydrofuran and added dropwise with stirring to a suspension of 925 mg of lithium aluminum hydride in 18 ml of tetrahydrofuran. The mixture was boiled under reflux for 12 hr and cooled, and a saturated aqueous solution of sodium sulfate was added dropwise until the metallic hydroxides separated as a granular precipitate. The organic layer was decanted and the reside extracted with ether. After the combined organic extracts had been dried and concentrated, the residual oil was subjected to molecular distillation at 100° and 19 mm to give 500 mg (66%) of a colorless oil: ir ($CCl_4$) 3333 $cm^{-1}$ (–OH) and 1100–1000 (–OH stretching); nmr ($CCl_4$) $\tau$ 6.42 (broad s, 2 H, O–*H*, lost on addition of $D_2O$), 7.47 (m, 1 H, $-CH-N<$), 7.70 (s, 3 H, $N-CH_3$), and 9.02 (t, 3 H, $-CH_2-CH_3$); mass spectrum (70 eV) *m/e* 181 ($m^+ - 18$), 167, 152, 124, 110, and 96.

*Anal.* Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62. Found: C, 66.32; H, 10.44.

Treatment of 100 mg of **15** with 500 mg of acetic anhydride in 3 ml of pyridine followed by addition of 10 ml of ice water caused separation of an oil which was extracted with ether. After the ether extract was dried and concentrated, the residual oil was taken up in chloroform and chromatographed over Florisil. The main eluate fraction gave 100 mg (70%) of a colorless oil (ir ($CCl_4$) 1750 $cm^{-1}$ ($-O-C(O)-CH_3$) and 1640 (>N–C(O)–$CH_3$)), whose spectral properties and elemental analysis are in accord with structure **17**.

*Anal.* Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.65; H, 8.98; N, 5.01.

***N*-(γ-Carbethoxypropyl)-5-bromo-7-ethylisatin (18).**—A mixture of 4.0 g of 5-bromo-7-ethylisatin and 830 mg of sodium hydride in a solution of 55 ml of benzene and 15 ml of dimethyl sulfoxide was boiled under reflux for 30 min before adding 3.40 g of ethyl γ-bromobutyrate. After the resulting mixture had been boiled under reflux for 12 hr, it was cooled and diluted to four times its volume with water. After acidification, the benzene layer was separated and the aqueous layer was extracted twice more with benzene. The combined benzene extracts were concentrated and the red residual oil was chromatographed over silica gel using a 5% ether–benzene mixture for elution. The main fraction of eluate gave red crystals which, after recrystallization from petroleum ether (60–90°), yielded 1.5 g (25%) of fine red needles; mp 83.5–84.5°; uv maxima (EtOH) 219 nm (log ε 4.11), 252 (3.80), 259 (sh, 3.78), 306 (3.20), 4.35 (2.36); ir (KBr), 1740 $cm^{-1}$ (C=O).

*Anal.* Calcd for $C_{15}H_{18}NO_4Br$: C, 52.20; H, 4.93; N, 3.81; Br, 21.71. Found: C, 52.40; H, 4.94; N, 4.05; Br, 21.75.

**Reaction of 18 with Hydrogen Peroxide and Base. Formation of 19.**—To a mixture of 1.30 g of **18** and 1.0 g of sodium hydroxide in 20 ml of water there was added 10 ml of a 3% aqueous hydrogen peroxide solution. After the mixture had stirred overnight at room temperature, it was brought to neutral pH and evaporated. The residue was taken up in 45 ml of absolute ethanol and saturated with dry hydrogen chloride. After the solution had been boiled under reflux for 2 hr, it was concentrated to dryness. The residue was taken up in chloroform and chromatographed over Florisil. The main eluate fraction was a yellow oil which, after molecular distillation at 155° and 0.1 mm, gave 541 mg of a pale yellow oil: ir (film) 1730 $cm^{-1}$ (C=O) and 1690 (>N–C(O)–); nmr ($CCl_4$) $\tau$ 2.45 (d, 1 H, Ar*H*), 2.62 (d, 1 H, Ar*H*), 5.75 (q, 2 H, $-OCH_2-$), 6.40 (m, 2 H, $-CH_2-N-C=O$), 7.62 (m, 6 H), and 8.72 (t, 3 H, $-CH_2CH_3$).

*Anal.* Calcd for $C_{15}H_{18}NO_3Br$: C, 52.93; H, 5.29; N, 4.10. Found: C, 53.03; H, 5.33; N, 4.13.

**Ethyl *N*-(β-Carbethoxypropionyl)-3-ethyl-5-carbethoxyanthranilate (20).**—A mixture of 530 mg of ethyl 3-ethyl-5-carbethoxyanthranilate (**4**), 360 mg of β-carbethoxypropionyl chloride, and 280 mg of anhydrous potassium carbonate in 10 ml of tetrahydrofuran was boiled under reflux for 10 hr. The mixture was then concentrated and the organic residue was taken up in 50 ml of benzene. The benzene extract was then washed with water, dried, and concentrated. The resulting yellow solid was recrystallized from petroleum ether (60–90°) to give 587 mg (75%) of colorless needles: mp 70–71°; ir ($CCl_4$) 3390 $cm^{-1}$ (N–H) and 1720 (broad, C=O); nmr ($CCl_4$) $\tau$ 0.75 (s, 1 H, NH), 1.71 (d, 1 H, Ar*H*), 1.98 (d, 1 H, Ar*H*), 5.73 (m, 6 H, $-OCH_2-$), 7.39 (m, 6 H, $Ar-CH_2-$ and $-C(O)-CH_2-$), and 8.68 (m, 12 H, $-CH_3$).

*Anal.* Calcd for $C_{20}H_{27}NO_7$: C, 61.05; H, 6.92; N, 3.56. Found: C, 61.12, H, 7.06; N, 3.47.

***N*-(2′,4′-Dicarbethoxy-6′-ethyl)phenylsuccinimide (21).**—To a vigorously stirred and boiling suspension of 28 mg of sodium hydride in 50 ml of toluene there was added dropwise over a period of 2 hr a solution of 200 mg of **20** in 40 ml of toluene. The mixture was then boiled under reflux for an additional 10 hr before being cooled and then washed successively with water, dilute aqueous acid, and water. Concentration of the organic layer gave a yellow solid which, on recrystallization from petroleum ether (60–90°), yielded 106 mg (61%) of shiny, colorless needles: mp 104.0–104.5°; ir ($CCl_4$) 1789 $cm^{-1}$ (imide C=O) and 1724 (imide and ester C=O); nmr ($CCl_4$) $\tau$ 1.45 (d, 1 H, Ar*H*), 1.82 (d, 1 H, Ar*H*), 5.68 (m, 4 H, $-O-CH_2-$), 7.22 (s, 4 H, $-C(O)-CH_2$), 7.47 (q, 2 H, $Ar-CH_2-$), and 8.71 (m, 9 H, $-CH_3$); uv maxima (EtOH) 213 nm (log ε 4.17), 230 (sh, 4.17), 287 (3.58), and 296 (3.59).

*Anal.* Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.10. Found: C, 62.46; H, 6.26.

**6-Acetyl-7-ethyl-2-azabicyclo[2.2.2]octan-3-one (23).**—Following the procedure of Corey and Chaykovsky,[12] 225 mg of 6-carbethoxy-7-ethyl-2-azabicyclo[2.2.2]octan-3-one in 10 ml of tetrahydrofuran was added to dimethyl sulfoxide containing 1 molar equiv of dimsyl anion. From the work-up there was obtained 128 mg of **22** as a colorless oil. This was treated directly with aluminum amalgam, again following the procedure of Corey and Chaykovsky.[12] On work-up there was isolated, after chromatography over alumina (Woelm, neutral, activity I) using chloroform for elution, 78 mg of a colorless oil: ir ($CHCl_3$) 1720 (ketone C=O) and 1680 (amide C=O); nmr ($CDCl_3$) $\tau$ 7.82 (s, 3 H, $-C(O)-CH_3$) and 9.09 (t, 3 H, $-CH_2CH_3$). The behavior of this oil on tlc and its spectral properties were completely identical in all respects with those of a sample of **23** prepared independently as described elsewhere.[8]

**Registry No.**—**4**, 34921-57-8; **4** *N*-acetyl derivative, 34921-58-9; **6**, 34921-59-0; **8**, 34921-60-3; **9**, 34921-61-4; **10**, 34921-62-5; **10** *N*-acetyl derivative, 34921-63-6; **11**, 34921-64-7; **12**, 34921-65-8; **13**, 34921-66-9; **15**, 34921-67-0; **17**, 34921-68-1; **18**, 34921-69-2; **19**, 34934-80-0; **20**, 34921-70-5; **21**, 34921-71-6; **23**, 34921-72-7; 5-cyano-7-ethylisatin, 34921-73-8; 3-ethyl-5-cyanoanthracetic acid, 34921-74-9.

# Stereoselective Syntheses of Isoquinuclidones. II[1]

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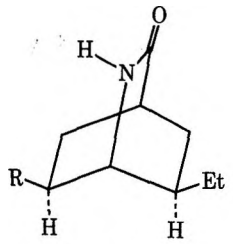
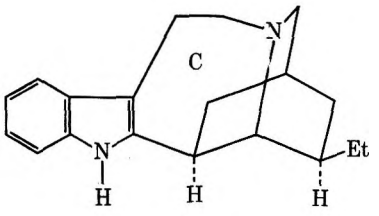
Syntheses of indole derivatives followed by cleavage of the indole ring is shown to be a convenient method of preparing 2,4,6-trisubstituted anilines. Hydrogenation of such 2,4,6-trisubstituted anilines over a ruthenium catalyst occurs in an all cis fashion, providing a stereoselective synthesis of isoquinuclidone derivatives.

In an accompanying paper we have described the stereoselective synthesis of the isoquinuclidine moiety (1) of the ibogamine molecule (2) by hydrogenation appropriate 2,4,6-trisubstituted anilines over a ruthenium catalyst.[2] Important to the success of such a scheme is the availability of convenient syntheses of appropriately substituted anilines. In our previous study,[2] such syntheses were accomplished *via* conversion of a substituted aniline to the corresponding isatin followed by cleavage of the isatin ring and hydrolysis. This scheme, although efficient, is limited to the synthesis of 6-carbethoxy isoquinuclidones (**1a**) or easily derived analogs (**1b**). For a total synthesis of ibogamine and the related iboga alkaloids, it would be desirable to have a more flexible synthesis of 2,4,6-trisubstituted anilines which would allow the stereoselective synthesis of an isoquinuclidine moiety such as **3**, containing the seven-membered C ring of ibogamine (2). The present report describes a study directed toward this end utilizing indole derivatives as intermediates.

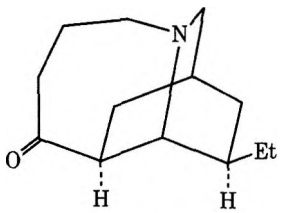


**1a**, R = $-CO_2Et$

**1b**, R = $-C(=O)-CH_3$



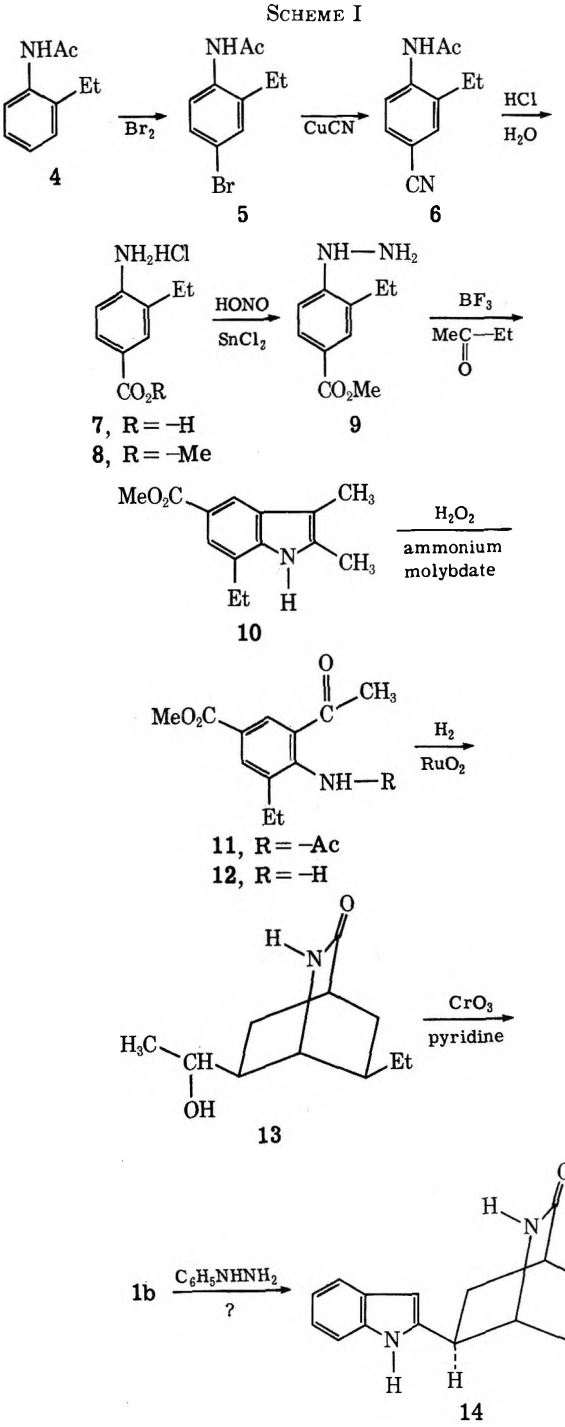
**2**



**3**

To explore the use of indoles as intermediates the first experiments were directed toward preparing the 6-acetyl-7-ethylisoquinuclidone (**1b**), previously synthesized *via* the isatin route.[2] For this purpose and as shown in Scheme I, 2-ethylacetanilide (**4**) was brominated to give 4-bromo-2-ethylacetanilide (**5**) in 93% yield and this in turn was converted in 77% yield *via* a von Braun reaction to the corresponding 4-cyano-2-ethylacetanilide (**6**). Hydrolysis of **6** proceeded quantitatively to the 4-carboxy-2-ethylaniline hydrochloride (**7**). Diazotization and reduction of the corresponding methyl ester (**8**) led in 90% yield to 4-carboethoxy-2-ethylphenylhydrazine (**9**). Reaction of **9** with methyl ethyl ketone under conditions of the Fischer indole synthesis then gave 2,3-dimethyl-5-carbomethoxy-7-ethylindole (**10**) in 68% yield.

SCHEME I



(1) We thank the Public Health Service, National Heart Institute Grant No. 5-ROI-HE 09813, for financial support of this investigation.

(2) V. A. Snieckus, T. Onouchi, and V. Boekelheide, *J. Org. Chem.*, **37**, 2845 (1972).

At this stage it was necessary to develop a procedure for cleavage of the indole nucleus. Oxidative methods have been investigated extensively.[3-7] The use of chromium trioxide in acetic acid, as studied by Koelsch,[4] is very effective but appears to be useful only for 2-acylinodoles. The elegant method of Dolby and Booth using periodate apparently is only moderately successful when electron-withdrawing substituents are present at the 5 position,[7] as in the present case. Therefore, we chose the hydrogen peroxide and ammonium molybdate procedure of Mentzen and Berguer.[5] Under their conditions **10** gave the corresponding acetanilide **11** in 60% yield. Hydrolysis of **11** then led to the desired 2,4,6-trisubstituted aniline (**12**). Although this route requires seven steps, all of them proceed in high yield and are convenient to carry out.

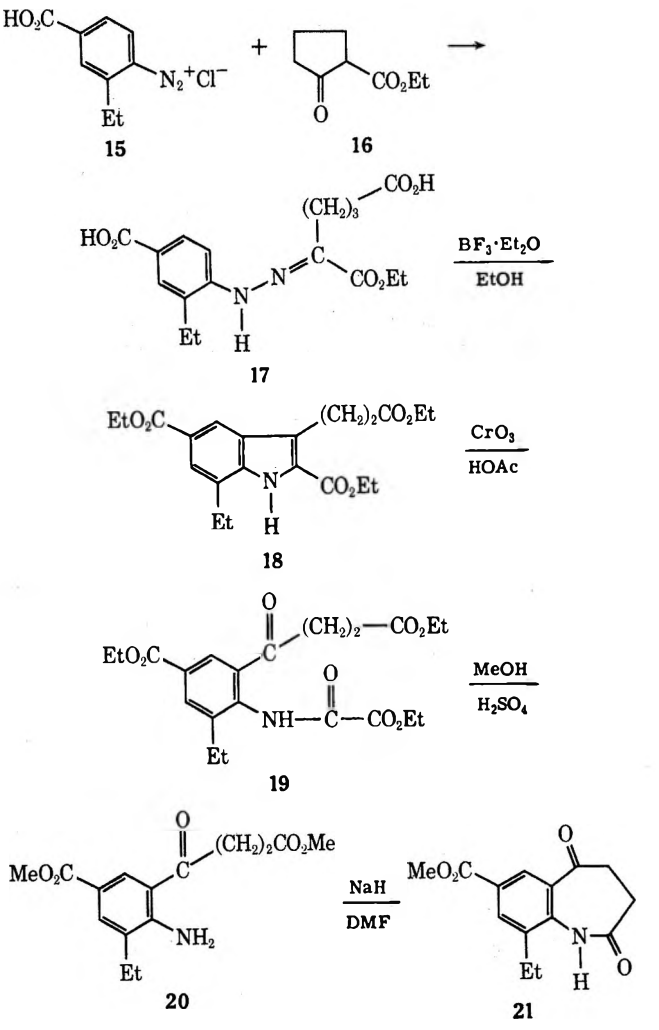
Catalytic hydrogenation of **12** over a ruthenium oxide catalyst at 150° and 2000 psi proceeded smoothly to yield the isoquinuclidone **13**. Oxidation of **13** with chromium trioxide–pyridine readily regenerated the ketone and provided **1b** in 50% yield overall from **12**.

Various experimental procedures were investigated for the conversion of **1b** *via* its phenylhydrazone to the indole derivate **14**, Although ultraviolet spectral data on the crude products indicated the presence of indole derivatives, the yield of **14**, if formed, was too low to be useful. We then turned to exploring the possibility for utilizing the indole approach for the synthesis of **3**. For this purpose **7** was diazotized and the corresponding diazonium salt (**15**) was allowed to react with 2-carbethoxycyclopentanone (**16**) in a Japp–Klingemann reaction. This gave the phenylhydrazone **17** in 77% yield overall from **7**. The Fischer indole cyclization of **17** was then accomplished in 65% yield using boron trifluoride etherate in ethanol, which simultaneously effected esterification of the carboxyl groups to give **18**. In this case with a carbethoxyl group present at the 2 position, oxidative cleavage with chromium trioxide in acetic acid was selected preferentially for cleavage of the indole nucleus and proceeded in 60% yield to give **19**. Hydrolysis of **19** readily gave the free aniline derivative **20** (Scheme II).

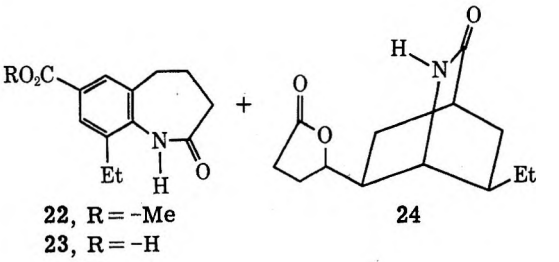
Although the cyclization of *o*-(β-carbethoxypropionyl)anilines has been reported to occur readily on sublimation or heating in boiling decalin,[8] **20** was recovered unchanged after subjection to these conditions. Apparently, the carbethoxyl group in the 4 position has a marked deactivating effect on such cyclizations to the amino group. To overcome this **20** was treated with sodium hydride in dimethylformamide and the resulting anion readily cyclized in 67% yield to give **21**.

It was hoped that hydrogenation of **21** might occur as before to give directly the isoquinuclidone skeleton of **3**. However, when **21** was subjected to hydrogenation over a ruthenium oxide catalyst at 135° and 2000 psi, three products were obtained in yields of 17, 15, and 42%. Based on their spectral data and elementary composition, the three products have been assigned structures **22**, **23**, and **24**. Apparently, spontaneous ring closure to the isoquinuclidone moiety does not occur with amides but rather requires a free, basic, amino group.

SCHEME II




**21** $\xrightarrow[RuO_2]{H_2}$

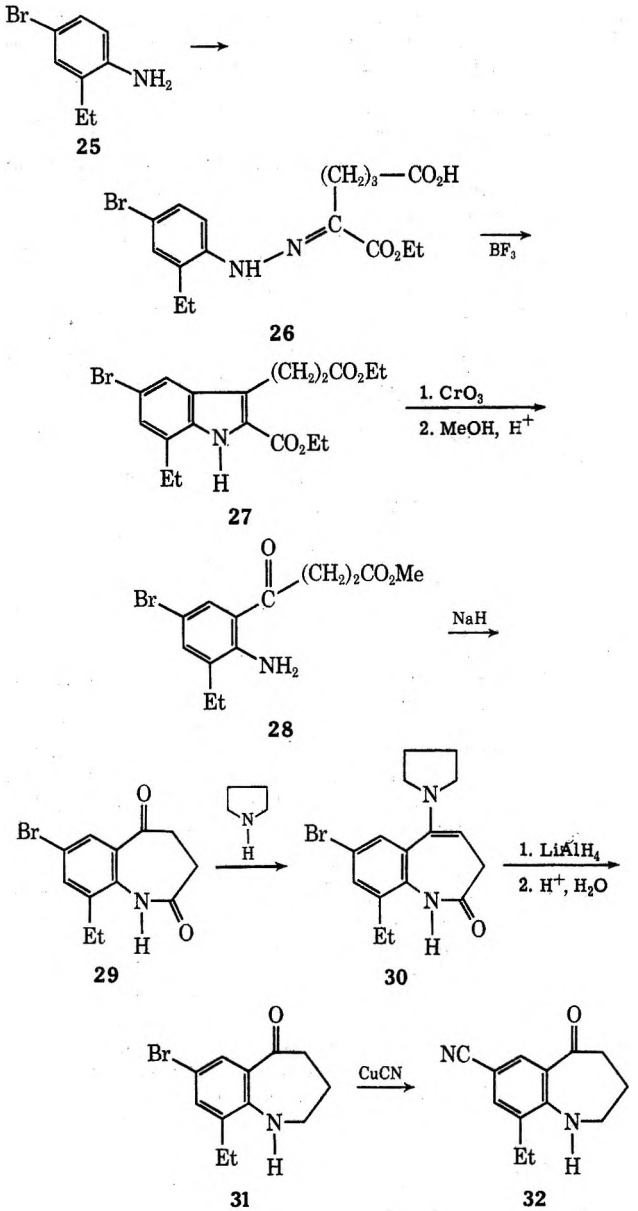



With this outcome it seemed necessary to modify the synthetic sequence to provide a basic amine prior to catalytic hydrogenation so that spontaneous cyclization to the isoquinuclidone moiety would occur. With this goal in mind we converted 4-bromo-2-ethylaniline (**25**) to its diazonium salt and subjected this to a Japp–Klingemann reaction with 2-carbethoxycyclopentanone. The resulting hydrazone derivative **26**, formed in 81% yield, was then cyclized with boron trifluoride etherate in ethanol to give **27**. Oxidation of **27** with chromium trioxide in acetic acid followed by methanolysis of the product yielded **28**. This was cyclized as before with sodium hydride to give **29**. At this stage it was desired to reduce the amide linkage

(3) B. Witkop and S. Goodwin, *J. Amer. Chem. Soc.*, **75**, 337 (1953).
(4) C. F. Koelsch, *J. Org. Chem.*, **8**, 295 (1943).
(5) C. Mentzen and Y. Berguer, *Bull. Soc. Chim., Fr.*, 218 (1952).
(6) L. J. Dolby and D. L. Booth, *J. Amer. Chem. Soc.*, **88**, 1049 (1966).
(7) D. L. Booth, Doctoral Dissertation, University of Oregon, 1965.
(8) A. H. Rees, *J. Chem. Soc.*, 3111 (1959).

while leaving the ketone carbonyl intact. To do this **29** was first converted to the corresponding enamine **30** with pyrrolidine and then **30** was subjected to reduction with lithium aluminum hydride. Hydrolysis of this product gave the desired keto amine **31** in 85% yield. Treatment of **31** with cuprous cyanide in a von Braun reaction gave the cyano derivative **32** in 75% yield (Scheme III).

SCHEME III




Work was discontinued at this stage in view of the reports of total syntheses of ibogamine by other investigators.[9]

## Experimental Section[10]

**4-Cyano-2-ethylacetanilide** (6).—The reaction of bromine in acetic acid with *o*-ethylacetanilide at 5° gave 4-bromo-2-ethylacetanilide (5) in 93% yield as white needles: mp 147.0–147.5°.[11] A solution of 5 and 4.5 g of cuprous cyanide in 50 ml of *N*-methyl-2-pyrrolidone was boiled under reflux for 3 hr. The cold solution was then poured into a mixture of 100 ml of concentrated ammonium hydroxide and 400 ml of water, causing the separation of a brown solid. This was collected, treated with activated charcoal in ethanol, and recrystallized from a water–ethanol mixture to give 5.8 g (77%) of colorless needles: mp 177–178°; ir ($CHCl_3$) 3520 $cm^{-1}$ (NH), 2250 (C≡N), and 1715 (C=O).

*Anal.* Calcd for $C_{11}H_{12}N_2O$: C, 70.23; H, 6.38; N, 14.89. Found: C, 70.42; H, 6.43; N, 14.52.

**3-Ethyl-4-aminobenzoic Acid Hydrochloride** (7).—A suspension of 5.0 g of 6 in 25 ml of concentrated hydrochloric acid was boiled under reflux for 12 hr. During this time the suspended solid went into solution and then reprecipitated. The precipitate was collected and recrystallized from water to give 5.2 g (99%) of white crystals: mp 210–211°.

*Anal.* Calcd for $C_9H_{12}ClNO_2$: C, 53.63; H, 5.95; N, 6.95. Found: C, 53.59; H, 6.03; N, 7.01.

**2-Ethyl-4-carbomethoxyphenylhydrazine** (9).—A solution of 20.0 g of 7 in 250 ml of methanol saturated with dry hydrogen chloride was boiled under reflux for 2 hr and then concentrated to dryness. The white crystalline residue (8) was dissolved in 100 ml of concentrated hydrochloric acid, cooled to −10°, and stirred vigorously while adding a solution of 6.9 g of sodium nitrite in 100 ml of water dropwise over a period of 1.0 hr. The stirring was continued during the addition of a cold solution of 90.0 g of stannous chloride in 90 ml of concentrated hydrochloric acid, the rate of addition being adjusted so that the temperature of the reaction mixture never rose above −5°. After the addition was complete, the pH of the reaction mixture was brought to 14 and the product was extracted with chloroform. When the chloroform extract had been washed with water and dried, concentration gave a white solid which, after recrystallization from an ether–cyclohexane mixture, yielded 17.5 g (90%) of white needles: mp 75–76°; ir ($CHCl_3$), 3450 $cm^{-1}$ (broad NH) and 1690 (C=O); nmr ($CDCl_3$) $\tau$ 2.00–2.30 (m, 2 H, Ar*H*), 3.00 (d, 1 H, Ar*H*), 5.10–5.50 (m, 6 H, -N*H* and $CH_3O$-), 6.53 (q, 2 H, $ArCH_2$-), and 8.75 (t, 3 H, $-CH_2CH_3$).

*Anal.* Calcd for $C_{10}H_{14}N_2O_2$: C, 61.86; H, 7.22; N, 14.44. Found: C, 62.13; H, 7.01; N, 14.71.

**2,3-Dimethyl-5-carbomethoxy-7-ethylindole** (10).—A mixture of 17.5 g of 9, 10.8 g of methyl ethyl ketone, and 0.2 ml of acetic acid in 200 ml of methanol was boiled under reflux for 2 hr. After concentration to remove most of the methanol, 50 ml of boron trifluoride etherate was added and the reaction mixture was heated at 130° for 10 min. It was then added to 300 ml of cold water and extracted with chloroform. After the chloroform extract had been washed with water and dried, it was concentrated to give a brown oil. This was taken up in benzene and chromatographed over silica gel. The white solid obtained from the main fraction of eluate was recrystallized from methanol to give 14.1 g (68%) of white needles: mp 77–78°; ir ($CHCl_3$) 3450 $cm^{-1}$ (NH) and 1700 (C=O); nmr ($CDCl_3$) $\tau$ 1.73 (broad s, 1 H, N*H*), 1.90 (d, 1 H, Ar*H*), 2.31 (d, 1 H, Ar*H*), 6.10 (s, 3 H, $-OCH_3$), 7.19 (q, 2 H, $ArCH_2$-), 7.67 (s, 3 H, $CH_3$), 7.79 (s, 3 H, $CH_3$), and 8.80 (t, 3 H, $-CH_2CH_3$).

*Anal.* Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.67; H, 7.32; N, 5.95.

***N*-Acetyl-2-acetyl-4-carbomethoxy-6-ethylaniline** (11).—To a suspension of 13.8 g of 10 and 300 mg of ammonium molybdate in 300 ml of acetic acid there was added dropwise with stirring over a period of 0.5 hr 50 ml of a 30% aqueous hydrogen peroxide solution. The reaction mixture was held at 35° until all of the suspended indole had dissolved and then it was stirred at room temperature for an additional 8 hr. After dilution with 1.0 l. of water, it was extracted with chloroform. The chloroform extract was washed successively with water, dilute aqueous sodium bicarbonate, and water, before drying. Concentration of the chloroform extract gave a brown oil which was chromatographed over silica gel using benzene for elution. The yellow solid from the main fraction of eluate was recrystallized from a methanol–water mixture to give 9.4 g (60%) of yellow needles: mp 132–133°; nmr ($CDCl_3$) $\tau$ 0.63 (broad s, 1 H, N*H*,), 1.84 (d, 1 H,

(9) (a) G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *J. Amer. Chem. Soc.*, **87**, 2073 (1965); *ibid.*, **88**, 3099 (1966); (b) Y. Ban, T. Wakamatsu, U. Fujimoto, and T. Oishi, *Tetrahedron Lett.*, 3383 (1968); (c) W. Nagata, S. Hirai, T. Okumura, and K. Kawata, *J. Amer. Chem. Soc.*, **90**, 1650 (1968); (d) S. Sallay, *ibid.*, **89**, 6762 (1967); (e) J. P. Kutney, W. J. Cretney, P. LeQueane, B. McHague, and E. Piers, *ibid.*, **88**, 4756 (1967); (f) J. Harley-Mason, Alta-ur-Rahman, and J. A. Beisler, *Chem. Commun.*, 743 (1966); *ibid.*, 208 (1967).

(10) Elemental analyses are by Bernhardt Laboratories and MicroTech Laboratories. Infrared spectra were measured with a Perkin-Elmer Model 202 spectrophotometer, ultraviolet and visible spectra with a Cary 15, nmr spectra with a Varian A-60, and mass spectra by Morgan-Schaffer Corp.

(11) A. Kövendi and M. Kircz, *Chem. Ber.*, **97**, 1896 (1964).

ArH), 2.01 (d, 1 H, ArH), 6.08 (s, 3 H, $-OCH_3$), 7.07–7.66 (m, 5 H), 7.68 (s, 3 H, $-CH_3$), and 8.83 (t, 3 H, $-CH_2CH_3$).

*Anal.* Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.77; H, 6.38; N, 5.27.

**2-Acetyl-4-carbomethoxy-6-ethylaniline (12).**—A solution of 9.1 g of **11** and 10 ml of concentrated sulfuric acid in 200 ml of absolute methanol was boiled under reflux for 4 hr. After the solution had been poured into 1.0 l. of water, it was brought to pH 5 and extracted with chloroform. Concentration of the chloroform extract gave a yellow solid which was chromatographed over silica gel using a 1:1 benzene–chloroform mixture for elution. The crystalline solid from the main fraction of eluate was recrystallized from methanol to give 5.1 g (68%) of yellow needles: mp 114–115°; ir ($CHCl_3$) 3450 and 3350 $cm^{-1}$ ($NH_2$) and 1690 (broad C=O); nmr ($CDCl_3$) $\tau$ 1.58 (d, 1 H, ArH), 2.12 (d, 1 H, ArH), 2.5 (broad s, 1 H, NH), 6.04 (s, 3 H, $-OCH_3$), 7.22–7.71 (m, 5 H), and 8.88 (t, 3 H, $-CH_2-CH_3$).

*Anal.* Calcd for $C_{12}H_{15}NO_3$: C, 65.16; H, 6.79; N, 6.34. Found: C, 65.11; H, 6.85; N, 6.25.

**6-Acetyl-7-ethyl-2-azabicyclo[2.2.2]octan-3-one (1b).**—A solution of 5.0 g of 12 in 100 ml of isopropyl alcohol containing 1.0 g of a ruthenium oxide catalyst was subjected to hydrogenation at 150° and 2000 psi for 8 hr. After removal of the catalyst and solvent, the colorless, residual oil was added to a solution of 35.6 g of the dipyridine–chromium(VI) oxide complex in 700 ml of methylene chloride. The mixture was stirred at room temperature for 15 min before adding 5 ml of isopropyl alcohol and stirring an additional 5 min. The mixture was then filtered and the filtrate concentrated. The resulting dark oil was chromatographed over alumina (Woelm, activity I) using chloroform for elution. The main eluate fraction gave 2.6 g (54%) of a colorless oil: ir ($CHCl_3$) 1720 $cm^{-1}$ (ketone C=O) and 1680 (–C(O)–NH); nmr ($CDCl_3$) $\tau$ 7.82 (s, 3 H, $-C(O)-CH_3$) and 9.09 (t, 3 H, $-CH_2-CH_3$).

*Anal.* Calcd for $C_{11}H_{17}NO_2$: C, 67.69; H, 8.71; N, 7.23. Found: C, 67.58; H, 8.77; N, 7.12.

A solution of 1.5 g of **1b** plus 1 drop of acetic acid and 840 mg of phenylhydrazine in 5 ml of benzene was heated for a short period of time. After removal of the benzene, the residue was dissolved in 2.0 g of polyphosphoric acid and heated at 100–110°. Work up of the reaction mixture followed by thin layer chromatography over silica gel using a 5% ethanol–chloroform mixture for elution gave three spots. The material corresponding to the spot of highest $R_f$ was resubjected to preparative tlc chromatography several times. A sample of this material showed a typical indole ultraviolet spectrum (uv maxima at 225 and 275 nm) but it was insufficient in amount and purity for further characterization.

**2-Ethyl-4-carboxyphenylhydrazone of Ethyl δ-Carboxy-α-oxovalerate (17).**—To a solution of 51.0 g of 3-ethyl-4-aminobenzoic acid hydrochloride (**7**) in a mixture of 10 ml of concentrated hydrochloric acid and 500 ml of water held at 0° there was added dropwise with stirring a solution of 17.5 g of sodium nitrite in 40 ml of water. Then, with continued stirring, a solution of 50 g of sodium acetate in 100 ml of water was added dropwise. This was followed by addition of 46.5 g of 2-carbethoxycyclopentanone with vigorous stirring. Over the course of 1 hr of stirring a yellow oil deposited and crystallized. This yellow solid was removed by decantation and added to 400 ml of a boiling 7% aqueous sodium carbonate solution. After 2 min the solution was cooled and acidified. The yellow solid, which separated, was collected and recrystallized from ethanol to give 77.3 g (77%) of yellow crystals, mp 218–219°.

*Anal.* Calcd for $C_{17}H_{22}N_2O_6$: C, 58.27; H, 6.34; N, 8.00. Found: C, 58.01; H, 6.25; N, 7.82.

**2,5-Dicarbethoxy-7-ethyl-3-(β-carbethoxyethyl)indole (18).**—A suspension of 35.0 g of **17** in 200 ml of absolute ethanol containing 100 ml of boron trifluoride etherate was boiled under reflux until solution was complete and then for an additional 0.5 hr. After removal of most of the solvent, the residue was poured onto cracked ice and extracted with dichloromethane. When the dichloromethane extract had been washed with water and dried, it was concentrated giving a yellow-brown solid. This was chromatographed over alumina (Woelm, activity I) using ether for elution. The solid from the main eluate fraction was recrystallized from an ethanol–water mixture to give 25.2 g (65%) of white needles: mp 125–126°; ir ($CHCl_3$) 3650 $cm^{-1}$ (NH) and 1760 (C=O); nmr ($CDCl_3$) $\tau$ 0.43 (broad s, 1 H, NH), 1.67 (d, 1 H, ArH), 2.15 (d, 1 H, ArH), 5.65 (q, 4 H, $-OCH_2CH_3$), 6.82 (q, 2 H, $-CH_2CH_3$), and 8.68 (m, 12 H, $-CH_2CH_3$).

*Anal.* Calcd for $C_{21}H_{27}NO_6$: C, 63.68; H, 7.15; N, 3.71. Found: C, 64.10; H, 7.11; N, 3.50.

**Ethyl β-(5-Carbethoxy-3-ethyl-2-ethoxalylaminobenzoyl)propionate (19).**—To a suspension of 5.0 g of **18** in 25 ml of acetic acid there was added dropwise with stirring a solution of 3.85 g of chromium trioxide and 2 ml of water in 13 ml of acetic acid. After the reaction had been stirred overnight at room temperature, it was diluted with water and extracted with chloroform. The chloroform extract was washed successively with water, aqueous sodium carbonate, and water. The yellow solid resulting on concentration of the chloroform extract was recrystallized from an ethanol–water mixture to give 3.3 g (60%) of yellow crystals: mp 69–70°; ir ($CHCl_3$) 3450 $cm^{-1}$ (NH) and 1754–1690 (broad C=O); nmr ($CDCl_3$) $\tau$ −0.28 (s, 1 H, NH), 1.68 (d, 1 H, ArH), 1.88 (d, 1 H, ArH), 5.75 (m, 6 H, $-OCH_2CH_3$), 6.67 (m, 2 H, $-C(O)-CH_2-$), 7.25 (q, 2 H, $-CH_2CH_3$), and 8.67 (m, 12 H, $-CH_2CH_3$).

*Anal.* Calcd for $C_{21}H_{27}NO_8$: C, 59.86; H, 6.41; N, 3.33. Found: C, 60.43; H, 6.37; N, 3.14.

**Methyl β-(2-Amino-3-ethyl-5-carbomethoxybenzoyl)propionate (20).**—A solution of 8.4 g of 19 and 5 ml of concentrated sulfuric acid in 100 ml of absolute methanol was boiled under reflux for 3 hr. The reaction mixture was then cooled, poured on to 500 g of ice, made basic, and extracted with chloroform. After the chloroform extract had been washed with water and dried, it was concentrated to give a yellow solid. This was recrystallized from a methanol–water mixture to yield 5.2 g (90%) of yellow crystals: mp 87–88°; ir ($CHCl_3$) 3530 and 3345 $cm^{-1}$ ($NH_2$) and 1720 and 1700 (C=O); nmr ($CDCl_3$) $\tau$ 1.57 (d, 1 H, ArH), 2.16 (d, 1 H, ArH), 6.13 (s, 3 H, $OCH_3$), 6.20 (s, 3 H, $-OCH_3$), 6.62 (m, 4 H, $-C(O)-CH_2-$), 7.42 (q, 2 H, $-CH_2CH_3$), and 8.75 (t, 3 H, $-CH_2CH_3$).

*Anal.* Calcd for $C_{15}H_{19}NO_5$: C, 59.40; H, 6.27; N, 4.62. Found: C, 59.19; H, 6.25; N, 4.51.

**2,3,4,5-Tetrahydro-7-carbomethoxy-9-ethyl-2,5-dioxobenz[f]azepine (21).**—To a suspension of 2.4 g of sodium hydride in 200 ml of tetrahydrofuran held at −40° there was added dropwise with stirring a solution of 15.0 g of 20 in 20 ml of dimethylformamide. The mixture was allowed to warm to room temperature while being stirred over a period of 1.5 hr. It was then poured onto ice, brought to pH 4 with acetic acid, and extracted with chloroform. After concentration of the chloroform extract, the resulting brown solid was chromatographed over Florisil using an 80% hexane–chloroform mixture for elution. The pale yellow solid from the main fraction of eluate was recrystallized from an ethanol–water mixture giving 10.0 g (67%) of yellow crystals: mp 161–162°; ir ($CHCl_3$) 3450 $cm^{-1}$ (NH) and 1725 and 1670 (C=O); nmr ($CDCl_3$) $\tau$ 1.53 (s, 1 H, NH), 7.15 (m, 6 H), and 8.68 (t, 3 H, $-CH_2CH_3$).

*Anal.* Calcd for $C_{14}H_{15}NO_4$: C, 64.75; H, 5.75; N, 5.36. Found: C, 64.37; H, 6.00; N, 5.18.

**Catalytic Hydrogenation of 21.**—A mixture of 1.0 g of **21** and 200 mg of a ruthenium oxide catalyst in 50 ml of ethanol was subjected to hydrogenation at 135° and 2000 psi for 12 hr. After removal of the catalyst and solvent, the residual oil was taken up in chloroform and chromatographed over silica gel. Elution with a 1% methanol–chloroform mixture (fraction A) gave a white solid. This was recrystallized from a methanol–water mixture to yield 170 mg (17%) of white crystals: mp 111–112°; ir ($CHCl_3$) 3470 $cm^{-1}$ (NH), 1730 (–C(O)–O), and 1658 (–C(O)–NH). This has been assigned structure **22**.

*Anal.* Calcd for $C_{14}H_{23}NO_2$: C, 66.40; H, 9.09; N, 5.53. Found: C, 66.56; H, 8.93; N, 5.42.

Further elution with a 3% methanol–chloroform mixture (fraction B) gave a second white solid. This, on recrystallization from benzene, yielded 420 mg (42%) of white crystals: mp 199–200°; ir ($CHCl_3$) 3340 $cm^{-1}$ (NH), 1770 (γ-lactone C=O), and 1670 (–C(O)–NH); nmr ($CDCl_3$) $\tau$ 3.10 (broad s, 1 H, –C(O)–NH–). This has been assigned structure **24**.

*Anal.* Calcd for $C_{13}H_{19}NO_3$: C, 65.27; H, 8.79; N, 5.86. Found: C, 65.09; H, 8.80; N, 6.01.

Finally, elution with a 6% methanol–chloroform mixture (fraction C) gave a third white solid. This, on recrystallization from a methanol–water mixture yielded 150 mg (15%) of white crystals: mp 133–134°; ir ($CHCl_3$) 3280 $cm^{-1}$ (broad, OH and NH), 1695 (broad, –C(O)–OH and –C(O)–NH–); nmr ($CDCl_3$) $\tau$ −1.34 (broad s, 1 H, –C(O)–OH) and 2.02 (d, 1 H, –NH). This has been assigned structure **23**.

*Anal.* Calcd for $C_{13}H_{21}NO_3$: C, 65.27; H, 8.79; N, 5.86. Found: C, 65.23; H, 8.75; N, 5.98.

**2-Ethyl-4-bromophenylhydrazone of Ethyl δ-Carboxy-α-oxovalerate** (26).—To a solution of 100.0 g of 4-bromo-2-ethylaniline in 1.0 l. of water and 190 ml of concentrated hydrochloric acid held at 0° there was added dropwise with stirring a solution of 34.5 g of sodium nitrite in 200 ml of water. After the mixture had been stirred an additional 0.5 hr at 0°, there was added 400 g of sodium acetate followed by 80.0 g of 2-carbethoxycyclopentanone. The yellow oil which separated was extracted with chloroform. Concentration of the chloroform extract gave a residual yellow oil which was added to 600 ml of a 7% aqueous sodium carbonate solution and boiled for 2 min. The solution was then cooled, brought to pH 2, and again extracted with chloroform. The combined chloroform extracts were washed with water, dried, and concentrated. The resulting yellow solid was recrystallized from an ethanol–water mixture to give 172 g (81%) of yellow crystals: mp 133–134°.

*Anal.* Calcd for $C_{16}H_{21}N_2O_4Br$: C, 49.91; H, 5.45; N, 7.27. Found: C, 49.74; H, 5.37; N, 7.53.

**2-Carbethoxy-3-(β-carbethoxyethyl)-5-bromo-7-ethylindole** (27).—A solution of 30.0 g of **26** and 65 ml of boron trifluoride etherate in 250 ml of absolute ethanol was boiled under reflux for 1 hr. After concentration to remove most the solvent, the reaction mixture was poured into ice water and extracted with chloroform. The chloroform extract was washed with water, dried, and concentrated. The residual oil was taken up in ether and chromatographed over neutral alumina (Woelm, activity I). The solid from the main fraction of eluate was recrystallized from an ethanol–water mixture to give 21.0 g (59%) of white crystals: mp 117–118°; nmr ($CDCl_3$) τ 1.13 (s, 1 H, N*H*), 2.32 (d, 1 H, Ar*H*), 2.80 (d, 1 H, Ar*H*), 5.32–6.12 (m, 4 H, Ar$CH_2$–), 6.66 (t, 2 H, –$CH_2$C(O)–), 6.99–7.55 (m, 4 H), and 8.35–9.05 (m, 6 H).

*Anal.* Calcd for $C_{18}H_{22}NO_4Br$: C, 54.58; H, 5.55; N, 3.53. Found: C, 54.27; H, 5.52; N, 3.46.

**Methyl γ-(2-Amino-3-ethyl-5-bromobenzoyl)propionate** (28).—To a solution of 36.0 g of chromium trioxide and 18 ml of water in 120 ml of acetic acid there was added dropwise with stirring a solution of 43.7 g of **27** in 230 ml of acetic acid. The temperature of the reaction mixture was maintained at 25–30° during the addition and stirring was continued for 4 hr at that temperature after the addition was complete. Then the reaction mixture was diluted with 1.0 l. of water and extracted with chloroform. After the chloroform extract had been washed successively with water, dilute aqueous acid, and water, it was concentrated, leaving a brown oil. This was dissolved in 500 ml of methanol containing 40 ml of concentrated sulfuric acid and boiled under reflux for 18 hr. The reaction mixture was then poured into ice water and the brown solid which separated was collected. This was recrystallized from methanol to give 10.0 g (54%, based on **27**) of yellow plates: mp 87–88°; nmr ($CDCl_3$) τ 2.24 (d, 1 H, ArH), 2.75 (d, 1 H, Ar*H*), 6.33 (s, 3 H, –$OCH_3$), 6.76 (t, 2 H, –$CH_2$–C(O)–), 7.42 (m, 4 H), and 8.78 (t, 3 H, –$CH_2CH_3$).

*Anal.* Calcd for $C_{13}H_{16}NO_3Br$: C, 49.68; H, 5.10; N, 4.46; Br, 25.48. Found: C, 49.77; H, 4.97; N, 4.23; Br, 25.52.

**2,3,4,5-Tetrahydro-7-bromo-9-ethyl-2,5-dioxobenz[*f*]azepine** (29).—To a suspension of 3.6 g of sodium hydride in 150 ml of tetrahydrofuran held at −45° there was added dropwise with stirring a solution of 23.6 g of **28** in 100 ml of dimethylformamide. After the addition was complete, the reaction mixture was allowed to warm to room temperature and was stirred for an additional 0.5 hr. It was then poured into 300 ml of water and extracted with chloroform. Concentration of the chloroform extract gave a yellow solid which was chromatographed over silica gel using chloroform for elution. The solid obtained from the main fraction of eluate was recrystallized from methanol to give 13.6 g (66%) of yellow needles: mp 92–93°; ir ($CHCl_3$) 3430 $cm^{-1}$ (NH) and 1680 (broad C=O); nmr ($CDCl_3$) τ 1.25 (s, 1 H, NH), 2.27 (d, 1 H, Ar*H*), 2.50 (d, 1 H, Ar*H*), 6.80–7.50 (m, 6 H), and 8.78 (t, 3 H, –$CH_2CH_3$).

*Anal.* Calcd for $C_{12}H_{12}NO_2Br$: C, 51.06; H, 4.25; N, 4.96; Br, 28.37. Found: C, 51.13; H, 4.17; N, 5.01; Br, 28.08.

**2,3,4,5-Tetrahydro-7-bromo-9-ethyl-5-oxobenz[*f*]azepine** (31).—A solution of 5.0 g of **29**, 3.6 g of pyrrolidine, and 5 mg of *p*-toluenesulfonic acid in 100 ml of toluene was boiled under reflux until no further water was collected in a Dean–Stark trap attached to the system. The mixture was concentrated to less than half-volume, 200 ml of ether was added, and then 1.1 g of lithium aluminum hydride was added. The reaction mixture was boiled under reflux for 8 hr before adding an aqueous saturated sodium sulfate solution dropwise to effect separation of the metallic hydroxides as a granular precipitate. After filtration, the filtrate was concentrated to give a yellow oil. This was taken up in 3 *N* aqueous hydrochloric acid and allowed to stand at room temperature for 3 hr. The solution was then made basic and extracted with chloroform. After concentration of the chloroform extract, the resulting yellow solid was chromatographed over silica gel using a 50% chloroform–benzene mixture for elution. The yellow solid from the main fraction of eluate was recrystallized from methanol to give 4.0 g (85%) of yellow plates: mp 91–92°; ir ($CHCl_3$) 3490 $cm^{-1}$ (NH) and 1665 (C=O); nmr ($CDCl_3$) τ 2.28 (d, 1 H, Ar*H*), 2.79 (d, 1 H, Ar*H*), 5.93 (broad s, 1 H, N*H*), 6.67–8.06 (m, 8 H), 8.73 (t, 3 H, –$CH_2CH_3$).

*Anal.* Calcd for $C_{12}N_{14}NOBr$: C, 53.73; H, 5.41; N, 5.41. Br, 29.85. Found: C, 53.48; H, 5.28; N, 5.27; Br, 30.19

**2,3,4,5-Tetrahydro-7-cyano-9-ethyl-5-oxobenz[*f*]azepine** (32).—A solution of 3.5 g of **31** and 1.8 g of cuprous cyanide in 25 ml of *N*-methyl-2-pyrrolidone was heated at 200° for 2.5 hr. After the reaction mixture had been cooled, it was poured into 100 ml of an aqueous 10% sodium cyanide solution and extracted with chloroform. The chloroform extract was washed with water, dried, and concentrated. The residual brown solid was chromatographed over silica gel using a 50% chloroform–benzene mixture for elution. The crystalline solid obtained from the main fraction of eluate was recrystallized from methanol to give 2.1 g (75%) of yellow crystals: mp 95–96°; ir ($CHCl_3$) 3450 $cm^{-1}$ (NH), 2250 (C≡N), and 1670 (C=O); nmr ($CDCl_3$) τ 2.10 (d, 1 H, Ar*H*), 2.67 (d, 1 H, Ar*H*), 4.33 (broad t, 1 H, NH), 6.39–7.87 (m, 8 H), and 8.87 (t, 3 H, –$CH_2CH_3$).

*Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.89; H, 6.54; N, 13.08. Found: C, 73.05; H, 6.33; N, 12.97.

**Registry No.**—**1b**, 34921-72-7; **6**, 34921-76-1; **7**, 34921-77-2; **9**, 34921-78-3; **10**, 34921-79-4; **11**, 34921-80-7; **12**, 34921-81-8; **17**, 34921-82-9; **18**, 34934-81-1; **19**, 34921-83-0; **20**, 34921-84-1; **21**, 34921-85-2; **22**, 34921-86-3; **23**, 34921-87-4; **24**, 34921-88-5; **26**, 34921-89-6; **27**, 34921-90-9; **28**, 34921-91-0; **29**, 34921-92-1; **31**, 34921-93-2; **32**, 34921-94-3.

# Reactions of 4-(2-Hydroxyethylamino)-2-phenyl-5-pyrimidinecarboxylic Acid with Acetic Anhydride. Syntheses of 8,9-Dihydro-6a-methyl-2-phenyl-5*H*,6a*H*-oxazolo-[2,3-*b*]pyrimido[4,5-*d*][1,3]oxazin-5-one and 8,9-Dihydro-8,8-dimethyl-2-phenyl-5*H*-oxazolo[2′,3′:6,1]pyrido[2,3-*d*]pyrimidin-5-one

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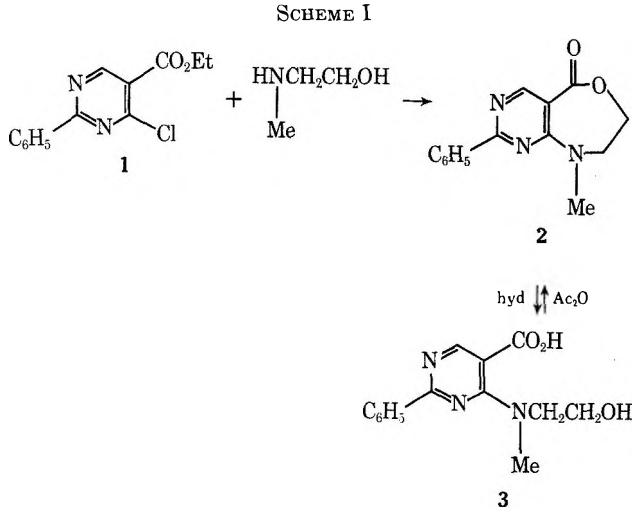
8,9-Dihydro-6a-methyl-2-phenyl-5*H*,6a*H*-oxazolo[2,3-*b*]pyrimido[4,5-*d*][1,3]oxazin-5-one (**7a**), the first member of a new heterocyclic system, oxazolo[2,3-*b*]pyrimido[4,5-*d*][1,3]oxazine, was obtained from the reaction of 4-(2-hydroxyethylamino)-2-phenyl-5-pyrimidinecarboxylic acid (**5a**) with acetic anhydride. The reaction of 5-carboethoxy-4-chloro-2-phenylpyrimidine and 2-hydroxyethylamine, and subsequent hydrolysis, afforded **5a**. Additional members of the new ring system, **7b–e**, were prepared in an analogous fashion. 8,9-Dihydro-8,8-dimethyl-2-phenyl-5*H*-oxazolo[2′,3′:6,1]pyrido[2,3-*d*]pyrimidin-5-one (**11**) was the main product of the reaction of 4-(2-hydroxy-2-methylpropylamino)-2-phenyl-5-pyrimidinecarboxylic acid (**10**) with acetic anhydride. Possible reaction mechanisms for the formation of the new compounds were discussed.

In a previous paper[1] we described the synthesis of a new heterocyclic class, the pyrimido[4,5-*e*][1,4]-oxazepin-5-ones, made directly from 5-carboethoxy-4-chloropyrimidines and 2-(N-substituted)aminoethanols. Further investigation in this area led us to prepare a number of novel compounds which represent new ring systems, *i.e.*, the oxazolo[2,3-*b*]pyrimido[4,5-*d*][1.3]oxazines and oxazolo[2′,3′:6,1]pyrido[2,3-*d*]-pyrimidines. This paper describes the syntheses of such compounds and possible reaction mechanisms for their formation.

Contrary to our previous observation that the 2-(N-substituted)aminoethanols reacted smoothly with 5-carboethoxy-4-chloro-2-phenylpyrimidine (**1**) in refluxing ethanol to give the corresponding 9-substituted 8,9-dihydro-2-phenylpyrimido[4,5-*e*][1,4]oxazepin-5-(7*H*)-one[1] such as **2** (Scheme I), the 2-(N-unsubstituted)-

SCHEME I




aminoethanols such as 2-aminoethanol failed to give a cyclized product under similar conditions, but instead afforded only the corresponding open-chain compound, 5-carboethoxy-4-(2-hydroxyethylamino)-2-phenylpyrimidine (**4a**). Neither extension of the reaction time nor elevation of the reaction temperature was effective in bringing about the cyclization.[2] The inability of **4a** to cyclize may be due to an unfavorable steric relationship of the hydroxyl group relative to the ester carbonyl, which is held by the amino hydrogen through intramolecular hydrogen bonding.

As an alternative route for the cyclization, we turned our attention to the reaction of 4-(2-hydroxyethylamino)-2-phenyl-5-pyrimidinecarboxylic acid (**5a**) with acetic anhydride. Such a ring closure was readily effected in the case of 4-[(2-hydroxyethyl)methylamino]-2-phenyl-5-pyrimidinecarboxylic acid (**3**). Thus, treatment of **3** with acetic anhydride under refluxing conditions gave **2** in 66% yield. Saponification of **4a** with dilute aqueous sodium hydroxide solution and subsequent acidification afforded the corresponding pyrimidinecarboxylic acid **5a**. However, the treatment of **5a** with acetic anhydride under conditions similar to those used for the preparation of **2** resulted in the isolation, not of **6a**, but of 8,9-dihydro-6a-methyl-2-phenyl-5*H*,6a*H*-oxazolo[2,3-*b*]pyrimido-[4,5-*d*][1,3]oxazin-5-one (**7a**),[3] as shown by the elemental analyses and spectral data. The infrared spectrum of **7a** showed only one absorption band at 5.80 $\mu$ in the carbonyl region. The nmr spectrum showed the methyl proton signal at $\delta$ 1.77 ppm, in support of the tricyclic structure. The nmr signal for the methyl protons in **6a** would be expected to appear in the region of $\delta$ 2.0–2.2 ppm.[4] Other proton signals of **7a** were a multiplet at $\delta$ 5.15 (4 H), which was attributed to the protons of the ethylene linkage; an aromatic multiplet centered at 7.70 (3 H) and 6.50 (2 H); and a pyrimidine proton at 9.17 ppm. In the presence of acid or base, **7a** was rapidly hydrolyzed, giving back the starting material **5a**. To our best knowledge, **7a** represents the first example of the oxazolo[2,3-*b*]pyrimido[4,5-*d*][1,3]oxazine ring system. Several other examples of this new heterocyclic system (**7b–e**) were similarly prepared, as shown in Scheme II.

A plausible mechanism of the cyclization appears to involve intermediates **8** and **9**. Initial acetylation on the hydroxy and the carboxylic acid groups of **5** forms

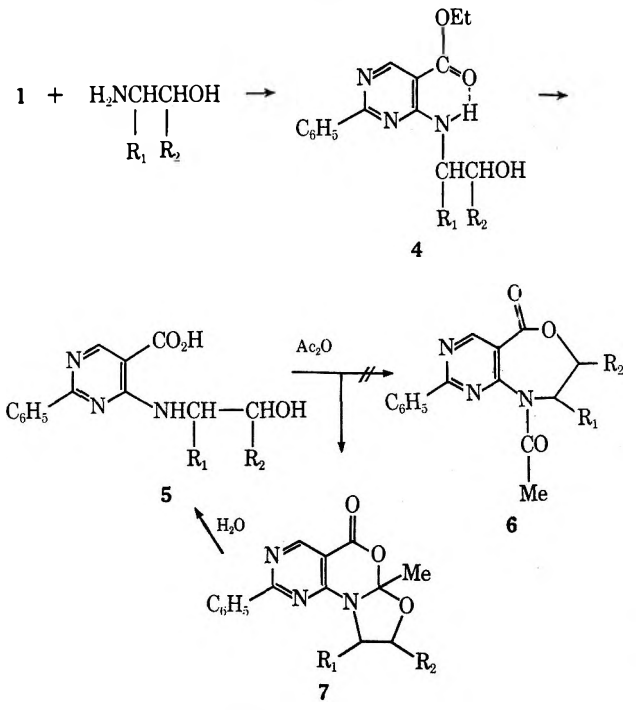
(1) A. A. Santilli, D. H. Kim, and S. V. Wanser, *J. Heterocycl. Chem.*, **9**, 309 (1972).

(2) After submission of our manuscript, there appeared a paper which described an observation similar to ours: S. Yunugi, M. Hieda, T. Fushima, and M. Tomimoto, *Chem. Pharm. Bull.*, **19**, 2354 (1971).

(3) This structure was suggested by Dr. S. C. Bell of these laboratories, to whom the authors are indebted.

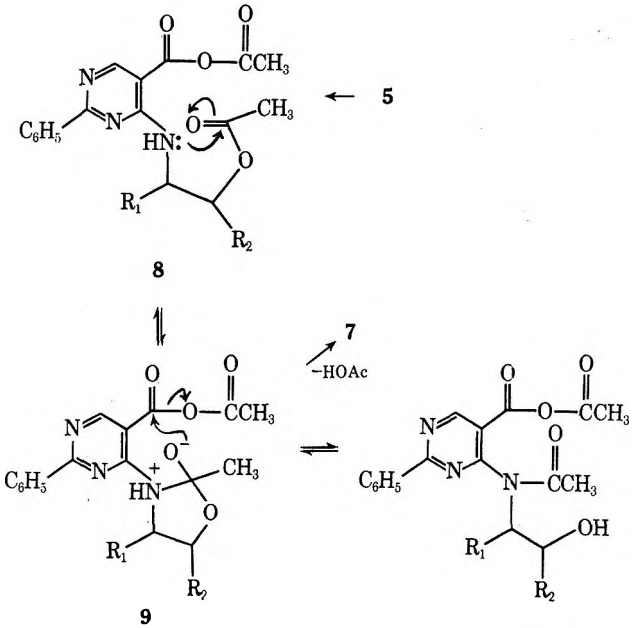
(4) Unpublished result obtained by D. H. Kim.

SCHEME II



**a**, $R_1 = H; R_2 = H$
**b**, $R_1 = H; R_2 = Me$
**c**, $R_1 = H; R_2 = o$-chlorophenyl
**d**, $R_1 = Et; R_2 = H$

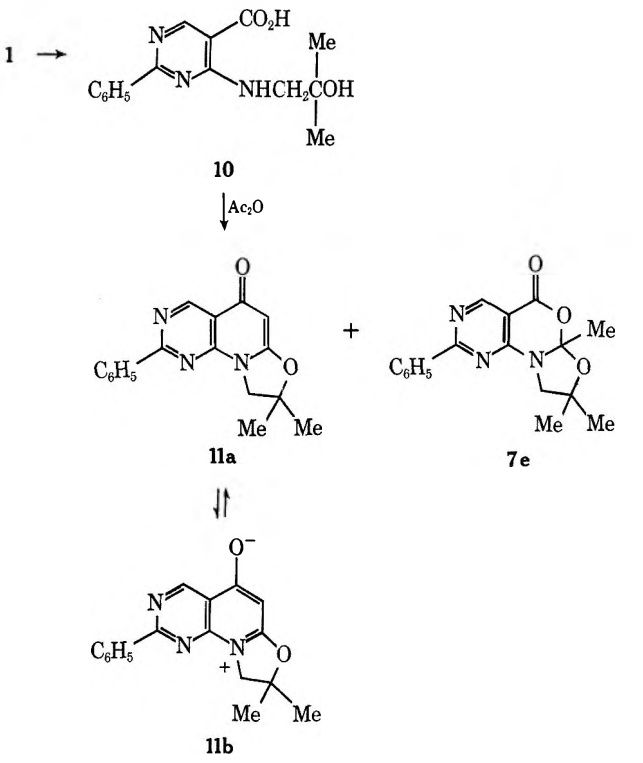
**8**. An intramolecular nucleophilic attack by the $C_4$-amino group in **8** on the *O*-acetyl carbonyl group generates **9**. An intermediate such as **9** has been postu-



lated by Amundsen and Ambrosio for the process of O to N migration of an acyl group in *o*-aminophenyl esters.[5] Subsequent intramolecular nucleophilic attack on the anhydride carbonyl group by the newly generated nucleophilic center in **9** affords the product **7** with elimination of acetate ion.[6] In support of the proposed mechanism, treatment of 4-(2-hydroxyethylamino)-*N*-methyl-2-phenyl-5-pyrimidinecarboxamide with acetic anhydride under similar conditions failed to cause cyclization, but afforded, instead, 4-(2-acetoxyethylamino)-*N*-methyl-2-phenyl-5-pyrimidinecarboxamide.

Interestingly, cyclization of 4-(2-hydroxy-2-methylpropylamino)-2-phenyl-5-pyrimidinecarboxylic acid (**10**) with acetic anhydride took still another reaction course. Thus when **10**, which was prepared from **1** and 2-hydroxy-2-methylpropylamine by the method described earlier in this paper, was allowed to react with a large excess of acetic anhydride for 1 hr under reflux, 8,9-dihydro-8,8-dimethyl-2-phenyl-5*H*-oxazolo-[2′,3′:6,1]pyrido[2,3-*d*]pyrimidin-5-one (**11**), the first example of another new ring system, was isolated in a yield of 49%, along with a very small amount of **7e** (Scheme III). The main product analyzed for $C_{17}H_{15}$-

SCHEME III



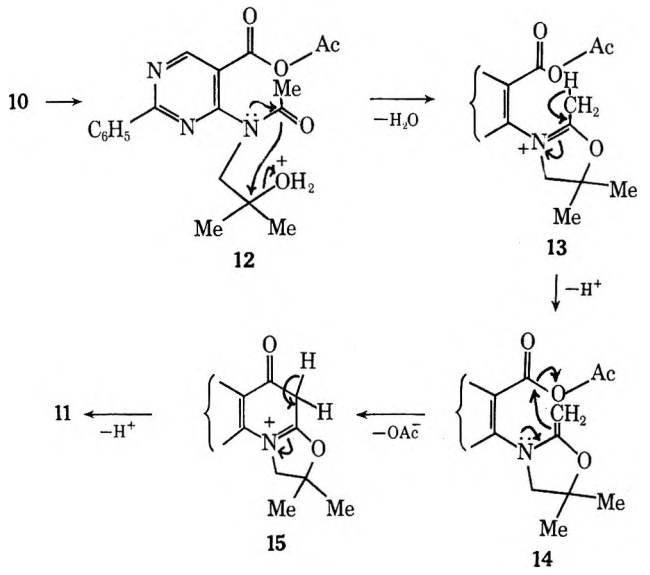
$N_3O_2$, which was confirmed by the mass spectral data as shown by $M \cdot^+$ *m/e* 293. The nmr spectrum of **11** (DMSO-$d_6$) showed, apart from the aromatic proton signals, a 6-methyl proton signal at $\delta$ 1.75 as a sharp singlet, a methylene proton signal as a singlet at $\delta$ 4.47, and a vinyl proton signal at $\delta$ 5.73 as a singlet. The absence of an absorption band in the carbonyl region of the ir spectrum and the downfield shift of the magnetic resonance signal of the methylene protons of **11** compared with that of corresponding protons in **7e** suggests that the product exists as **11b**. In this form it is expected to be thermodynamically more stable in the ground state.

The formation of **11** from **10** can be envisioned by the sequence shown in Scheme IV. Due to the greatly reduced nucleophilicity of the hydroxy group as being *tert*-carbinol, the initial acetylation now takes place at the $C_4$-amino nitrogen, with concurrent or stepwise

(5) L. H. Amundsen and C. Ambrosio, *J. Org. Chem.*, **31**, 731 (1966).

(6) Recently a similar mechanism was presented by Bain and Smalley for the formation of 2-substituted 4*H*-3,1-benzoxazin-4-ones from anthranilic acid and benzoyl chloride: D. I. Bain and R. K. Smalley, *J. Chem. Soc. C*, 1593 (1968).

SCHEME IV



formation of a mixed anhydride, to give an intermediate (12). Cyclization of the intermediate then follows, with displacement of the hydroxy group, which is protonated by acetic acid generated *in situ*, resulting in formation of an oxazolium salt.[7] The latter then transforms, with loss of a proton, into chemically reactive **14**. The final ring-closure reaction now takes place, with elimination of acetate ion from the mixed anhydride of **14**, by a process resembling an enamine reaction. Subsequent deprotonation of **15** affords the isolated product, **11**.

It is worthy to note that in the nmr spectrum of **7e** (DMSO-$d_6$) there appeared two broad singlet proton signals at $\delta$ 3.85 and 4.22, of equal intensity, both attributed to the methylene protons. When the spectrum was determined at 100°, however, there was only one singlet, which appeared at the midpoint of the two peaks. The broad singlet of the *gem*-dimethyl protons which appeared at $\delta$ 1.43 ppm sharpened without change in its position at 100°. A similar phenomenon was observed with **7a**. This observation suggests that 8,9-dihydro-6a-methyl-5*H*,6a*H*-oxazolo[2,3-*b*]pyrimido[4,5-*d*][1,3]oxazin-5-one (**7a–e**) exists in two difficultly interchangeable conformational states at room temperature.[8]

## Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained in KBr discs using a Perkin-Elmer 21 spectrophotometer, and nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as the internal reference. Elemental analyses were performed by the analytical section of Wyeth Laboratories, Inc.

**5-Carboethoxy-4-(2-hydroxyethylamino)-2-phenylpyrimidine** (**4a**).—5-Carboethoxy-4-chloro-2-phenylpyrimidine (**1**) (18 g) was added in small portions to a solution containing 30 ml of 2-hydroxyethylamine in 70 ml of absolute ethanol. Heat was evolved during the addition. The resulting mixture was heated on a steam bath for 7 min. The solvent was removed under reduced pressure, giving an oil which solidified on chilling and scratching. The product weighed 6.0 g and melted at 128–133°. Recrystallization from absolute ethanol increased the melting point to 134–136°; ir 5.90 $\mu$ (C=O); nmr ($CDCl_3$) $\delta$ 1.33 (t, 3 H, $CH_2CH_3$), 2.07 (broad s, 1 H, OH), 3.86 (s) and 3.83 (shoulder) (4 H, $CH_2CH_2$), 4.30 (q, 2 H, $CH_2CH_3$), 7.47 (m, 3 H, aromatic), 8.39 (m, 3 H, 2 aromatic and NH), and 9.05 ppm (s, 1 H, pyrimidine).

*Anal.* Calcd for $C_{15}H_{17}N_3O_3$: C, 62.70; H, 5.96; N, 14.63. Found: C, 62.59; H, 5.76; N, 14.77.

**5-Carboethoxy-4-(2-hydroxypropylamino)-2-phenylpyrimidine** (**4b**) was prepared in the same fashion as **4a** from **1** and 2-hydroxypropylamine in 57% yield, mp 98–100°, ir 5.90 $\mu$ (C=O).

*Anal.* Calcd for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.95. Found: C, 63.45; H, 6.11; N, 14.00.

**5-Carboethoxy-4-(2-*o*-chlorophenyl-2-hydroxyethylamino)-2-phenylpyrimidine** (**4c**) was prepared in a similar fashion to **4a** from **1** and 2-(*o*-chlorophenyl)ethanolamine, then recrystallized from absolute ethanol, mp 164–166°, ir 5.93 $\mu$ (C=O).

*Anal.* Calcd for $C_{21}H_{20}ClN_3O_3$: C, 63.40; H, 5.07; N, 10.56; Cl, 8.91. Found: C, 63.55; H, 5.00; N, 10.83; Cl, 8.76.

**5-Carboethoxy-4-(1-hydroxymethylpropylamino)-2-phenylpyrimidine** (**4d**).—**1** (2.6 g) was added in small portions under mechanical stirring to 12 ml of DMF containing 0.9 g of 2-aminobutanol and 1.0 g of powdered sodium carbonate. After being stirred for 30 min at room temperature, the reaction mixture was heated to boiling for 5 min and then poured into 250 ml of cold water, causing separation of an oil. The aqueous layer was decanted and fresh water was added. The oil solidified on chilling and scratching to give 2.5 g of product, mp 91–100°. Recrystallization from methanol increased the melting point to 103–105°, ir 5.91 $\mu$ (C=O).

*Anal.* Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.33. Found: C, 64.75; H, 6.88; N, 13.51.

**4-(2-Hydroxyethylamino)-2-phenyl-5-pyrimidinecarboxylic Acid** (**5a**).—**4a** (13 g) was added to a mixture of 20% aqueous NaOH solution (50 ml) and absolute ethanol (20 ml) and the resulting mixture was refluxed for 15 min. Acidification of the reaction mixture with dilute HCl caused separation of a precipitate, which was collected on a filter and washed with water. The product (Table I) weighed 10 g and melted at 244–246° dec, ir 3.85 and 6.05 $\mu$ (COOH).

**5-Carboethoxy-4-(2-hydroxy-2-methylpropylamino)-2-phenylpyrimidine.**—To a solution containing 26 g of 2-hydroxy-2-methylpropylamine in 60 ml of absolute ethanol was added 15 g of **1**, in small portions and with gentle heating and stirring. The resulting mixture was heated on a steam bath for 10 min. After most of the ethanol had been removed under reduced pressure, the concentrated reaction mixture was poured into 300 ml of cold water, whereby an oil separated. Chilling and scratching of the oil caused solidification. The solid material was collected on a filter and washed with water several times, giving 16 g of product, mp 76–87°. Recrystallization of the crude product from petroleum ether (bp 30–60°) raised the melting point to 89.5–92°; ir 5.90 $\mu$ (C=O); nmr ($CDCl_3$) $\delta$ 1.32 (s, 6 H, $CH_3CCH_3$), 1.37 (t, 3 H, $CH_3CH_2$), 3.08 (broad s, 1 H, OH), 3.72 (d, 2 H, $NHCH_2$), 4.38 (t, 2 H, $OCH_2$), 7.50 (m, 3 H, aromatic), 8.47 (m, 2 H, aromatic), 8.55 (t, 1 H, NH), and 9.00 (s, 1 H, pyrimidine).

*Anal.* Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.33. Found: C, 65.10; H, 6.84; N, 13.53.

**4-(2-Hydroxy-2-methylpropylamino)-2-phenyl-5-pyrimidinecarboxylic acid** (**10**) was prepared by the hydrolysis of its corresponding ethyl ester in a similar fashion to **5a**: mp 239–241° dec; ir 3.65 and 6.10 $\mu$ (COOH); nmr (DMSO-$d_6$) $\delta$ 1.22 (s, 6 H, $CH_3CCH_3$), 3.68 (d, 2 H, $J$ = 6 Hz, $NHCH_2$), 7.55 (m, 3 H, aromatic), 8.48 (m, 2 H, aromatic), 8.76 (t, 1 H, $J$ = 6 Hz, NH), and 8.92 (s, 1 H, pyrimidine).

*Anal.* Calcd for $C_{13}H_{17}N_3O_3$: C, 62.70; H, 5.96; N, 14.63. Found: C, 62.45; H, 5.65; N, 14.43.

**8,9-Dihydro-9-methyl-2-phenylpyrimido[4,5-*e*][1,4]oxazepin-5(7*H*)-one** (**2**).—A mixture of 4-[(2-hydroxyethyl)methylamino]-2-phenyl-5-pyrimidinecarboxylic acid[1] (1.8 g) and acetic anhydride (20 ml) was heated under reflux for 40 min. Most of the excess acetic anhydride was removed by distillation under reduced pressure. Chilling of the concentrated solution in ice caused separation of 1.1 g of crystalline product, mp 161–167°.

(7) Amides of 2-hydroxyethylamines are known to cyclize to oxazolines under acidic conditions. See J. A. Frump, *Chem. Rev.*, **71**, 483 (1971).

(8) One of the referees suggested that the observed nmr changes might be due to ionization of **7e** to its opened zwitterionic form at 100°.

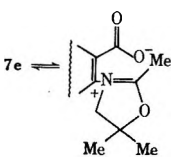


TABLE I

4-(2-HYDROXYETHYLAMINO)-2-PHENYL-5-PYRIMIDINECARBOXYLIC ACIDS[a]

| Compd | Mp, °C | Formula | Calcd, % C | Calcd, % H | Calcd, % N | Found, % C | Found, % H | Found, % N |
|---|---|---|---|---|---|---|---|---|
| **5a** | 244–246 dec | $C_{13}H_{13}N_3O_3$ | 60.22 | 5.05 | 16.21 | 60.49 | 5.29 | 16.01 |
| **5b** | 241.5–242.5 dec | $C_{14}H_{15}N_3O_3$ | 61.53 | 5.53 | 15.38 | 61.48 | 5.24 | 15.34 |
| **5c** | 238–240 dec | $C_{19}H_{16}ClN_3O_3$ | 61.71 | 4.36 | 11.36 | 61.63 | 4.69 | 11.50 |
| **5d** | 258–261 dec | $C_{15}H_{17}N_3O_3$ | 62.70 | 5.96 | 14.63 | 62.63 | 5.94 | 14.33 |

[a] Microanalytical results for C, H, and N agreed with theoretical values within ±0.4%.

TABLE II

8,9-DIHYDRO-6a-METHYL-2-PHENYL-5*H*,6a*H*-OXAZOLO[2,3-*b*]PYRIMIDO[4,5-*d*][1,3]OXAZIN-5-ONES[a]

| Compd | Mp, °C | Yield, % | Formula | Calcd, % C | Calcd, % H | Calcd, % N | Found, % C | Found, % H | Found, % N |
|---|---|---|---|---|---|---|---|---|---|
| **7a** | 176–179 | 70 | $C_{15}H_{13}N_3O_3$ | 63.59 | 4.63 | 14.83 | 63.75 | 4.63 | 14.86 |
| **7b** | 166–168.5 | 64 | $C_{16}H_{15}N_3O_3$ | 64.63 | 5.09 | 14.14 | 64.31 | 4.78 | 13.93 |
| **7c** | 189–191 | 80 | $C_{21}H_{16}ClN_3O_3$ | 64.04 | 4.10 | 10.67 | 64.04 | 4.05 | 10.74 |
| **7d** | 179–183 | 12 | $C_{17}H_{17}N_3O_3$ | 65.58 | 5.50 | 13.50 | 65.79 | 5.51 | 13.51 |

[a] Microanalytical results for C, H, and N agreed with theoretical values to within ±0.4%.

Recrystallization from absolute ethanol improved the melting point to 170–173° (lit.[1] mp 170–173°). A mixture melting point with an authentic sample was not depressed.

**8,9-Dihydro-6a-methyl-2-phenyl-5*H*,6a*H*-oxazolo[2,3-*b*]pyrimido[4,5-*d*][1,3]oxazin-5-one (7a).**—A mixture of **5a** (1.5 g) and acetic anhydride (30 ml) was heated to obtain a clear solution. The resulting solution was refluxed for 0.5 hr. The excess acetic anhydride was distilled off under reduced pressure, giving an oil which solidified on chilling. The solid was collected on a filter and washed with acetone, yielding 1.1 g of product, mp 176–178°. Recrystallization from acetone afforded an analytical sample.

In a similar fashion, **7b–d** (Table II) were prepared from acetic anhydride and **5b–d**, respectively, and recrystallized from acetic anhydride.

**8,9-Dihydro-8,8-dimethyl-2-phenyl-5*H*-oxazolo[2′,3′:6,1]pyrido[2,3-*d*]pyrimidin-5-one (11) and 8,9-Dihydro-6a,8,8-trimethyl-2-phenyl-5*H*,6a*H*-oxazolo[2,3-*b*]pyrimido[4,5-*d*][1,3]oxazin-5-one (7e).**—A mixture of **10** (3.0 g) and acetic anhydride (50 ml) was heated to obtain a clear solution. The resulting solution was refluxed for 0.5 hr, and most of the excess acetic anhydride was distilled under reduced pressure. The concentrated solution was filtered under suction while hot. Chilling of the filtrate caused separation of a crystalline product which was collected on a filter, giving 1.5 g of **11**, mp 243–248°. Recrystallization from acetic anhydride raised the melting point to 251–252°, uv max (95% EtOH) 274 mμ (ε 28.4 × 10³) and 304 (19.2 × 10³).

*Anal.* Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.69 H, 5.22; N, 14.35.

Concentration of the mother liquor under reduced pressure and subsequent chilling in ice caused separation of a small amount of **7e**, which was collected on a filter and recrystallized from acetic anhydride: mp 138–140.5°; ir 5.80 μ (C=O); nmr (DMSO-$d_6$) δ 1.43 (s, 6 H, $CH_3CCH_3$), 1.73 (s, 3 H, $CH_3$), 3.85 and 4.22, which at 100° merged into a singlet at 4.03 (2 H, $CH_2$), 7.65 (m, 3 H, aromatic), 8.50 (m, 2 H, aromatic), and 9.05 (s, 1 H, pyrimidine).

*Anal.* Calcd for $C_{17}H_{17}N_3O_3$: C, 65.68; H, 5.50; N, 13.50. Found: C, 65.63; H, 5.21; N, 13.23.

**4-(2-Hydroxyethylamino)-*N*-methyl-2-phenyl-5-pyrimidinecarboxamide.**—A mixture of 10 g of **4a** and 100 ml of methylamine–ethanol solution which was obtained by saturating methylamine in ethanol at room temperature was charged in a steel bomb. The bomb was heated in a steam bath for 5 hr. After the bomb was cooled to room temperature, it was opened. Evaporation of most of the unreacted amine caused separation of 9.1 g of product, mp 206–208°. Recrystallization from absolute ethanol afforded an analytical sample, mp 205–207°, ir 6.12 μ (amide C=O).

*Anal.* Calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.88 H, 6.28; N, 20.52.

**4-(2-Hydroxyethylamino)-*N*-methyl-2-phenyl-5-pyrimidinecarboxamide Acetate Ester.**—A mixture of 2.0 g of 4-(2-hydroxyethylamino)-*N*-methyl-2-phenyl-5-pyrimidinecarboxamide and 45 ml of acetic anhydride was heated under reflux for 2 hr. Removal of the excess acetic anhydride under reduced pressure afforded a solid residue which was collected on a filter and recrystallized from absolute ethanol, giving 1.0 g of product, mp 147–149°, ir 5.76 (ester C=O) and 6.11 μ (amide C=O).

*Anal.* Calcd for $C_{16}H_{18}N_4O_3$: C, 61.13; H, 5.77; N, 17.83. Found: C, 61.41; H, 6.01; N, 17.96.

**Registry No.**—**4a**, 32515-49-4; **4b**, 32412-64-9; **4c**, 32556-42-6; **4d**, 32412-65-0; **5a**, 32412-66-1; **5b**, 32412-67-2; **5c**, 32412-68-3; **5d**, 32412-69-4; **7a**, 32412-72-9; **7b**, 32412-73-0; **7c**, 32412-74-1; **7d**, 32412-75-2; **7e**, 32412-77-4; **10**, 32412-71-8; **11**, 34111-38-1; 5-carboethoxy-4-(2-hydroxy-2-methylpropylamine)-2-phenylpyrimidine, 32412-70-7; 4-(2-hydroxyethylamino)-*N*-methyl-2-phenyl-5-pyrimidinecarboxamide, 34922-22-0; 4-(2-hydroxyethylamino)-*N*-methyl-2-phenyl-5-pyrimidinecarboxamide acetate ester, 34922-23-1.

# Pyrimidines. XII. A Propargyl Claisen Rearrangement in the Pyrimidine Series. Synthesis of Furo- and Pyrano[3,2-*d*]pyrimidines[1]

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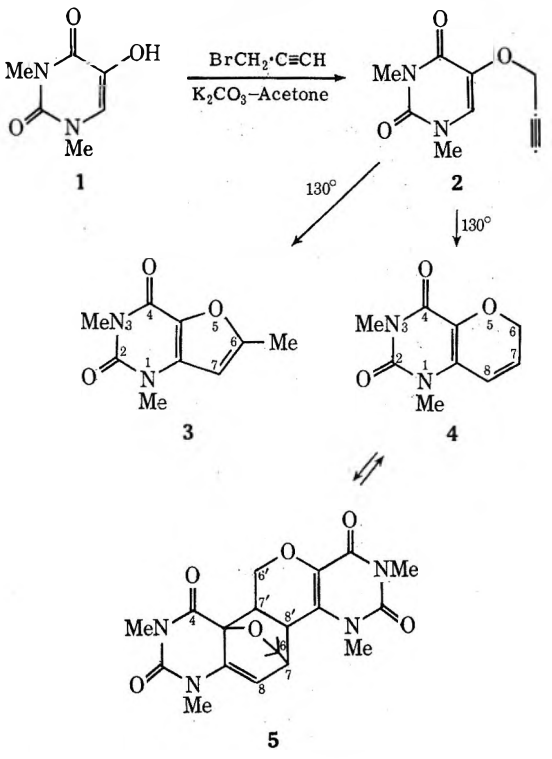
1,3-Dimethyl-5-(2-propynyloxy)uracil (**2**) readily undergoes thermal rearrangement at 130° to give mixtures of 1,3,6-trimethylfuro[3,2-*d*]pyrimidine-2,4-dione (**3**) and 1,3-dimethyl-6*H*-pyrano[3,2-*d*]pyrimidine-2,4-dione (**4**). The course of the rearrangement is markedly dependent on solvent and can be directed to give mostly **3** (in DMF), equal amounts of **3** and **4** (in DMSO), or predominantly **4** (in xylene). With prolonged reaction times in xylene, compound **4** dimerizes to give a Diels–Alder adduct (**5**). The observed incorporation of deuterium from labeled **2** into **3** and **4** is consistent with a mechanism involving Claisen-type rearrangement of **2** to give 6-allenyl-1,3-dimethyl-5-hydroxyuracil (**8**), which then rearranges to give either **3** or **4**. An independent synthesis of **8** by photolysis of **4** in chloroform is described, and it is further shown that **8** reverts to **4** at 35° and rearranges to **3** under ionizing conditions. Photolysis of **4** in ethanol affords **3** directly. The 2-propynyl ether of 5-hydroxyuridine rearranges in boiling water to give the corresponding furo[3,2-*d*]pyrimidine nucleoside (**10**). In refluxing toluene, tri-*O*-acetyl-5-(2-propynyloxy)uridine affords the pyrano[3,2-*d*]pyrimidine nucleoside (**11**).

In a recent paper[2] we described a new method for the synthesis of 6-carbon-substituted pyrimidines which involves, as a key step, the Claisen rearrangement of 5-allyloxyuracils to 6-allyl-5-hydroxyuracils. These rearrangements proceed rapidly (10 min) under relatively mild conditions (120°), and this suggested that the corresponding 2-propynyl (propargyl) ethers might also rearrange to products having a newly established carbon–carbon bond at C-6.

Claisen rearrangement of suitable 2-propynyl ethers are known in both the aliphatic and aromatic series.[3] Thus 2-propynyl vinyl ethers rearrange, *via* a cyclic transition state, to allenic carbonyl compounds. Phenyl 2-propynyl ethers afford the corresponding 2*H*-1-benzopyrans (3-chromenes)[4] and these products are apparently formed by rearrangement of an intermediate *o*-allenylphenol.[5] We therefore expected that pyrolysis of 2-propynyl ethers of 5-hydroxyuracils would lead to either 6-allenyl-5-hydroxyuracils or, by further cyclization, to pyrano[3,2-*d*]pyrimidines. At the nucleoside level, these products would serve as intermediates in our program[2] directed toward the synthesis and biological evaluation of 6-substituted pyrimidine nucleosides.

For the present study, the 2-propynyl ether **2** (Scheme I) was prepared by alkylation of 1,3-dimethyl-5-hydroxyuracil (**1**) and subjected to pyrolysis at 130° in a variety of solvents. In dimethylformamide, compound **2** rearranged completely within 60 min, and afforded two products in a ratio of about 10:1. The major component, which crystallized directly from the reaction mixture in 70% yield, was not one of the expected products and was identified as 1,3,6-trimethylfuro[3,2-*d*]pyrimidine-2,4-[1*H*,3*H*]-dione (**3**). The structure of **3** was evident from the nmr spectrum, which shows H-7 as a narrow quartet (δ 6.17) coupled

SCHEME I




(*J* = 0.8 Hz) to the 6-methyl signal at δ 2.45.[6] Compound **3** is identical with a by-product noted during the preparation of **2** from **1** in acetone, and we confirmed that isolated **2** is indeed converted slowly into **3** in acetone at 56°. The minor product formed from **2** in DMF was obtained in larger amounts when the pyrolysis was conducted in DMSO-$d_6$. The nmr spectrum of the reaction mixture revealed the presence of **3** and showed clearly that the second product was the expected 1,3-dimethyl-6*H*-pyrano[3,2-*d*]pyrimidine-2,4-[1*H*,3*H*]-dione[7] (**4**). In addition to the signals of **3**, this spectrum shows the C-6 protons as a double doublet (δ 4.63 $J_{6,7}$ = 3.8, $J_{6,8}$ = 1.5 Hz) coupled to H-7 and H-8 which each appear as double triplets ($J_{7,8}$

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08478).

(2) B. A. Otter, A. Taube, and J. J. Fox, *J. Org. Chem.*, **36**, 1251 (1971).

(3) For reviews covering these rearrangements see (a) D. R. Taylor, *Chem. Rev.*, **67**, 317 (1967); (b) A. Jefferson and F. Scheinmann, *Quart. Rev., Chem. Soc.*, **22**, 391 (1968); (c) H. J. Hansen in "Mechanism of Molecular Migrations," Vol. 3, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1971, p 227.

(4) (a) I. Iwai and J. Ide, *Chem. Pharm. Bull.*, **11**, 1042 (1963); (b) J. Hlubucek, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.*, **24**, 2347 (1971); (c) *ibid.*, **23**, 1881 (1970).

(5) J. Zsindely and H. Schmid, *Helv. Chim. Acta*, **51**, 1510 (1968).

(6) (a) Only one example of a furo[3,2-*d*]pyrimidine has been reported previously,[6b] but this was prepared by an ambiguous method and may be a furo[2,3-*d*]pyrimidine. (b) R. G. Jones, *J. Org. Chem.*, **25**, 956 (1960).

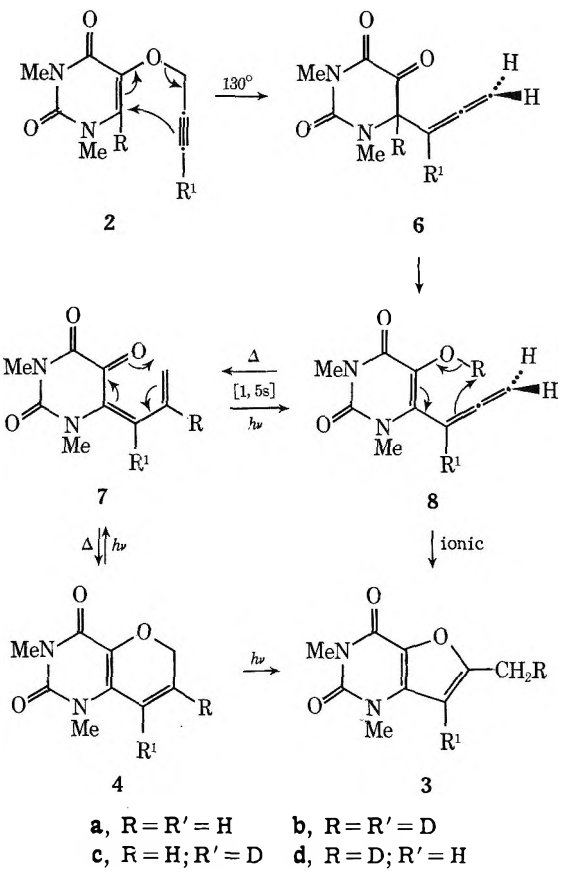
(7) This compound appears to be the first example of the pyrano[3,2-*d*]-pyrimidine ring system.

= 10 Hz), centered at δ 6.25 and 6.65, respectively. These parameters are similar to those reported for 2*H*-1-benzopyran.[8] The relative amounts of the two products (**3** and **4**) formed from **2** in DMSO vary according to the dryness of the solvent. Thus **3** and **4** are formed in nearly equal amounts in DMSO-$d_6$ containing ~1% of added water, whereas in anhydrous DMSO-$d_6$ the ratio changes to 3:1 in favor of the pyranopyrimidine **4**. Compound **4** was also obtained as the major product (49% yield) from the pyrolysis of **2** in a nonpolar solvent, namely xylene, and in this case the furopyrimidine **3** was formed in only ~3% yield. The reaction in xylene was not as clear-cut as in DMF and DMSO-$d_6$ and some decomposition occurred. Moreover, with longer reaction times, the yield of **4** decreased at the expense of a third product (**5**), which appears to be a Diels–Alder adduct formed from two molecules of **4**. Evidence for the basic structure of **5** came from molecular weight determination and from the nmr spectrum, which confirmed that **5** was an asymmetrical dimer. The 220-MHz spectrum showed signals attributable to four methyl groups and eight other protons. The low-field proton (H-8) occurs as a doublet (δ 5.75, $J_{7,8}$ = 7 Hz) coupled to a multiplet (H-7, ~3.28) that is partially obscured by the methyl signals. The 6′ methylene protons were well separated at δ 4.30 and 3.63 ($J_{gem}$ = 12, $J_{6'a,7'} \cong 0$, $J_{6'b,7'}$ = 4 Hz), presumably because of the proximity of the 4-oxo group in both the endo and exo configurations.[9] A two-proton signal at δ 4.14 was assigned to the C-6 methylene protons; the remaining multiplets at δ 3.10 and 2.88 were assigned to H-7′ and H-8′. Step **4** → **5** is reversible, in agreement with the Diels–Alder formulation, and heating **5** in DMSO-$d_6$ at 130° leads to the partial reappearance of **4** as shown by the nmr spectrum. The furopyrimidine **3**, unlike **4**, is thermally stable and was unchanged during 24 hr in DMSO-$d_6$ at 130°.

The above results demonstrate that the course of rearrangement of **2** at 130° is markedly dependent on solvent and can be directed to give mixtures in which either **3** or **4** (or **5**) predominate. In contrast, aryl 2-propynyl ethers are reported to give *only* 2*H*-1-benzopyran derivatives when heated in either *N*,*N*-diethylaniline (~215°)[4a,b] or DMF.[4c] However, the mechanism proposed by Zsindely and Schmid[5] to account for the formation of these 2*H*-1-benzopyrans can also be used to account for the formation of both **3** and **4** from **2**. This mechanism (Scheme II) involves a Claisen-type rearrangement (**2** → **6**), followed by enolization to give the 6-allenyl-5-hydroxyuracil **8**. A [1,5] sigmatropic hydrogen shift in **8a** leads to **7a**, which then cyclizes to the pyranopyrimidine **4a**. This sequence predominates in xylene and to a lesser extent in dry DMSO. Alternatively, the allene **8a** can undergo an ionic ring closure to give the furopyrimidine **3a** in a manner similar to the ring closure of *o*-allenylphenol to 2-methylbenzofuran catalyzed by sodium methoxide.[5] This route predominates in DMF, which presumably contains basic impurities, competes favorably in moist DMSO, but becomes negligible in xylene.

As noted above, the rearrangement **2a** → **3a** has no parallel occurrence in the thermal rearrangement of

SCHEME II




**a**, R = R′ = H **b**, R = R′ = D
**c**, R = H; R′ = D **d**, R = D; R′ = H

phenyl 2-propynyl ethers.[10] A possible reason for this difference is that the electron-withdrawing effect of the uracil ring in intermediate **8a** would be greater than that of the phenyl ring in the analogous *o*-allenylphenols. The central allene carbon atom in **8a** would therefore be electron deficient relative to the corresponding phenyl compounds, and hence would be more susceptible to nucleophilic attack by the hydroxyl group.

The overall mechanism requires that the acetylenic hydrogen (R′) of **2** becomes located at C-8 of **4** and C-7 at **3**. Similarly, H-6 (R) of **2** becomes H-7 in **4** and incorporates into the methyl group of **3**. The observed incorporation of deuterium into both **3** and **4** is consistent with these requirements. Labeled starting material was prepared by adding sodium deuterioxide and $D_2O$ to a solution of **2a** in DMSO-$d_6$. This resulted in rapid exchange of both H-6[11] and the acetylenic hydrogen, and afforded **2b** in crystalline form. Pyrolysis of **2b** in DMSO-$d_6$ at 130° gave the furopyrimidine **3b**, which was characterized by absence of the H-7 signal in the nmr spectrum and the appearance of the deuterated methyl group as a two-proton triplet with $J_{H,D}$ = 2.3 Hz. This product also contained a small amount of monodeuterated material (**3c**), and this could arise

(8) J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, 981 (1964).

(9) As shown by examination of Dreiding models. Diels–Alder condensation can lead to eight isomers and a definitive structure is not offered at this time.

(10) (a) However, Kwart and George[10b] have shown that phenyl 2-propynyl sulfide does rearrange to 2-methylbenzothiopene. This compound is formed in part *via* a mechanism analogous to that above, but the main route involves a thermal thiopropynylic rearrangement (Ph S·$CH_2$·C:CH → Ph S·CH:C:$CH_2$) to give phenyl allenyl sulfide, which itself undergoes thio-Claisen rearrangement. Ring closure of the resulting *o*-propynylthiophenol then gives the benzothiophene. These authors further state that thermal propynylic rearrangements do not occur with oxy substrates, and it is therefore unlikely that the furopyrimidine **3** is formed *via* a similar route. (b) H. Kwart and T. J. George, *Chem. Commun.*, 433 (1970).

(11) Base-catalyzed deuterium exchange of H-6 appears to be a general reaction of 1,3,5-trisubstituted 5-hydroxyuracils and is currently under further investigation in this laboratory.

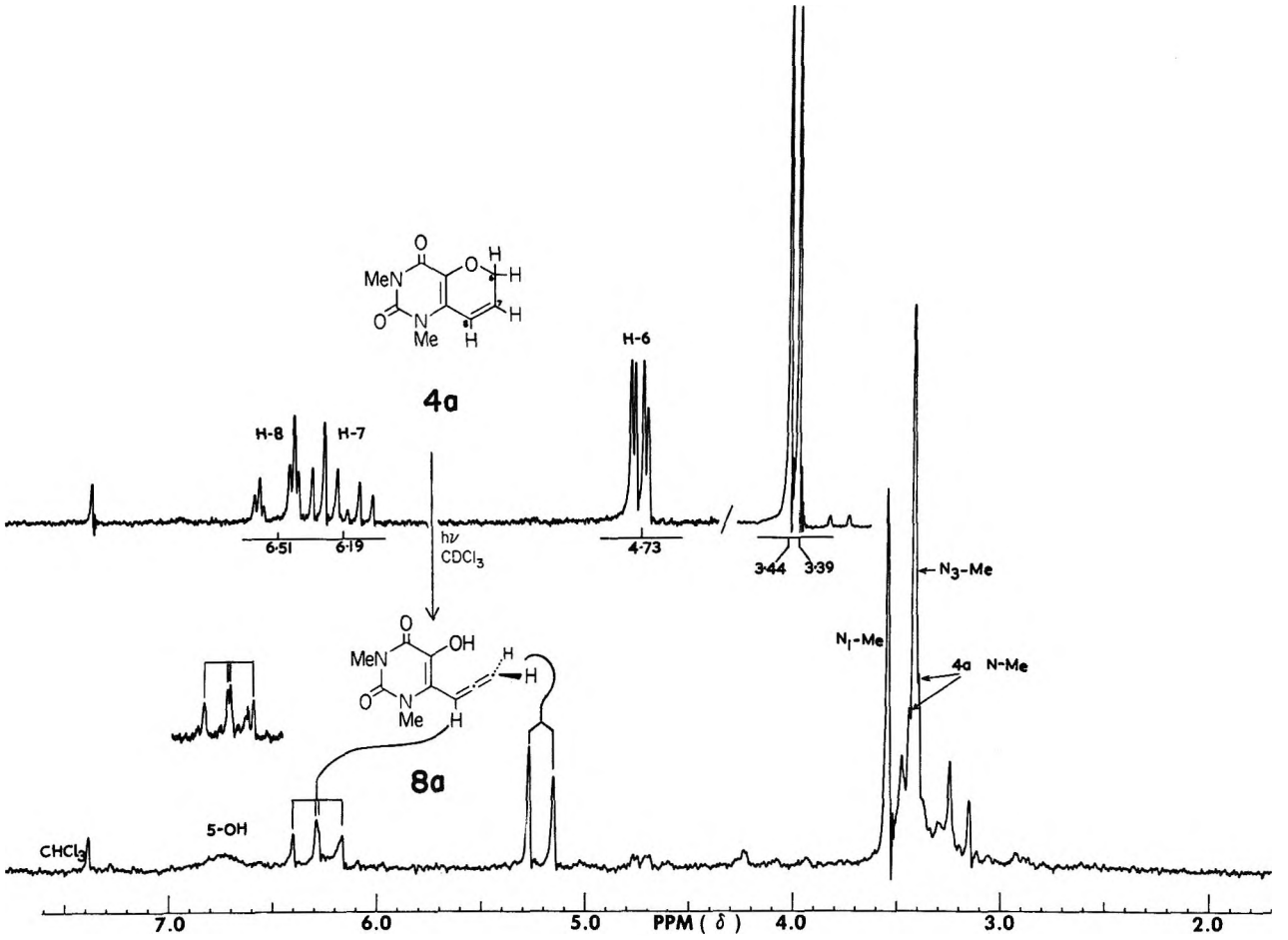



Figure 1.—60-MHz spectrum of compound 4a in $CDCl_3$ (above) and spectrum obtained with the same solution after 3-hr uv irradiation (below). The 5-OH signal was shifted from ~δ 6.3 by addition of 1 drop of DMSO-$d_6$. The allenic protons give an $AB_2$ spectrum in which the ratio $J/\delta_B - \delta_A$ is such (0.11) that the A band appears as a four-line multiplet rather than as a triplet expected for a first-order system [P. L. Corio, *Chem. Rev.*, 60, 363 (1960)]. The inset spectrum, showing the A band multiplicity more clearly, was obtained from a different run.

either from partially deuterated starting material (**2c**) or by reexchange of the **8b** 5-OD group by water invariably present in DMSO-$d_6$. Pyrolysis of **2b** in xylene afforded the 7,8-dideuterio compound **4b**, as required by the mechanism, but this product was accompanied by substantial amounts of the monodeuterated **4c**. Again, this could be formed from **2c** or from **8c** generated by reexchange of **8b**, although the source of hydrogen in this case is not clear.

Further evidence for the mechanism shown in Scheme II was obtained from a study of the photochemistry of the pyranopyrimidine **4**. This study was undertaken because of the serendipitous finding that storage of dilute alcohol solutions of **4** under fluorescent lighting for several days resulted in a gradual shift of the uv absorption maximum from 350 (**4**) to ~280 mμ, a value close to that of the furopyrimidine **3**.[12] Controlled irradiation of **4** ($2 \times 10^{-4}$ *M*) in ethanol, using a high-pressure mercury lamp, afforded a set of uv-spectral curves passing through isosbestic points and a final curve (20 min) identical with the spectrum of **3**. On a preparative scale, crystalline **3** was isolated in 90% yield. No intermediates were observed spectrally in the photolysis of **4** in ethanol, but irradiation in methanol resulted in the rapid appearance of a broad peak at 315 mμ which subsequently disappeared in a dark reaction to form **3**. This difference may be caused by the presence of water in the ethanol solutions of **4**. The absorption at 315 mμ also appeared when **4** was irradiated in chloroform, and by conducting the photolysis in deuteriochloroform it was possible to monitor the formation of the intermediate by nmr spectroscopy. After 2 hr, the nmr spectrum (Figure 1) shows a major product which gives rise to a hydroxyl signal, and a doublet at δ 5.21 coupled to a four-line multiplet at δ 6.28. The multiplicity and large coupling constant[3a] (7.0 Hz) is fully consistent with the allene structure **8a** for the photointermediate. This assignment is supported by the ir spectrum of the reaction mixture, which shows a hydroxyl peak at 3450 $cm^{-1}$ and peaks at 1930 and 1960 $cm^{-1}$ characteristic[3a] of allenes. The first step in the ring contraction **4a** → **3a** presumably involves the formation of intermediate **7a**; a similar ring opening has been proposed previously[13] to account for the formation of colored photoproducts from 2*H*-1-benzopyrans. A photochemical [1,5] hydrogen shift then converts **7a** into allene **8a**,[14] the postulated inter-

(12) A similar, but smaller difference is seen in the uv spectra of 2*H*-1-benzopyrans ($\lambda_{max}$ ~310 mμ, ref 4) and benzofuran [$\lambda_{max}$ 244, 281 mμ: G. M. Badger and B. J. Christie, *J. Chem. Soc.*, 3438 (1956)].

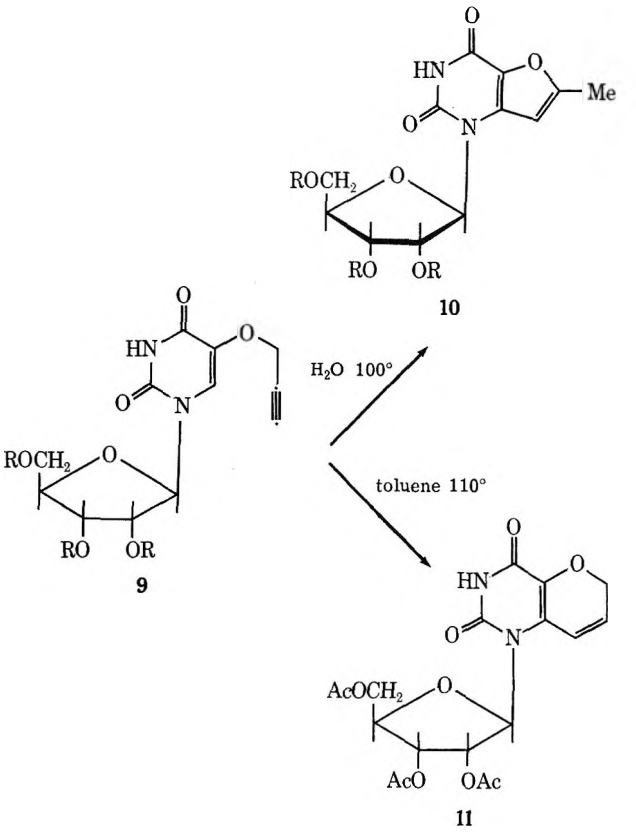
(13) J. Kolc and R. S. Becker, *J. Phys. Chem.*, **71**, 4045 (1967).

(14) Similar photochemical formation of allenes involving 1,5 hydrogen shifts has been observed previously with acyclic conjugated trienes [for example, H. Prinzbach and E. Druckrey, *Tetrahedron Lett.*, 2959 (1965), and references cited therein] and conjugated dienoic acids [K. J. Crowley, *J. Amer. Chem. Soc.*, **85**, 1210 (1963), discussed in R. O. Kan, "Organic Photochemistry," McGraw-Hill, New York, N. Y., 1966, p 32].

mediate in the thermal rearrangement of 2. Allene **8a** was detected on thin layer chromatograms as a ferric chloride positive spot but an attempt to isolate it by preparative chromatography was unsuccessful. It was not possible, therefore, to subject compound **8a** to the pyrolytic conditions described earlier. However, **8a** does revert slowly to pyranopyrimidine **4a** when kept overnight at the nmr probe temperature (~35°), and can be converted into **3** by dilution of the deuteriochloroform solution with ethanol or methanol. Addition of sodium deuterioxide to the solution of **8a** resulted in instantaneous deuteration of the 5-OH group and very rapid ring closure of the resulting **8d** to **3d**.[15] Compound **3d** was identified from the nmr spectrum, which shows the deuteriomethyl signal as a six-line multiplet ($J_{H,D}$ = 2.3, $J_{allylic}$ = 0.8 Hz), and by comparison of the uv spectrum and chromatographic mobility with **3a** prepared by pyrolysis of **2a**.

Extension of these pyrolysis procedures to the uridine series has led to the synthesis of both furo- and pyrano-[3,2-*d*]pyrimidine nucleosides. The 2-propynl ether **9** (R = H, Scheme III) was prepared by selective alkylation of 5-hydroxyuridine. That **9** contains an O-5 rather than an N-3 alkyl substituent was confirmed by a negative ferric chloride test, and by the uv spectrum which failed to show the bathochromic shift (~280 → 305 mμ) in alkali with results from ionization of the 5-hydroxy group in 1,3-disubstituted 5-hydroxyuracils.[16] Compound **9** (R = H) rearranged smoothly in boiling water to give the corresponding furopyrimidine **10**, which was identified by comparison of the uv and nmr spectral parameters with **3**. The pyranopyrimidine **11** was not observed in this solvent, as would be expected from the mechanism. Refluxing the tri-*O*-acetate (**9**, R = $COCH_3$) in toluene, however, afforded an amorphous product whose nmr and uv characteristics (compared with **4**) were fully consistent with the pyranopyrimidine structure **11**. Studies on the chemistry of nucleosides **10** and **11** are currently in progress.

SCHEME III




## Experimental Section

**General Procedures.**—Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Ultraviolet, infrared, and nuclear magnetic resonance spectra were determined on Unicam SP800, Perkin-Elmer Infracord, and Varian A-60 spectrometers, respectively. Nmr data for compound 5 were obtained with a Varian HR-200 instrument at Rockefeller University; in all cases first-order values are given for chemical shifts (δ, measured from internal tetramethylsilane) and coupling constants (hertz, obtained from spectra recorded at expanded sweep widths). Ultraviolet irradiations were carried out with a Hanovia 450-W high-pressure mercury lamp equipped with a Pyrex filter. Thin layer chromatography was performed on Merck silica gel $GF_{254}$; preparative separations were carried out on 20 × 20 cm plates coated with 30 g of silica gel $PF_{254}$. All evaporations were carried out under reduced pressure. Microanalyses were determined by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Spang Microanalytical Laboratory, Ann Arbor, Mich.

**1,3-Dimethyl-5-(2-propynyloxy)uracil (2).**—Propargyl bromide (23.8 g, 0.2 mol) and potassium carbonate (13.8 g, 0.1 mol) were added to a solution of 1,3-dimethyl-5-hydroxyuracil[17] (1) (15.6 g, 0.1 mol) in acetone (300 ml). The mixture was stirred and refluxed for 14 hr, at which time tlc (EtOAc–benzene, 4:1, $FeCl_3$ spray) indicated absence of starting material. The solids were removed and the filtrate was concentrated to give several crops (14 g, 72%) of crystalline material, mp 137–139°. Recrystallization from acetone afforded pure **2**: mp 140–142°; uv $\lambda_{max}^{EtOH}$ 278, $\lambda_{min}$ 245 mμ; ir (KBr disc) 3250 (≡CH stretch) and 2130 $cm^{-1}$ (C≡C stretch); nmr (DMSO-$d_6$) δ 7.64 (s, 1, H-6), 4.65 (d, 2, $CH_2$, $J$ = 2.4 Hz), 3.57 (t, 1, CH), 3.30 (s, 3, $NCH_3$), and 3.18 ppm (s, 3, $NCH_3$); nmr ($CDCl_3$) δ 7.15 (s, 1, H-6), 4.70 (d, 2, $CH_2$, $J$ = 2.4 Hz), 3.39 and 3.34 (s, 6, $N_{1,3}CH_3$), and 2.56 ppm (t, 1, CH). The propynyl signals are closely similar to those reported[18] for phenyl-2-propynyl ether ($CCl_4$, $CH_2$, d at δ 4.63 and CH, t at δ 2.35 ppm, $J$ = 2.4 Hz).

*Anal.* Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.62; H, 5.09; N, 14.46.

A final crop (1.6 g) of crystals, mp 108–110°, obtained from the concentrated reaction mixture was shown (nmr) to be a mixture of **2** and **3**.

**Rearrangement of 2 in DMF. Preparation of 1,3,6-Trimethylfuro[3,2-*d*]pyrimidine-2,4-[1*H*,3*H*]-dione (3).**—A solution of **2** (3 g) in 25 ml of analytical grade DMF was kept at 130° for 1 hr. The crystals that separated on cooling were collected and washed with petroleum ether (bp 30–60°). Recrystallization from hot ethanol afforded pure **3** (2 g, 66%): mp 210–211°; uv $\lambda_{max}^{EtOH}$ 281, 241 sh, $\lambda_{min}$ 258, 234 mμ; nmr ($CDCl_3$) δ 6.17 (q, 1, H-7, $J_{7,CH_3}$ = 0.8 Hz), 3.41 and 3.45 (two singlets, 6 protons,

(15) A similar attempt to follow the incorporation of deuterium from **8d** into the pyranopyrimidine led to some interesting results. Compound **8d** was prepared *in situ* by adding a drop of $D_2O$ to the $CDCl_3$ solution containing **8a**, and kept at room temperature for 36 hr. The nmr spectrum then showed the presence of residual **8d**, the furopyrimidine **3d**, and some nondeuterated pyranopyrimidine (**4a**), which must have been formed from **8a** *via* reexchange of the **8d** 5-OD group by HOD present in the reaction mixture. None of the expected deuterated pyranopyrimidine **4d** was observed. In contrast, a control experiment where **8a** was treated with water instead of $D_2O$ showed that all the allene had disappeared in 36 hr and that pyranopyrimidine **4a** was the sole rearrangement product. These results indicate that the rate of the conversion **8d** → **4d** is so slow relative to the nondeuterated case that furopyrimidine formation becomes competitive under these conditions. A similar conclusion follows from pyrolysis of the dideuterated 2-propynyl ether **2b** in DMSO-$d_6$, which leads *only* to the dideuterated furopyrimidine **3b**; the same experiment with **2a** leads to both **3a** and **4a**. The magnitude of these effects seems to be too great to attribute solely to the deuterium isotope effects expected in the various steps leading to **4**, and merits further study.

(16) B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, **34**, 2636 (1969).

(17) Prepared according to the procedure described for the corresponding 3-benzyl-1-methyl compound.[16]

(18) M. P. Simonnin, *C. R. Acad. Sci.*, **257**, 1075 (1963).

*N*-methyls), and 2.45 ppm (d, 3, 6-$CH_3$); nmr (DMSO-$d_6$) $\delta$ 6.65 (narrow m, 1, H-7, $J_{7,CH_3}$ not fully resolved), 3.35 and 3.21 (two singlets, 6 protons, *N*-methyls), and 2.41 ppm (broadened s, 3, 6-$CH_3$).

*Anal.* Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.54; H, 5.10; N, 14.31.

On a smaller scale, the rearrangement of **2** (40 mg) in 0.4 ml of DMF was monitored using nmr spectroscopy. The H-6 ($\delta$ 7.67) and $CH_2$ (4.71) signals of **2** (the remaining signals being obscured by DMF peaks and side bands) disappeared within 1 hr, and were replaced by peaks (H-7, $\delta$ 6.67; 6-$CH_3$, $\delta$ 2.47) corresponding to **3**. A small double doublet at $\delta$ 4.68 was subsequently identified as the 6-methylene signal of compound **4**. By integration, the **3**:**4** ratio was 10:1.

**Rearrangement of 2 in Xylene. Preparation of 1,3-Dimethyl-6*H*-pyrano[3,2-*d*]pyrimidine-2,4-[1*H*,3*H*]-dione (4) and Adduct 5. Run A.**—A solution of **2** (1.0 g) in xylene (20 ml) was kept at 130° for 2 hr, at which time tlc (EtOAc–benzene, 4:1) indicated complete loss of starting material. The yellow solution was concentrated to dryness and the residue was dissolved in chloroform. Fractionation of this mixture on four thick layer chromatography plates (EtOAc–benzene, 4:1) and elution of the uv-absorbing zones afforded three fractions (a–c). The nmr spectrum ($CDCl_3$) of the fastest moving component (fraction a, 66 mg) showed it to be a complex mixture containing about 50% of compound **3**. The yield of **3** was therefore ~3%. Concentration of fraction b afforded compound **4** as yellow crystals (485 mg, 48.5%): mp 202–204°; uv $\lambda_{max}^{EtOH}$ 350, $\lambda_{min}$ 282 m$\mu$; nmr ($CDCl_3$) $\delta$ 6.51 (double triplets, 1, H-8, $J_{8,7}$ = 10 Hz), 6.19 (double triplets, 1, H-7), 4.73 (d d, 2, H-6a,b, $J_{6,8}$ = 1.2, $J_{6,7}$ = 3.8 Hz), and 3.44 and 3.39 ppm (two singlets, 6 protons, *N*-methyls).

*Anal.* Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.62; H, 5.09; N, 14.46.

Concentration of the remaining fraction (c, $R_f$ ~0) and recrystallization of the dark residue from $CH_2Cl_2$–EtOH afforded adduct **5** as colorless crystals (268 mg, 27%) which melted indistinctly at 240–246° dec (yellows from 200°): mol wt, found 377 (osmotic pressure), calcd 388; uv $\lambda_{max}^{EtOH}$ 278, sh 305, $\lambda_{min}$ 250 m$\mu$; nmr (220 MHz, $CDCl_3$) $\delta$ 5.75 (d, 1, H-8, $J_{7,8}$ = 7 Hz), 4.30 (d, 1, H-6'a, $J_{gem}$ = 12, $J_{6'a,7'} \cong$ 0 Hz), 4.14 (m, 2, H-6a, H-6b), 3.63 (q, 1, H-6'b, $J_{6'b,7'}$ = 4 Hz), 3.23 (s, 3, *N*-methyl), 3.10 [4, *N*-methyl superimposed on H-7' (or H-8')], and 2.88 ppm [m, 1, H-8' (or H-7')]. The remaining protons appeared as a seven-proton group in which two *N*-methyl singlets ($\delta$ 3.30 and 3.29) overlapped the H-7 multiplet. Compound **5** was unstable at 130° in DMSO-$d_6$, as shown by the partial reappearance of signals corresponding to **4** in the nmr spectrum.

*Anal.* Calcd for $C_{18}H_{20}N_4O_6$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.68; H, 5.14; N, 14.41.

**Run B.**—A sample of **2** (1.75 g) was heated in 35 ml of xylene at 130° for 4 hr (instead of 2 hr as above). Concentration of the reaction mixture and fractionation of the residue on a column containing 200 g of Merck silica gel G afforded 407 mg (23%) of compound **4** (eluted with EtOAc–benzene, 4:1) and 713 mg (41%) of compound **5** (eluted with EtOAc–MeOH, 4:1).

**Rearrangement of 2 in Acetone.**—A solution of **2** (225 mg) in acetone (10 ml) was refluxed for 90 hr and then concentrated to dryness. The nmr spectrum ($CDCl_3$) of the residue showed peaks corresponding to starting material (**2**) and the furopyrimidine **3** in the ratio (by integration) of 6:1.

**Rearrangement of 2 in DMSO-$d_6$.**—A sample of **2** (40 mg) in an nmr tube was dissolved (under nitrogen) in 0.4 ml of anhydrous DMSO-$d_6$. The tightly stoppered tube was heated at 130° in a silicon–oil bath for 45 min, at which time the nmr spectrum showed absence of starting material and presence of **3** and **4**. Integration of the spectrum indicated a **3**:**4** ratio of 1:3. A repeat of this experiment using DMSO-$d_6$ containing 1% of added water gave a **3**:**4** ratio of 1:1.

**1,3-Dimethyl-5-(2-propynyloxy)uracil-6,3'-$d_2$ (2b).**—Two drops of 1 *N* sodium deuterioxide solution was added to a solution of **2a** (125 mg) in 1 ml of DMSO-$d_6$. After ~1 min the solution was neutralized with 1 *N* DCl, diluted with 2 ml of $D_2O$, and then cooled. The resulting crystals were washed thoroughly with $D_2O$ and then dried (100°, $P_2O_5$). The yield of **2b** was 90 mg: mp 139–142°; nmr (DMSO-$d_6$) $\delta$ 4.65 (s, 2, $CH_2$), 3.30 (s, 3, $NCH_3$), and 3.18 ppm (s, 3, $NCH_3$). The original H-6 resonance was just visible at high spectrum amplitudes, indicating that **2c** was present in trace amounts.

**1,3,6-Trimethylfuro[3,2-*d*]pyrimidine-2,4-[1*H*,3*H*]-dione-6$\alpha$,-7-$d_2$ (3b).**—The nmr solution from above (35 mg of **2b** in 0.4 ml of DMSO-$d_6$) was heated at 130° for 45 min. The nmr spectrum of the cooled solution indicated that the pyranopyrimidine **4** was absent (*cf.* pyrolysis of **2a** in DMSO-$d_6$ above) and that the product was the furopyrimidine **3b**. Since the deuteriomethyl signal was partially obscured by the residual $CD_2H$–solvent peaks, the product was precipitated with water, dried, and dissolved in $CDCl_3$. The nmr spectrum of this solution showed $\delta$ 3.45 (s, 3, $NCH_3$), 3.41 (s, 3, $NCH_3$), and 2.43 ppm (t, 2, $CH_2D$, $J_{H,D}$ = 2.3 Hz). A small peak at $\delta$ 2.45, partially overlapped by the $-CH_2D$ triplet, indicated the presence of **3c**. The small chemical shift difference (0.8 Hz, measured at 100 Hz sweep width) between the **3b** $CH_2D$ and **3c** $CH_3$ signals is consistent with previous studies.[19]

**1,3-Dimethyl-6*H*-pyrano[3,2-*d*]pyrimidine-2,4-[1*H*,3*H*]-dione-7,8-$d_2$ (4b) and 1,3-Dimethyl-6*H*-pyrano[3,2-*d*]pyrimidine-2,4-[1*H*-3*H*]-dione-8-*d* (4c).**—Pyrolysis (130°) of 170 mg of **2b** in 3.5 ml of xylene for 3 hr, and isolation of the pyranopyrimidine component as in the preparation of **4a** (run A) above, afforded a mixture of **4b** and **4c** with the following nmr spectrum ($CDCl_3$): $\delta$ 6.20 (broad t, 0.4, H-7 of **4c**), 4.73 (2, 6-methylene singlet of **4b** overlapping 6-methylene doublet of **4c**), and 3.44 and 3.39 ppm (two singlets, six protons, **4b** and **4c** *N*-methyls). The line widths of the H-7 signal (2.5 Hz) of **4c** indicate a substantial H-7–D-8 coupling constant (expected $J \cong$ 1.5 Hz). Similarly, broadening of the 6-methylene singlet of **4b** (width at half-height = 1.5 Hz, height = 6 cm; *cf.* width of *N*-methyl singlets = 1.0 Hz, height = 25 cm) indicates vicinal and possibly long-range coupling of H-6 with D-7 and D-8.

**Photolysis of 4 in Ethanol.**—A $2 \times 10^{-4}$ *M* solution of **4** in ethanol (unprotected from moisture) was irradiated for five 4-min periods. Uv spectral examination at the end of each irradiation period revealed gradual loss of the original absorption (350 m$\mu$) and appearance of a new peak at 281 m$\mu$. Serial curves passed through isosbestic points at 248 and 303 m$\mu$, and the final curve (20 min) was identical with the spectrum of **3**.

For preparative purposes, a solution of **4** (40 mg) in ethanol (200 ml) was irradiated for 1 hr. Concentration of the solution afforded crystalline material (36 mg, 90%), identical (nmr, mixture melting point) with **3** prepared by rearrangement of **2**.

**Photolysis of 4 in Methanol.**—The uv spectrum obtained after irradiation of **4** in methanol ($2 \times 10^{-4}$ *M*) for 6 min showed a broad peak with $\lambda_{max}$ 315, $\lambda_{min}$ 265 m$\mu$. On standing, this peak gradually descreased (half-life ~1 hr) with the concomitant appearance (isosbestics at 291.5 and 237 m$\mu$) of absorption at 281 m$\mu$ corresponding to **3**.

**Photolysis of 4 in Deuteriochloroform. Preparation of 6-Allenyl-1,3-dimethyl-5-hydroxyuracil (8a).**—A sample of **4** (30 mg) was dissolved in $CDCl_3$ (0.5 ml) in an nmr tube, and the solution was irradiated with the tube ~1 cm from the lamp. Nmr monitoring showed that a 2.5–3-hr period was required for almost complete disappearance of **4**. A typical spectrum recorded after 3 hr of irradiation is reproduced in Figure 1; parameters for **8a** measured from the original spectrum are $\delta$ ~6.7 (broad peak, 5-OH, shifted from ~6.3 by addition of 1 drop of DMSO-$d_6$), 6.28 (four-line m, $-CH=$), 5.21 (d, $=CH_2$, $J$ = 7 Hz), 3.53 (s, $N_1CH_3$), 3.40 ppm (s, $N_3CH_3$). A sample of the 3-hr reaction mixture diluted with $CDCl_3$ showed peaks at 3450 (OH) and 1930 and 1960 $cm^{-1}$ (allene) in the ir spectrum. Storage of the reaction mixture at ~35° (nmr probe) resulted in complete disappearance of the **8a** signals, and reappearance of signals corresponding to **4**, within a 14-hr period.

**Conversion of 8a into 3. A. In Alcohols.**—The initial uv spectrum obtained after dilution of the $CDCl_3$ solution containing **8a** with ethanol showed a broad peak with $\lambda_{max}$ 314, $\lambda_{min}$ 265 m$\mu$, which rapidly decreased (half-life ~10 min) with simultaneous formation of absorption at 281 m$\mu$ corresponding to **3**. Dilution of the $CDCl_3$ solution of **8a** with methanol caused a much slower disappearance of the 314-m$\mu$ peak (half-life ~1 hr), with the overall transformation to **3** (isobestics at 237, 291.5 m$\mu$) closely resembling the curves obtained above in the photolysis of **4** in methanol.

**B. In Alkali.**—Addition of ~0.01 ml of 1 *N* NaOD in $D_2O$ to the $CDCl_3$ solution containing **8a** resulted in almost instantaneous appearance of peaks corresponding to **3d**. Pure material was isolated by thick layer chromatography: nmr ($CDCl_3$) $\delta$ 6.17 (narrow m, H-7), 3.41, 3.45 (two singlets, 6 protons,

(19) See J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Spectroscopy," Vol. 2, Pergamon Press, Elmsford, N. Y., 1966, p 1092.

*N*-methyls), and 2.44 ppm (six-line m, 2, $CH_2D$, $J_{allylic}$ = 0.8, $J_{H,D}$ = 2.3 Hz); uv $\lambda_{max}^{EtOH}$ 281, 241 mμ (sh).

**5-(2-Propynyloxy)uridine (9, R = H).**—Propargyl bromide (19.04 g 0.16 mol) was added to a solution of 5-hydroxyuridine[20] (20.8 g 0.08 mol) in 50% aqueous methanol (500 ml) containing sodium hydroxide (3.2 g 0.08 mol). The mixture was stirred at room temperature for 10 hr, by which time most of the starting material had reacted (tlc, $CH_2Cl_2$–MeOH, 5:1; $FeCl_3$ spray). Removal of solvent and crystallization of the syrupy residue from methanol afforded 14.7 g (61%) of product, mp 152–153°. A single recrystallization gave pure material: mp 155–156°; uv (pH 1) $\lambda_{max}$ 276, $\lambda_{min}$ 242 mμ; (pH 12) $\lambda_{max}$ 275, $\lambda_{min}$ 252 mμ; nmr (DMSO-$d_6$–$D_2O$) δ 7.80 (s, 1, H-6), 5.81 (m, 1, H-1′), 4.67 (d, 2, $-OCH_2-$, $J$ = 2.3 Hz), ~4.27–3.55 (m, HOD + H-2′, 3′, 4′, 5′a, 5′b), and 3.49 ppm (t, 1, $CCH_3$).

*Anal.* Calcd for $C_{12}H_{14}N_2O_7$: C, 48.32; H, 4.73; N, 9.39. Found: C, 48.16; H, 4.80; N, 9.46.

**Tri-*O*-acetyl-5-(2-propynyloxy)uridine (9, R = $COCH_3$).**—Acetylation of 9 (R = H) (1.5 g) in acetic anhydride (5 ml)–pyridine (20 ml) for 1 hr at room temperature, and isolation of the product by the standard chloroform extraction and washing procedure, afforded the tri-*O*-acetate as a chromatographically pure amorphous foam (2.1 g, 89%): nmr ($CDCl_3$) δ 7.43 (s, 1, H-6), 6.20 (m, 1, H-1′), 5.37 (m, 2, H-2′ and H-3′), 4.72 d (1, $-OCH_2-$, $J$ = 2.2 Hz), 4.37 (broad s, 3, H-4′ and H-5′a,b), 2.66 (t, 1, CH), and 2.20, 2.12, and 2.10 (three singlets, 9 protons, acetyls). This compound contained considerable amounts of entrapped chloroform which was not removed on storage at 40° under vacuum for 24 hr. At higher temperatures, darkening and partial rearrangement to **11** took place. The nmr spectrum showed more $CHCl_3$ than did a $CDCl_3$ blank run at the same amplitude; the presence of $CHCl_3$ was confirmed by elemental analysis.

*Anal.* Calcd for $C_{18}H_{20}N_2O_{10}\cdot 0.13\ CHCl_3$: C, 49.50; H, 4.61; N, 6.37; Cl, 3.29. Found: C, 49.52; H, 4.55; N, 6.13; Cl, 3.29.

**1-(β-D-Ribofuranosyl)-6-methylfuro[3,2-*d*]pyrimidine-2,4-[1*H*,3*H*]-dione (10, R = H). Method A.**—A solution of 9 (R = H) (1 g) in DMSO (20 ml) was heated at 135° for 1.5 hr. Concentration of the solution to a semisolid (bath 55–60°) and recrystallization from hot water furnished 835 mg (83.5%) of **10** (R = H): mp 246–248°; uv (pH 1) $\lambda_{max}$ 248, 280, $\lambda_{min}$ 233, 257; (pH 12) $\lambda_{max}$ 242 sh, 282; $\lambda_{min}$ 259 mμ; nmr (DMSO-$d_6$) δ 10.45 (s 1, NH), 6.95 (broadened s, 1, H-7 allylic coupling not resolved), 5.93 (d, 1, H-1′, $J_{1',2'}$ = 6 Hz), ~5.33–4.90 (m, 3, hydroxyls), ~4.50–4.00 (m, 2, H-2′, H-3′), ~4.00–3.50 (m, 3, H-4′, H-5′a,b), and 2.45 ppm (broadened s, 3, 6-$CH_3$).

*Anal.* Calcd for $C_{12}H_{14}N_2O_7$: C, 48.32; H, 4.73; N, 9.39. Found: C, 48.10; H, 4.79; N, 9.19.

**Method B.**—A solution of **9a** (3 g) in water (75 ml) was refluxed for 3.5 hr (tlc, $CH_2Cl_2$–MeOH, 5:1). The concentrated solution deposited 2.66 g (88%) of **10** (R = H), mp 246–247°.[21]

**1-(Tri-*O*-acetyl-β-D-ribofuranosyl)-6*H*-pyrano[3,2-*d*]pyrimidine-2,4-[1*H*,3*H*]-dione (11).**—A solution of **9** (R = $COCH_3$) (400 mg) in toluene (20 ml) was refluxed for 3.5 hr, at which time all the starting material had rearranged as shown by the nmr spectrum of an evaporated sample of the reaction mixture. Removal of solvent afforded **11** as an amorphous, yellow solid. Thick layer chromatography (EtOAc–benzene, 4:1; zone eluted with $CHCl_3$) afforded the analytical sample as a rigid foam: uv (pH ~1) $\lambda_{max}^{EtOH}$ 341, $\lambda_{min}$ 276; (pH ~ 12) $\lambda_{max}^{EtOH}$ 343, $\lambda_{min}$ 294 mμ; nmr ($CDCl_3$) δ 6.55 (m, 1, H-8, $J_{7,8}$ = 10 Hz, $J_{6,8}$ not fully resolved), 6.10 (double triplet, 1, H-7, $J_{6,7}$ = 4 Hz), 5.87–5.25 (m, 3, H-1′, 2′, 3′), 4.68 (dd, 2, H-6a,b, $J_{6,8}$ ~1 Hz), ~4.50–4.08 (m, 3, H-4′,5′a,b), and 2.09 ppm (s, 9, acetyls). Chloroform entrapped in this compound was not removed during 24 hr at 40° under vacuum. Partial decomposition took place at higher temperatures as reflected by darkening and appearance of a peak at ~450 mμ in the uv spectrum at pH 12. Nmr and elemental analysis indicated chloroform.

*Anal.* Calcd for $C_{18}H_{20}N_2O_{10}\cdot 0.17CHCl_3$: C, 49.08; H, 4.57; N, 6.30; Cl, 4.06. Found: C, 48.81; H, 4.86; N, 5.90; Cl, 3.93.

**Registry No.**—**2**, 35042-03-6; **3**, 35042-04-7; **4**, 35042-05-8; **5**, 35042-06-9; **9** (R = H), 35042-07-0; **9** (R = $COCH_3$), 35042-08-1; **10** (R = H), 35042-09-2; **11**, 35042-10-5.

(20) D. W. Visser in "Synthetic Methods in Nucleic Acid Chemistry," Vol. 1, W. W. Zorbach and R. S. Tipson, Ed., Interscience, New York, N. Y., 1968, p 428.

(21) Boiling water is also the solvent of choice for the Claisen rearrangement of 5-allyloxyuridine to 6-allyl-5-hydroxyuridine (>90% yield). The rearrangement in boiling DMF (79% yield) has been reported[2] previously.

# Aminoacyl Derivatives of Nucleosides, Nucleotides, and Polynucleotides. XIV. A General Synthesis of Adenosine 2′(3′)-*O*-Peptidyl Derivatives[1]

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Reaction of the adenosine 2′(3′)-*O*-L-phenylalanyl, -L-leucyl, and -L-alanyl derivatives (**1a–c**) with 5-chloro-8-hydroxyquinoline esters of protected amino acids or dipeptide (**2b–e**) affords the protected adenosine 2′(3′)-*O*-peptidyl derivatives (**3b, 3c, 3g, 3e** and **3f**) in good yields. Removal of protecting groups gives 2′(3′)-*O*-L-phenylalanylphenylalanyl, -L-lysylphenylalanyl, -L-phenylalanylleucyl, -L-leucylalanyl, and -L-serylphenylalanylphenylalanyl adenosines (**3i–m**) in excellent yields. Similarly, 5-chloro-8-hydroxyquinoline acetate (**2a**) acylates 2′(3′)-*O*-L-phenylalanyl adenosine (**1a**) and 2′(3′)-*O*-L-leucyladenosine (**1b**) to give 2′(3′)-*O*-(*N*-acetyl-L-phenylalanyl)-adenosine (**3a**) and 2′(3′)-*O*-(*N*-acetyl-L-leucyl)adenosine (**3d**) in high yields. The usefulness of the described acylation reaction for the synthesis of peptidyl or *N*-acylaminoacyl oligoribonucleotides is discussed.

The 2′(3′)-*O*-aminoacyl derivatives of nucleosides and oligonucleotides may be used as suitable substrates in investigation of the mechanism of the transpeptidation process in ribosomal systems.[3,4] The adenosine 2′,3′-*O*-bisaminoacyl derivatives and 2′(3′)-*O*-peptidyl derivatives represent potential substrates for detailed investigations of the formation of the peptide bond on ribosomes.[5]

In the present paper, we report a general synthesis of adenosine 2′(3′)-*O*-peptidyl derivatives starting from 2′(3′)-*O*-aminoacyladenosines[6] as key intermediates. An earlier paper of this series[7] described the preparation of adenosine 2′(3′)-*O*-peptidyl derivatives con-

(1) Part XIII: I. Rychlík, J. Černá, S. Chládek, P. Pulkrábek, and J. Žemlička, *Eur. J. Biochem.*, **16**, 136 (1970).

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(3) I. Rychlík, S. Chládek, and J. Žemlička, *Biochim. Biophys. Acta*, **138**, 640 (1967).

(4) I. Rychlík, J. Černá, S. Chládek, J. Žemlička, and Z. Haladová, *J. Mol. Biol.*, **43**, 13 (1969).

(5) J. Černá, S. Chládek, I. Rychlík, and J. Žemlička, *Biochim. Biophys. Acta*, **199**, 291 (1970).

(6) S. Chládek, P. Pulkrábek, J. Sonnenbichler, J. Žemlička, and I. Rychlik, *Collect. Czech. Chem. Commun.*, **35**, 2296 (1970).

(7) S. Chládek and J. Žemlička, *ibid.*, **33**, 4299 (1968).

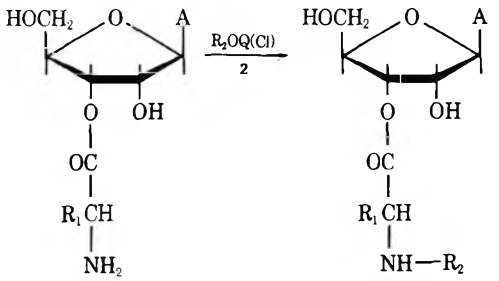
taining glycine as the C-terminal unit with the use of a selective acylation of the ortho ester type intermediates by the action of active esters of protected amino acids.

Later on,[8,9] this method was also applied to the synthesis of analogous dinucleoside phosphate derivatives, and the esters of 5-chloro-8-hydroxyquinoline[10] (chloroxine) were used as selective acylating agents (for a detailed discussion, see ref 8).

The use of chloroxine esters **2** has been now extended to the acylation of various adenosine 2′(3′)-*O*-aminoacyl derivatives **1**. As the starting material, adenosine esters of the amino acids L-phenylalanine, L-leucine, and L-alanine[11] (**1a-c**) were used.

The latter were condensed (see Scheme I) in di-

SCHEME I




1 3

A = adenine
Q(Cl) = 5-chloroquinolin-8-yl

**1a**, $R_1 = C_6H_5CH_2$
**b**, $R_1 = (CH_3)_2CHCH_2$
**c**, $R_1 = CH_3$

**2a**, $R_2 = CH_3CO$
**b**, $R_2 =$ ZPhe
**c**, $R_2 =$ ZLys (Z)
**d**, $R_2 =$ ZLeu
**e**, $R_2 =$ ZSer(*t*-Bu)Phe

**3a**, $R_1 = C_6H_5CH_2$; $R_2 = CH_3CO$
**b**, $R_1 = C_6H_5CH_2$; $R_2 =$ ZPhe
**c**, $R_1 = C_6H_5CH_2$; $R_2 =$ ZLys (Z)
**d**, $R_1 = (CH_3)_2CHCH_2$; $R_2 = CH_3CO$
**e**, $R_1 = (CH_3)_2CHCH_2$; $R_2 =$ ZPhe
**f**, $R_1 = CH_3$; $R_2 =$ ZLeu
**g**, $R_1 = C_6H_5CH_2$; $R_2 =$ ZSer(*t*-Bu)Phe
**h**, $R_1 = C_6H_5CH_2$; $R_2 =$ ZSerPhe
**i**, $R_1 = C_6H_5CH_2$; $R_2 =$ Phe
**j**, $R_1 = C_6H_5CH_2$; $R_2 =$ Lys
**k**, $R_1 = (CH_3)_2CHCH_2$; $R_2 =$ Phe
**l**, $R_1 = CH_3$; $R_2 =$ Leu
**m**, $R_1 = C_6H_5CH_2$; $R_2 =$ SerPhe

methylformamide with chloroxine esters of *N*-benzyloxycarbonylamino acids **2b–d** or with chloroxine acetate (**2a**). The reaction mixture was separated by preparative thin layer chromatography on silica gel. The yields of peptidyl and *N*-acetylaminoacyl derivatives **3** are shown in Table I. The following compounds were detected as by-products: the unreacted aminoacyl derivative **1** (or a trace of adenosine due to its decomposition) and small amounts of *N*-acetylaminoacyl

TABLE I
REACTION OF ACTIVE ESTERS **2** WITH ADENOSINE 2′(3′)-*O*-AMINOACYL DERIVATIVES **1**

| Acyl-adenosine | Active ester | Product | Yield,[a] % |
|---|---|---|---|
| A-Phe (**1a**) | Ac-OQ(Cl) (**2a**) | A(Ac-Phe) (**3a**) | 78 |
| A-Phe (**1a**) | Z-Phe-OQ(Cl) (**2b**) | A(Z-Phe-Phe) (**3b**) | 89 |
| A-Phe (**1a**) | Z-Lys(Z)-OQ(Cl) (**2c**) | A(Z-Lys(Z)-Phe) (**3c**) | 94 |
| A-Phe (**1a**) | Z-Ser(*t*-Bu)Phe-OQ(Cl) (**2e**) | A(Z-Ser(*t*-Bu)Phe-Phe) (**3g**) | 42 |
| A-Leu (**1b**) | Ac-OQ(Cl) (**2a**) | A(Ac-Leu) (**3d**) | 70 |
| A-Leu (**1b**) | Z-Phe-OQ(Cl) (**2b**) | A(Z-Phe-Leu) (**3e**) | 77 |
| A-Ala (**1c**) | Z-Leu-OQ(Cl) (**2d**) | A(Z-Leu-Ala) (**3f**) | 66 |

[a] The yields were determined by weight.

derivatives (*e.g.*, **3a** accompanying the reaction of compound **1a** with the ester **2b**). Formation of the by-products (*e.g.*, **3a**) may be explained by an exchange reaction[12] between the active esters **2b–e** and the acetate ions (their presence in the reaction mixture is due to dissociation of acetates of bases **1** which represent the virtual starting material; *cf.* ref 6). The extent of this side reaction is negligible with chloroxine esters under conditions used.

By the action of hydrogen bromide in acetic acid, the chloroxine ester of *N*-benzyloxycarbonyl-L-phenylalanine was converted to L-phenylalanine chloroxine ester dihydrobromide.[10] Condensation of the latter with *N*-benzyloxycarbonyl-*O*-*tert*-butyl-L-serine, according to the anhydride method,[13] afforded the required dipeptide ester. In the synthesis of the derivative **3g**, the protected active ester of the dipeptide **2e** was condensed with the aminoacyl derivative **1a**. After the usual isolation, the yield of the protected tripeptide ester was 42%. The above procedure precludes racemization of the phenylalanine unit in the resulting tripeptide ester during aminolysis of the active ester **2e** (*cf.* ref 14).

Lapidot and coworkers[15,16] used *N*-hydroxysuccinimide esters of protected oligopeptides in a recent synthesis of a tRNA oligopeptidyl derivative. Esterification of *N*-hydroxysuccinimide was effected with *N*,*N*′-dicyclohexylcarbodiimide. This procedure, however, does not guarantee the optical purity of the product, since the carboxylic function of the peptide is activated by the action of *N*,*N*′-dicyclohexylcarbodiimide.[14] Similarly, Gottikh, *et al.*,[17,18] have prepared imidazoyl derivatives of protected peptides by the esterification used with *N*,*N*′-carbonyldiimidazol. The activated esters of peptides were used for the acylation of 5′ nucleotides, but again the optical purity of resulting compounds [2′(3′)-*O*-peptidyl-5′ nucleotides] is subject to question.[14]

(8) S. Chládek and J. Žemlička, *Chem. Commun.*, **35**, 89 (1970).
(9) V. Gut, S. Chládek, and J. Žemlička, *ibid.*, **35**, 2398 (1970).
(10) H. D. Jakubke and A. Voigt, *Chem. Ber.*, **99**, 2944 (1966).
(11) All amino acids and their derivatives were of the L configuration. For abbreviations, see ref 6 and 7. The symbol -OQ(Cl) designates an ester of 5-chloro-8-hydroxyquinoline.
(12) J. Žemlička and S. Chládek, *Biochim. Biophys. Acta*, **246**, 487 (1971).
(13) J. R. Vaughn, Jr., *J. Amer. Chem. Soc.*, **73**, 3547 (1951).
(14) F. Weygand, A. Prox, and W. König, *Chem. Ber.*, **99**, 1451 (1966).
(15) Y. Lapidot and N. de Groot, *Biochim. Biophys. Acta*, **179**, 521 (1969).
(16) Y. Lapidot, N. de Groot, and S. Rappoport, *ibid.*, **182**, 105 (1969).
(17) B. P. Gottikh, A. A. Krayevsky, and P. P. Purygin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1104 (1970).
(18) P. P. Purygin, A. A. Krayevsky, and B. P. Gottikh, *ibid.*, 1369 (1970).

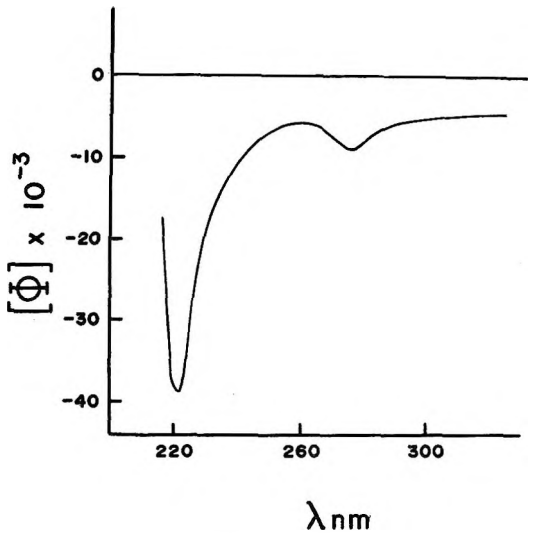



Figure 1.—Optical rotatory dispersion curve of a mixture of products obtained by dissolving compound **3i** in dimethylformamide (methanol).

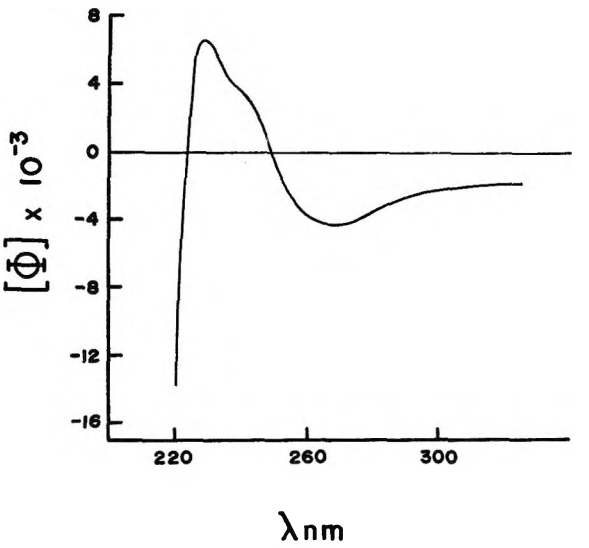



Figure 2.—Optical rotatory dispersion curve of compound **3i** (0.1 *M* HCl).

The protected peptides and the *N*-acetylaminoacyl derivatives **3a–g** were characterized by thin layer chromatography on silica gel and paper chromatography as well as by ultraviolet and infrared spectra when a sufficient amount of material was available. In the case of derivatives **3b**, **3c**, **3e**, and **3f**, the protecting *N*-benzyloxycarbonyl group was removed by the usual procedure of hydrogenolysis over a palladium catalyst in acetic acid as the solvent.[6] In the synthesis of the tripeptidyl derivative **3m**, the *O*-*tert*-butyl group in the serine unit of compound **3g** was quantitatively removed by the action of trifluoroacetic acid prior to hydrogenolysis. The final products were characterized by paper chromatography, electrophoresis at pH 3.4, alkaline hydrolysis to adenosine, and the corresponding peptide derivative, as well as by ratio of amino acids to adenosine (see Table II).

TABLE II

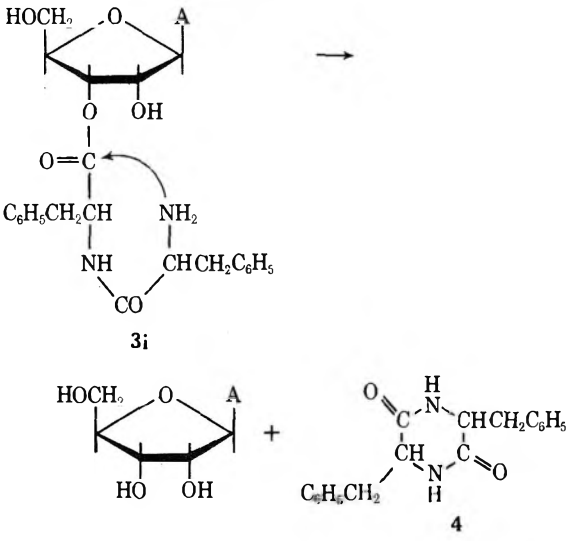
ADENOSINE 2′(3′)-*O*-PEPTIDYL DERIVATIVES **3**

| Compd | Yield, % | Ratio of components[a] |
|---|---|---|
| A(Phe-Phe) (**3i**) | 74 | Phe:A = 1.90:1 |
| A(Lys-Phe) (**3j**) | 53 | Lys:Phe:A = 0.96:1.09:1 |
| A(Phe-Leu) (**3k**) | 61 | Phe:Leu:A = 0.63:0.87:1 |
| A(Leu-Ala) (**3l**) | 88 | Leu:Ala:A = 0.90:0.95:1 |
| A(Ser-Phe-Phe) (**3m**) | 50 | Ser:Phe:A = 1.00:2.36:1 |

[a] See ref 7.

2′(3′)-*O*-L-Phenylalanyl-L-phenylalanyladenosine (**3i**) rapidly decomposes when dissolved in dimethylformamide even in the absence of a base, in contrast to the 2′(3′)-*O*-aminoacyl derivatives **1** which are relatively stable in dimethylformamide. The dipeptide ester[19] **3i** is readily cyclized to the corresponding 2,5-piperazinedione **4** with the simultaneous removal of adenosine (Scheme II). The optical rotatory dispersion spectrum of the reaction mixture (Figure 1) differs considerably from that of the starting compound (Figure 2). A distinct Cotton effect in the 220-nm region strongly favors the presence of 2,5-piperazinedione **4** in the reaction mixture. A similar Cotton effect of an unusually high amplitude has been observed[20] with 2,5-piperazinedione derived from L-phenylalanine. This observation is in accordance with a report of Lapidot and coworkers,[15,16] who recorded the formation of cyclopeptides during hydrolysis of several tRNA peptidyl derivatives.

SCHEME II




In our opinion, the present procedure is applicable to the synthesis of various oligonucleotide peptidyl derivatives. In this respect, the chloroxine esters fulfill all fundamental requirements; namely, they are selective, do not react with other functions present in the molecule of aminoacyl oligonucleotides (especially with the phospho diester linkage[8,9]), and do not acylate the cytidine amino group in contrast to other active esters.[9] Consequently, the chloroxine esters are highly advantageous from the preparative point of view.

## Experimental Section

**General Procedures.**—All evaporations were carried out *in vacuo* at <35° bath temperature. Some general methods used

(19) It has been well established that aminoacyl and peptidyl derivatives of nucleosides, oligonucleotides, or tRNA behave as active esters; *e.g.*, see H. G. Zachau and H. Feldmann, *Progr. Nucleic Acid Res. Mol. Biol.*, **4**, 217 (1965).

(20) K. Bláha and I. Frič, *Collect. Czech. Chem. Commun.*, **35**, 619 (1970).

in this study were described in an earlier paper.[6] Adenosine aminoacyl derivatives 1a–c were prepared according to ref 6. The active esters 2a–d were prepared by known procedures.[9,10,21] Protected amino acids and peptides were prepared in the Peptide Department of this institute. Descending chromatography was performed on Whatman No. 1 paper in the solvent systems $S_1$, 2-propanol–concentrated ammonium hydroxide–water (7:1:2); $S_2$, 1-butanol–acetic acid–water (5:2:3), and $S_3$, 1-butanol–water–pyridine–acetic acid (90:72:60:18). Thin layer chromatography was performed with aluminum foils precoated with silica gel and starch as binder (Silufol, Kavalier Glassworks, Votice, Czechoslovakia) in the solvent systems $S_4$, methylene chloride–methanol (95:5), and $S_5$, methylene chloride–methanol (9:1). Preparative thin layer chromatography employed the method described previously.[6] Spots were detected under ultraviolet light and, whenever possible, by the ninhydrin spray. For $R_f$ values, see Table III. Electrophoresis was performed on Whatman No. 1 paper in 0.05 *M* sodium hydrogen citrate (pH 3.4). For electrophoretic mobilities, see Table IV. Melting points were taken on a heated microscope stage (Kofler block). Infrared spectra (Table V) were measured on a UR-10 spectrophotometer in chloroform at a concentration of 5% or, in the region of hydrogen bonds, of $3 \times 10^{-3}$ *M*. ORD spectra were recorded on a Jasco ORD/UV apparatus without temperation in 1 mm cells at a concentration of 1 μmol per 1 ml.

TABLE III

$R_f$ VALUES IN PAPER AND THIN LAYER CHROMATOGRAPHY OF STARTING COMPOUNDS, PRODUCTS, AND AUTHENTIC SPECIMENS

| Compd | $S_1$ | $S_2$ | $S_3$ | $S_4$ | $S_5$ |
|---|---|---|---|---|---|
| A | 0.51 | 0.56 | 0.55 | start | 0.08 |
| Phe | 0.59 | 0.70 | 0.53 | | |
| A-Phe (1a) | *a* | 0.73 | | | 0.09 |
| A(Z-Phe-Phe) (3b) | *a* | 0.90 | | 0.26 | 0.57 |
| A(Ac-Phe) (3a) | *a* | 0.80 | | 0.05 | 0.32 |
| Ac-Phe | 0.74 | | | | |
| A(Phe-Phe) (3i) | *a* | 0.85 | | | |
| Phe-Phe | 0.79 | 0.89 | | | |
| A(Z-Lys(Z)-Phe) (3c) | *a* | 0.94 | | | 0.65 |
| A(Lys-Phe) (3j) | *a* | 0.55 | 0.49 | | |
| Lys-Phe | 0.61 | 0.57 | 0.39 | | |
| Lys | 0.32 | 0.29 | 0.11 | | |
| A(Z-Ser(*t*-Bu)-Phe-Phe) (3g) | *a* | 0.92 | | 0.08 | 0.47 |
| A(Z-Ser-Phe-Phe) (3h) | *a* | 0.90 | | 0.03 | 0.35 |
| A(Ser-Phe-Phe) (3m) | *a* | 0.78 | 0.80 | | |
| Ser | 0.38 | 0.29 | 0.17 | | |
| Ser-Phe-Phe | 0.72 | 0.89 | 0.70 | | |
| A-Leu (1b) | *a* | 0.68 | | | 0.06 |
| Leu | 0.62 | 0.70 | 0.54 | | |
| A(Ac-Leu) (3d) | *a* | 0.85 | | | 0.35 |
| A(Z-Phe-Leu) (3e) | *a* | 0.95 | | | 0.20 |
| A(Phe-Leu) (3k) | *a* | 0.82 | | | |
| Phe-Leu | 0.82 | 0.88 | | | |
| A-Ala (1c) | *a* | 0.44 | | | 0.04 |
| Ala | 0.47 | 0.41 | 0.21 | | |
| A(Z-Leu-Ala) (3f) | *a* | 0.90 | | 0.10 | 0.20 |
| A(Leu-Ala) (3l) | *a* | 0.64 | | | |
| Leu-Ala | 0.67 | 0.72 | 0.63 | | |

[a] Decomposition.

TABLE IV

RELATIVE MOBILITY OF PRODUCTS IN THE PAPER ELECTROPHORESIS (pH 3.4; ADENOSINE MOBILITY, 1.00)

| Compd | Mobility | Compd | Mobility |
|---|---|---|---|
| A-Phe (1a) | 2.1 | Leu | 0.71 |
| Phe | 0.47 | Phe-Leu | 1.29 |
| A(Phe-Phe) (3i) | 1.30 | A-Ala (1c) | 2.40 |
| Phe-Phe | 0.83 | Ala | 0.74 |
| A(Lys-Phe) (3j) | 3.00 | A(Leu-Ala) (3l) | 1.80 |
| Lys | 4.00 | Leu-Ala | 1.02 |
| Lys-Phe | 2.2 | A(Ser-Phe-Phe) (3m) | 1.50 |
| A-Leu (1b) | 2.1 | Ser | 0.72 |
| A(Phe-Leu) (3k) | 1.37 | Ser-Phe-Phe | 0.54 |

**Authentic Samples.**—L-Phenylalanyl-L-phenylalanine was prepared by removal of the benzyloxycarbonyl group from *N*-benzyloxycarbonyl-L-phenylalanyl-L-phenylalanine[22] with hydrogen bromide in acetic acid. L-Phenylalanyl-L-leucine was obtained according to ref 23. L-Leucyl-L-alanine was prepared by condensation of L-alanine benzyl ester *p*-toluenesulfonate with *N*-benzyloxycarbonyl-L-leucine by the action of *N,N'*-dicyclohexylcarbodiimide and the subsequent hydrogenolysis of protecting groups.[7] L-Lysyl-L-phenylalanine was obtained analogously by condensation of $N^{\alpha}$,$N^{\epsilon}$-bisbenzyloxycarbonyl-L-lysine with L-phenylalanine benzyl ester *p*-toluenesulfonate[24] and the subsequent hydrogenolysis. L-Seryl-L-phenylalanyl-L-phenylalanine was obtained by hydrogenolysis of *N*-benzyloxy-L-seryl-L-phenylalanyl-L-phenylalanine (*vide infra*). Amino acid analysis: LysPhe,Lys, Phe = 1.02; SerPhePhe,Ser, Phe = 0.445.

***N*-Benzyloxycarbonyl-*O*-*tert*-butyl-L-seryl-L-phenylalanine 5-Chloro-8-hydroxyquinoline Ester (2e).**—A mixture of *N*-benzyloxycarbonyl-*O*-*tert*-butyl-L-serine (3.1 mmol, 0.92 g), *N*-ethyl piperidine (3.1 mmol, 0.43 ml), and chloroform (10 ml) was cooled to −20°, treated with *sec*-butyl chloroformate (3 mmol, 0.4 ml), and then held at 5° for 10 min. The solution was cooled again to −20° and treated with L-phenylalanine 5-chloro-8-hydroxyquinoline ester dihydrobromide[10] (3.1 mmol, 1.52 g), and the resulting mixture was stirred for 1 hr at −20° and for an additional 2 hr at room temperature. The solvent was evaporated under diminished pressure and the residue was dissolved in chloroform (50 ml). The solution was washed successively with water, two portions of 20% aqueous citric acid, water, 5% aqueous sodium hydrogen carbonate, and water again. The dried ($Na_2SO_4$) solution was evaporated to dryness under diminished pressure. The residue solidified on trituration with a mixture of nitromethane and water. Recrystallization from aqueous 2-propanol afforded 0.83 g (44%) of compound **2e**, mp 151–153°.

*Anal.* Calcd for $C_{33}H_{34}ClN_3O_6$: C, 65.61; H, 5.67; N, 6.95; Cl, 5.87. Found: C, 65.90; H, 5.76; N, 7.09; Cl, 6.03.

***N*-Benzyloxycarbonyl-L-seryl-L-phenylalanyl-L-phenylalanine Benzyl Ester.**—A solution of the active ester **2e** (0.3 g, 0.5 mmol) in dimethylformamide (5 ml) was added to a 1 *M* solution (0.5 ml) of L-phenylalanine benzyl ester (liberated from the *p*-toluenesulfonate by the action of triethylamine[24]) in ethyl acetate. The resulting mixture was kept at room temperature for 60 hr and then diluted with ethyl acetate (40 ml). The solution was washed successively with water and five 20-ml portions of 0.5 *M* $H_2SO_4$, and then once more with water. The dried ($Na_2SO_4$) ethyl acetate solution was evaporated under diminished pressure. The residual oil was dissolved in ethyl acetate and a solid was precipitated with petroleum ether (bp 30–60°). The gelatinous precipitate was collected and dissolved in trifluoroacetic acid (2 ml), the solution was allowed to stand at room temperature for 2 hr and evaporated to dryness under diminished pressure, and the residue was coevaporated twice with dioxane to remove the traces of trifluoroacetic acid. Crystallization from ethyl acetate–petroleum ether afforded 128 mg of a crude product, mp 143–145°, which was recrystallized twice from ethyl acetate to afford 50 mg of the title compound, mp 161–163°.

*Anal.* Calcd for $C_{36}H_{37}N_3O_7$: C, 69.33; H, 5.97; N, 6.74. Found: C, 69.08; H, 6.12; N, 6.89.

**Reaction of 2′(3′)-*O*-Aminoacyl Derivatives of Adenosine 1 with the Active Esters 2.**—Compound 1 (50 μmol obtained from a stock solution in 80% aqueous acetic acid by lyophilization, dried at $10^{-3}$ Torr, and washed with two portions of ether) in dimethylformamide (0.5 ml) was treated with a solution of the active ester 2 (100 μmol) in dimethylformamide (0.5 ml), and the entire mixture was allowed to stand at room temperature for

(21) H. Vogt and D. Jeske, *Arch. Chem. Pharm.*, **291**, 168 (1958).

(22) K. Bláha, unpublished results.

(23) Z. Pravda, K. Poduška, and K. Bláha, *Collect. Czech. Chem. Commun.*, **29**, 2626 (1964).

(24) J. P. Greenstein and M. Winitz, "Chemistry of Amino Acids," Wiley, New York, N. Y., 1959, p 942.

TABLE V

INFRARED SPECTRA ($cm^{-1}$) AND ULTRAVIOLET SPECTRA (nm) OF PRODUCTS

| Compd[a] | ν(CO) Ester | ν(CO) Urethane | ν(CO) Amide | Adenine | $\nu(NH_2)$ | ν(NH) | $\lambda_{max}$ | Log ε |
|---|---|---|---|---|---|---|---|---|
| **3a** | 1750, 1729[b] | | 1664 | 1632 | 3526, 3412 | 3438 | 260[c] | 3.97 |
| **3b** | 1745 | 1718 | 1679 | 1634 | 3526 | 3413[d] | 259[c] | 4.14 |
| **3d** | 1743, 1730[b] | | 1658 | 1643[e] | 3521, 3415 | 3442 | 260[f] | |
| **3g**[g] | 1746 | 1726 | 1676, 1510 | 1639[e] | 3526, 3414 | 3431[d] | 260[c] | |
| **3e** | 1750 | 1715 | 1680 | | 3524, 3414 | 3431[d] | 260[c] | |

[a] ν(OH) 3200 $cm^{-1}$ (hydrogen bonding) for all compounds. [b] Hydrogen bonding. [c] In ethanol. [d] Together with $\nu(NH_2)_{sym}$, shoulder. [e] Together with ν(CO) amide bonded. [f] 0.01 *M* HCl. [g] A weak band at 3357 $cm^{-1}$, probably NH bonded; *cf.* the spectra of adenosine 2′(3′)-*O*-bisaminoacyl derivatives.[6]

20–24 hr and evaporated to dryness under diminished pressure. The residue was dissolved in the solvent system $S_5$ and chromatographed on a thin layer (loose, 3 mm thick, 20 × 50 cm) of silica gel in the same solvent system. Detection showed a band of the unreacted starting compound **1**, a very weak band of the *N*-acetyl derivative of compound **1**, and the principal band of the main product **3**. The latter band was eluted with the above solvent system and the eluate was evaporated under diminished pressure (when traces of chloroxine were present, the product was rechromatographed). Powdered products were obtained by lyophilization of dioxane solutions. For yields, see Table I. The products were homogeneous as shown by paper and thin layer chromatography; some of them were characterized by infrared spectra.

**2′(3′)-*O*-(*N*-Benzyloxycarbonyl-L-seryl-L-phenylalanyl-L-phenylalanyl)adenosine (3h).**—Compound **3g** (50 μmol) was dissolved in trifluoroacetic acid[6] (1 ml), and the solution was allowed to stand at room temperature for 45 min and evaporated to dryness under diminished pressure. The residue was repeatedly lyophilized with five portions of dioxane until colorless. The resulting powder was chromatographically homogeneous in the solvent systems $S_2$ and $S_5$ and different from the starting derivative **3g**.

**Adenosine 2′(3′)-*O*-Peptidyl Derivatives (3i–3m).**—The hydrogenolysis of the *N*-benzyloxycarbonyl group was performed over 5% palladium oxide on barium sulfate catalyst in 80% aqueous acetic acid, as reported earlier.[6] Yields of the peptidyl derivatives **3i–3m** were determined spectrophotometrically with the use of aliquots of stock solutions in 80% acetic acid diluted with 0.01 *M* HCl. For yields of products and the corresponding amino acid analyses, see Table II. The products were also characterized by paper chromatography in the solvent systems $S_2$ and $S_3$ (Table III), electrophoresis at pH 3.4 (Table IV), and alkaline hydrolysis in the solvent system $S_1$ or in 0.2 *M* NaOH (30 min at 20°) to adenosine and the parent peptide. Products of hydrolysis were compared with authentic specimens in the solvent systems $S_1$, $S_2$, and $S_3$ as well as in electrophoresis at pH 3.4.

**Cleavage of Compound 3i in Dimethylformamide.**—Compound **3i** (1.09 μmol) was dissolved in dimethylformamide (0.2 ml). After 4 hr at room temperature the reaction mixture was analyzed by chromatography in the solvent systems $S_1$ and $S_2$. Adenosine was determined as the single reaction product (detection under ultraviolet light and with ninhydrin). The solution was evaporated to dryness under diminished pressure, and the residue was repeatedly lyophilized with water and dried at $10^{-4}$ Torr. The residue was finally dissolved in hot methanol and the small amount of insoluble material was removed by filtration. The ORD measurements (Figures 1 and 2) were performed with the filtrate as well as with the starting compound **3i**.

**Registry No.**—**1a**, 2′-isomer, 25164-30-1; **1a** 3′-isomer, 5956-81-0; **1b** 2′-isomer, 34996-43-5; **1b** 3′-isomer, 5957-19-7; **1c** 2′-isomer, 4217-73-6; **1c** 3′-isomer, 4217-74-7; **2a**, 10173-02-1; **2b**, 7797-44-6; **2c**, 27785-02-0; **2d**, 7797-39-9; **2e**, 34996-31-1; **3a** 2′-isomer, 44996-45-7; **3a** 3′-isomer, 34996-32-2; **3b** 2′-isomer, 34996-46-8; **3b** 3′-isomer, 34969-19-2; **3c** 2′-isomer, 34996-47-9; **3c** 3′-isomer, 34996-33-3; **3d** 2′-isomer, 34996-48-0; **3d** 3′-isomer, 34996-34-4; **3e** 2′-isomer, 34996-49-1; **3e** 3′-isomer, 35000-88-5; **3f** 2′-isomer, 35000-98-7; **3f** 3′-isomer, 35000-89-6; **3g** 2′-isomer, 35000-99-8; **3g** 3′-isomer, 35000-90-9; **3h** 2′-isomer, 35001-00-4; **3h** 3′-isomer, 35000-91-0; **3i** 2′-isomer, 35001-01-5; **3i** 3′-isomer, 35000-92-1; **3j** 2′-isomer, 35001-02-6; **3j** 3′-isomer, 35000-93-2; **3k** 2′-isomer, 35001-03-7; **3k** 3′-isomer, 35000-94-3; **3l** 2′-isomer, 35001-04-8; **3l** 3′-isomer, 35000-95-4; **3m** 2′-isomer, 35001-05-9; **3m** 3′-isomer, 35000-96-5; *N*-benzyloxycarbonyl-L-seryl-L-phenylalanyl-L-phenylalanine benzyl ester, 35000-97-6.

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# Formation of a Long-Chain Alcohol Ester of Hydroxy Fatty Acid Sophoroside by Fermentation of Fatty Alcohol by a *Torulopis* Species[1]

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Fermentation of oleyl alcohol by *Torulopsis bombicola* produces the oleyl alcohol ester of the sophoroside of 17-hydroxyoleic acid (40%) together with lactonic and acidic hydroxy acid sophorosides. The major product was characterized as the octadecyl derivative **3** and the structure was established by degradation and by synthesis of the $\alpha$ anomer of the heptaacetate. The composition of the fermentation product was obtained by gas–liquid chromatographic analysis of the trimethylsilyl ethers of the hydrogenated deacetylated products.

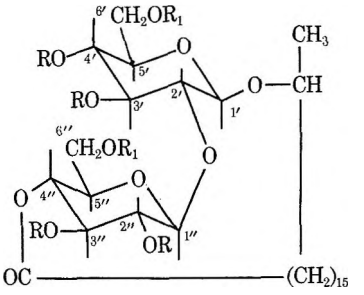
We have previously shown that when long-chain fatty acids are fermented by a species of yeast of the genus *Torulopsis* the acids are hydroxylated at the penultimate or terminal carbon atom and the hydroxy acids produced are converted to sophorosides.[2] The products exist mainly in lactonic (**1**) and acidic forms (**2**) both having acetate groups at the 6′ and 6″ positions.[3] The fermentation of fatty alcohols has now been investigated in the hope that alcohol sophorosides with surface-active properties would be obtained. Another possible result hoped for was that alcohol sophoroside would be formed first, then the terminal methyl group oxidized to carboxyl, thus producing a larger proportion of $\omega$-hydroxy acid sophoroside than is usually obtained from fatty acids.

Oleyl alcohol was used in these experiments since being liquid it was more readily taken up by the yeast cells. There was, however, no appreciable formation of alcohol sophoroside nor was there an increase in the proportion of $\omega$-hydroxy acid sophoroside. About 40% of the product, examined after hydrogenation, consisted of octadecyl ester **3** octadecyl 17-L-[(2′-*O*-$\beta$-D-glucopyranosyl-$\beta$-D-glucopyranosyl)oxy]octadecanoate 6′,6″-diacetate.

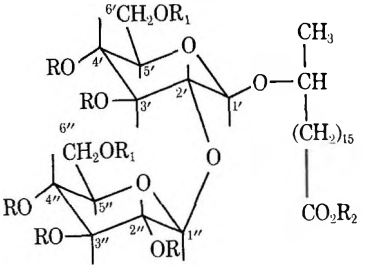
Thin layer chromatography indicated that the crude fermentation product also contained appreciable amounts of lactone and acid. After removal of about one-third of the lactone by crystallization, the remainder of the product was hydrogenated. Subsequently, a combination of column chromatography and crystallization yielded about 15% of the original amount of ester **3** in pure form.

Alkaline hydrolysis gave octadecanol and sophorosyl hydroxy acid isolated as methyl ester **4**,[3] and methanolysis with sodium methoxide gave deacetylated octadecyl ester **5**. Acetylation of **3** gave heptaacetate **6**. This compound was also prepared from crude neutral product (obtained by chromatographic removal of **2**) by acetylation and separation from lactone hexaacetate (**7**).

The nmr spectrum of **3** in dimethyl sulfoxide-$d_6$ was similar to that of methyl ester **8**,[3] except for additional signals due to the octadecyl portion. In particular, it contained five low-field proton doublets assigned to the five secondary hydroxyl groups of the sophorose portion, showing that the acetate groups are at the 6′ and 6″ positions.



**1**, R = H; $R_1$ = Ac
**7**, R = $R_1$ = Ac



**2**, R = $R_2$ = H; $R_1$ = Ac
**3**, R = H; $R_1$ = Ac; $R_2$ = $CH_3(CH_2)_{17}$
**4**, R = $R_1$ = H; $R_2$ = $CH_3$
**5**, R = $R_1$ = H; $R_2$ = $CH_3(CH_2)_{17}$
**6**, R = $R_1$ = Ac; $R_2$ = $CH_3(CH_2)_{17}$
**8**, R = H; $R_1$ = Ac; $R_2$ = $CH_3$

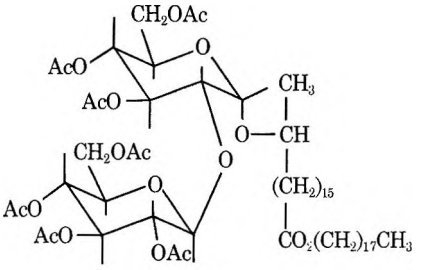
The formation of **3** in the fermentation was surprising, and, to confirm that **3** was in fact an octadecyl ester, synthesis of heptaacetate **6** by the Koenigs–Knorr reaction was attempted. 17-L-Formyloxyoctadecanoyl chloride[4] was allowed to react with octadecanol and the formate group was removed from the product to give octadecyl 17-L-hydroxyoctadecanoate. Reaction of acetobromosophorose[3] with this hydroxy ester, however, yielded a heptaacetate which resembled but was not identical with **6**. The product was dextrorotatory, whereas **6** is levorotatory, indicating that the reaction had produced a mixture of $\alpha$ and $\beta$ anomers. This was confirmed by the nmr spectrum ($CDCl_3$) of the product, which showed a doublet at $\delta$ 4.61, assigned to H-1″ of the $\alpha$ form **9** by analogy with the spectrum of the heptaacetate of the $\alpha$ form of **4**,[3] and a doublet at $\delta$ 4.46 assigned to H-1′ of **6**. The relative intensities of these signals showed that about 30% of $\alpha$ anomer was present. The Koenigs–Knorr reaction was repeated, but 30–50% of the $\alpha$ anomer was always produced. Accordingly, both the synthetic

(1) (a) NRCC No. 12527. (b) Part VIII in the series "Fermentation of Long-Chain Compounds by *Torulopsis* sp." Part VII: E. Heinz, A. P. Tulloch, and J. F. T. Spencer, *Biochem. Biophys. Acta*, **202**, 49 (1970).

(2) A. P. Tulloch, J. F. T. Spencer, and P. A. J. Gorin, *Can. J. Chem.*, **40**, 1326 (1962).

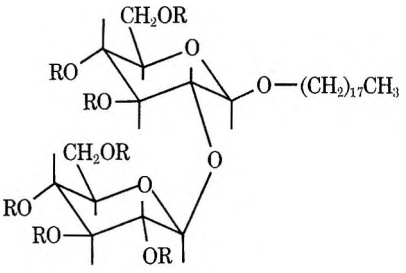
(3) A. P. Tulloch, A. Hill, and J. F. T. Spencer, *ibid.*, **46**, 3337 (1968).

(4) A. P. Tulloch, *Chem. Phys. Lipids*, **6**, 235 (1971).



9

mixture and compound **6** were completely inverted to $\alpha$-heptaacetate **9** by treatment with 3% hydrogen bromide in acetic acid.[3] The two products were indistinguishable.



**10**, R = Ac
**11**, R = H

To make it easier to detect possible minor amounts of oleyl alcohol $\beta$-sophoroside in the fermentation product by chromatography, octadecyl $\beta$-sophoroside heptaacetate (**10**) was synthesized by the Koenigs–Knorr reaction. About 35% of the product crystallized as pure $\beta$ anomer, but nmr spectroscopy indicated that the mother liquors contained the $\alpha$ form in quantities corresponding to the formation of 20% of $\alpha$ anomer in the reaction. Deacetylation of **10** gave octadecyl $\beta$-sophoroside (**11**).

The possibility of analyzing the fermentation products as trimethylsilyl ethers by gas–liquid chromatography (glc) was investigated. Although trimethylsilyl ethers of pure diacetates **1** or **8** could be separated, the natural product also contained compounds lacking one or both acetate groups which had shorter retention times (as trimethylsilyl ethers), resulting in a complex mixture which could not be analyzed satisfactorily. Trimethylsilyl ethers of the deacetylated compounds sophoroside **11**, methyl ester **4**, and octadecyl ester **5**, however, were well separated by glc. A mixture of these three compounds was used to determine relative response factors for flame ionization detectors, making possible quantitative analysis of the fermentation products.

The fermentation mixture was hydrogenated, treated with diazomethane to produce esters from acidic products, deacetylated, and converted to trimethylsilyl ethers. Proportions of lactonic and acidic products were estimated by first separating **1** and **3** together from **2** (and compounds lacking acetate groups) by silicic acid column chromatography and analyzing these fractions separately by glc. A peak (2%) with the same emergence temperature as the trimethylsilyl ether of **11** was detected, and, although the presence of **11** was not confirmed further, it clearly did not form more than 2% of the total product. The approximate composition of the product was thus shown to be **11**, 2%; **1**, 20%; **2** (also acids lacking acetates), 25%; **3**, 40%; octadecyl esters lacking acetates, 5%; and unidentified, 8%. Compound **11** was probably originally present as the 6′,6″-diacetate.

Fermentation of long-chain fatty acids and hydrocarbons previously[3] gave mixtures containing about 60% lactones and 40% acids. It appears that, when oleyl alcohol is fermented, part of the alcohol is first oxidized to oleic acid, which is then hydroxylated mainly at the penultimate carbon atom;[2] sophorosidic acid is then formed; about half is enzymatically converted to oleyl alcohol ester; and the rest either is converted to lactone or remains as free acid. Further investigations are being carried out to find out if other alcohols are also converted to esters of type **3** by *Torulopsis* species.

## Experimental Section[5]

**Fermentation of Oleyl Alcohol.**—Strain 319-67 of *Torulopsis bombicola*[6] was used and the medium (3 l. in 5 l. of fermentor) was glucose (10%), yeast extract (1%), and urea (0.1%). The medium was inoculated and 2 days later oleyl alcohol[7] was added (50 g on each of 4 successive days). The medium was agitated at 400 rpm at 23° with air flow of 1 l./min. One day after the last oleyl alcohol addition the clear medium was decanted from the sludge of cells and heated to 70°, when a mixture of product and water (1:1) separated as a heavy, amber-colored "oil" (470 ml). Product (220 g) was obtained by extraction of the "oil" with ethyl acetate.

**Thin Layer Chromatography.**—All products were examined by tlc. $R_f$ values were as follows: in diethyl ether, 6 and 9, 0.57; **7**, 0.51; **10**, 0.50; in chloroform–acetone–acetic acid (50:50:1), **1**, 0.26; **3**, 0.20; **2**, 0.11; in chloroform–methanol (3:1), **1**, 0.71; **3**, 0.72; **5**, 0.48; **4**, 0.37; **11**, 0.31.

**Octadecyl 17-L-[(2′-*O*-β-D-Glucopyranosyl-β-D-glucopyranosyl)-oxy]octadecanoate 6′,6″-Diacetate (3).**—A solution of 55 g of fermentation product in 220 ml of ethanol was kept at 2° for 1 week and then filtered from 5 g of crystalline lactone (similar to compound **1** but with a 9,10-double bond in the fatty acid chain). The filtrate was made up to 500 ml with ethanol and hydrogenated at 45° over 1 g of 10% palladium on charcoal. After removal of the catalyst, the solution deposited 16.3 g of amorphous lumps. This material was applied to a column of 200 g of silicic acid, and elution with 2 l. of chloroform–methanol (50:1) gave 8.5 g of crude **3**. Rechromatography on a further 200 g of silicic acid and elution with 5 l. of chloroform–acetone (9:1) gave 2.55 g of **3** free from **1**. Recrystallization from ethanol gave 2.30 g of pure **3**: mp 109–111°; $[\alpha]^{25}D$ −15.5° (*c* 2.3, $CHCl_3$); nmr (dimethyl sulfoxide-$d_6$, 55°) $\delta$ 0.84 (t), 1.08 (d), 1.24 (s), 1.98 (s, $CH_3CO$–), 2.22 (t, $-CH_2CO_2$–), 3.98 (t, $-CH_2OCO$–), 4.37, 4.41 (both d, $J$ = 7.5 Hz, H-1′ and H-1″), 4.86, 4.94, 5.10, 5.20, 5.40 (all d, OH)

*Anal.* Calcd for $C_{52}H_{96}O_{15}$: C, 64.97; H, 10.07. Found: C, 64.72; H, 9.85. Saponification equivalent calcd, 320.43; found, 323.9; mol acetic acid/mol calcd, 2.0; found, 1.97.

**Alkaline Hydrolysis of 3.**—A solution of 0.156 g of compound **3** in 20 ml of ethanol, 20 ml of water, and 10 ml of 0.1 *N* aqueous sodium hydroxide was refluxed for 18 hr and then neutralized with 0.1 *N* hydrochloric acid. After addition of 50 ml of methanol and 50 ml of water the solution was extracted twice with

(5) Nmr spectra were measured at 100 MHz using a Varian HA-100 spectrometer; the temperature was 32° except where otherwise stated; chemical shifts are in parts per million from internal tetramethylsilane. Specific rotations were measured in a 1-dm cell using a Perkin-Elmer Model 141 polarimeter. Silica gel G was used for tlc; compounds were detected by spraying with 50% sulfuric acid and heating with an infrared lamp. Bio-Sil A silicic acid, from Bio-Rad Laboratories, Richmond, Calif., was used for column chromatography. Glc was carried out using an F & M Model 402 gas chromatograph with flame ionization detectors; the column was 3 ft × 0.125 in. stainless steel packed with 80–100 mesh, silanized, acid-washed Chromosorb W coated with 2% silicone SE-30.

(6) J. F. T. Spencer, P. A. J. Gorin, and A. P. Tulloch, *Antonie van Leeuwenhoek*; *J. Microbiol. Serol.*, **36**, 129 (1970).

(7) Oleyl alcohol was prepared by lithium aluminum hydride reduction of pure methyl oleate.

hexane. Evaporation of the hexane extract gave 0.042 g of octadecanol, after crystallization from methanol, mp and mmp 58–59°. The aqueous alcohol solution was treated with Dowex 50, 2 ml of pyridine was added, and the solution was evaporated to dryness. The product was dissolved in methanol and treated with diazomethane, and the solvent removed. Crystallization of the residue from methanol–water (1:2) gave 0.100 g of **4**, mp and mmp with authentic **4**[3] 145–148°.

**Octadecyl 17-L-[(2′-*O*-β-D-Glucopyranosyl-β-D-glucopyranosyl)-oxy]octadecanoate (5).**—Compound **3** (0.151 g) was dissolved in 5 ml of chloroform, 5 ml of 0.022 *N* methanolic sodium methoxide was added, and the mixture was kept at room temperature for 30 min and then neutralized with 15 μl of acetic acid. Solvents were evaporated and the residue was crystallized from ethanol, giving 0.139 g of **5**: mp 159–162°; $[\alpha]^{25}D$ −13.8° (c 1.1, pyridine); nmr (pyridine) δ 4.48 (d, $J$ = 7.5 Hz, H-1′), 5.14 (d, $J$ = 7.5 Hz, H-1″).

*Anal.* Calcd for $C_{48}H_{92}O_{13}$: C, 65.72; H, 10.57. Found: C, 65.72; H, 10.76.

**Octadecyl 17-L-[2′-*O*-β-D-Glucopyranosyl-β-D-glucopyranosyl)-oxy]octadecanoate 2″,3′,3″,4′,4″,6′,6″-Heptaacetate (6).**—A solution of 1.30 g of **3** in 5 ml of pyridine and 5 ml of acetic anhydride was kept at 25° for 18 hr. Removal of the reagents at 70° and crystallization from methanol gave 1.53 g of **6**: mp 63–65°; $[\alpha]^{25}D$ −6.9° (c 2.4, $CHCl_3$); nmr ($CDCl_3$) δ 4.46 (d, $J$ = 7.5 Hz, H-1′, assigned as before[3]).

*Anal.* Calcd for $C_{62}H_{106}O_{20}$: C, 63.56; H, 9.12. Found: C, 63.27; H, 8.91.

Compound **6** was also prepared directly from crude fermentation product. Chromatography of 2.65 g of product on silicic acid gave 2.07 g of neutral material on elution with chloroform–methanol (50:1). After hydrogenation, neutral material was acetylated as above and chromatographed on 200 g of silicic acid; elution with 1500 ml of chloroform–hexane (1:1) gave 0.63 g of **6**. Further elution with the same solvent gave mixtures of **6** and **7**.

**Octadecyl 17-L-Formyloxyoctadecanoate.**—A solution of 5.0 g of 17-L-formyloxyoctadecanoyl chloride[4] in 10 ml of methylene chloride was added to 6.4 g of octadecanol dissolved in 25 ml of methylene chloride and 1.5 ml of pyridine, and the mixture was refluxed for 48 hr. The solution was washed with 2 *N* hydrochloric acid and solvent was evaporated, giving 10.65 g of crude product. This material, chromatographed on 200 g of silicic acid, gave on elution with 3 l. of hexane–chloroform (9:1) 1.53 g of octadecyl formate. Further elution with 4 l. of hexane–chloroform (4:1) gave 2.95 g of formate ester, and elution with 3 l. of hexane–chloroform (3:2) gave 2.45 g of hydroxy ester (see below). Crystallization of formate ester from ethyl acetate gave 1.45 g of pure product, mp 59.5–62.5°, $[\alpha]^{25}D$ −2.6° (c 2.1, $CHCl_3$).

*Anal.* Calcd for $C_{37}H_{72}O_4$: C, 76.49; H, 12.49. Found: C, 76.50; H, 12.52.

**Octadecyl 17-L-Hydroxyoctadecanoate.**—It had been intended to selectively hydrolyze the formate group (as was done previously[4] in a similar synthesis), but since some formate ester was hydrolyzed on the silicic acid column (above) the hydroxy ester so obtained was used. Crystallization from ethyl acetate gave 1.95 g of pure hydroxy ester, mp 70–72°, $[\alpha]^{25}D$ +2.0° (c 2.4, $CHCl_3$).

*Anal.* Calcd for $C_{36}H_{72}O_3$: C, 78.19; H, 13.13. Found: C, 78.03; H, 13.25.

**Octadecyl 17-L-[(2′-*O*-β-D-Glucopyranosyl-α,β-D-glucopyranosyl)oxy]octadecanoate 2″,3′,3″,4′,4″,6′,6″-Heptaacetate (6 + 9).**—A solution of 0.33 g of octadecyl 17-L-hydroxyoctadecanoate in 5 ml of methylene chloride was shaken for 1 hr with 0.5 g of silver carbonate and 0.5 g of Drierite, a solution of 0.42 g of acetobromosophorose[3] was then added, and shaking was continued for 3 days. The reaction mixture was applied to a silicic acid column, and elution with chloroform–hexane (1:1) gave 0.35 g of **6** + **9**. Crystallization from ethanol gave 0.12 g of **6** + **9**: mp 55–56°; $[\alpha]^{25}D$ +5.6° (c 3.2, $CHCl_3$); nmr ($CDCl_3$) δ 4.46 (d, $J$ = 7.5 Hz, H-1′ of **6**), 4.61 (d, $J$ = 7.5 Hz, H-1″ of **9**) (the ratio of the first signal to the second was about 2:1), 5.36 (t, H-3′ of **9**).

*Anal.* Calcd for $C_{62}H_{106}O_{20}$: C, 63.56; H, 9.12. Found: C, 63.42; H, 9.23.

**Octadecyl 17-L-[(2′-*O*-β-D-glucopyranosyl-α-D-glucopyranosyl)-oxy]octadecanoate 2″,3′,3″,4′,4″,6′,6″-Heptaacetate (9).**—A solution of 1.53 g of **6** in 20 ml of glacial acetic acid was prepared, 2 ml of 33% hydrogen bromide in acetic acid was added, and the mixture was kept for 2 hr. The mixture was poured into ice–water and extracted three times with chloroform. Solvent was removed, giving 1.28 g of crude **9**, which was purified by silicic acid chromatography (elution with hexane–chloroform, 1:1) and two crystallizations from methanol. The yield of pure **9** was 0.68 g: mp 61–64°; $[\alpha]^{25}D$ +33.7° (c 2.8, $CHCl_3$); nmr ($CDCl_3$) δ 4.61 (d, $J$ = 7.5 Hz, H-1″), 5.36 (t, H-3′).

*Anal.* Calcd for $C_{62}H_{106}O_{20}$: C, 63.56; H, 9.12. Found: C, 63.26; H, 9.22.

Compound **9** was also prepared in the same way from the synthetic mixture of **6** + **9**, it did not depress the melting point of the above product, and the nmr spectra of the two compounds were indistinguishable; $[\alpha]^{25}D$ was +31.6° (c 0.9, $CHCl_3$).

**Octadecyl 2-*O*-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (10).**—Octadecanol (0.16 g) in 5 ml of methylene chloride was shaken with 0.5 g of silver carbonate, 0.5 g of Drierite, and 0.40 g of acetobromosophorose for 2 days. The mixture was filtered, and solvents were removed and applied to a silicic acid column in hexane–chloroform (3:1). Hexane–chloroform (1:1) eluted 0.33 g of crude **10**, which on crystallization from ethanol gave 0.13 g of pure **10** as long needles: mp 85–87°; $[\alpha]^{25}D$ −6.1° (c 1.8, $CHCl_3$); nmr ($CDCl_3$) δ 4.44 (d, $J$ = 7.5 Hz, H-1).

*Anal.* Calcd for $C_{44}H_{72}O_{18}$: C, 59.44; H, 8.16. Found: C, 59.32; H, 8.07.

Deacetylation of 0.09 g of **10** with methanolic sodium methoxide and crystallization from methanol gave 0.05 g of octadecyl 2-*O*-(β-D-glucopyranosyl)-β-D-glucopyranoside (**11**): mp 195–197°; $[\alpha]^{25}D$ −19.5° (c 0.4, pyridine); nmr (pyridine) δ 4.85 (d, $J$ = 7.5 Hz, H-1), 5.26 (d, $J$ = 7.5 Hz, H-1′).

*Anal.* Calcd for $C_{30}H_{58}O_{11}$: C, 60.58; H, 9.83. Found: C, 60.54; H, 9.83.

Deacetylation of the mother liquors left after isolation of crystalline **10** gave an amorphous product, nmr (pyridine) δ 5.22 (d, $J$ = 7.5 Hz, H-1′ of **11**), 5.42 (d, $J$ = 4 Hz, presumably H-1 of α form of **11**); the ratio of the first signal to the second was about 2:1.

**Glc Analysis of Trimethylsilyl Ethers of Fermentation Products.**—Trimethylsilyl ethers were prepared as described by Sweeley, *et al.*[8] Isothermal analysis at 280° gave relative emergence times for trimethylsilyl ethers: **11**, 1.00; **1**, 1.26; **4**, 1.44; **8**, 2.29. Temperature programming from 250° to 385° at 5°/min gave emergence temperatures: **11**, 300°; **4**, 310°; **5**, 360°. Correction factors required for quantitative analysis were: **11**, 1.00; **4**, 1.33; **5**, 1.96. Before preparation of trimethylsilyl ethers 10-mg samples were dissolved in 100 μl of methanol and treated with ethereal diazomethane, solvents were removed, the samples were warmed with 100 μl of 0.022 *N* methanolic sodium methoxide for 10 min, the solution was neutralized with acetic acid in methanol, solvents were removed, and the residue was taken up in 100 μl of pyridine.

**Composition of Hydroxy Acid Portion of Crude Product.**—The percentage of ω-hydroxy acid in the crude product, determined as previously described,[2] was 12%, which is very similar to that formed when oleic acid was fermented.[2]

**Registry No.**—**3**, 34991-59-8; **4**, 23071-19-4; **5**, 34991-60-1; **6**, 34991-61-2; **9**, 34991-62-3; **10**, 34991-63-4; **11**, 34991-64-5; oleyl alcohol, 143-28-2; octadecyl 17-L-formyloxyoctadecanoate, 34991-65-6; octadecyl 17-L-hydroxyoctadecanoate, 34991-66-7.

(8) C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, **85**, 2497 (1963).

# Studies with Bicyclo[2.2.2]octenes. V.[1] The Total Synthesis of (±)-Patchouli Alcohol

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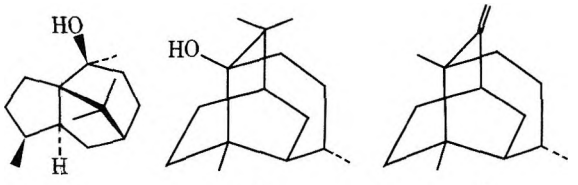
A stereospecific total synthesis of (±)-patchouli alcohol (2) *via* the key intermediate alcohol **14a** is described. A modified Reformatsky procedure was used to convert ketone **4** in high yield into a mixture of the conjugated esters **9a** and **10a** without concurrent formation of nonconjugated esters. Dissolving metal reduction of the conjugated esters gave alcohols **14a** and **15a** (4:1), whose relative configurations were readily assigned by pmr spectroscopy. The sequence was completed *via* the intermediates **14c**, **16**, **18a**, **18c**, and **18e**.

Patchouli alcohol and seychellene are two tricyclic sesquiterpenes which have been isolated from patchouli oil, an important raw material for the composition of perfumes.

Patchouli alcohol has been the subject of a large volume of both degradative and synthetic work, the most recent of which, up to the commencement of our work, was that of Büchi and coworkers.[3-6] The original structure **1** which Büchi attempted to synthesize was, however, incorrect, and it was only by a fortuitous rearrangement in the final steps of the synthesis that he arrived at patchouli alcohol, which was later shown to have a different structure (**2**) by X-ray investigations.[7] It was this ambiguity which led us to design a more direct synthesis of the revised structure based on bicyclo[2.2.2]octene intermediates.



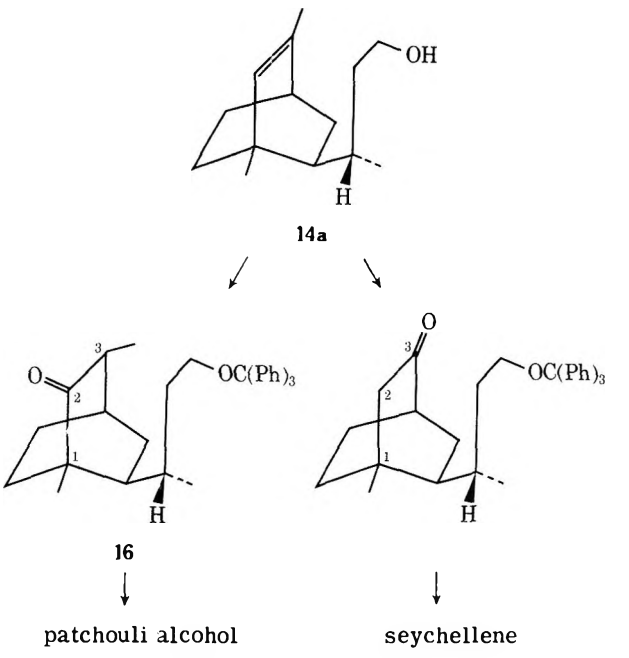
**1** **2** **3**

(−)-patchouli alcohol (−)-seychellene

The hydrocarbon seychellene (**3**) was isolated recently by Ourisson and Wolff[8] from patchouli oil obtained from the Seychelles Islands. The similarity in structure between seychellene and patchouli alcohol suggested a synthetic route to seychellene utilizing intermediates which had previously been prepared for the synthesis of patchouli alcohol.

The crucial intermediate in both syntheses was the olefin **14a**. The plan involved the modification of the olefinic bridge of this compound to yield a bicyclo[2.2.2]octanone **16** with the ketone function at $C_2$ for patchouli alcohol, and a bicyclo[2.2.2]octanone with the ketone at $C_3$ for seychellene.

This paper describes the synthesis of (±)-patchouli alcohol, while the accompanying paper[9] outlines details of the synthesis of (±)-seychellene.



**14a**

**16**

patchouli alcohol seychellene

## Results and Discussion

Entry into the bicyclo[2.2.2]octane ring system was gained *via* the Diels–Alder reaction of 1,3-dimethyl-1,3-cyclohexadiene with methyl vinyl ketone to give ketone **4** as the major product,[10] whose structure and stereochemistry have been rigorously established. The conversion of **4** to the planned intermediate **14a** appeared to be a simple task in theory, since a wide variety of methods are available for extending carbon chains by a two-carbon fragment.[11] The immediate objective was thus a simple and effective method of preparing the conjugated esters **9a** and/or **10a** from the ketone **4**.

The Wadsworth–Emmons method[12] proved disappointing, since only low yields of conjugated esters were obtained, together with a high proportion of starting material. Similarly, other workers[13] have found that many ketones, including a substituted pregnan-20-one, were inert to the Wadsworth–Emmons reagent; this was attributed to the stringent steric requirements of the reagent.

On the other hand, it was gratifying to find that the β-hydroxy ester **6** could be obtained consistently in

(1) Part IV: R. P. Gregson, R. N. Mirrington, and K. J. Schmalzl, *Aust. J. Chem.*, **25**, 531 (1972).

(2) (a) Abstracted in part from the Ph.D. thesis of K. J. Schmalzl, University of Western Australia, May 1971. (b) The award of a Commonwealth Postgraduate Scholarship to K. J. S. is gratefully acknowledged.

(3) G. Büchi and R. E. Erickson, *J. Amer. Chem. Soc.*, **78**, 1262 (1956).

(4) G. Büchi, R. E. Erickson, and N. Wakabayashi, *ibid.*, **83**, 927 (1961).

(5) G. Büchi and W. D. MacLeod, Jr., *ibid.*, **84**, 3205 (1962).

(6) G. Büchi, W. D. MacLeod, Jr., and J. Padilla O., *ibid.*, **86**, 4438 (1964).

(7) M. Dobler, J. D. Dunitz, B. Gubler, H. P. Weber, G. Büchi, and J. Padilla O., *Proc. Chem. Soc.*, 383 (1963).

(8) G. Wolff and G. Ourisson, *Tetrahedron*, **25**, 4903 (1969).

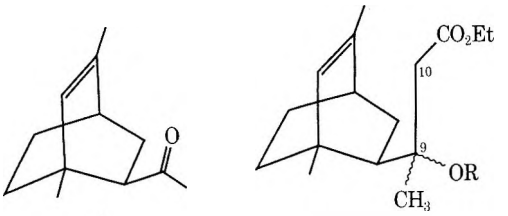
(9) R. N. Mirrington and K. J. Schmalzl, *J. Org. Chem.*, **37**, 2877 (1972).

(10) R. N. Mirrington and K. J. Schmalzl, *ibid.*, **34**, 2358 (1969).

(11) See H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, Chapter 8, for many leading references.

(12) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

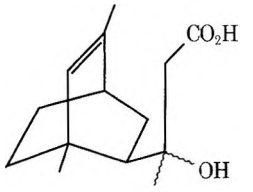
(13) A. K. Bose and R. T. Dahill, Jr., *J. Org. Chem.*, **30**, 505 (1965).



4

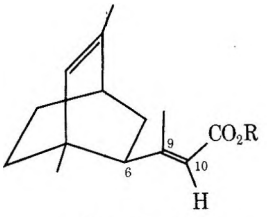


5, R = ZnBr
6, R = H
7, R = $COCH_3$

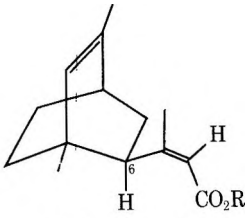


8

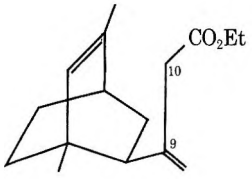
yields of up to 90% *via* the Reformatsky reaction on the ketone **4**. The difficulty with this approach soon became apparent, however, when attempted dehydration of the β-hydroxy ester by a number of the usual methods under acidic conditions resulted in rearrangement of the bicyclo[2.2.2]octene skeleton to an aromatic compound. Some aspects of this rearrangement and of its mechanism have been reported in an earlier paper.[1]



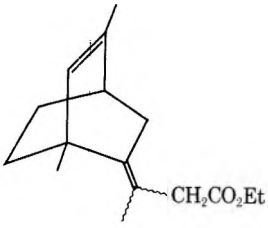
**9a**, R = Et
**b**, R = H



**10a**, R = Et
**b**, R = H



**11**



**12**

Dehydration of **6** without rearrangement was accomplished using phosphorus oxychloride in pyridine. The conjugated esters **9a** and **10a** were obtained, contaminated with the nonconjugated ester **11**. The other β,γ-unsaturated ester **12** was not detected, and this was not unexpected as there would be serious $A^{(1,3)}$ strain[14,15] between the $C_1$ methyl group and the substituents on the exocyclic double bond. The preparation of conjugated esters by dehydration of β-hydroxy esters[16] has this obvious weakness in the general case, since significant quantities of the nonconjugated esters are usually formed.

The product of the Reformatsky reaction was itself of some interest, because it might have been expected that a mixture of the 9*R* and 9*S* epimers of **6** would have been obtained. It appeared, however, that only one, or certainly predominantly one epimer was formed, but no positive identification has been possible. This question was not pursued further at the time as it obviously had little or no bearing on the structure of the conjugated esters **9a** and **10a** obtained from **6**, either by dehydration or by acetylation and elimination (see below).

In view of the problems associated with the dehydration of the hydroxy ester **6**, an alternative procedure was designed involving acetylation of the tertiary alcohol and subsequent elimination of acetic acid from the acetate **7** by base, to yield the conjugated esters **9a** and **10a** exclusively.[17] The acetate **7** was obtained in good yield from the hydroxy ester **6** using acetyl chloride and *N*,*N*-dimethylaniline.[18] An alternate and more convenient procedure was to treat the Reformatsky complex **5** directly with acetyl chloride and *N*,*N*-dimethylaniline.

The acetate **7** was readily converted to a mixture of the conjugated *Z* and *E* esters **10a** and **9a** by elimination of acetic acid with sodium ethoxide. A variety of other bases were tried, including sodium hydride, potassium *tert*-butoxide, and even basic alumina. Sodium ethoxide was found to be the most convenient and would be especially useful when the conjugated esters were prone to isomerization under strongly basic conditions.

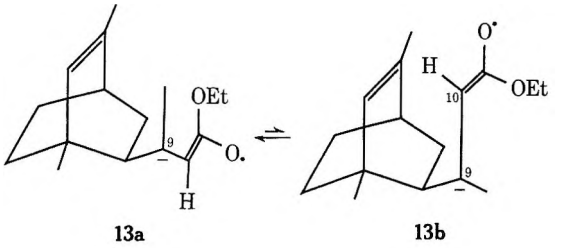
Even in cases where the β,γ-unsaturated esters were more stable than the α,β-unsaturated esters, the latter could be formed almost exclusively by this method.[17] This observation, together with the simplicity of the procedure and low cost of the reagents, make this a very useful high-yielding method for large-scale preparation of α,β-unsaturated esters *via* the Reformatsky reaction,[19] particularly in view of the great variety of ketones reactive under Reformatsky conditions.[16]

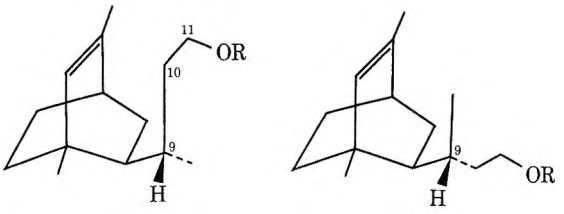
The conjugated esters **9a** and **10a** were easily distinguished by their pmr spectra. The characteristic signals were due to $H_6$ and the $C_9$ vinyl methyl group. In the *Z* ester **10a** there was strong deshielding of $H_6$ by the coplanar carboxyl group. This signal, a doublet of doublets, was obscured by the quartet of the ester resonance in **10a**, but was clearly visible in the spectrum of the corresponding *Z* acid **10b** at 4.05 ppm. The signal for $H_6$ in the pmr spectrum of the *E* acid **9b** was situated much further upfield at 2.27 ppm as expected, since the carboxyl group was now remote from $H_6$. The strong deshielding of $H_6$ in the *Z* ester and acid also indicated that the preferred conformation was as shown, since rotation about the $C_6$–$C_9$ bond to alternative conformations would not be expected to give rise to such a strong deshielding effect on $H_6$. In addition, other conformations would be unlikely because of prohibitive steric interactions between either the ester group or the $C_9$ methyl group and other functions in the molecule.

(14) F. Johnson and S. K. Malhotra, *J. Amer. Chem. Soc.*, **87**, 5492 (1965).
(15) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).
(16) R. L. Shriner, *Org. React.*, **1**, 1 (1942).
(17) K. H. Fung, K. J. Schmalzl, and R. N. Mirrington, *Tetrahedron Lett.*, 5017 (1969).
(18) J. D. Cocker and T. G. Halsall, *J. Chem. Soc.*, 4262 (1956).
(19) Since the completion of this section and the subsequent appearance of our communication,[17] a similar procedure has been reported by Engel, *et al.*,[20] using steroidal substrates. This procedure is analogous to that of Linstead, *et al.*,[21] who used *aqueous* bases to obtain conjugated *acids* from β-acyloxy esters.
(20) C. R. Engel, V. S. Salvi, and L. Ruest, *Can. J. Chem.*, **48**, 3425 (1970).
(21) R. P. Linstead, L. N. Owen, and R. F. Webb, *J. Chem. Soc.*, 1211 (1953).

Further evidence for the preferred conformation of both the *Z* and *E* esters was obtained from the chemical shifts of the $C_9$ vinyl methyl doublets. In the *Z* ester **10a** there was strong shielding of this methyl to $\delta$ 1.57 by the olefinic bridge. In the *E* ester **9a** this shielding effect was counteracted by the strong deshielding effect of the coplanar carboxyl group so that the net effect was to shift the signal to $\delta$ 1.92. An alternative preferred conformation for the *E* ester, obtained by rotating the side chain around the $C_6$–$C_9$ bond through 180°, was unlikely, since no strong shielding of the $C_{10}$ olefinic proton was observed. In fact, the $C_{10}$ olefinic proton signals of the *Z* and *E* esters both occurred near 5.5 ppm. This value is very similar to that of the olefinic proton signals in the pmr spectra of the conjugated esters ethyl $\beta,\beta$-diethylacrylate and ethyl cyclohexylideneacetate, obtained from diethyl ketone and cyclohexanone, respectively.[17]

Reduction of the conjugated esters **9a** and **10a** with lithium in ammonia and ethanol yielded the alcohols **14a** and **15a** in a ratio of 4:1, respectively. This ratio could be accounted for by consideration of the two most likely conformations **13a** and **13b** of the intermediate radical anion (only one canonical form represented). The conformer **13b** would be somewhat less preferred than **13a** because the steric interaction of the $\pi$ cloud of the olefinic bridge with the protons of the freely rotating $C_9$ methyl group in **13a** should be less severe than with the rigidly fixed $H_{10}$ in **13b**. If protonation of the radical anion at $C_9$ were mainly occurring from the less hindered side (remote from the $C_1$ methyl group), **13a** would give **14a** while **13b** would give **15a**. The most important single factor determining the success of the synthesis of patchouli alcohol as well as of seychellene[9] was the ability to distinguish these two epimers **14a** and **15a**, and the finding that the major one had the desired stereochemistry.




a, R = H
b, R = Ac
c, R = $C(Ph)_3$

The reduction was usually carried out on a mixture of *Z* and *E* esters. To eliminate the very remote possibility that the *Z* ester was yielding **15a** almost exclusively, while the *E* ester was yielding **14a**, the reduction was also carried out on pure *E* ester **9a**. The ratio of products **14a** and **15a** obtained was unchanged.

Isolation of a minor product from any reaction mixture, except in the most trivial cases, must be regarded with great caution and always raises the question of rearrangement. The pmr spectrum of the alcohol of minor abundance, however, showed all the characteristic signals of the bicyclo[2.2.2]octene skeleton and, furthermore, apart from the position of the $C_9$ methyl doublet, these signals were virtually superimposable on those of the major epimer **14a**. The methyl doublet of the minor epimer was more shielded than that of the major epimer (0.55 ppm compared to 0.78 ppm) and we have observed as expected[22] that in all cases where the side chain was endo to the olefinic bridge, the pmr signals were strongly shielded relative to signals in the corresponding exo isomers. It was inconceivable, therefore, that the minor epimer with the highly shielded $C_9$ methyl group could have an exo side chain. In addition, hydrochlorination of the acetate **15b** caused a downfield shift of the $C_9$ methyl doublet in the pmr spectrum, confirming that the shielding effect was due to the olefinic bridge. The major epimer **14a** was also shown to have its side chain endo when the system was cyclized in the final steps of the synthesis.

In short, no epimerization about $C_6$ or rearrangement had occurred during the reduction, and the two anticipated products **14a** and **15a** were obtained.

It was the simple observation of the difference in chemical shift of the $C_9$ methyl doublets which formed the basis of the assignment of stereochemistry to the major and minor epimers. If both alcohols **14a** and **15a** were to adopt that conformation which minimized the 1,3-diaxial-like interactions with the methyl group at $C_1$, the $C_9$ methyl would be close to the olefinic bridge in **15a**, whereas in **14a** it would be much more remote. It was then apparent that the major epimer with the less shielded $C_9$ methyl signal in its pmr spectrum was **14a**, which had the stereochemistry required for the synthesis of (±)-patchouli alcohol and (±)-seychellene.

This large difference in the chemical shift of the $C_9$ methyl doublets was quite consistent, regardless of the function at the end of the side chain (Table I), although with triphenylmethyl (trityl) ethers the difference was significantly smaller. The effect was similar when either the olefinic bridge or the carbonyl group at $C_2$ was the shielding function.

TABLE I
CHEMICAL SHIFTS[a] OF $C_9$ METHYL GROUPS

| Compd | $C_9$ methyl doublet[b] | Compd | $C_9$ methyl doublet[b] | Difference[c] |
|---|---|---|---|---|
| **14a** | 0.78 | **15a** | 0.55 | 0.23 |
| **14b**[d] | 0.81 | **15b**[d] | 0.57 | 0.24 |
| **14c** | 0.62 | **15c** | 0.48 | 0.14 |
| **16** | 0.67 | **17** | 0.50 | 0.17 |

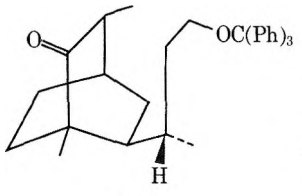
[a] Measured for $CCl_4$ solutions on a Varian A-60 spectrometer. Chemical shifts in parts per million downfield from TMS as internal standard. [b] $J$ = 6.5 Hz. [c] Parts per million. [d] The preparation and spectral properties of this compound appear in the accompanying paper.[9]

The trityl ether **14c** was treated with diborane in tetrahydrofuran[23] and the organoborane was oxidized

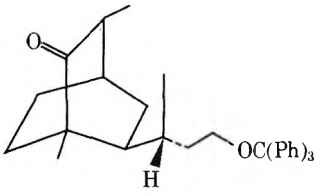
(22) I. Botica and R. N. Mirrington, *Aust. J. Chem.*, **24**, 1467 (1971), and references cited therein; A. A. Othman, M. A. Qasseem, and N. A. J. Rogers, *Tetrahedron*, **23**, 87 (1967).

(23) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).

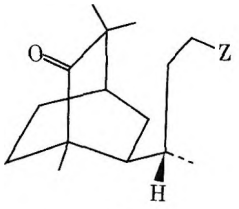
*directly* with chromium trioxide–pyridine to yield the ketone **16**. This direct procedure not only saved time and material but was also found to be necessary in the present case. Much difficulty was experienced in the oxidation of the organoborane to the intermediate alcohol with aqueous alkaline hydrogen peroxide because of the extreme insolubility of the trityl ether in the reaction medium. Organoboranes have been oxidized directly before using chromic acid,[24] but this method is obviously not applicable to the oxidation of acid-sensitive systems. It was found that chromium trioxide–pyridine could be used without any complications; this method could be of general applicability especially with water-insoluble compounds.




**16**

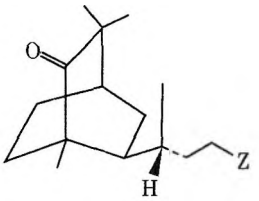



**17**




**18**

a, Z = OH
b, Z = OC(Ph)$_3$
c, Z = OTs
d, Z = OCONHPh




**19**

e, Z = I
f, Z = Br
g, Z = H

The relative stereochemistry of the $C_3$ methyl group in the ketone **16** was assigned as depicted, since one would anticipate exclusive attack of diborane from the less hindered side[23] of the olefin **14c**, and the above oxidation conditions should not cause epimerization. In any case this stereochemistry was not vital, since alkylation in the next step destroyed the asymmetric center at $C_3$.

Potassium triphenylmethide was found to be a vastly superior base to sodium hydride or potassium *tert*-butoxide for the alkylation of the ketone **16**. The ketone was converted quantitatively by titration to its enolate anion, which reacted rapidly with methyl iodide at 20°. The usual objection to the use of potassium triphenylmethide as the base in alkylation reactions is the difficulty in separation of the alkylated ketones from the triphenylmethane produced in the titration.[25] This was not a problem in the present case, because the ketone **18b** was not isolated, but converted to the alcohol **18a** by hydrogenolysis of the trityl ether function. Chromatography at this stage of the synthesis readily separated the triphenylmethane formed in the titration and in the hydrogenolysis from the alcohol **18a**. The tosylate **18c**, prepared in the usual way, was converted to the iodide **18e** by treatment with sodium iodide in acetone.

Magnesium metal was used with great success by Leroux[26] in the cyclization of γ-halo ketones to the corresponding cyclobutanols. However, the iodide **18e** was found to be completely inert to magnesium. Prolonged heating with magnesium in tetrahydrofuran, even on addition of equimolar amounts of mercuric chloride,[26] resulted in *recovery of the iodide unchanged.* Similarly, the bromide **18f** was found by Danishefsky[27] to be inert to magnesium.

The iodide **18e** was successfully cyclized using sodium in tetrahydrofuran at 100° in a sealed tube. The two products isolated were (±)-patchouli alcohol (**2**) and the acyclic ketone **18g**. These results are in agreement with those of Danishefsky and Dumas, who cyclized the bromide **18f** to (±)-patchouli alcohol using similar conditions.[27]

The reasons for the inertness of **18e** and **18f** to the action of magnesium are not clear at present. Further studies of the scope and mechanism of this interesting intramolecular cyclization[28] using various reagents and substrates are currently in progress in this laboratory.

## Experimental Section

Analyses were carried out by the CSIRO Microanalytical Service, Melbourne. Melting points and boiling points are uncorrected; the latter refer to the bath temperature. Infrared spectra were measured on a Perkin-Elmer 337 grating infracord spectrophotometer using carbon tetrachloride solutions. Pmr spectra were measured with a Varian A-60 spectrometer using carbon tetrachloride solutions unless otherwise specified, with TMS as internal standard. A Varian Aerograph Series 1400 gas chromatograph was used for vpc analysis with nitrogen carrier gas at a flow rate of 15 ml/min. Columns were 5 ft × 0.125 in. of 5% UCON and 5% DEGS on nonacid-washed Chromosorb W (80–100 mesh), and 3% SE-30 on Varaport 30 (100–120 mesh). Preparative vpc was carried out using a Wilkens Aerograph Autoprep, Model A-700 with helium as the carrier gas. The aluminum column was 12 ft × 0.375 in. of 10% Carbowax 20M on non-acid-washed Chromosorb W (44–60 mesh).

**Reformatsky Reaction with Ketone 4.**—Zinc powder (15 g), which had been activated by washing successively with 5% hydrobromic acid, water, ethanol, and acetone and dried at 100°, was added to a solution of 17 g of the ketone **4** and 24 g of bromoacetic ester in 350 ml of dry benzene. The mixture was stirred and heated, and 0.3 g of iodine was added to initiate the reaction. Stirring and heating were continued so that the mixture refluxed gently for 2 hr after the commencement of the reaction. After cooling, the solution was decanted and the excess sludge of zinc powder was washed with benzene. The zinc complex was destroyed by shaking the combined benzene solutions with 20% aqueous sulfuric acid at 0°, and the benzene layer was subsequently washed with 5% aqueous sulfuric acid, aqueous sodium carbonate, and water, then dried over anhydrous sodium sulfate. Evaporation of the solvent yielded 23.5 g (92%) of the crude hydroxy ester **6**: ir 3520 (OH), 1720 cm$^{-1}$ (ester); pmr δ 5.44 (br s, 1, $H_2$), 4.12 (q, $J$ = 7 Hz, 2, ester), 3.44 (br s, 1, OH), 2.23 (br s, 2, $C_{10}$ methylene), 1.73 (d, $J$ = 1.6 Hz, 3, $C_3$ vinyl methyl), 1.27 (t, $J$ = 7 Hz, 3, ester), 1.27 (s, 3, $C_1$ methyl), 0.95 (s, 3, $C_9$ methyl). The analytical sample was prepared by microdistillation, bp 102° (0.1 mm). *Anal.* Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.49; H, 9.64.

**Hydrolysis of Hydroxy Ester 6.**—A solution of 2 g of the hydroxy ester in 50 ml of 50% aqueous ethanol containing 5 g of sodium hydroxide was refluxed for 45 min. The solution was cooled, acidified with dilute hydrochloric acid at 0°, and extracted with ether. The ethereal solution was extracted with aqueous sodium carbonate and, after acidification at 0° with dilute hydrochloric acid, the precipitated organic acid was extracted with ether. The extract was washed with water and dried over anhydrous sodium sulfate, and the solvent was evaporated to yield 1.5 g (84%) of the crude crystalline hydroxy acid **8**, which crystallized from hexane as colorless prisms: mp

(24) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2951 (1961).
(25) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 188–189.
(26) Y. Leroux, *Bull. Soc. Chim. Fr.*, 359 (1968).
(27) S. Danishefsky and D. Dumas, *Chem. Commun.*, 1287 (1968).
(28) H. O. House, J. Riehl, and C. G. Pitt, *J. Org. Chem.*, **30**, 650 (1965).

134–135°; ir 3525 (OH), 1695 $cm^{-1}$ (acid); pmr ($CDCl_3$) $\delta$ 6.70 (very br, 2, OH), 5.47 (br s, 1, $H_2$), 2.46, 2.30 (AB q, $J_{AB}$ = 16 Hz, 2, $C_{10}$ methylene), 2.30 (br s, 1, $H_4$), 1.75 (d, $J$ = 1.5 Hz, 3, $C_3$ vinyl methyl), 1.30 (s, 3, $C_1$ methyl), 1.10 (s, 3, $C_9$ methyl). *Anal.* Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.55; H, 9.38.

**Dehydration of Hydroxy Ester 6 with Phosphorus Oxychloride in Pyridine.**—A solution of 0.9 g of the hydroxy ester in 5 ml of dry pyridine was treated with 1 g of redistilled phosphorus oxychloride, and the solution was stirred for 3 hr at 60°. The reaction mixture was then poured into water and extracted with hexane. The extract was washed with dilute hydrochloric acid and water, then dried over anhydrous sodium sulfate. Evaporation of the solvent yielded 0.63 g of a mixture of the esters **9a**, **10a**, and **11**, in a ratio of *ca.* 3:1:1, respectively, by pmr. The ir and pmr spectra of **9a** and **10a** are described below. No attempt was made to isolate the nonconjugated ester **11**, which gave rise to characteristic pmr signals at $\delta$ 4.79 (s, $C{=}CH_2$), 2.78 (s, $C_{10}$ methylene), and 1.00 (s, $C_1$ methyl).

**Acetylation of Hydroxy Ester 6.**—A mixture of 5 ml of acetyl chloride, 20 ml of *N*,*N*-dimethylaniline (purified to remove traces of *N*-methylaniline), 20 ml of chloroform, and 0.99 g of the hydroxy ester were refluxed for 20 hr. The resultant blue solution was diluted with water, acidified at 0° with dilute hydrochloric acid, and extracted with ether. The ether extract was washed with dilute HCl and water and dried over anhydrous sodium sulfate, and the solvent was evaporated to yield 1.1 g of the crude acetate, which was purified by rapid chromatography over 30 g of neutral activity I alumina.[29] The yield of purified acetate **7** was 0.90 g (78%): ir 1730 $cm^{-1}$ (ester and acetate); pmr $\delta$ 5.43 (br s, 1, $H_2$), 4.06 (q, $J$ = 7 Hz, 2, ester), 2.69 (s, 2, $C_{10}$ methylene), 2.28 (br s, 1, $H_4$), 1.91 (s, 3, acetate methyl), 1.75 (d, $J$ = 1.6 Hz, 3, $C_3$ vinyl methyl), 1.23 (t, $J$ = 7 Hz, 3, ester), 1.23 (s, 3, tertiary methyl), 1.19 (s, 3, tertiary methyl). The analytical sample was obtained by microdistillation, bp 130° (0.4 mm). *Anal.* Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 69.95; H, 9.23.

**Modified Acetylation Procedure.**—A mixture of 50 g of ketone **4**, 58 g of bromoacetic ester, and 45 g of activated zinc powder in 800 ml of dry benzene was treated as previously described and the resultant benzene solution of the zinc complex was decanted. The excess sludge of zinc powder was washed with small portions of dry benzene, and the combined solutions were treated at 0° with 450 ml of purified *N*,*N*-dimethylaniline and 150 ml of acetyl chloride. An immediate blue-black tarry deposit separated and, after stirring for several minutes at 20°, the mixture was heated on a steam bath under gentle reflux overnight. The reaction mixture was then poured into excess dilute HCl at 0°, and the tarry residue was stirred and washed with hexane. The washings were combined with the hexane extract of the acidified reaction mixture and the hexane solution was then washed with dilute HCl, aqueous sodium carbonate, and water and dried over anhydrous sodium sulfate and the solvent was evaporated to yield 82 g (95%) of the crude acetate **7**.

**Unsaturated Esters 9a and 10a.**—The acetate **7** (0.17 g) was treated at 20° with sodium ethoxide solution (0.12 g of sodium in 2 ml of ethanol) for 30 min, the reaction mixture was then poured into water, and the unsaturated esters were extracted with hexane. The extract was washed with water and dried over anhydrous sodium sulfate, and the solvent was evaporated to yield 0.12 g (89%) of the mixture of esters **9a** and **10a** (2.5:1).

In large-scale preparations the crude acetate prepared by the modified acetylation procedure was used without further purification. Treatment of 84 g of acetate with sodium ethoxide solution (14 g of sodium in 400 ml of ethanol) for 80 min at 20° with stirring gave 60 g of the crude unsaturated esters, isolated as above. The esters were separated by chromatography over neutral activity I alumina. The *Z* ester **10a** was eluted first with hexane: ir 1710 (ester), 1630 $cm^{-1}$ (conjugated double bond); pmr $\delta$ 5.50 (br s, 2, olefinic protons), 4.06 (q, $J$ = 7 Hz, 2, ester) (superimposed on the doublet of doublets for $H_6$), 2.32 (br s, 1, $H_4$), 1.79 (d, $J$ = 1.6 Hz, 3, $C_3$ vinyl methyl), 1.57 (d, $J$ = 1.2 Hz, 3, $C_9$ vinyl methyl), 1.24 (t, $J$ = 7 Hz, 3, ester), 0.97 (s, 3, $C_1$ methyl). The analytical sample was obtained by preparative vpc at 190°, followed by microdistillation, bp 95° (0.4 mm). *Anal.* Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.52; H, 9.89.

The *E* ester **9a** was eluted with hexane and hexane–benzene (9:1): ir 1710 (ester), 1630 $cm^{-1}$ (conjugated double bond); pmr $\delta$ 5.50 (br s, 2, olefinic protons), 4.05 (q, $J$ = 7 Hz, 2, ester), 2.3[30] (br s, 1, $H_4$), 1.92 (d, $J$ = 1.3 Hz, 3, $C_9$ vinyl methyl), 1.81 (d, $J$ = 1.8 Hz, 3, $C_3$ vinyl methyl), 1.23 (t, $J$ = 7 Hz, 3, ester), 0.98 (s, 3, $C_1$ methyl). The analytical sample was obtained by preparative vpc at 190°, followed by microdistillation, bp 115° (1 mm). *Anal.* Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.21; H, 9.90.

**Hydrolysis of Esters 9a and 10a. A. The *E* Ester 9a.**—A solution of 0.63 g of the ester in 25 ml of 50% aqueous ethanol containing 2.5 g of sodium hydroxide was refluxed for 8 hr. The crude acid **9b** (0.53 g, 94%) was isolated in the manner described for **8**. The acid crystallized from hexane as colorless prisms: mp 138–139°; ir 1685 (acid), 1625 $cm^{-1}$ (conjugated double bond); pmr $\delta$ 12.11 (br s, 1, OH), 5.60 (br s, 1, $H_{10}$), 5.50 (br s, 1, $H_2$), 2.34[30] (br s, 1, $H_4$), 1.93 (br s, 3, $C_9$ vinyl methyl), 1.82 (d, $J$ = 1.8 Hz, 3, $C_3$ vinyl methyl), 1.00 (s, 3, $C_1$ methyl). *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 75.93; H, 9.31.

B. **The *Z* Ester 10a.**—A solution of 0.45 g of the ester in 25 ml of 50% aqueous ethanol containing 2 g of sodium hydroxide was refluxed for 10 hr. The crude *Z* acid **10b** (0.37 g, 92%) was isolated in the manner described for **8**. The acid crystallized from hexane as colorless, flat needles which sublimed readily on heating: mp 162–163°; ir 1685 (acid), 1625 $cm^{-1}$ (conjugated double bond); pmr $\delta$ 11.62 (br s, 1, OH), 5.61 (q, $J$ = 1.3 Hz, 1, $H_{10}$), 5.48 (br s, 1, $H_2$), 4.05 (dd, $J_{6,5n} + J_{6,5x}$ = 16 Hz, 1, $H_6$), 2.33 (br s, 1, $H_4$), 1.80 (d, $J$ = 1.5 Hz, 3, $C_3$ vinyl methyl), 1.64 (d, $J$ = 1.3 Hz, 3, $C_9$ vinyl methyl), 1.00 (s, 3, $C_1$ methyl). *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.45; H, 9.02.

**Lithium–Ammonia Reduction of Esters 9a and 10a.**—Following the general procedure of Stork and Darling,[31] 17 g of the mixture of esters **9a** and **10a** (2.5:1) in 200 ml of dry ethanol and 150 ml of ether was added to 1000 ml of liquid ammonia. Lithium metal (11 g) was added in portions with stirring over 1 hr. The blue color persisted throughout the solution for some time after the addition of the last few portions of lithium metal. The ammonia was evaporated by stirring and the cautious addition of water. The aqueous alkaline reaction mixture was extracted with ether. The extract was washed with water and dried over anhydrous sodium sulfate, and the solvent was evaporated to yield 13.5 g (94%) of the crude mixture of alcohols **14a** and **15a**. A portion (7.5 g) was chromatographed on 300 g of neutral activity I alumina, and elution with benzene–ether (9:1) yielded 4.8 g (60%) of the major epimer **14a**: ir 3630, 3430 $cm^{-1}$ (OH); pmr $\delta$ 5.47 (br s, 1, $H_2$), 3.51 (m, 2, $C_{11}$ methylene), 2.35 (br s, 1, OH), 2.27 (br s, 1, $H_4$), 1.73 (d, $J$ = 1.7 Hz, 3, $C_3$ methyl), 1.08 (s, 3, $C_1$ methyl), 0.78 (d, $J$ = 6.5 Hz, 3, $C_9$ methyl). The analytical sample was prepared by microdistillation, bp 97° (0.1 mm). *Anal.* Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.75; H, 11.67.

The minor epimer **15a** (1.2 g, 15%) was eluted with benzene–ether (9:1) and benzene–ether (4:1): ir 3630, 3430 $cm^{-1}$ (OH); pmr $\delta$ 5.46 (br s, 1, $H_2$), 4.11 (br s, 1, OH), 3.55 (t, $J$ = 7 Hz, 2, $C_{11}$ methylene), 2.27 (br s, 1, $H_4$), 1.73 (d, $J$ = 1.7 Hz, 3, $C_3$ vinyl methyl), 1.07 (s, 3, $C_1$ methyl), 0.55 (d, $J$ = 6.5 Hz, 3, $C_9$ methyl). The analytical sample was obtained by preparative vpc at 190°, followed by microdistillation, bp 100° (0.1 mm). *Anal.* Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.95; H, 11.56.

**Preparation of the Trityl Ether 14c.**—A solution of 3.3 g of the alcohol **14a** in 50 ml of benzene and 3 ml of pyridine was heated with 6.0 g of trityl chloride under gentle reflux for 5 hr. The solution was cooled to 0° and the crystalline pyridine hydrochloride was filtered by suction. The filtrate was evaporated almost to dryness and the residue was dissolved in hexane and applied to a column of 300 g of neutral activity I alumina. Elution with hexane and hexane–benzene (4:1) yielded 6.0 g (85%) of the trityl ether **14c**, which crystallized from ethanol as colorless prisms: mp 105–106°; pmr $\delta$ 5.47 (br s, 1, $H_2$), 3.02 (m, 2, $C_{11}$ methylene), 2.24 (br s, 1, $H_4$), 1.74 (d, $J$ = 1.7 Hz, 3, $C_3$ vinyl methyl), 1.15 (s, 3, $C_1$ methyl), 0.62 (d, $J$ = 6.5 Hz, 3, $C_9$ methyl). *Anal.* Calcd for $C_{33}H_{38}O$: C, 87.95; H, 8.50. Found: C, 88.12; H, 8.48.

(29) The grade of alumina was important as the acetate was unstable on basic alumina, from which the only products eluted were unsaturated esters.

(30) The signal for $H_6$ at about $\delta$ 2.2 was superimposed on this broad singlet.

(31) G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **86**, 1761 (1964).

A mixture of alcohols **14a** and **15a** (4:1) was also tritylated as above, and, in the pmr spectrum of the mixture of trityl ethers **14c** and **15c** obtained, the characteristic signals of the minor epimer **15c** were seen to be $\delta$ 1.04 (s, $C_1$ methyl), 0.48 (d, $J$ = 6.5 Hz, $C_9$ methyl).

**Hydroboration–Oxidation of Trityl Ether 14c.**—Diborane was passed through a stirred solution of 27 g of the trityl ether in 140 ml of dry tetrahydrofuran under nitrogen at 20°,[23] until pmr analysis of an aliquot of the reaction mixture showed the complete disappearance of the olefinic signal due to the starting material. Water was then added dropwise to destroy excess hydride. The mixture was then poured into water and the organoborane was extracted with benzene. The solvents were evaporated and the residue was dissolved in 250 ml of pyridine. The pyridine solution was added to chromium trioxide–pyridine complex[32] (40 g of chromium trioxide in 400 ml of pyridine) and the mixture was left overnight at 20°. The reaction mixture was then poured into 1500 ml of ether and the red precipitate was filtered by suction and washed several times with ether. The combined filtrate and washings were then shaken with excess 10% hydrochloric acid at 0° to remove the pyridine. The ether solution was washed exhaustively with dilute HCl at 0° and then with dilute aqueous sodium carbonate and water, and dried over anhydrous sodium sulfate. Evaporation of solvent yielded the crude ketone **16**, which was purified by recrystallization from ethanol. The yield after one recrystallization was 14 g (50%). The ketone crystallized from ethyl acetate as colorless prisms: mp 154–155°; ir 1710 $cm^{-1}$ (ketone); pmr $\delta$ 3.02 (m, 2, $C_{11}$ methylene), 2.15 (br q, $J$ = 7.5 Hz, 1, $H_3$), 1.10 (d, $J$ = 7.5 Hz, 3, $C_3$ methyl), 1.01 (s, 3, $C_1$ methyl), 0.67 (d, $J$ = 6.5 Hz, 3, $C_9$ methyl). *Anal.* Calcd for $C_{33}H_{38}O_2$: C, 84.93; H, 8.21. Found: C, 84.72; H, 8.14.

A mixture of the trityl ethers **14c** and **15c** (4:1) was converted *via* hydroboration–oxidation (as above) to a mixture of the ketones **16** and **17**. Pmr analysis of the mixture showed the characteristic signals of the minor epimer **17** to be $\delta$ 0.90 (s, $C_1$ methyl), 0.50 (d, $J$ = 6.5 Hz, $C_9$ methyl).

**Preparation of Keto Alcohol 18a.**—The ketone **16** (6 g) was dissolved in 100 ml of 1,2-dimethoxyethane (glyme) in a flask sealed with a rubber septum cap. By means of a syringe, potassium triphenylmethide solution, prepared by stirring potassium with triphenylmethane in glyme in a septum-sealed flask,[33] was added to the ketone until the red color of the triphenylmethide ion just persisted. Methyl iodide (20 ml) was then injected; the solution warmed noticeably; and potassium iodide precipitated immediately. The mixture was left overnight at 20°, poured into water, and extracted with ether. The ether extract was washed with water and dried over anhydrous sodium sulfate and the solvent was evaporated to yield the trityl ether **18b**, which was of course contaminated with triphenylmethane. The crude product was not purified but was dissolved in 400 ml of ethanol; 1 g of 5% palladium on charcoal was added; and the mixture was shaken under 2.5 atm of hydrogen at 20° for 17 hr. After filtration of the catalyst and evaporation of the ethanol, the product was separated from the triphenylmethane by chromatography over 300 g of neutral activity I alumina. Elution with hexane and hexane–ether (9:1) yielded triphenylmethane together with minor amounts of other aromatic products,[33] while 2.4 g (78%) of the alcohol **18a** was eluted with hexane–ether (1:2) and ether. Vpc analysis showed a single peak on 3% SE-30 at 170°: ir[34] 3625, 3480 (OH), 1715 $cm^{-1}$ (ketone); pmr[34] $\delta$ 3.52 (m, 2, $C_{11}$ methylene), 3.12 (br s, 1, OH), 1.11 (s, 6, 2 tertiary methyls), 0.93 (s, 3, tertiary methyl), 0.90 (d, $J$ = 6.5 Hz, 3, $C_9$ methyl). The analytical sample was prepared by microdistillation, bp 112° (0.02 mm). *Anal.* Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.52; H, 10.78.

The phenylurethane **18d** of this alcohol was prepared in the usual manner[35] and crystallized from hexane–benzene as colorless prisms: mp 142–143° (lit.[27] mp 165°);[36] ir 3430 (NH), 1735 (urethane carbonyl), 1710 $cm^{-1}$ (ketone); pmr ($CDCl_3$) $\delta$ 4.13 (br t, $J$ = 6.5 Hz, 2, $C_{11}$ methylene), 1.14 (s, 6, two tertiary methyls), 0.96 (s, 3, tertiary methyl), 0.92 (d, $J$ = 6.5 Hz, 3, $C_9$ methyl). *Anal.* Calcd for $C_{22}H_{31}O_3N$: C, 73.91; H, 8.74. Found: C, 74.24; H, 8.89.

**Preparation of Tosylate 18c.**—The alcohol **18a** (0.25 g) was treated with 0.60 g of *p*-toluenesulfonyl chloride in 18 ml of pyridine at −15° for 12 hr. Ten drops of water were then added and the reaction mixture was left for an additional 45 min at −15°. After addition to excess dilute HCl at 0°, the reaction mixture was extracted with hexane. The extract was washed with dilute aqueous sodium carbonate and water and then dried over anhydrous sodium sulfate. Evaporation of solvent yielded 0.38 g (92%) of the crude tosylate **18c** which crystallized from benzene–hexane as colorless prisms: mp 99–100°; ir 1710 $cm^{-1}$ (ketone); pmr $\delta$ 3.95 (m, 2, $C_{11}$ methylene), 2.47 (s, 3, aromatic methyl), 1.08 (s, 3, tertiary methyl), 1.00 (s, 3, tertiary methyl), 0.83 (s, 3, tertiary methyl), 0.83 (d, $J$ = 6.5 Hz, 3, $C_9$ methyl). *Anal.* Calcd for $C_{22}H_{32}O_4S$: C, 67.32; H, 8.22; S, 8.15. Found: C, 67.62; H, 8.38; S, 7.90.

**Preparation of Iodide 18e.**—Following an established procedure,[37] 0.50 g of the tosylate **18c** was stirred with 1.5 g of sodium iodide in 20 ml of acetone at 20° for 20 hr, after which time a considerable quantity of sodium tosylate had precipitated. The reaction mixture was poured into water and the iodide was extracted with hexane. The extract was washed with water and dried over anhydrous sodium sulfate, and the solvent was evaporated to yield the crude iodide **18e**, which was purified by chromatography over 40 g of neutral activity I alumina. Elution with hexane–ether (9:1) yielded 0.40 g (90%) of the iodide **18e** as a colorless liquid. Vpc analysis showed a single peak on 3% SE-30 at 170°: ir 1710 $cm^{-1}$ (ketone); pmr $\delta$ 3.65–2.8 (very complex m, 2, $C_{11}$ methylene), 1.10 (s, 3, tertiary methyl), 1.06 (s, 3, tertiary methyl), 0.93 (s, 3, tertiary methyl), 0.86 (d, $J$ = 6.5 Hz, 3, $C_9$ methyl). When an attempt was made to obtain an analytical sample of **18e**, either by preparative vpc or by microdistillation, it decomposed slightly to give a pale yellow oil, which analyzed about 2% high for carbon and 0.8% low for iodine.

**Attempted Cyclization of 18e with Magnesium and Mercuric Chloride.**—The iodide **18e** (50 mg) in 1.5 ml of tetrahydrofuran which had been freshly distilled from sodium–naphthalene was treated with 15 mg of magnesium powder and 45 mg of mercuric chloride. The mixture was heated in a sealed flask at 80–90° for 2 hr and then poured into water. Extraction with hexane resulted in recovery of the iodide unchanged (pmr and vpc).

**Cyclization of Iodide 18e with Sodium.**—A solution of 0.20 g of the iodide in 5 ml of tetrahydrofuran, which had been freshly distilled from sodium–naphthalene, was transferred to a thick-walled glass tube. Fine sodium sand (0.15 g), prepared by shaking molten sodium in paraffin oil, was added and the tube was sealed and heated at 90–100° for 4 hr. The surface of the metal became coated with a powdery deposit which soon crumbled and revealed the shiny metallic surface of the residual sodium. The tube was left overnight at 20°, the seal was broken, and the red solution was poured into water. After acidification with dilute HCl, the product was extracted with hexane. The extract was washed with water and dried over anhydrous sodium sulfate, and the solvent was evaporated to leave 0.12 g of a colorless oil. The ir spectrum of this crude product showed some free hydroxyl absorption (3610 $cm^{-1}$) and carbonyl absorption (1705 $cm^{-1}$). Analysis of the mixture by vpc showed it to contain two major products, A and B, which accounted for 62% of the total area under all the peaks (40 and 22%, respectively). When the reaction was carried out in more dilute solution (10–20 mg of iodide in 5 ml of tetrahydrofuran), a cleaner reaction product was obtained. Vpc analysis in this case showed A to constitute 45% of the total area and B 31%. The retention times of A and B on 5% DEGS at 120° were 6 and 2.5 min, respectively. A and B were isolated by preparative vpc on 10% Carbowax 20M at 200°.

The constituent A was a colorless semisolid which was readily purified by sublimation to give (±)-patchouli alcohol (**2**): mp 46–47° (lit.[27] mp 39–40°); ir 3610 (free OH), 1380, 1370, and 1363 $cm^{-1}$ (methyls);[38] pmr $\delta$ 1.06 (s, 6, two tertiary methyls),

(32) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

(33) H. O. House and V. Kramar, *J. Org. Chem.*, **27**, 4146 (1962).

(34) The ir and pmr spectra were identical with copies of spectra of the alcohol kindly forwarded by Dr. Danishefsky.

(35) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Longmans, Green and Co., London, 1962, p 264.

(36) In a recent letter Dr. Danishefsky has conceded the possibility of having confused the melting points of the epimers **18d** and **19d**. He reported[27] the melting point for **19d** as 145°.

(37) R. S. Tipson, M. A. Clapp, and L. H. Cretcher, *J. Org. Chem.*, **12**, 133 (1947).

(38) A noteworthy feature of the ir spectrum of patchouli alcohol was these three strong, well-resolved absorptions. Presumably the "doublet" at 1380 and 1370 $cm^{-1}$ was due to symmetric and asymmetric *gem*-dimethyl stretching vibrations.

0.82 (s, 3, tertiary methyl), 0.80 (d, $J$ = 6.5 Hz, 3, secondary methyl). The vpc retention time[39] (5% UCON, 5% DEGS) and ir and pmr spectra were superimposable on those of naturally occurring (−)-patchouli alcohol.[40] The mass spectrum was also identical with that of the natural product.

Constituent B was the oily acyclic ketone **18g**: ir 1705 cm$^{-1}$ (ketone); pmr $\delta$ 1.09 (s, 3, tertiary methyl), 1.07 (s, 3, tertiary methyl), 0.88 (s, 3, tertiary methyl), 0.86 (d, $J$ = 6.5 Hz, 3, $C_9$ methyl); mass spectrum $m/e$ 222 ($M^+$).

(39) The synthetic material was mixed with naturally occurring (−)-patchouli alcohol and peak enhancement was observed on the two columns at various temperatures.

(40) Naturally occurring (−)-patchouli alcohol, mp 56°, was isolated from patchouli oil which was generously donated by Plaimar Ltd., Perth. The higher boiling fractions of the oil were chromatographed over neutral alumina to give patchouli alcohol of high purity.

**Registry No.**—(±)-**2**, 5986-55-0; **4**, 34996-60-6; **6**, 34996-61-7; **7**, 34996-62-8; **8**, 34996-63-9; **9a**, 34996-28-3; **9b**, 34996-64-0; **10a**, 34996-65-1; **10b**, 34996-66-2; (±)-**14a**, 29450-72-4; (±)-**14c**, 29448-20-2; (±)-**15a**, 29448-21-3; (±)-**16**, 34996-70-8; (±)-**18a**, 21682-97-3; (±)-**18c**, 34996-72-0; (±)-**18d**, 21683-01-2; (±)-**18e**, 34996-74-2; (±)-**18g**, 21682-98-4.

# Studies with Bicyclo[2.2.2]octenes. VI.[1] The Total Synthesis of (±)-Seychellene[2]

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A stereospecific total synthesis of (±)-seychellene is described from the alcohol **2**, which was previously prepared for the synthesis of patchouli alcohol. The key stage in the sequence was the relatively efficient conversion of the olefinic bridge in **2** to the exocyclic methylene function in **21** *via* a modified hydrochlorination–dehydrochlorination procedure. The sequence was completed *via* the intermediates **22**, **25**, **26a**, and **26c**. Attempts to acylate the olefinic ester **7** gave none of the desired ketone **11**, but afforded instead the rearranged acetate **8** and/or the ketone **9**, depending on the reaction temperature.

The sesquiterpenoid (−)-seychellene was isolated from patchouli oil obtained from the Seychelles Islands, and was assigned the structure and absolute stereochemistry depicted in **1**.[4] The similarity in structure between seychellene and patchouli alcohol suggested a synthetic route to seychellene utilizing alcohol **2**, a key intermediate for the synthesis of patchouli alcohol.[1]

Two approaches to an intramolecular alkylation which could be used to construct the tricyclic seychellene skeleton are outlined in Scheme I. Path A suffers from the disadvantage that either the nitrile, aldehyde, or methyl ketone function of the cyclized product **4** must be converted to a methyl group in seychellene. On the other hand, norseychellanone (**5**), the path B intramolecular alkylation product, ought to be readily converted to seychellene by the reported procedure[5] of reaction with methyllithium, followed by dehydration of the resultant tertiary alcohol with thionyl chloride–pyridine.

Preliminary investigations were carried out on both pathways to assess their relative merits. The unsaturated aldehyde **3b** would have been the most useful of the type A alkylations from the point of view of generation of the $C_2$ methyl by a Wolff–Kishner reduction.[6] The preparation of this unsaturated aldehyde from the ketone **6**,[1] however, would be far from trivial.[7] The preparation of the unsaturated nitrile **3a** *via* the corresponding cyanohydrin was abandoned when difficulty was experienced in preparing the latter in good yield from the ketone **6** using acetone cyanohydrin.[8]

It is known[9] that acylation of 1-methylcyclohexene with polyphosphoric acid in acetic acid under specified conditions yields 2-acetyl-1-methylcyclohexene, and therefore it was envisaged that a compound of the type **3c** might be prepared by acylation of the corresponding olefin with the same reagent. Initially we studied the acylation of the readily available[10] model ester **7**.

At 55–60°, the major product of the reaction of **7** with polyphosphoric acid in acetic acid was the rearranged secondary acetate **8**. There was little or no tertiary acetate **10**, which was perhaps the expected major product, and furthermore, none of the desired ketone **11** was detected. At 75–80°, a mixture of compounds was isolated of which greater than 90% (pmr and vpc) were **8** and **9** in a ratio of 1:1.7. At 85–90°, the sole product was the ketone **9**. The movement of the double bond from the endocyclic to the exocyclic position prior to acylation has also been observed by other workers in the acylation of 1-ethylcyclohexene catalyzed by stannic chloride.[11] It was the remarkable isolation of **9** in good yield which aroused interest in the present case, since ozonolysis of **9** to the corresponding ketone **12** provided the analogy for a useful method of preparing a type B intramolecular alkylation precursor such as **25**. It was found, however, that, when the primary acetate **13** was treated with polyphosphoric acid in acetic acid under identical conditions to those used for the methyl ester **7**, none of the expected conjugated ketone analogous to **9** was obtained. The mixture of

(1) Part V: R. N. Mirrington and K. J. Schmalzl, *J. Org. Chem.*, **37**, 2871 (1972), accompanying paper.

(2) Some of the work described herein has appeared in a preliminary communication: K. J. Schmalzl and R. N. Mirrington, *Tetrahedron Lett.*, 3219 (1970).

(3) (a) Abstracted in part from the Ph.D. thesis of K. J. Schmalzl, University of Western Australia, May 1971. (b) The award of a Commonwealth Postgraduate Scholarship to K. J. S. is gratefully acknowledged.

(4) G. Wolff and G. Ourisson, *Tetrahedron Lett.*, 3849 (1968); *Tetrahedron*, **25**, 4903 (1969).

(5) J. E. McMurry, *J. Amer. Chem. Soc.*, **90**, 6821 (1968).

(6) F. E. King, D. H. Godson, and T. J. King, *J. Chem. Soc.*, 1117 (1955).

(7) M. de Botton, *Bull. Soc. Chim. Fr.*, 2466 (1966).

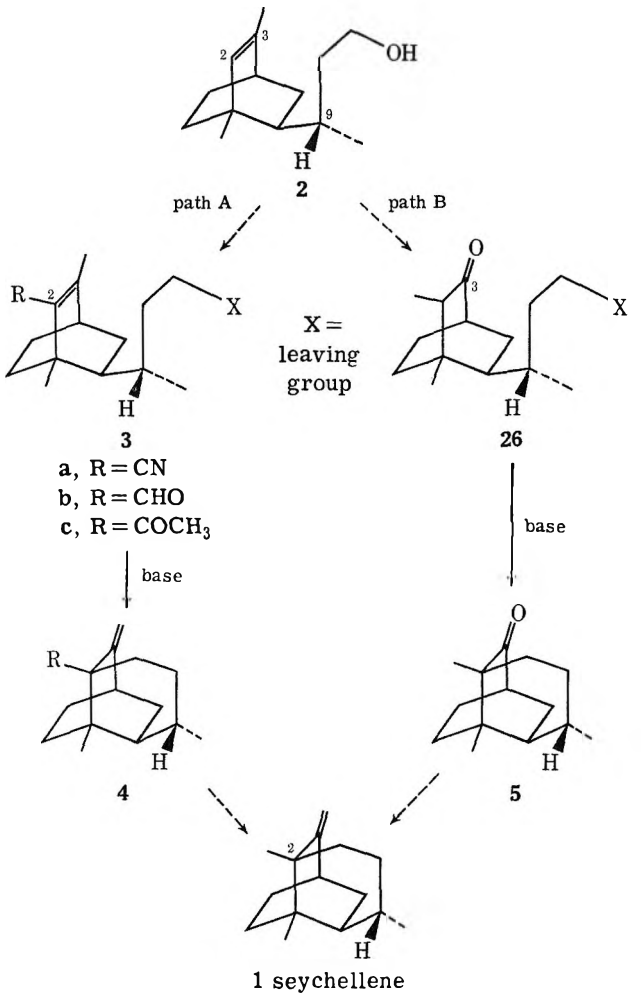
(8) (a) R. Gardi, P. P. Castelli, R. Gandolfi, and A. Ercoli, *Gazz. Chim. Ital.*, **91**, 1250 (1961); (b) A. Ercoli and P. de Ruggieri, *J. Amer. Chem. Soc.*, **75**, 650 (1953).

(9) S. B. Kulkarni and Sukh Dev, *Tetrahedron*, **24**, 561 (1968).

(10) R. N. Mirrington and K. J. Schmalzl, *J. Org. Chem.*, **34**, 2358 (1969).

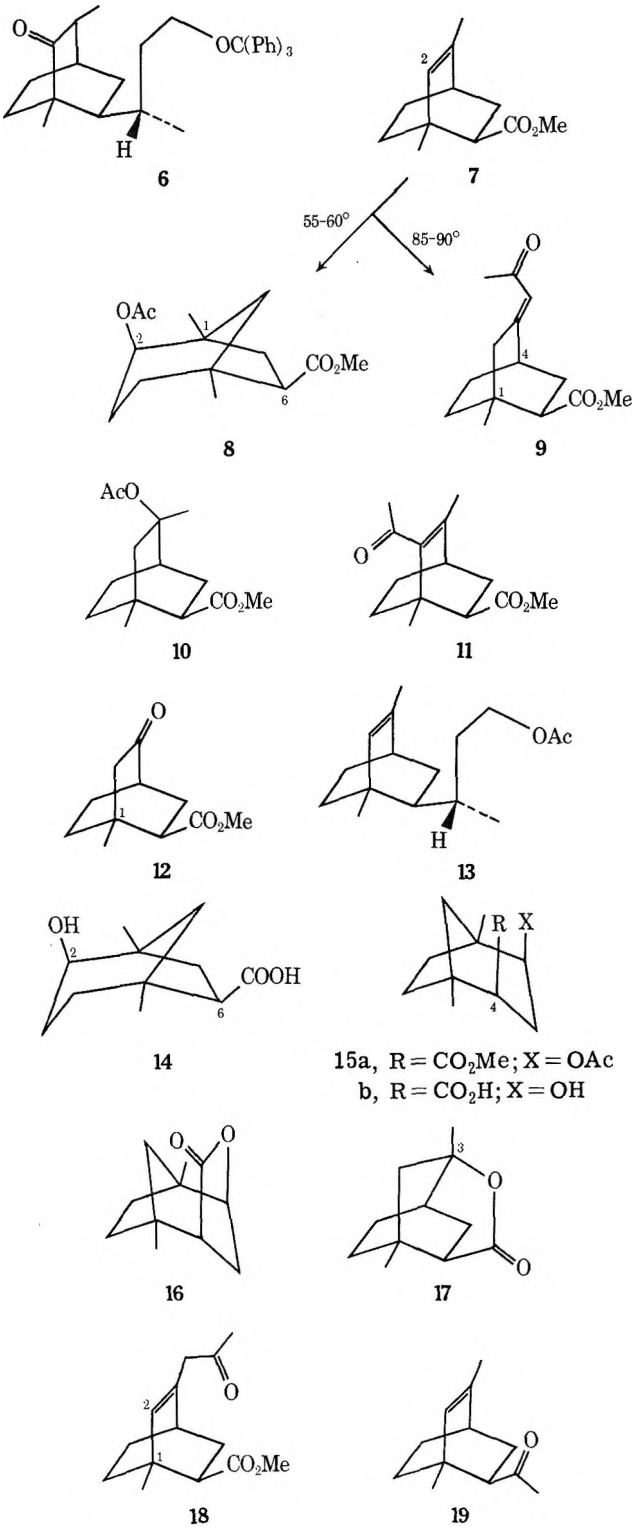
(11) J. K. Groves and N. Jones, *Tetrahedron Lett.*, 1161 (1970).

SCHEME I




acetates that was obtained was not investigated further.

The structures **8** and **9** were assigned to the two products isolated from the attempted acylation of **7** at $C_2$ on the basis of the following evidence. The pmr spectrum of the acetate **8** showed a broad singlet of width at half height 4.5 Hz, at $\delta$ 4.60. The shape of the signal was characteristic of an equatorial proton on the chair form of a six-membered ring.[12] The chemical shift of the signal was consistent with a methine proton on a carbon bearing an acetate function. There were two tertiary methyl singlets and the doublet of doublets for $H_6$ was also clearly visible. Mild hydrolysis yielded the corresponding hydroxy acid **14**, the pmr spectrum of which showed the expected diamagnetic shift of $H_2$ to 3.54 ppm, and the doublet of doublets for $H_6$. The appearance of the doublet of doublets for $H_6$ ruled out the alternative structure **15a** for the rearranged secondary acetate, since the equatorial proton $H_4$ in **15a** should give rise to a broad singlet in the pmr spectrum.[12] In addition, if the rearranged secondary acetate had the structure **15a**, the corresponding hydroxy acid **15b** would have been expected to lactonize readily to **16**. The only lactone obtained, however, on treatment of the hydroxy acid with formic acid and sulfuric acid for 20 hr at 20° was the known[10] $\delta$-lactone **17** in low yield. This presumably arose *via* a reversal of the original rearrangement, although the remote possibility of it having been formed from traces of the tertiary hydroxy acid corresponding to **10**, which may have been present in the starting material, could not be overlooked. Acid-catalyzed rearrangements are well known in the bicyclo[2.2.2]octane series[13] and hence the isolation of the rearranged secondary acetate **8** was not exceptional.




The proposed structures for the conjugated ketone **9** and the corresponding ketone **12** obtained by ozonolysis are supported by their spectroscopic data (Experimental Section). Of the two possible configurations, *Z* and *E*, for the conjugated ketone, the more stable *E*

(12) F. A. L. Anet, *J. Amer. Chem. Soc.*, **84**, 1053 (1962).

(13) For example; H. L. Goering and M. F. Sloan, *ibid.*, **83**, 1397 (1961).

configuration depicted in **9** was assigned to the product. If the product had the alternative *Z* configuration, the pmr spectrum would have been expected to show strong deshielding of $H_4$. The absence of any signals downfield from 3.2 ppm, apart from those due to the methyl ester and olefinic protons, thus supported the *E* configuration.

When an attempt was made to purify **9** by preparative vpc, it partly isomerized to the ketone **18**. The characteristic pmr signals of the latter offered supporting evidence for the proposed structures, and, in particular, the paramagnetic shift of the $C_1$ methyl singlet from $\delta$ 0.92 in **9** to $\delta$ 1.13 in **18** was found to be entirely consistent with the established trend in related compounds, as shown in Table I.

TABLE I

DESHIELDING EFFECT OF THE $C_2$=$C_3$ DOUBLE BOND ON THE $C_1$ METHYL GROUP[a]

| Compounds with olefinic bridge | $C_1$ methyl singlet[b] | Compounds without olefinic bridge | $C_1$ methyl singlet[b] |
|---|---|---|---|
| **7** | 1.09 | **12** | 0.96 |
| **13** | 1.07 | **23** | 0.87 |
| **2** | 1.08 | **21** | 0.91 |
| **20** | 1.15 | **22** | 0.94 |
| **18** | 1.13 | **9** | 0.92 |

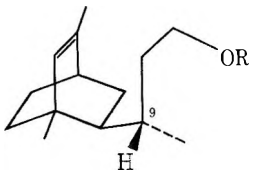
[a] There were obviously many other factors which influenced chemical shift of the $C_1$ methyl group. Nevertheless, these data gave a rough estimate for the magnitude of the deshielding effect of the olefinic bridge. [b] Pmr spectra were measured for $CCl_4$ solutions on a Varian A60 spectrometer. Chemical shifts are in parts per million downfield from TMS as internal standard.

The obvious sequel to this work on the acylation reactions was the search for a more reliable method of introducing a carbonyl group at $C_3$ (path B, Scheme I). Some preliminary experiments using Brown's hydrochlorination–elimination procedure[14] on the model compound **19**[10] showed some promise, although the ratio of exocyclic to endocyclic olefin, obtained from the reaction of potassium triethylmethoxide[14] with the hydrochloride of **19**, was disappointingly low (1:2). However, elimination with the weaker base sodium ethoxide not only gave a much more favorable ratio (up to 2:1), but also avoided the problem, when using triethyl methoxide, of separating the products from the relatively nonvolatile triethylmethanol.

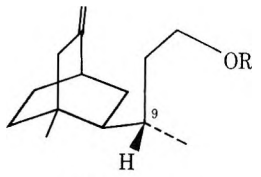
The alcohol **2**[1] was protected as its acetate **13**, which was then hydrochlorinated to give **23**. Dehydrochlorination of **23** with sodium ethoxide proceeded with concomitant transesterification of the protecting acetate group as desired to yield a mixture of olefins **2** and **21** in the ratio 2:3. After chromatography on silver nitrate–alumina the alcohol **21** was isolated in a yield of 50%, based on unrecovered **2**. A by-product was assigned the structure **24** on the basis of its pmr spectrum, which contained no signals for olefinic protons but an ethyl quartet at $\delta$ 3.30.

The preparation of the exocyclic olefin **21** by this simple and relatively high-yielding procedure from the endocyclic isomer **2** was an important contribution to the success of the total synthesis of (±)-seychellene.

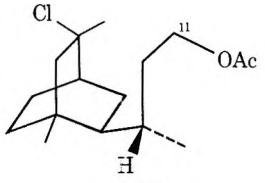
The alcohol function in **21** was protected as the trityl



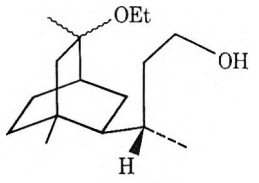
**2**, R = H
**13**, R = Ac
**20**, R = C(Ph)$_3$



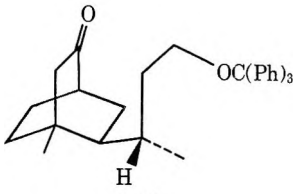
**21**, R = H
**22**, R = C(Ph)$_3$



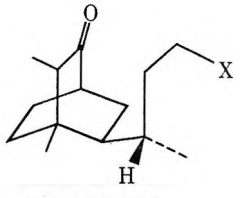
**23**



**24**



**25**



**26a**, X = OH
**b**, X = OC(Ph)$_3$
**c**, X = OTs
**d**, X = Cl

ether **22**, whose exocyclic double bond was cleaved, using osmium tetroxide and sodium metaperiodate in aqueous dioxane,[15] to yield the ketone **25**. Originally this cleavage was attempted on a mixture of exocyclic and endocyclic olefins **22** and **20** using catalytic amounts of osmium tetroxide, but the unreacted olefins were recovered. The color of the reaction mixture in these cases was a deep green. When pure exocyclic olefin **22** was used, the reaction proceeded smoothly and the color of the reaction mixture was deep brown. It was thus apparent that the endocyclic olefin **20** reacted with osmium tetroxide, but that the intermediate osmate ester was not breaking down readily to regenerate the osmium tetroxide, and hence the reaction did not proceed. Similarly, 1-methylcyclohexene has been reported[15] to undergo oxidative cleavage very slowly.

The ketone **25** was monomethylated using potassium triphenylmethide and methyl iodide. The relative stereochemistry of the $C_2$ methyl group in the product **26b** was assigned on the basis of the assumption that the enolate would be attacked by the alkylating agent from the less hindered side.[16] This issue was not crucial, since the system could be cyclized to norseychellanone regardless of the relative stereochemistry at $C_2$.

Hydrogenolysis of the trityl ether **26b** afforded the alcohol **26a**. This was converted to the tosylate **26c**, which readily cyclized to norseychellanone (**5**) when treated with potassium triphenylmethide in 1,2-dimethoxyethane. An indication of the speed of this reaction was gained from the fact that, upon dropwise addition of the triphenylmethide solution to the tosylate **26c** in 1,2-dimethoxyethane at 20°, an instantaneous

(14) (a) S. P. Acharya and H. C. Brown, *Chem. Commun.*, 305 (1968); (b) H. C. Brown and Min-Hon Rei, *J. Org. Chem.*, **31**, 1090 (1966).

(15) R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).

(16) E. J. Corey, R. Hartmann, and P. A. Vatakencherry, *J. Amer. Chem. Soc.*, **84**, 2611 (1962).

precipitate of potassium tosylate was observed. The chloride **26d** did not cyclize at 20° under similar conditions, but heating at 90° for 1.5 hr was required before complete precipitation of potassium chloride was observed. This chloride **26d** was prepared by accident from the alcohol **26a**, when the temperature during tosylation and subsequent hydrolysis of excess reagent was not kept below 20°. The chloride ion present in solution presumably displaced the initially formed tosylate group. Analogous observations have been made by other workers.[17]

This synthesis of (±)-norseychellanone (**5**) constitutes a total synthesis of (±)-seychellene, because the conversion of **5** to (±)-seychellene has been carried out by Piers, Britton, and de Waal, who synthesized the racemic ketone by quite a different route.[18]

## Experimental Section

For general details, refer to the previous paper.[1] An aluminum column 10 ft × 0.375 in. of 15% Apiezon on nonacid-washed Chromosorb W (60–80 mesh) was also used for preparative vpc.

**Reaction of Methyl Ester 7 with Polyphosphoric Acid in Acetic Acid. A. At 55–60°.**—The polyphosphoric acid in acetic acid reaction medium was prepared according to the method of Kulkarni and Dev[9] using 7 g of phosphorus pentoxide, 3 ml of 85% orthophosphoric acid, and 12 g of acetic acid. To one third of this solution at 55–60°, 0.50 g of the methyl ester[10] was added dropwise over 2 min and the temperature was maintained at 55–60° for 1 hr. The product was then poured into ice water and extracted with hexane. The hexane extract was washed with dilute aqueous sodium carbonate and water, then dried over anhydrous sodium sulfate. Evaporation of solvent yielded 0.55 g of a yellow oil, identified as predominantly the rearranged secondary acetate **8** (see below).

**B. At 75–80°.**—The reaction medium was prepared as above using 35 g of phosphorus pentoxide, 15 ml of 85% orthophosphoric acid, and 60 g of acetic acid. The olefin **7** (5 g) was added dropwise with stirring over 2 min to the reaction medium at 75–80°, and this temperature was maintained for 1 hr. Work-up as above yielded 5.6 g of product; vpc analysis showed the presence of two major components, A and B (1.7:1), which accounted for approximately 90% of the mixture. The retention times of A and B on 3% SE-30 at 160° were 4.7 and 2.8 min, respectively. A and B were separated by preparative vpc on 15% Apiezon at 180°.

B, a colorless oil, was the rearranged secondary acetate **8**: ir 1730 $cm^{-1}$ (ester and acetate); pmr $\delta$ 4.60 (br s, 1, $H_2$), 3.60 (s, 3, methyl ester), 2.48 (dd, $J_{6,7n} + J_{6,7x}$ = 14.5 Hz, 1, $H_6$), 2.00 (s, 3, acetate methyl), 1.02 (s, 3, tertiary methyl), 0.93 (s, 3, tertiary methyl); mass spectrum *m/e* 194 ($M^+ - 60$) (the molecular ion was of negligible abundance). The analytical sample was obtained by microdistillation, bp 86° (0.1 mm). *Anal.* Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.38; H, 8.85.

The higher retention time component A was found to be a mixture of the two double bond isomers **9** and **18** (2.5:1). Since **18** was not present in the crude product (pmr), it must have been formed by isomerization of **9** on the preparative column. The ir and pmr spectra of **9** are given below. The characteristic pmr signals of the nonconjugated ketone **18** were $\delta$ 5.67 (br s, $H_2$), 3.14 (br s, $-CH_2CO-$), 1.13 (s, $C_1$ methyl).

**C. At 85–90°.**—The reaction medium was prepared as before using 7 g of phosphorus pentoxide, 3 ml of 85% orthophosphoric acid, and 12 g of acetic acid. The olefin **7** (1.0 g) was added with stirring over 2 min to the reaction medium at 85–90° and this temperature was maintained for 1 hr. Work-up as before yielded 1.0 g of the oily conjugated ketone **9**: ir 1730 (ester), 1680 (conjugated ketone), 1610 $cm^{-1}$ (conjugated double bond); pmr $\delta$ 5.99 (br t, $J_t$ = 2.3 Hz, 1, olefinic proton), 3.62 (s, 3, methyl ester), 2.10 (s, 3, methyl ketone), 0.92 (s, 3, $C_1$ methyl).

(17) B. W. Metcalf, Ph.D. Thesis, University of Western Australia, 1970.

(18) E. Piers, R. W. Britton, and W. de Waal, *Chem. Commun.*, 1069 (1969); E. Piers, W. de Waal, and R. W. Britton, *J. Amer. Chem. Soc.*, **93**, 5113 (1971).

The analytical sample was prepared by chromatography over neutral alumina and subsequent microdistillation, bp 90° (0.08 mm). *Anal.* Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.89; H, 8.29.

**Ozonolysis of Conjugated Ketone 9.**—Ozone was bubbled through a solution of 0.50 g of the ketone in 35 ml of purified acetone at −70° until a faint blue color was apparent. The solution was allowed to warm to 20° and 1.5 ml of Jones reagent was added dropwise. After standing for 30 min, excess reagent was destroyed by the addition of ethanol and the reaction mixture was poured into water. Extraction with ether and evaporation of the washed and dried extracts yielded 0.35 g of the ketone **12** as a colorless liquid: ir 1720–1730 $cm^{-1}$ (ketone and ester); pmr $\delta$ 3.67 (s, 3, methyl ester), 0.96 (s, 3, $C_1$ methyl); mass spectrum *m/e* 196 ($M^+$). *Anal.* Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.44; H, 8.24.

**Hydrolysis of Acetate 8.**—The acetate (45 mg) was refluxed with 400 mg of sodium hydroxide in 5 ml of 50% aqueous ethanol for 12 hr. The mixture was poured into water, acidified with dilute hydrochloric acid, and extracted with ether. The extract was washed with water and dried over anhydrous sodium sulfate, and the solvent was evaporated to yield 26 mg (74%) of glassy hydroxy acid **14** which crystallized from benzene–ethanol as colorless prisms: mp 160–161°; ir 3620 (OH), 1695 $cm^{-1}$ (acid); pmr ($CDCl_3$) $\delta$ 6.16 (very br s, 2, OH protons), 3.54 (br s, 1, $H_2$), 2.52 (dd, $J_{6,7n} + J_{6,7x}$ = 14 Hz, 1, $H_6$), 1.11 (s, 3, tertiary methyl), 1.07 (s, 3, tertiary methyl); mass spectrum *m/e* 198 ($M^+$).

**Attempted Lactonization of Hydroxy Acid 14.**—A solution of 70 mg of the hydroxy acid in 5 ml of formic acid containing 5 drops of concentrated sulfuric acid was left at 20° for 22 hr. The solution was then poured cautiously into excess aqueous sodium bicarbonate and extracted with ether. The extract was washed with aqueous sodium carbonate and water, then dried over anhydrous sodium sulfate. Evaporation of solvent yielded 5 mg of the crude $\delta$-lactone **17**.[10]

**Acetylation of Alcohol 2.**—A solution of 9.9 g of the alcohol[1] in 70 ml of pyridine and 70 ml of acetic anhydride was left overnight at 20°. The reaction mixture was then poured into ice water and extracted with hexane. The extract was washed with water and dried over anhydrous sodium sulfate. Evaporation of solvent yielded 11.6 g (97%) of the acetate **13**: ir 1735 $cm^{-1}$ (acetate); pmr $\delta$ 5.46 (br s, 1, $H_2$), 3.98 (m, 2, $C_{11}$ methylene), 2.29 (br s, 1, $H_4$), 1.98 (s, 3, acetate methyl), 1.75 (d, $J$ = 1.5 Hz, 3, $C_3$ vinyl methyl), 1.07 (s, 3, $C_1$ methyl), 0.81 (d, $J$ = 6.5 Hz, 3, $C_9$ methyl). The analytical sample was obtained by microdistillation, bp 100° (0.7 mm). *Anal.* Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 77.11; H, 10.40.

A 4:1 mixture of the alcohol **2** and its $C_9$ epimer[1] was also acetylated according to the above procedure to yield a mixture of acetates whose pmr analysis showed the characteristic $C_9$ methyl doublet of the minor epimer at $\delta$ 0.57 ($J$ = 6.5 Hz).

**Preparation of Olefin 21.**—Gaseous hydrogen chloride was passed through a stirred solution of 41 g of the acetate **13** in 200 ml of ether at −70°, using apparatus similar to Brown's automatic hydrochlorinator.[14b] Evaporation of the ether at low temperature yielded the unstable chloride **23**, which was used in the next reaction without delay: pmr $\delta$ 4.02 (br t, $J$ = 6.5 Hz, 2, $C_{11}$ methylene), 1.97 (s, 3, acetate methyl), 1.68 (s, 3, $C_3$ methyl), 0.87 (s, 3, $C_1$ methyl).

The total amount of hydrochloride above was refluxed for 30 min with sodium ethoxide solution (16 g of sodium in 650 ml of ethanol). The reaction mixture was poured into water and extracted with hexane. The extract was washed with water and dried over anhydrous sodium sulfate, and the solvent was evaporated to yield 33 g of crude alcohols. A portion (3.2 g) of this mixture was chromatographed on a column of 165 g of 10% silver nitrate–alumina. Elution with hexane–ether (9:1) yielded 0.8 g of the endocyclic olefin **2**. The substitution product **24** (0.3 g) was eluted with hexane–ether (4:1) and 1.3 g of the desired exocyclic olefin **21** was eluted with ether. The isolated yield of **21** was 38% (50% based on unrecovered endocyclic olefin **2**): pmr $\delta$ 4.65 (m, 1, exocyclic olefinic proton), 4.47 (m, 1, exocyclic olefinic proton), 3.56 (m, 2, $C_{11}$ methylene), 3.25 (br s, 1, OH), 0.91 (s, 3, $C_1$ methyl), 0.88 (d, $J$ = 6.5 Hz, 3, $C_9$ methyl). The analytical sample was obtained by microdistillation, bp 80° (0.03 mm). *Anal.* Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.37; H, 11.45.

**Tritylation of Alcohol 21.**—A mixture of 1.15 g of the alcohol in 50 ml of benzene and 1 ml of pyridine was refluxed gently with

1.9 g of trityl chloride for 12 hr. The trityl ether **22** (2.1 g, 84%), which was isolated in the manner previously described[1] for **20**, crystallized from ethanol as colorless prisms: mp 104–105°; pmr $\delta$ 4.66 (m, 1, exocyclic olefinic proton), 4.49 (m, 1, exocyclic olefinic proton), 3.10 (m, 2, $C_{11}$ methylene), 0.94 (s, 3, $C_1$ methyl), 0.73 (d, $J$ = 6.5 Hz, 3, $C_9$ methyl). *Anal.* Calcd for $C_{33}H_{38}O$: C, 87.95; H, 8.50. Found: C, 88.09; H, 8.50.

**Preparation of Ketone 25.**—To a solution of 4.9 g of the trityl ether **22** in 450 ml of purified dioxane and 150 ml of water was added 0.19 g of osmium tetroxide; the solution rapidly became dark brown. Finely powdered sodium metaperiodate (26 g) was added to the stirred solution over a period of 30 min and a flocculent precipitate of sodium iodate soon appeared. The mixture was stirred at 20° for an additional 22.5 hr, after which time the dark brown color of the solution had faded to a light yellow. The reaction mixture was poured into water and extracted with ether. The extract was washed with water and dried over anhydrous sodium sulfate, and the solvent was evaporated. The crude product was purified by chromatography on 240 g of neutral activity I alumina. Elution with benzene yielded 3.45 g (75%) of the ketone **25**, which crystallized from ethyl acetate as colorless prisms: mp 176°; ir 1720 $cm^{-1}$ (ketone); pmr $\delta$ 3.11 (m, 2, $C_{11}$ methylene), 1.06 (s, 3, $C_1$ methyl), 0.73 (d, $J$ = 6.5 Hz, 3, $C_9$ methyl). *Anal.* Calcd for $C_{32}H_{36}O_2$: C, 84.91; H, 8.02. Found: C, 84.72; H, 7.80.

**Preparation of Alcohol 26a.**—A solution of 0.89 g of the ketone **25** in 30 ml of 1,2-dimethoxyethane was alkylated using potassium triphenylmethide[19] and methyl iodide (4 ml) in the manner described[1] for the ketone **6**. The trityl ether **26b** was not isolated, but the crude product was dissolved in 250 ml of ethanol and hydrogenated (2.5 atm) with 0.5 g of 5% palladium on charcoal at 20° for 14 hr. After removal of the catalyst by filtration and evaporation of ethanol, the product was purified by chromatography on 150 g of neutral activity I alumina. Elution with hexane and hexane–ether (9:1) yielded triphenylmethane, while 0.35 g (80%) of the alcohol **26a** was eluted with hexane–ether (1:1). Vpc analysis showed a single peak on 3% SE-30 at 160°: ir 3630 and 3450 (OH), 1715 $cm^{-1}$ (ketone); pmr $\delta$ 3.56 (m, 2, $C_{11}$ methylene), 3.37 (br s, 1, OH), 2.46 (br q, $J$ = 7 Hz, 1, $H_2$), 0.99 (d, $J$ = 7 Hz, 3, $C_2$ methyl), 0.98 (s, 3, $C_1$ methyl), 0.93 (d, $J$ = 6.5 Hz, 3, $C_9$ methyl). The analytical sample was obtained by microdistillation, bp 114° (0.04 mm). *Anal.* Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.30; H, 10.99.

**Preparation of Chloride 26d.**—A mixture of 0.14 g of the alcohol **26a** and 0.17 g of *p*-toluenesulfonyl chloride in 5 ml of pyridine was left at 20° for 42 hr. Water (0.15 ml) was then added and the mixture was left for a further 6 hr at 20°, after which it was poured into excess dilute hydrochloric acid at 0° and extracted with hexane. The hexane extract was washed with dilute aqueous sodium carbonate and water, and then dried over anhydrous sodium sulfate. Evaporation of solvent yielded 0.11 g of a colorless oil, identified as the chloride **26d**: pmr $\delta$ 3.55 (m, 2, $C_{11}$ methylene), 1.00 (d, $J$ = 7 Hz, 3, $C_2$ methyl), 0.99 (s, 3, $C_1$ methyl), 0.97 (d, $J$ = 6.5 Hz, 3, $C_9$ methyl). The ir spectrum showed no hydroxyl absorption.

**Preparation of Tosylate 26c.**—A mixture of 0.10 g of the alcohol **26a** and 0.23 g of *p*-toluenesulfonyl chloride in 3 ml of cold pyridine was left at −15° for 12 hr, and water (0.15 ml) was then added. The reaction mixture was left for a further 45 min at −15°, after which it was poured into excess dilute hydrochloric acid at 0° and extracted with hexane. The extract was washed with dilute aqueous sodium carbonate and water and dried over anhydrous sodium sulfate, and the solvent was evaporated to yield 0.16 g (93%) of the crude tosylate **26c** which crystallized from benzene–hexane as colorless prisms: mp 91–93°; ir 1715 $cm^{-1}$ (ketone); pmr $\delta$ 4.02 (m, 2, $C_{11}$ methylene), 2.46 (s, 3, aromatic methyl), 0.93 (d, $J$ = 7 Hz, 3, $C_2$ methyl), 0.89 (s, 3, $C_1$ methyl), 0.85 (d, $J$ = 6.5 Hz, 3, $C_9$ methyl). *Anal.* Calcd for $C_{21}H_{30}O_4S$: C, 66.64 H, 7.99 S, 8.46. Found: C, 66.98; H, 8.12; S, 8.20.

**Cyclization of Tosylate 26c.**—Potassium triphenylmethide solution[19] was added dropwise with a syringe to 80 mg of the tosylate in 3 ml of 1,2-dimethoxyethane. An immediate white precipitate of potassium tosylate was observed at 20°. The base was added until the red color of the triphenylmethide ion just persisted. The reaction mixture was left at 20° for 1.5 hr and then poured into water. Extraction with hexane followed by evaporation of the dried extracts yielded a crude product which was purified by chromatography on a small column of 10 g of neutral activity I alumina. Elution with hexane and hexane–benzene (9:1) gave triphenylmethane, while 35 mg (80%) of norseychellanone **5** was eluted with hexane–benzene (1:1). Vpc analysis (5% Ucon) showed the product to be homogeneous. The pmr, ir, and mass spectra of this compound were identical with the spectra[20] of authentic norseychellanone: ir (liquid film) 1715 $cm^{-1}$ (ketone); pmr ($CDCl_3$) $\delta$ 0.97 (s, 3, tertiary methyl), 0.94 (s, 3, tertiary methyl), 0.79 (d, $J$ = 6.5 Hz,[21] 3, secondary methyl).

**Cyclization of Chloride 26d.**—Potassium triphenylmethide solution was added with a syringe to 50 mg of the chloride in 2 ml of 1,2-dimethoxyethane until the red color of the triphenylmethide ion just persisted. The sealed flask was heated at 80–90° for 1.5 hr and by this time precipitation of potassium chloride was complete. The reaction mixture was then poured into water and the cyclic ketone norseychellanone (30 mg, 70%) was isolated as above.

**Registry No.**—(±)-**1**, 24568-69-2; (±)-**2**, 29450-72-4; (±)-**5**, 24461-21-0; **8**, 34993-78-7; **9**, 34993-79-8; **12**, 34996-50-4; (±)-**13**, 29448-19-9; **14**, 34996-52-6; **18**, 34996-53-7; (±)-**21**, 34996-54-8; (±)-**22**, 29448-16-6; (±)-**25**, 29448-15-5; (±)-**26a**, 29448-22-4; (±)-**26c**, 29448-23-5; (±)-**26d**, 34996-59-3.

(19) H. O. House and V. Kramar, *J. Org. Chem.*, **27**, 4146 (1962).

(20) Copies of spectra were very kindly forwarded by Professor Ourisson.

(21) This coupling constant was incorrectly reported[4] as 5.5 Hz.

# The Oxidation of Tetramethylethylene in the Presence of Rhodium(I) and Iridium(I) Complexes

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The oxidation of tetramethylethylene (TME) was studied in the presence of the oxygen-carrying complexes *trans*-$MCl(CO)(Ph_3P)_2$ (M = Rh, Ir). The oxidation was found to be rapid and quite selective under mild conditions, yielding 2,3-dimethyl-2,3-epoxybutane and 2,3-dimethyl-3-hydroxybutene-1 as the major oxidation products. The reactions are inhibited by hydroquinone, which is consistent with a free radical initiated autoxidation. The reaction of TME with oxygen was far more rapid than was oxidation of less substituted olefins in the presence of the Rh(I) and Ir(I) complexes, suggesting that initial coordinative interaction between the olefin and the metal center is not an important factor. A mechanistic pathway involving an allylic hydroperoxide intermediate is proposed.

Current interest in the oxidation of olefins in the presence of hydrocarbon-soluble, oxygen-carrying transition metal complexes has been stimulated by the possibility of novel oxidation pathways in these systems. The results of recent studies concerning the role of transition metal complexes in the oxidation of olefinic

TABLE I

THE OXIDATION OF TETRAMETHYLETHYLENE[a] IN THE PRESENCE OF $MCl(CO)(Ph_3P)_2$ (M = Rh, Ir)

| Metal complex | Radical inhibitor | Yield of products, %[b] I | II | III | Acetone | Unreacted TME, %[c] |
|---|---|---|---|---|---|---|
| None[d] | None | 2 | 0.5 | 2 | | 92 |
| $RhCl(CO)(Ph_3P)_2$ | None | 25 | 22 | 11 | 4 | 34 |
| $RhCl(CO)(Ph_3P)_2$ | HQ[e] | 3 | 5 | 2 | 0.5 | 88 |
| $IrCl(CO)(Ph_3P)_2$ | None | 19 | 15 | 11 | 3 | 47 |
| $IrCl(CO)(Ph_3P)_2$ | HQ[e] | 3 | 3 | 1 | 0.3 | 92 |

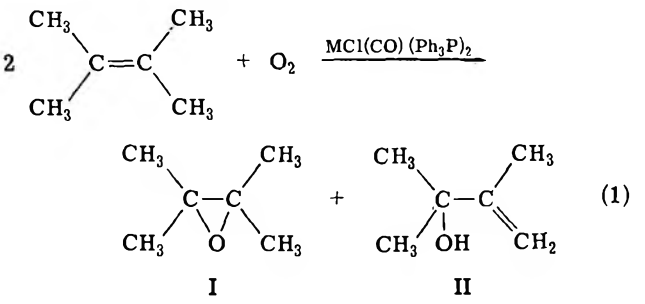
[a] Oxygen bubbled through 12 ml of TME containing $8 \times 10^{-5}$ mol metal complex for 4 hr at 50°. [b] Conversions, mol %, of TME to the indicated products. [c] Unidentified high-boiling by-products were also formed in 2–5% yield. [d] Reaction run in the presence of $4 \times 10^{-4}$ mol of azobisisobutyronitrile. [e] Hydroquinone present in 3.3 mol %.

hydrocarbons have been interpreted in two different ways. There is evidence which suggests[1,2] that the oxidation of cyclohexene using iridium(I) and rhodium(I) phosphine complexes, first reported by Collman,[3] proceeds *via* a radical pathway similar to autoxidation in the presence of metal salts.[4] Takao, *et al.*,[5,6] have investigated the oxidation of styrene in the presence of iridium(I) and rhodium(I), but these authors suggest that the observed catalytic activity is due to coordination of molecular oxygen by the metal center causing an increased oxygen–oxygen bond length and enhanced reactivity with olefin in the coordination sphere of the metal. James and Ochiai[7] have proposed a mechanism for the oxidation of a cyclooctene–rhodium(I) complex which involves oxygen activation and transfer to the olefin. These authors suggest that this mechanism may be operative in the oxidation of cyclohexene in the presence of Rh(I) and Ir(I).

We have studied the oxidation of tetramethylethylene in the presence of the metal complexes *trans*-$MCl(CO)(Ph_3P)_2$ (M = Rh,[8] Ir[9]) and have compared the results with autoxidation using a free-radical initiator. Tetramethylethylene was found to be an excellent model compound for study since it was rapidly and selectively oxidized at low temperatures in the presence of these metal complexes. In contrast to the oxidation of cyclohexene,[2] little polymerization occurred during the oxidation of TME in the presence of the rhodium(I) and iridium(I) complexes.

## Results and Discussion

The oxidation of tetramethylethylene (TME) in the presence of $MCl(CO)(Ph_3P)_2$ (M = Rh, Ir) at 50° gives two major reaction products: 2,3-dimethyl-2,3-epoxybutane (I) and 2,3-dimethyl-3-hydroxybutene-1 (II) (eq 1). Acetone and small amounts of high molecular weight by-products are also formed. The reaction mixtures are completely homogeneous throughout with no observable deposits of insoluble materials. Little oxidation of TME occurs under the same conditions in the absence of the metal complexes, but low




(1)

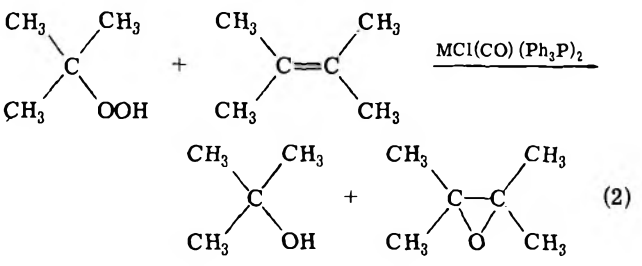
yields of I and II are obtained in the presence of a radical source.[10] Reactions are severely inhibited by hydroquinone (3.3 mol %). The results are summarized in Table I.

In an attempt to explain the formation of II, we have shown that the epoxide I does not rearrange to form II under reaction conditions in the presence of the metal complexes. Furthermore, II is not formed from 2,3-dimethylbutene-1 in detectable amounts under the reaction conditions, thus eliminating the possibility of isomerization of TME to 2,3-dimethylbutene-1 followed by allylic oxidation. Despite the fact that the rhodium(I) and iridium(I) complexes are catalysts for olefin isomerization when used in an inert atmosphere,[11,12] little or no isomerization occurs under oxidation conditions.

We were able to observe the formation of 2,3-dimethyl-3-hydroperoxybutene-1 (III) in as much as 10% yield during the course of the oxidation of TME in the presence of $RhCl(CO)(Ph_3P)_2$ and $IrCl(CO)(Ph_3P)_2$. We have also shown that these complexes are capable of catalytically decomposing *tert*-butyl hydroperoxide in toluene solution with liberation of oxygen and formation of *tert*-butyl alcohol at room temperature (Table II). However, when the $MCl(CO)(Ph_3P)_2$-catalyzed reaction of *tert*-butyl hydroperoxide was carried out in TME rather than in toluene, little or no oxygen was liberated and the products were I and *tert*-butyl alcohol (eq 2, Table II). No observable epoxidation of TME occurred under similar conditions in the absence of the catalyst. Therefore, it is reasonable to suggest that the allylic hydroperoxide III formed during the reaction of TME with oxygen reacts with TME to give I and II in the presence of the metal complexes (eq 3).

James and Ochiai have cited spectral evidence for hydroperoxide intermediates, and Fusi, *et al.*,[2] invoked the intermediacy of an allylic hydroperoxide in explaining the oxidation of cyclohexene in the presence of

(1) V. P. Kurkov, J. Z. Pasky, and J. B. Lavigne, *J. Amer. Chem. Soc.*, **90**, 4744 (1968).
(2) A. Fusi, R. Ugo, F. Fox, A. Pasini, and S. Cenini, *J. Organometal. Chem.*, **26**, 417 (1971).
(3) J. P. Collman, M. Kubota, J. W. Hosking, *J. Amer. Chem. Soc.*, **89**, 4811 (1967).
(4) (a) A. J. Chalk and J. F. Smith, *Trans. Faraday Soc.*, **53**, 1214 (1957); (b) E. S. Gould and M. Rado, *J. Catal.*, **13**, 238 (1969).
(5) K. Takao, Y. Fujiwara, T. Imanaka, and S. Teranishi, *Bull. Chem. Soc. Jap.*, **43**, 1153 (1970).
(6) K. Takao, M. Wayaku, Y. Fujiwara, T. Imanaka, and S. Teranishi, *ibid.*, **43**, 3898 (1970).
(7) B. R. James and E. Ochiai, *Can. J. Chem.*, **49**, 975 (1971).
(8) L. Vallarino, *J. Chem. Soc.*, 2287 (1957).
(9) L. Vaska and J. DiLuzio, *J. Amer. Chem. Soc.*, **83**, 2784 (1961).
(10) D. E. VanSickle, F. R. Mayo, R. M. Arluck, and M. G. Syz, *J. Amer. Chem. Soc.*, **89**, 967 (1967).
(11) W. Strohmeier and W. Rehder-Sternweiss, *J. Organometal. Chem.*, **19**, 417 (1969).
(12) J. E. Lyons, *J. Org. Chem.*, **36**, 2497 (1971).



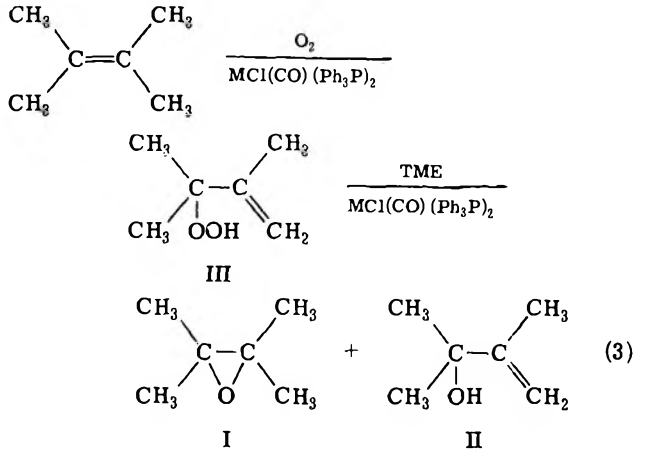
(2)

TABLE II

REACTIONS OF *tert*-BUTYL HYDROPEROXIDE IN THE PRESENCE OF $MCl(CO)(Ph_3P)_2$[a] (M = Rh, Ir)

| Metal complex | Medium | Yield of products, %[b] *tert*-Butyl alcohol | I | Unreacted *tert*-butyl hydroperoxide, % |
|---|---|---|---|---|
| $RhCl(CO)(Ph_3P)_2$ | Toluene | 14 | | 85 |
| $RhCl(CO)(Ph_3P)_2$ | TME | 25 | 26 | 71 |
| $IrCl(CO)(Ph_3P)_2$ | Toluene | 46 | | 53 |
| $IrCl(CO)(Ph_3P)_2$ | TME | 59 | 42 | 34 |

[a] *tert*-Butyl hydroperoxide (1 g) was added dropwise over 5 min to 0.08 mmol of the complex in 10 g of TME or toluene at 25° and the mixture was stirred for a total of 1 hr. [b] Conversions, mol %, based on *tert*-butyl hydroperoxide.



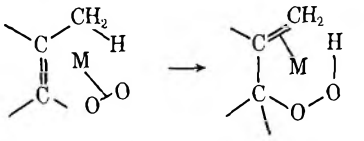
III

(3)

I II

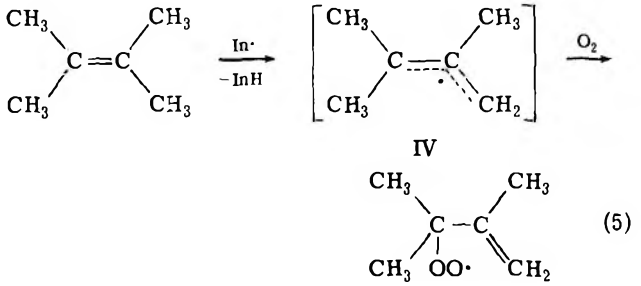
metal complexes, although hydroperoxides were not isolated from their reaction mixtures. Fusi, *et al.*,[2] showed further that such a hydroperoxide was decomposed in the presence of several metal complexes. Our results show that the metal-catalyzed reactions of *tert*-butyl hydroperoxide in the presence of TME follow a different course than in the absence of the olefin. When $RhCl(CO)(Ph_3P)_2$ is used, reaction occurs according to eq 2, although, with the iridium analog, some decomposition to oxygen and alcohol occurs simultaneously (Table II). Thus, *the Rh(I) and Ir(I) complexes are efficient catalysts for epoxidation of TME with an alkyl hydroperoxide.*[13]

Since the product of the reaction of TME with singlet oxygen is III,[14] we considered the possibility that we had generated singlet oxygen *in situ* during the course of this reaction. Fusi, *et al.*, however, failed to find evidence of singlet oxygen during the oxidation of cyclohexene in the presence of iridium(I) and rhodium(I) complexes. Similar experiments in our laboratories have also failed to detect singlet oxygen[15] when $O_2$ is liberated from the metal complex. Since the adducts formed from reaction of $d^8$ and $d^{10}$ group VIII metal complexes with molecular oxygen are generally diamagnetic,[16] formation of III by an "ene" reaction[17] between coordinated oxygen and olefin (eq 4) cannot be



(4)

disregarded. If a metal-catalyzed "ene" reaction (eq 4) were the pathway for the formation of III, the rate of reaction would be expected to parallel the coordinative ability of the olefin, as is found in many other metal-catalyzed reactions (hydrogenation,[18] hydroformylation,[19] isomerization,[12] etc.). Contrary to what would be expected of a coordinative mechanism, we have found that the relative rates of olefin oxidation using $MCl(CO)(Ph_3P)_2$ are just the reverse of this. The ease of the olefin oxidations *increases* with the degree of substitution: TME > 2-methyl-2-pentene > *cis*-2-hexene ≫ hexene-1. This holds true for *both* the hydroperoxide formation *and* the epoxidation steps. When TME is oxidized at 50° in the presence of $RhCl(CO)(Ph_3P)_2$, the total hydroperoxide content as determined titrimetrically was nearly 11% after 4 hr, while less than 1% hydroperoxide was detected in hexene-1 oxidation under the same conditions. Similarly, we have found that TME is epoxidized much faster than hexene-1 in the presence of the rhodium(I) and iridium(I) complexes. Furthermore, the tertiary allylic hydroperoxide III has been shown to be the product of radical-initiated oxidation due to the greater electron density at the tertiary carbon of the initial intermediate IV of a radical pathway (eq 5).[20] The observation



IV

(5)

that hydroquinone inhibits oxidation of TME by the Rh(I) and Ir(I) complexes (Table I) supports the existence of a radical chain mechanism for the formation of the allylic hydroperoxide. Our data do not enable us to distinguish between initiation by the metal center and initiation by radical species present due to metal-catalyzed decomposition of trace impurities.[21] Our results, however, are consistent with the existence of a mechanistic pathway in which the initial step is ini-

(13) It has been shown that several group Vb and VIb complexes catalyze the epoxidation of olefins by hydroperoxides: (a) N. Indictor and W. F. Brill, *J. Org. Chem.*, **30**, 2074 (1965); (b) N. N. Sheng and J. G. Zajacek, *Advan. Chem. Ser.*, **76**, 418 (1968).

(14) C. S. Foote and S. Wexler, *J. Amer. Chem. Soc.*, **86**, 3879 (1964).

(15) No reaction with tetracyclone.[14]

(16) J. P. Collman, *Accounts Chem. Res.*, **1**, 142 (1968).

(17) J. E. Baldwin and J. C. Swallow, *Angew. Chem.*, **81**, 571 (1969).

(18) J. E. Lyons, L. E. Rennick, and J. L. Burmeister, *Ind. Eng. Chem. Prod. Res. Develop.*, **9**, 2 (1970).

(19) C. K. Brown and G. Wilkinson, *Tetrahedron Lett.*, 1725 (1969).

(20) J. A. Howard and K. U. Ingold, *Can. J. Chem.*, **45**, 793 (1967).

(21) R. A. Sheldon, *Chem. Commun.*, 788 (1971).

tiated autoxidation of the olefin to form an allylic hydroperoxide and a subsequent epoxidation step which is catalyzed by the metal complexes.

## Experimental Section

Infrared spectra were determined using Perkin-Elmer infrared spectrophotometers Models 137-B and 21. Nmr spectra were run using Varian T-60 and A-60 spectrometers. Gas chromatographic analyses were carried out on a Hewlett-Packard Model 5750B instrument. Fractional distillations were performed on a Nester-Faust 18-in. semimicro spinning band column equipped with a stainless steel band.

**Materials.**—Olefinic hydrocarbons of at least 99% purity were obtained from Chemical Samples Co., distilled under nitrogen, and then passed through freshly activated silica gel under nitrogen prior to use. The complexes $RhCl(CO)(Ph_3P)_2$ and $IrCl(CO)(Ph_3P)_2$ were obtained from Strem Chemical Co. *tert*-Butyl hydroperoxide (92% by titration) was purchased from Lucidol. Oxygen cylinders were obtained from Linde Air Products Co.

**Oxidation of TME Using $MCl(CO)(Ph_3P)_2$ (M = Rh, Ir) as Catalyst.**—Oxygen was bubbled (1.5 l./hr) through 12.0 ml of TME containing $8 \times 10^{-5}$ mol of metal complex for 4 hr at 50°. The Rh(I) complex slowly dissolved to give a bright yellow solution, whereas the Ir(I) gave a clear green solution. Liquid was returned to the reaction flask by an efficient micro Dry Ice condenser. A small amount of liquid (~0.5 ml) was carried by the gas stream into a −78° trap, and was returned to the reaction flask at the conclusion of the run. After 4 hr the volatile reaction products were immediately flash evaporated away from the catalyst and 0.3–0.5 g of a viscous liquid which did not distil by gentle warming at 0.01 mm. The vacuum-transferred reaction mixture was then analyzed by glpc using a 6 ft × 0.125 in. column packed with 10% silicone UC-W98 on 80–100 mesh Chromosorb W (Hewlett-Packard) and an injection port temperature under 200°. It was established using pure standards that little or no decomposition of reaction products occurred during glpc analysis of product mixtures. I and II were unaffected by column conditions while a small amount of decomposition of III occurred in the injection port. For this reason III was also analyzed titrimetrically (iodometric method[22]) and results agreed to within ±1% of the glpc value. Compounds I, bp 90.5°, $n^{20}D$ 1.4014 (lit.[23] $n^{20}D$ 1.4010), >99.5% glpc purity, and II, bp 117°, $n^{20}D$ 1.4316 (lit.[23] $n^{20}D$ 1.4312), >99% glpc purity, were obtained by spinning band distillation of a run ten times the size of those reported above and were identified by comparison of their ir, nmr, and mass spectra with those of authentic samples. Pure III, $n^{20}D$ 1.4432 (lit.[14] $n^{20}D$ 1.4428), was obtained by preparative glpc and identified by comparison of ir and nmr spectra with those of an authentic sample. Spectral data for I, II, and III were identical with that reported in the literature.[23,24] When the reaction was run under conditions identical with those given above in the *absence* of a metal complex or an initiator, less than a 2% yield of oxidation products was observed (glpc) after 4 hr.

(22) L. S. Silbert and D. Swern, *Anal. Chem.*, **30**, 385 (1958).

(23) C. C. Price and D. D. Carmelite, *J. Amer. Chem. Soc.*, **88**, 4039 (1966).

(24) P. D. Bartlett and G. D. Mendenhall, *ibid.*, **92**, 210 (1970).

**Inhibition by Hydroquinone.**—Reactions were carried out under conditions identical with the above in TME which contained 3.3 mol % hydroquinone.

**Effect of the Catalyst and Reaction Conditions on Isomerization of TME, I, and II during Oxidation.**—Less than 0.5% isomerization of TME to 2,3-dimethylbutene 1 occurred during oxidation (glpc analysis).

When $O_2$ was bubbled through 12 ml of I at 50° for 4 hr in the presence of $8 \times 10^{-5}$ mol of either $RhCl(CO)(Ph_3P)_2$ or $IrCl(CO)(Ph_3P)_2$ no change was noted (glpc) and I was recovered in 98% yield.

When $O_2$ was bubbled through a solution of 1 g of II in 5 ml of benzene for 3 hr at 50° in the presence of $8 \times 10^{-5}$ mol of $RhCl(CO)(Ph_3P)_2$, then vacuum transferred at 0.01 mm, a 1.5% yield (by weight) of a nonvolatile gummy residue was left behind and II was recovered unchanged in 98% yield.

**Decomposition of *tert*-Butyl Hydroperoxide in the Presence of $MCl(CO)(Ph_3P)_2$ (M = Rh, Ir).**—*t*-Butyl hydroperoxide (1.0 g) was added dropwise over a 15-min period to 0.08 mmol of the complex in 10 g of toluene at 25° and the mixture was stirred for a total of 1 hr. The volatiles were immediately vacuum transferred from the catalyst and analyzed by glpc (Table II). No organic residue remained.

**Reaction of *tert*-Butyl Hydroperoxide with TME in the Presence of $MCl(CO)(Ph_3P)_2$.**—*tert*-Butyl hydroperoxide (1.0 g) was added dropwise over 15 min to 0.08 mmol of the complex in 10 g of TME at 25° and the mixture was stirred for a total of 1 hr. The volatiles were immediately vacuum transferred from the catalyst and analyzed by glpc (Table II). No organic residue remained.

**Relative Ease of Olefin Oxidation Using $MCl(CO)(Ph_3P)_2$.**—Using conditions identical with those for the oxidations above, the per cent conversions of TME, 2 methyl-2-pentene, *cis*-2-hexene, and hexene-1 to oxidation products were 66, 33, 3, and <1%, respectively, with the Rh(I) complex and 53, 8, 1, and <1%, respectively, with the Ir(I) complex. Titration of reaction mixtures by the standard iodometric method[22] showed that, in the case of TME, a buildup of 11% hydroperoxide had occurred after 4 hr at 50° using either the Rh(I) or the Ir(I) complex, whereas with either complex less than 1% hydroperoxide had formed from hexene-1. When TME was epoxidized using *tert*-butyl hydroperoxide at room temperature as described above, a 26% yield of I was obtained after 1 hr with the Rh(I) complex and a 42% yield of I was obtained using Ir(I). When hexene-1 was treated with *tert*-butyl hydroperoxide under the same conditions using the Rh(I) complex, *tert*-butyl alcohol was formed in 25% yield but less than 1% hexene oxide was detected (glpc). With the iridium(I) complex no epoxide could be detected under identical conditions.

**Registry No.**—I, 5076-20-0; II, 10473-13-9; tetramethylethylene, 563-79-1; $RhCl(CO)(Ph_3P)_2$, 13938-94-8; $IrCl(CO)(Ph_3P)_2$, 14871-41-1; *tert*-butyl hydroperoxide, 75-91-2; *tert*-butyl alcohol, 75-65-0.

**Acknowledgment.**—The authors with to express their thanks to Miss Caroline Link and Mr. Arthur Brown for their experimental assistance in this work.

# The Accelerated Decomposition of Benzoyl Peroxide in the Presence of Sulfides and Disulfides[1]

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Benzoyl peroxide (BPO) decomposes at an accelerated rate in the presence of aliphatic sulfides or disulfides. The effect is most dramatic for methyl sulfide: 0.5 *M* methyl sulfide in carbon tetrachloride increases the rate constant for BPO disappearance by about $10^4$ over that for pure $CCl_4$, and BPO decomposes with explosive speed in neat methyl sulfide. These reactions have been shown to be ionic processes by a series of experiments using free-radical scavengers, oxygen, and polymerizable and nonpolymerizable olefins. The sulfides and disulfides are oxidized to the sulfoxide or thiolsulfinate, respectively. Other products that have been isolated in one or more of these reactions include benzoic acid, benzoic anhydride, olefin, an $\alpha$-benzoyloxy sulfide, and polysulfides. The reactions are first order in disulfide or sulfide, and first order in peroxide. We suggest a mechanism for all of these reactions in which the O–O bond of BPO undergoes nucleophilic attack by the sulfur compound to produce an intermediate **1** which exists in two resonance structures, **2** and **3**. We have included the nonionic structure **3** in the description of the intermediate since the change from $CCl_4$ to methanol as solvent produces a rate enhancement of only a factor of 11, a smaller effect than would be expected for a totally ionic reaction. The intermediate **1** can decompose by a number of paths. For example, attack by the benzoate ion on the carbonyl carbon produces benzoic anhydride and the sulfoxide, and attack on the $\alpha$ hydrogen produces an ylide and benzoic acid. This system is compared and contrasted with similar work in the literature. In cases where a small concentration of a rather ineffective sulfur compound is used, some of the BPO undergoes normal homolysis in competition with the ionic decomposition. It is interesting, therefore, to inquire whether this homolysis might occur at an accelerated rate due to the presence of the sulfur compound. Several studies in the literature suggest that such an assisted homolysis might be expected.[3-5] Data on the rate of polymerization of styrene in the presence of BPO and disulfides, however, show that all of the radicals in this system are produced by the normal, unimolecular decomposition of BPO, and no assisted homolysis occurs. Some data on the effect of sulfur compounds on the rate of decomposition of *tert*-butyl perbenzoate, propionyl peroxide, lauroyl peroxide, *tert*-butyl peroxylate, and *n*-nitrophenylazotriphenylmethane also are given.

Benzoyl peroxide (BPO) decomposes at an accelerated rate in the presence of aliphatic sulfides or disulfides. The effect is most dramatic for methyl sulfide: 0.5 *M* methyl sulfide in $CCl_4$ increases the rate of BPO decomposition by $10^4$ over that for pure $CCl_4$, and BPO decomposes at an explosive rate in pure methyl sulfide. The sulfur compounds which we have studied (Table I) include compounds of the type RSR and RSSR where R = methyl, propyl, isobutyl, *sec*-butyl, *tert*-butyl, or phenyl. A mechanism which is consistent with all of our evidence involves the nucleophilic attack of the sulfur compound on the O–O bond of BPO and the initial formation of an intermediate **1**, where R is an alkyl group in the case of sulfides and a thiyl group for disulfides (eq 1).

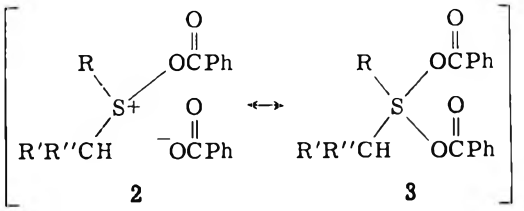
$$\underset{\text{BPO}}{\text{RSCHR'R''} + \text{PhC(=O)OOC(=O)Ph}} \longrightarrow \mathbf{1} \qquad (1)$$

$\mathbf{1} \longrightarrow$ products including sulfoxide (from sulfides) or thiolsulfinate (from disulfides), benzoic acid, benzoic anhydride, olefin, and polysulfides

In order to clarify the distinctions to be made later in this paper, it is useful to define the following terms. *Homolysis* implies simple, unimolecular bond scission to form free radicals;[3a] *assisted homolysis* is homolysis of higher molecularity than unity which occurs at an accelerated rate (a process we have previously referred to as molecule-induced homolysis[3b]); *heterolysis* is unimolecular bond scission to form ions (*e.g.*, SN1); and *assisted heterolysis* is heterolysis of molecularity greater than unity (*e.g.*, SN2). In the discussion to follow, we establish that sulfur compounds interact with BPO to accelerate the rate of its heterolysis, and that this process, eq 1, competes with the normal homolysis of BPO. Our data also show that no accelerated homolysis occurs.

The exact nature of the intermediate **1** requires discussion. An extensive series of studies using free-radical scavengers, which will be presented below, as well as the products produced in these reactions, prove conclusively that eq 1 is not a radical reaction.[3a] However, the small rate effect produced by increasing solvent polarity suggests that the transition state leading to **1** does not have unit charge separation.[3c] There are two possible explanations for this. In the first, **1** is an ion pair but the transition state leading to its formation is very reactantlike and has developed very little charge separation; in the second, intermediate **1** itself is not totally ionic in nature but has some covalent character. We cannot choose between these two possibilities conclusively, but because of analogies to other work in the literature we have formulated eq 1 in terms of the latter possibility. In this explanation, intermediate **1** is a resonance hybrid of ionic and covalent structures **2** and **3**.

There is precedent for both **2** and **3**. Structures




(1) Supported in part by Grants GM-11908 from NIH and GP-3820 from NSF.

(2) (a) John Simon Guggenheim Fellow, 1970–1971; NIH Special Postdoctoral Fellow, Summer, 1971. (b) Abstracted in part from the Ph.D. Dissertation of H. T. Bickley, Louisiana State University, 1971.

(3) (a) If the product of the reactivity and concentration of the sulfur compound is such that assisted heterolysis, eq 1, is slow, then the normal homolysis of BPO occurs in competition with the catalyzed ionic reaction. (b) W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, pp 118–126, 180–186, 290; (c) p 119; (d) pp 223–227; (e) p 244.

TABLE I

RATE CONSTANTS FOR THE REACTION OF BPO WITH SULFIDES AND DISULFIDES IN $CCl_4$[a]

| Sulfide or disulfide | $10^2$[BPO]$_0$ | $10^2$[RSR]$_0$ or $10^2$[RSSR]$_0$ | Temp, °C | $10^4k$, $sec^{-1}$ [b] | $10^4k'$, $M^{-1}$ $sec^{-1}$ [c] |
|---|---|---|---|---|---|
| None | 4.0 | | 41 | 0.002 | |
| Methyl sulfide | 4.0 | 48.6 | 41 | 46.5 | 100.0 |
| Propyl sulfide | 4.0 | 31.7 | 41 | 26.8 | 91.0 |
| Isobutyl sulfide | 4.0 | 4.80 | 41 | | 68.0[e] |
| Isobutyl sulfide | 4.0 | 9.84 | 41 | | 55.0[e] |
| Isobutyl sulfide | 4.0 | 19.1 | 41 | | 61.0[e] |
| Isobutyl sulfide | 4.0 | 31.9 | 41 | | 57.0[e] |
| Isobutyl sulfide | 4.0 | 37.3 | 41 | 25.0 | 67.0 |
| *sec*-Butyl sulfide | 4.0 | 31.8 | 41 | 3.8 | 12.6 |
| *tert*-Butyl sulfide | 4.0 | 32.5 | 41 | 1.19 | 3.90 |
| *tert*-Butyl disulfide | 1.1 | Neat | 41 | 3.9 | 0.72 |
| None | 5.0 | | 60 | 0.02 | |
| *tert*-Butyl sulfide | 4.1 | 64.2 | 60 | 15.0 | 23.0 |
| Methyl disulfide | 4.1 | 63.7 | 60 | 3.64 | 5.7 |
| Ethyl disulfide | 4.1 | 64.3 | 60 | 2.40 | 3.7 |
| *tert*-Butyl disulfide | 4.1 | 64.2 | 60 | 2.37 | 3.7 |
| Isobutyl disulfide | 4.1 | 63.8 | 60 | 2.24 | 3.5 |
| Propyl disulfide | 4.1 | 63.8 | 60 | 2.24 | 3.5 |
| Isopropyl disulfide | 4.1 | 64.1 | 60 | 1.03 | 1.7 |
| *sec*-Butyl disulfide | 4.1 | 64.1 | 60 | 0.90 | 1.4 |
| None | 0.8 | | 100 | 3.2 | |
| *tert*-Butyl sulfide | 1.2 | 17.7 | 100 | 61.0 | 360.0 |
| Phenyl sulfide | 1.1 | 84.2 | 100 | 25.8 | 31.0 |
| Methyl disulfide | 1.7 | 17.0 | 100 | 16.3 | 101.0 |
| Propyl disulfide | 1.2 | 17.9 | 100 | 15.1 | 87.0 |
| *tert*-Amyl disulfide | 1.1 | 17.8 | 100 | 12.2 | 71.0 |
| *tert*-Butyl disulfide | 1.1 | 5.06 | 100 | | 120.0[f] |
| *tert*-Butyl disulfide | 0.77 | 8.86 | 100 | 7.3 | 83.0 |
| *tert*-Butyl disulfide | 1.0 | 18.0 | 100 | 12.8 | 71.0 |
| *tert*-Butyl disulfide[d] | 1.1 | 18.6 | 100 | 12.1 | 65.0 |
| *tert*-Butyl disulfide | 8.90 | 17.5 | 100 | | 92.0[e] |
| *tert*-Butyl disulfide | 16.2 | 17.6 | 100 | | 50.0[f] |
| *tert*-Butyl disulfide[e] | 1.1 | 18.6 | 100 | 13.3 | 72.0 |

[a] The initial concentration of reactants is indicated by the subscript zero. [b] First-order rate constant $k$ for the disappearance of BPO; calculated by computer from raw data assuming that the sulfur compound's concentration does not change. [c] The second-order rate constant $k'$ in eq 4a; calculated by dividing the first-order rate constant $k$ by the average concentration of sulfide or disulfide for runs where the sulfur compound is present in eightfold excess or more. In the cases in which a value of $k$ is not given, $k'$ was determined directly using the integrated form of the second-order rate law, eq 4a. [d] Degassed. [e] 0.2 $M$ styrene added. [f] Calculated using eq 4b; see text.

analogous to **2** have been suggested in the reaction of amines with BPO[4] and in the decomposition of mercaptide-substituted peroxy esters.[5] Covalent compounds which have structures analogous to **3** have recently been isolated by Martin[6a,b] and by Kapovits and Kalman,[6c] and Martin has reviewed the support for such a formulation.[6a] Moffatt has postulated a related tetravalent sulfur compound as an intermediate in sulfoxide–carbodiimide reactions.[6d]

We have studied the reaction of a number of sulfides and disulfides with BPO (Table I). The product mixtures from both types of compounds are similar, suggesting that these reactions involve a similar mechanism and proceed through intermediate **1** (R is alkyl for sulfides and thiyl for disulfides).

After our investigation was completed we discovered that Horner[4b] previously had observed that sulfides enhance the rate of decomposition of BPO. He also postulated the involvement of the nonbonded electrons on sulfur in a reaction which is first order in sulfide and first order in peroxide. However, it is not clear from his report whether the reaction goes by a radical or ionic mechanism.

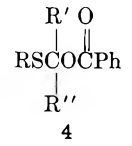
Horner observed the presence of sulfoxides, α-benzoyloxy substitution products (**4**),[7] benzoic anhydride, and benzoic acid as products from the reaction of BPO with sulfides,[4b] and he postulated that the reaction between BPO and sulfides involves the initial combination of two species followed by the decomposition of the intermediate complex by competitive radical and polar paths. Horner suggested that the most

(4) (a) C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 1957, pp 590–596; (b) L. Horner and E. Jurgens, *Justus Liebigs Ann. Chem.*, **602**, 135 (1957).

(5) (a) W. G. Bentrude and J. C. Martin, *J. Amer. Chem. Soc.*, **84**, 1561 (1962); (b) D. L. Tullen, W. G. Bentrude, and J. C. Martin, *ibid.*, **85**, 1938 (1963); (c) T. W. Koenig and J. C. Martin, *J. Org. Chem.*, **29**, 1520 (1964); (d) J. C. Martin and T. W. Koenig, *J. Amer. Chem. Soc.*, **86**, 1771 (1964).

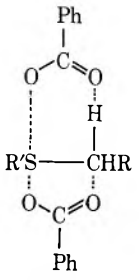
(6) (a) J. C. Martin and R. J. Arhart, *ibid.*, **93**, 2339 (1971); (b) J. C. Martin and R. J. Arhart, *ibid.*, **93**, 2341 (1971); (c) I. Kapovits and A. Kalman, *Chem. Commun.*, 649 (1971); (d) see, for example, J. C. Moffatt, *J. Org. Chem.*, **26**, 1909 (1971).

(7) (a) An α-substitution product also has been reported in a recent investigation of the reaction of BPO with $(RS)_2CH_2$; the products are benzoic acid and $PhCOOCH(SR)_2$: K. Gollmer and H. Ringsdorf, *Makromol. Chem.*, **121**, 227 (1969). (b) The α-substitution product is the only product in the reaction of sulfides with *tert*-butyl perbenzoate in the presence of copper salts as catalysts. The mechanism is probably the mixed ion–radical pathway of the Kharasch reaction. See G. Sosnovsky, *Tetrahedron*, **18**, 15 (1962), and for reviews, G. Sosnovsky, *Angew. Chem., Int. Ed. Engl.*, **3**, 269 (1964), and W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, pp 138–145. (c) L. Bateman and K. R. Hargrave, *Proc. Roy. Soc., Ser. A*, **224**, 389, 399 (1954); D. Barnard, *J. Chem. Soc.*, 489 (1956); K. R. Hargrave, *Proc. Roy. Soc., Ser. A*, **235**, 55 (1956). (d) The literature is reviewed by R. Hiatt in "Organic Peroxides," Vol. II, D. Swern, Ed., Wiley-Interscience, New York, N. Y., 1971, pp 73–78. (e) R. Curci, R. A. Di Prete, J. O. Edwards, and G. Modena, *J. Org. Chem.*, **35**, 740 (1970).



4

likely mechanism for the formation of the $\alpha$-substitution product involves the cyclic structure shown below.[4b]



5

This structure is similar to one proposed by Oae and Kise[8] to rationalize an $^{18}O$ exchange between a sulfoxide and acetic anhydride. They suggest that the exchange involves an equilibrium between a cyclic structure similar to **5** and one like **2** ↔ **3**.

Some years ago, Bateman and his coworkers discovered that hydroperoxides react with sulfides in a process that produces sulfoxide,[7c] and the groups of Modena and of Edwards have studied these reactions in detail.[7d,e] In the absence of oxygen, the reaction is ionic and involves nucleophilic attack by sulfur in a mechanism not unlike that proposed here, but the product mixture is simpler. One unexpected and interesting feature of the hydroperoxide reaction, which we will later see is shared by the reaction studied here, is that the rate is not markedly affected by solvent polarity.[7e] Another striking similarity of hydroperoxides and BPO is that both undergo an accelerated decomposition in amines, and, for both peroxidic materials, the amine-accelerated reaction appears to be complex and to involve both homolytic and heterolytic paths.[4,7d]

## Results

**Kinetic Studies.**—We have studied the kinetics of the reaction of BPO with sulfides and disulfides by monitoring the disappearance of BPO by infrared spectrometry. The reaction is first order in BPO and first order in the sulfur compound. All the sulfides are more reactive toward BPO than even the most reactive disulfide, probably because of the greater nucleophilicity of sulfides.[9] Data on the order of reactivities of a series of sulfides and disulfides are given in Table I. As R varies, the order of reactivity for the sulfides increases in the order phenyl < *tert*-butyl < *sec*-butyl < isobutyl < propyl < methyl. The disulfides follow a similar pattern but the rate constants are more compressed. This order suggests a steric effect which, as would be expected, is more pronounced in sulfides than in disulfides.[10] The lower nucleophilicity of aryl sulfides or disulfides relative to their alkyl analogs also is expected.[9]

**The Ionic Nature of the Reaction. Effects of Scavengers.**—We have eliminated the possibility that our results are due to a radical reaction of BPO which is accelerated by sulfur compounds by studying the effects of scavengers. If BPO is allowed to thermally decompose in $CCl_4$ in the presence of galvinoxyl, 89% of the radicals theoretically formed are scavenged. However, the addition of sulfur compounds diminishes the equivalents of galvinoxyl which are destroyed, indicating that an increasing fraction of the BPO decomposes by a nonradical process in the presence of increasing concentrations of disulfides. If a sufficient amount of sulfur compound is added, BPO reacts entirely by a nonradical process and no galvinoxyl is destroyed[3a] (see Table II).

TABLE II
THE REACTION OF BPO WITH DISULFIDES IN $CCl_4$ IN THE PRESENCE OF GALVINOXYL

| $10^3$ [BPO]$_0$ | $10^5$[G]$_0$[a] | Disulfide | [RSSR]$_0$ | Galvinoxyl decolorized, % | Temp, °C |
|---|---|---|---|---|---|
| 2.39 | 3.9[illegible] | Isobutyl | 0.281 | 0 | 60 |
| 8.79 | 3.60 | *tert*-Butyl | 3.05 | 0 | 80 |
| 0.046 | 3.59 | *tert*-Butyl | 0.170 | 19.2 | 80 |
| 0.015 | 4.16 | None | | 89.0 | 80 |

[a] Galvinoxyl.

The data of Table III show the effect of sulfur compounds on the rate of polymerization of styrene. As the concentrations of the sulfur compounds are increased, a larger fraction of the BPO decomposes by a nonradical mechanism and $R_P$ decreases. The rate constants for the assisted heterolysis of BPO, eq 1, are unaffected by the presence of styrene (Table I). Oxygen also does not affect these rate constants (Table I). (The last column in Table III will be discussed below.)

We also have used nonpolymerizable olefins to test for a radical component of the reaction. If BPO is allowed to decompose in $CCl_4$ in the presence of 2-methyl-1-butene, the olefin is consumed by the addition of $CCl_4$ to the double bond in a radical chain reaction. However, if the reaction is carried out in the presence of a sulfur compound, for example, *tert*-butyl disulfide (TSST), there is very little decrease in the olefin concentration, indicating that radicals are not formed (see Table IV).

It is known that if phenyl radicals from phenylazotriphenylmethane are generated in TSST–$CCl_4$ mixtures, 80% of the phenyl radicals can be accounted for as benzene, chlorobenzene, and *tert*-butyl phenyl sulfide.[11] However, the products of the decomposition of BPO in TSST–$CCl_4$ mixtures do not include these products; rather, the phenyl groups are accounted for as benzoic anhydride and benzoic acid, as is consistent with a nonradical mechanism. (It actually was this discrepancy that led to our study of the BPO system.)

**Assisted Homolysis.**—As the data of both Tables II and III show, in the presence of sufficiently low concentrations of sulfur compounds, and particularly those which are relatively inefficient at assisting heterolysis, a fraction of the BPO decomposes by a free-radical

(8) S. Oae and M. Kise, *Tetrahedron Lett.*, 2261 (1968).
(9) J. L. Kice, *Accounts Chem. Res.*, **1**, 58 (1968).
(10) G. Modena and L. Malioli, *Gazz. Chim. Ital.*, **87**, 1306 (1957).
(11) W. A. Pryor and K. Smith, *J. Amer. Chem. Soc.*, **92**, 273 (1970).

TABLE III

THE RATE OF POLYMERIZATION OF STYRENE INITIATED BY BPO AND OTHER INITIATORS AT 60° IN THE PRESENCE OF DISULFIDES

| Disulfide | [RSSR]$_0$ | Initiator | [Styrene]$_0$ | Time, hr | Polymer, mg | $10^5R_P$ ($M$ sec$^{-1}$)[d] obsd | $R_P/R_P$ Obsd[d] | $R_P/R_P$ Calcd[e] |
|---|---|---|---|---|---|---|---|---|
| None | | BPO[a] | 8.34 | 5.0 | 290, 306 | 4.23, 4.44 | | |
| *tert*-Butyl | 0.191 | BPO[a] | 8.14 | 5.0 | 129.0 | 1.91 | 0.4 | 0.5 |
| Isobutyl | 0.183 | BPO[a] | 8.05 | 5.0 | 94.0 | 1.83 | 0.4 | 0.4 |
| *tert*-Butyl | 0.596 | BPO[a] | 7.37 | 5.0 | 67.0 | 0.920 | 0.2 | 0.1 |
| *tert*-Butyl | 0.963 | BPO[a] | 6.75 | 5.0 | 47.0 | 0.581 | 0.1 | 0.03 |
| Methyl | 0.198 | BPO[a] | 8.13 | 5.0 | 54.0 | 0.817 | 0.2 | 0.4 |
| *tert*-Amyl | 0.234 | BPO[a] | 7.89 | 5.0 | 69.0 | 1.97 | | |
| None | | LPO[b] | 8.34 | 0.74 | 72.0 | 12.1 | | |
| *tert*-Butyl | 0.21 | LPO[b] | 7.99 | 0.74 | 115.0 | 11.6 | | |
| None | | AIBN[c] | 8.34 | 1.30 | 83.0 | 4.9 | | |
| *tert*-Butyl | 0.21 | AIBN[c] | 7.99 | 1.30 | 74.0 | 4.0 | | |

[a] Molarities are calculated at 60°. BPO is 0.01 $M$. [b] Lauroyl peroxide (LPO) is 0.011 $M$. [c] Azobisisobutyronitrile (AIBN) is 0.014 $M$. [d] $R_P$ is the rate of polymerization (in $M$/sec) for the control run in the absence of disulfide; $R_P'$ is that for the run containing sulfur compound. [e] Calculated using eq 3 and assuming that the sulfur compound diverts some BPO to decompose by an ionic reaction and does not accelerate the normal rate of homolysis of BPO. See text.

TABLE IV

EFFECT OF *tert*-BUTYL DISULFIDE ON THE DECOMPOSITION OF BPO IN THE PRESENCE OF 2-METHYL-1-BUTENE AT 60°[a]

| [TSST]$_0$ | Olefin concentration Initial | Olefin concentration Final |
|---|---|---|
| 0 | 0.458 | 0.0059 |
| 0.582 | 0.569 | 0.531 |

[a] BPO is 0.337 $M$.

mechanism.[3a] It is interesting, therefore, to inquire whether the rate at which this fraction undergoes homolysis is affected by the presence of the sulfur compounds. Such an effect would not be unexpected.[3b,4,5] A number of types of compounds which have nucleophilic character are able to interact with peroxides to accelerate homolysis.[3b] However, our studies using styrene demonstrate that the rate of homolysis of BPO is not affected by the presence of the sulfur compounds.

In the absence of sulfur compounds, the rate of the BPO-initiated polymerization of styrene is given by

$$R_P = \frac{[M]}{\delta}\{k_d f[\mathrm{BPO}]_0 e^{-k_d t}\}^{0.5} \qquad (2a)^{3d}$$

where $\delta = k_t^{0.5}/k_p$, $k_t$ and $k_p$ are the rate constants for termination and propagation in the polymerization of styrene, $k_d$ is the rate constant for unimolecular homolysis of BPO, $f$ is the efficiency of BPO at initiating polymerization, and $[M]$ is the molarity of styrene. In the presence of sulfur compound, the BPO undergoes a competing pseudo-unimolecular ionic decomposition, eq 1, and the rate of polymerization, $R_P$, is given by

$$R_P' = \frac{[M]}{\delta}\{k_d f[\mathrm{BPO}]_0 e^{-(k_d+k)t}\}^{0.5} \qquad (2b)$$

where $k$ is the first-order rate constant taken from Table I for the appropriate sulfur compound and concentration. Thus, the ratio $R_P'/R_P$, given in eq 3, depends only on $kt$. Table III compares values of this ratio calculated in this way with those observed, and the agreement is excellent. This agreement implies that all of the polymer produced in styrene–disulfide–BPO mixtures can be accounted for by the usual rate constant for unimolecular homolysis of BPO; no accelerated homolysis occurs.

$$R_P'/R_P = e^{-kt/2} \qquad (3)$$

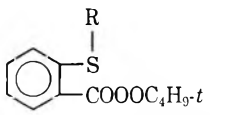
In this connection it is appropriate to make some remarks about the methods used to calculate rate constants. When only negligible amounts of homolysis occurs, $k'$ was calculated using eq 4a. (See the footnotes to Table I for details.) If an appreciable fraction of the BPO undergoes homolysis, eq 4a is not accurate and eq 4b was used. Values of $k_d$ were taken from runs in pure $CCl_4$ and the instantaneous concentration of the sulfur compound was expressed in terms of its initial concentration, the moles of BPO reacted, and the fraction of the reaction which was heterolytic. This gave satisfactory values of $k'$ even for runs in which the initial concentrations of the sulfur compound and the

$$-\mathrm{d[BPO]}/dt = k'[\mathrm{BPO}][\text{sulfur compound}] \qquad (4a)$$

$$-\mathrm{d[BPO]}/dt = k'[\mathrm{BPO}][\text{sulfur compound}] + k_d[\mathrm{BPO}] \qquad (4b)$$

BPO were equal and where a large fraction of the reaction was homolytic. For example, in a run at 100° with $[\mathrm{BPO}]_0 = 0.16$ $M$ and [*tert*-butyl disulfide]$_0$ = 0.17 $M$, $10^4k'$ is calculated to be 50 ± 20. This value can be compared with a value of about 78 ± 10 × $10^{-4}$ predicted from runs at higher concentrations of *tert*-butyl disulfide (Table I).

**The Effect of Sulfur Compounds on Other Peroxides and Initiators.**—The literature cited in the introduction suggests that eq 1 might be a general process. Furthermore, Martin, *et al.*, have found that the thiyl-substituted perester **6** gives a greatly accelerated homolysis relative to unsubstituted *tert*-butyl perbenzoate.[5] Quite surprisingly, they also find that the rate of de-



**6**, R = $C_6H_5$ or *t*-$C_4H_9$

composition of **6** increases on increasing the polarity of the solvent.[5b] Therefore, they have suggested that the transition state for the assisted homolysis of **6** includes the dipolar resonance structure **7**.[5]

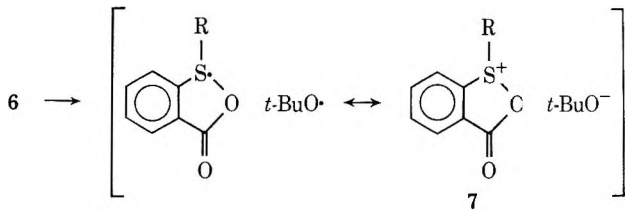
We have performed some preliminary experiments on other initiators to determine the generality of eq 1. Table V shows that sulfur compounds hardly affect the rate of decomposition of azo compounds, as would be expected.[3b] Interestingly, diacyl peroxides are much

TABLE V
THE EFFECT OF SULFUR COMPOUNDS ON THE RATE OF DECOMPOSITION OF SEVERAL OTHER INITIATORS

| Initiator[a] | $[I]_0 \times 10^2$ | Sulfur compd[b] | $[RSR]_0$ or $[RSSR]_0$ | Solvent | Temp, °C | $10^4k$, $sec^{-1}$ |
|---|---|---|---|---|---|---|
| TBP | 1.99 | None | | $CCl_4$ | 120 | 1.58 |
| TBP | 1.99 | None | | $CCl_4$ | 120 | 1.67 |
| TBP | 2.16 | TSST | 0.172 | $CCl_4$ | 120 | 1.44 |
| TBP | 2.56 | TSST | Neat[c] | | 120 | 1.38 |
| TBP | 2.02 | $Me_2S$ | 0.178 | $CCl_4$ | 120 | 29.3 |
| TBPOx | 1.59 | None | | $CCl_4$ | 39 | 0.79 |
| TBPOx | 1.72 | TSST | 0.204 | $CCl_4$ | 39 | 0.98 |
| TBPOx | 1.67 | TSST | Neat[c] | | 39 | 0.98 |
| PPO | 2.56 | None | | $CCl_4$ | 80 | 0.79 |
| PPO | 2.67 | *i*-$Bu_2S$ | 0.182 | $CCl_4$ | 80 | 5.8 |
| PPO | 2.57 | TSST | Neat[c] | | 80 | 3.4 |
| LPO | 1.26 | None | | $CCl_4$ | 80 | 1.23 |
| LPO | 1.28 | TSST | 0.178 | $CCl_4$ | 80 | 1.31 |
| LPO | 1.23 | TSST | Neat[c] | | 80 | 3.2 |
| NAT | 0.229 | None | | $CCl_4$ | 60 | 0.83 |
| NAT | 0.313 | TSST | Neat[c] | | 60 | 0.88 |

[a] The abbreviations are: TBP, *tert*-butyl perbenzoate; TBPOx, di-*tert*-butyl peroxylate; PPO, propionyl peroxide; LPO, lauroyl peroxide; NAT, *p*-nitrophenylazotriphenylmethane. [b] TSST is *tert*-butyl disulfide; $Me_2S$ is methyl sulfide; and *i*-$Bu_2S$ is isobutyl sulfide. [c] The sulfur compound is the solvent.

less accelerated than is BPO. For example, the decomposition of propionyl peroxide is increased in rate some tenfold by 0.2 *M* isobutyl sulfide, conditions under which the decomposition of BPO is increased over $10^3$.




(Compare Tables I and V.) Similarly, the decomposition of lauroyl peroxide is three times faster in neat *tert*-butyl disulfide than in $CCl_4$, whereas this change in solvent increases the rate of decomposition of BPO by $10^3$. The rate of decomposition of di-*tert*-butyl peroxylate is hardly affected by *tert*-butyl disulfide.

*tert*-Butyl perbenzoate (TBP) represents an intermediate case. As might be expected from Martin's work,[5] its rate of decomposition is substantially increased by sulfur compounds; however, it is much less sensitive than is BPO. For example, 0.2 *M* methyl sulfide in $CCl_4$ increases the rate of decomposition of TBP by 20-fold and BPO by $10^4$. (Compare Tables I and V.)

We did not perform the extensive scavenger and solvent variation studies with these initiators which would allow us to decide whether these increased rates are due to assisted heterolysis or homolysis. However, one piece of evidence indicates that the effect for TBP is due at least partially to an ionic process similar to that for BPO. A large-scale run at 120° with methyl sulfide and TBP modeled after the run shown in Table V gave a white precipitate which was collected and recrystallized, and the nmr was determined in $CCl_4$. Its spectrum was identical with that of the $\alpha$-substitution product 4 (R = $CH_3$, R′ = R″ = H) obtained from the methyl sulfide–BPO reaction (singlets at 2.22 and 5.32 ppm and aromatic absorption at about 7.8 ppm; relative intensity 3:2:5).

Thus, our results suggest that the enhanced homolysis found by Martin, *et al.*, for **6** represents a special case.[12] When the peroxide linkage and the sulfur atom are in separate molecules, as in TBP and methyl sulfide, the reaction appears to be ionic. Furthermore, it is much less accelerated than is the comparable reaction of BPO. Another interesting feature is that Martin, *et al.*, find that the *tert*-butyl perbenzoate **6** gives similar rate accelerations with R equal to either methyl or phenyl.[5] With BPO, phenyl sulfide is much less efficient at accelerating heterolysis than is methyl sulfide (Table I).

All of the data discussed above can be summarized by postulating that the intramolecular sulfur atom of **6**, for a reason not entirely clear, accelerates homolytic scission more than heterolytic, but that the opposite is true when external sulfur compounds interact with BPO or TBP.

**Effects of Solvent Polarity.**—The rate of disappearance of BPO in the BPO–TSST system was studied in a series of solvents with different values of Kosower's *Z* values.[13a] (See Table VI.) The reaction rate does increase with increasing solvent polarity but less so than would be expected for a typical ionic reaction.[13b] There are two possible explanations for this. One is that the transition state leading to **1** is not far along the reaction coordinate and little charge separation has

(12) One of the most striking features of the work reported here is the contrast between the BPO–sulfide reaction and the decomposition of *tert*-butyl *o*-phenylthiolperbenzoate (**6**) studied by Martin, *et al.*[5] Our reaction shows a smaller effect of solvent polarity than does Martin's, yet our reaction is ionic and his seems to be entirely radical. One possibility which could partially reconcile the two sets of data should be mentioned. We showed that our reaction was ionic by scavenger studies carried out in the least polar solvents we studied (such as $CCl_4$ and styrene), and, therefore, it is clear that our reaction remains ionic in more polar solvents. Martin, *et al.*, carried out most of their scavenger studies in chlorobenzene,[5a] and it is conceivable that a portion of the decomposition of their perester **6** occurs in more polar solvents such as methanol by an ionic mechanism. Professor Martin has informed us that the evidence for formation of radicals from **6** in methanol solution lay in the observation of zero-order galvinoxyl disappearance. Clearly, more research is necessary both on the decomposition of **6** in very polar solvents and on that of *tert*-butyl perbenzoate in sulfide solvents to unravel ionic and radical components of these reactions, and both we and Professor Martin intend to pursue these studies further.

(13) (a) For a discussion of $E_T$ see E. M. Kosower, "Introduction to Physical Organic Chemistry," Wiley, New York, N. Y., 1968, p 305. (b) W. A. Pryor, "Mechanisms of Sulfur Reactions," McGraw-Hill, New York, N. Y., 1962, pp 106–107, discusses the rate increases to be expected from increasing solvent polarity in ionic and radical reactions involving sulfur compounds.

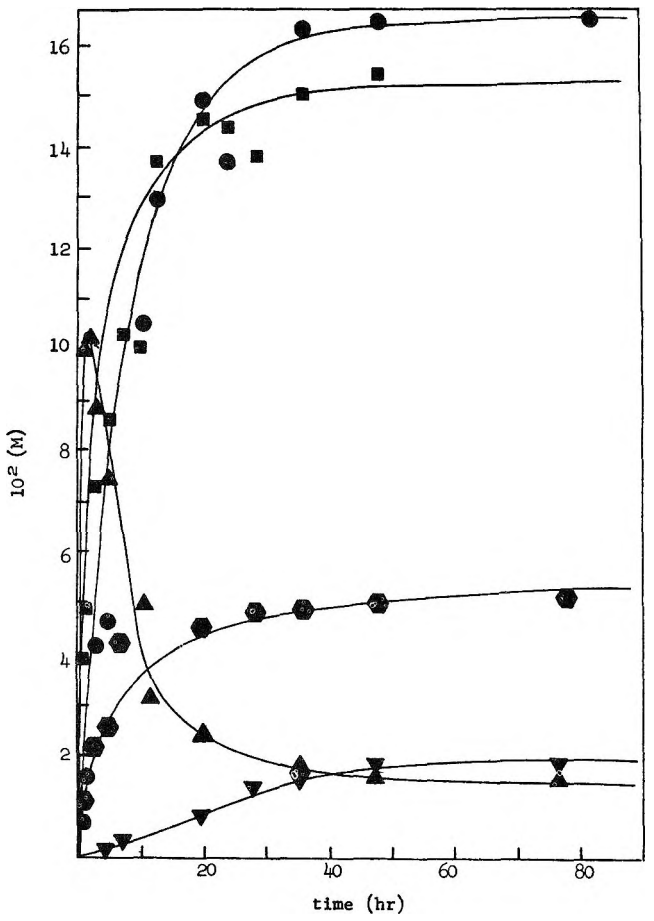



Figure 1.—A plot of the products of the reaction of 0.102 *M* BPO and 0.632 *M* *tert*-butyl sulfide (TST) in $CCl_4$ at 80° as a function of time. The products are coded as follows: benzoic acid ●, benzoic anhydride ▲, isobutylene ■, TSST ⬢, $TS_3T$ ▼.

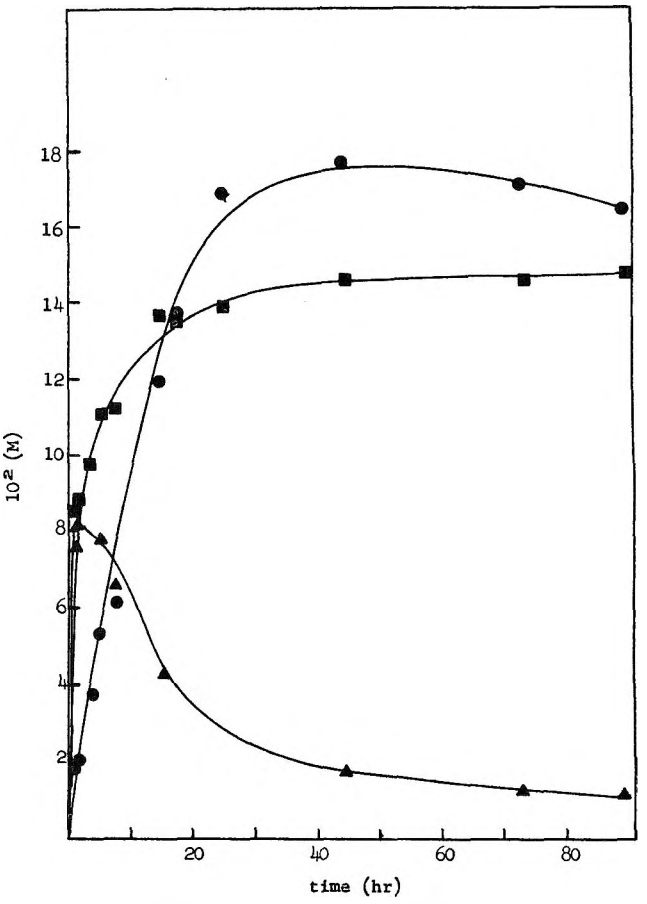



Figure 2.—A plot of the products of the reaction of BPO and TSST in $CCl_4$ at 80° as a function of time: $(BPO)_0$ = 0.102, $(TSST)_0$ = 0.632; benzoic acid ●, benzoic anhydride ▲, isobutylene ■.

TABLE VI

RATE OF REACTION OF BPO WITH *tert*-BUTYL DISULFIDE AS A FUNCTION OF SOLVENT POLARITY AT 80° [a]

| Solvent | $10^4k$, $sec^{-1}$ | $E_T$[b] |
|---|---|---|
| $CCl_4$ | 2.72 | 32.5 |
| $CHCl_3$ | 6.3 | 39.1 |
| PhH | 3.66 | 34.5 |
| PhCl | 4.00 | 37.5 |
| $CCl_4$[c] | 3.17 | 32.5 |
| $CCl_4$[d] | 3.42 | 32.5 |
| $(CH_2Cl)_2$ | 6.5 | 42.0 |
| $CH_2Cl_2$ | 7.4 | 41.1 |
| $CH_3OH$ | 27.7 | 55.0 |

[a] The initial concentration of BPO is 0.02 *M*; that of TSST is 0.2 *M*. [b] See ref 13a. [c] This sample contains 0.0072 *M* $Cl_3CCO_2H$. [d] This sample contains 0.0256 *M* $Cl_3CCO_2H$.

developed. In the second possibility, the transition state is similar to the intermediate **1**, but **1** is a resonance hydride of structures like **2** and **3** with an appreciable contribution from the covalent structure.[14]

The small effect which we find for eq 1 when the polarity of the solvent is increased is even more surprising when compared with the results of Martin, *et al.*,[5] for the decomposition of **6**. They find that the solvents cyclohexane, chlorobenzene, and methanol give rate constants for the decomposition of **6** which increase in the ratio 0.07:1:47. The rate increase they observed in going from chlorobenzene to methanol is about six times greater than we find (Table VI). It certainly is unexpected that the BPO–sulfide reaction, with a small solvent effect, is entirely ionic in mechanism, whereas the decomposition of **6**, with a large solvent effect, is entirely radical.[12] However, it should be stressed that *neither* eq 1 nor the decomposition of **6** is accelerated by more polar solvents to the degree that a completely ionic reaction would be.[13] Thus, the transition state both for eq 1 and for the decomposition of **6** has some dipolar character but does not involve unit charge separation.

**Products.**—Table VII shows typical data on the nature of the products from both BPO–sulfide and BPO–disulfide reactions, and Figures 1 and 2 plot product data for *tert*-butyl sulfide and disulfide, respectively. The products consist of benzoic acid and benzoic anhydride, olefin, polysulfides, and the α-substitution product **4** for those sulfur solvents that possess an α hydrogen. The material balance for the phenyl groups is quite good throughout the reaction (Table VII). Since the sulfur solvents were usually present in excess, material balances in sulfur are difficult to obtain. Polysulfide–sulfur (formally in the zero valance state) is produced. Both disulfide and trisulfide products were isolated from the reactions of *tert*-butyl sulfide (Figure 1), and mass spectral evidence for the presence

(14) The solvent studies (Table V) were done using *tert*-butyl disulfide, the least reactive sulfur solvent which was studied. It seemed possible that a larger solvent effect might have been observed if a more reactive sulfur solvent were used. However, preliminary results using isobutyl sulfide indicate that the rate enhancement due to changing the solvent from $CCl_4$ to methanol is about the same with this more reactive sulfide as that shown in Table VI for *tert*-butyl disulfide.

TABLE VII
REACTION PRODUCTS OF BPO WITH SULFIDES AND DISULFIDES IN $CCl_4$ AT 80°

| $[BPO]_0$, $M$ | Sulfide or disulfide | Initial [RSR] or [RSSR], $M$ | Time, hr | $10^2[PhCO_2H]$, $M$ | $10^2[(PhCO)_2O]$, $M$ | $10^2[R(-H)]$,[a] $M$ | $10^2$ [α-substituted product],[b] $M$ |
|---|---|---|---|---|---|---|---|
| 0.102 | *tert*-Butyl sulfide | 0.632 | 0.5 | 0.6 | 10.0 | 4.0 | |
| | | | 1.0 | 1.6 | 10.2 | 5.0 | |
| | | | 3.0 | 4.2 | 8.9 | 7.3 | |
| | | | 5.0 | 4.7 | 7.4 | 8.7 | |
| | | | 10.3 | 10.6 | 5.0 | 10.0 | |
| | | | 20.0 | 15.0 | 2.5 | 14.7 | |
| | | | 36.0 | 16.0 | 1.9 | 15.1 | |
| 0.104 | Methyl sulfide | 0.397 | 0.5 | 3.3 | 6.9 | | 3.9 |
| | | | 5.0 | 6.1 | 4.2 | | 5.9 |
| | | | 10.0 | 6.1 | 3.4 | | 6.0 |
| 0.0503 | *tert*-Butyl disulfide | 0.704 | 0.5 | 1.0 | 3.9 | 4.2 | |
| | | | 1.0 | 1.2 | 4.2 | 4.2 | |
| | | | 5.0 | 2.1 | 4.0 | 5.0 | |
| | | | 7.5 | 3.4 | 2.8 | 5.2 | |
| | | | 17.0 | 8.2 | 1.7 | 7.1 | |
| 0.0491 | *tert*-Amyl disulfide | 1.70 | 0.5 | 2.0 | 3.0 | 3.6 | |
| | | | 2.0 | 2.2 | 2.6 | 4.0 | |
| | | | 3.0 | 2.4 | 2.6 | 4.6 | |
| | | | 12.0 | 2.9 | 2.5 | 4.9 | |
| | | | 22.0 | 5.0 | 2.1 | 4.9 | |

[a] Olefin formed from R group on sulfide or disulfide. [b] This is 4 shown in text.

of tetra- and pentasulfides was obtained from reaction mixtures of the BPO–TSST system.

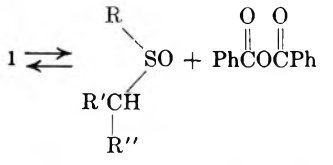
The order in which products are formed is revealing. Anhydride is produced early in the reaction and then disappears (Figures 1 and 2). Notice particularly that the olefin is formed earlier than is benzoic acid (Figures 1 and 2).

**Temperature Coefficients.**—The Arrhenius activation energies for the reaction of BPO with *tert*-butyl sulfide, *tert*-butyl disulfide, methyl disulfide, and propyl disulfide are 17, 18, 19, and 20 kcal/mol, respectively, calculated from the data in Table I. The Arrhenius $A$ factor is approximately $10^9\ M^{-1}\ sec^{-1}$ for all of these reactions, a rather typical value for a second-order ionic reaction.

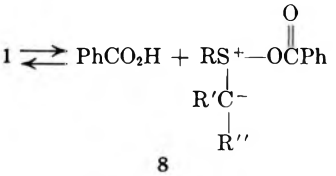
## Discussion

**Sulfides.**—Several modes of decomposition are available to **1**, and sulfides and disulfides give somewhat different product mixtures. We will discuss the reactions of sulfides first. (1) Intermediate **1** can revert to starting materials. (2) The benzoate anion can attack the carbonyl carbon of the cation fragment in **1** to produce benzoic anhydride and a sulfoxide (eq 5). (3) If the sulfide possesses a hydrogen $\alpha$ to sulfur, the benzoate anion can abstract a proton to form benzoic acid and an ylide (eq 6) which can subsequently rearrange to produce the $\alpha$-substitution product (eq 7).

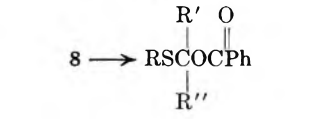
Johnson and Phillips[15] have studied the Pummerer rearrangement of sulfonium salts. Their results indicate the initial formation of an ylide in a rate- and product-determining step; the ylide then leads to product *via* a sulfur-stabilized carbonium ion. It is likely, therefore, that the reaction shown in eq 7 involves the formation of an ion pair and the subsequent



(5)

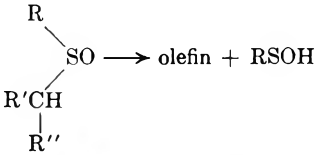


(6)

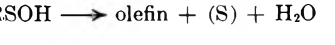


(7)

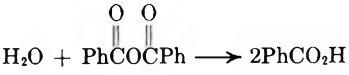
recombination of the ions to form the $\alpha$-substitution product. The subsequent reactions are shown in eq 8–11 and will be discussed below.



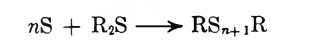
(8)



(9)



(10)



(11)

We believe that the sulfoxide produced in eq 5 is the precessor of the olefin produced in these reactions (eq 8). However, it is possible to rationalize the products of eq 8–10 by different mechanisms. For example, the benzoate ion in **1** could be postulated to abstract a $\beta$ hydrogen to yield olefin, benzoic acid, and RSOCOPh directly (eq 12).[16]

(15) (a) C. R. Johnson and W. G. Phillips, *J. Amer. Chem. Soc.*, **91**, 682 (1969); (b) K. F. O'Driscoll, "Organic Peroxides," Vol. I, D. Swern, Ed., Wiley, New York, N. Y., 1970, pp 630–632; (c) K. F. O'Driscoll, "Structure and Mechanism in Vinyl Polymerization," T. Tsura and K. F. O'Driscoll, Ed., Marcel Dekker, New York, N. Y., 1969, pp 87–89.

(16) This possibility was suggested by a referee.

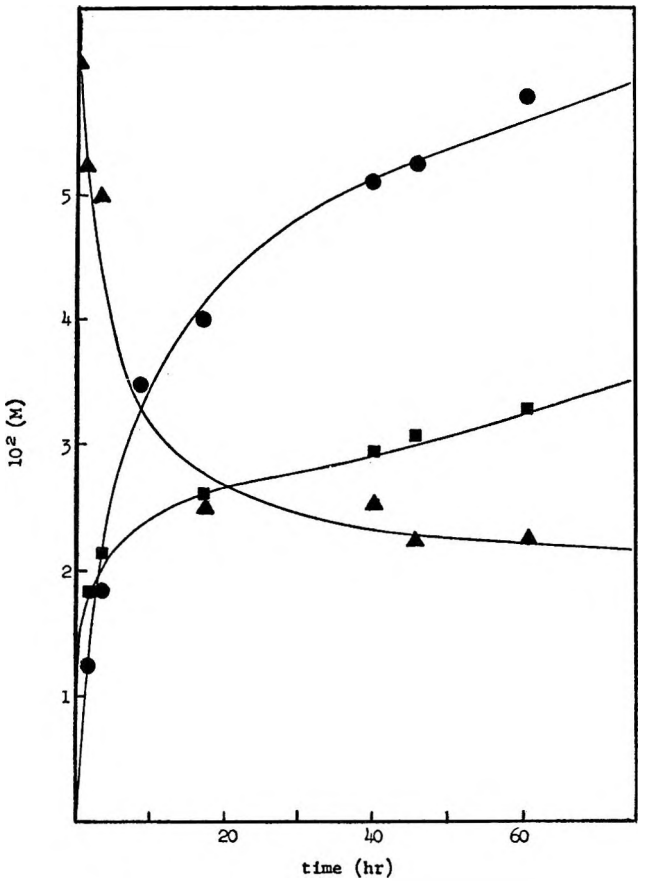
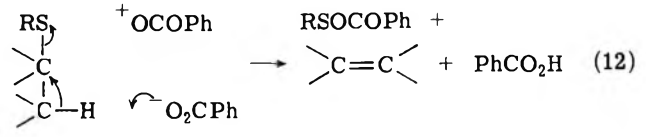



Figure 3.—A plot of the products of decomposition of *tert*-butyl sulfoxide in $CCl_4$ at 80° in the presence of benzoic anhydride: $(sulfoxide)_0 = 0.0661$, $(anhydride)_0 = 0.0614$; benzoic acid ●, benzoic anhydride ▲, isobutylene ■.

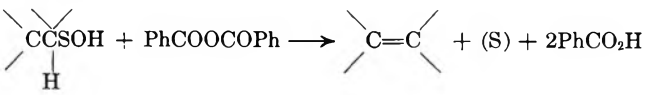



The RSOCOPh would then react with benzoic acid to yield sulfenic acid and anhydride.

$$RSOCOPh + PhCO_2H \longrightarrow RSOH + PhCOOCOPh \quad (13)$$

This mechanism is not consistent with our data. Firstly, Figures 1 and 2 show that olefin formation precedes benzoic acid, whereas they would be produced together in eq 12. Secondly, in an independent study, *tert*-butyl sulfoxide was found to decompose to form isobutylene and, presumably, *tert*-butylsulfenic acid, and the rate of isobutylene formation did not change when benzoic anhydride was present. Furthermore, the rates of olefin and benzoic acid formation are similar in the BPO–*tert*-butyl sulfide and the sulfoxide–benzoic anhydride system (compare Figures 1 and 3).

Another possibility would be to formulate eq 9 and 10 as synchronous.




We prefer to formulate eq 9 and 10 separately, since Block[17] has evidence that water is produced in the similar decomposition of thiolsulfinates, RS(O)SR. He has proposed a mechanism involving a Cope rearrangement and the production of thiolsulfinic acid (RSSOH) as an intermediate. Note that the BPO reaction with disulfides would give thiolsulfinates in eq 1 and RSSOH in eq 8 instead of the sulfoxide and RSOH produced from sulfides.

Sulfur atoms have been formulated as intermediates in eq 9 and 11, but it is probable that the polysulfide products are produced directly. A possible sequence could be

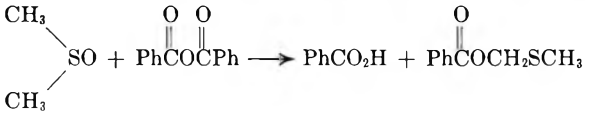
$$RSOH + H^+ \longrightarrow RSOH_2^+$$

$$RSOH_2^+ + R_2S \longrightarrow R_2\overset{+}{S}SR + H_2O$$

$$R_2\overset{+}{S}SR \longrightarrow RSSR + R^+$$

$$R^+ \longrightarrow \text{olefin} + H^+$$

There is evidence in the literature to support our postulation that the benzoate ion abstracts an $\alpha$ hydrogen from the dialkylbenzoxysulfonium cation in **1**. It is known, for example, that benzoic anhydride reacts with DMSO to produce benzoic acid and the $\alpha$-substitution product (the Pummerer reaction).[15a] A Hammett plot of the reaction of substituted anhydrides with DMSO indicates that the rate-determining step is the nucleophilic attack of the sulfoxide oxygen on the carbonyl carbon of the anhydride.[18] Oae and Kise[8] have studied the reaction of acetic anhydride with phenyl methyl-$d_3$ sulfoxides. They found a $\rho$ value of $-1.60$ and a $k_H/k_D$ value of 2.85 at 120°. Sorenson[19] has postulated an analogous mechanism in the reaction of a mixed carboxylic–carbamic anhydride with DMSO.




**Disulfides.**—Disulfides react with BPO to produce benzoic acid, benzoic anhydride, olefin, and polysulfides in analogy with the reactions of sulfides. (See Table II and Figures 1 and 2.) However, disulfides give thiolsulfinates in eq 5 rather than sulfoxides. Attempts were not made to isolate thiolsulfinates from BPO–disulfide reaction mixtures, but there is indirect evidence that they are produced. In the methyl disulfide reaction mixture, an nmr peak at 5.50 ppm was observed which could arise from the presence of methyl thiolsulfinate. *tert*-Butyl thiolsulfinate was synthesized and shown to decompose to form isobutylene and polysulfides under the reaction conditions of the BPO–disulfide experiments. Block[17] studied the decomposition of several thiolsulfinates; the products are polysulfides, water, and either sulfenic acids or olefins (depending on whether the thiolsulfinate does or does not have $\alpha$ hydrogens).

## Experimental Section

**Materials.**—Benzoyl peroxide was purchased from Matheson Coleman and Bell and was recrystallized several times from $CCl_4$–methyl alcohol. All sulfides and disulfides were purchased from either Eastman or Columbia and were distilled before use. Re-

(17) E. Block, personal communication. We have independently found polysulfides as a decomposition product of both thiolsulfinates and sulfoxides. Since the submission of this paper, two communications of Block's have been published: *J. Amer. Chem. Soc.*, **94**, 642, 644 (1972).

(18) S. Iwanami, S. Arita, and K. Takeshita, *Yuki Gosei Kagaku Shi*, **26**, 375 (1968).

(19) W. R. Sorenson, *J. Org. Chem.*, **24**, 978 (1959).

agent grade $CCl_4$ was purchased from Matheson Coleman and Bell and was distilled before use.

**Benzoyloxy Dimethyl Sulfide (BOMS).**—BOMS has been isolated and purified from the reaction of BPO and methyl sulfide by using preparative gc. A 6-ft SE-30 column was used with the column temperature 110° and the inlet and detector temperature 205°. The nmr showed sharp singlets at 2.2 (3) and 5.32 ppm (2) and two broad peaks in the aromatic region, one centered at 7.45 (3) and the other at 8.05 ppm (2). The ir showed peaks at 5.78 (s), 6.21 (sh), 6.29 (sh), 6.70 (sh), 6.88 (m), 7.00 (b), 7.49 (sh), 7.60 (sh), 7.92 (b), 8.45 (sh), 9.15 (b), 9.32 (sh), 9.72 (sh), 10.70 (b), 12.40 (w), 13.30 (b), 14.03 (b), 14.54 $\mu$ (w). The boiling point was 83–84° (0.2 mm). *Anal.* Calcd for $C_9H_{10}O_2S$: C, 59.32; H, 5.53. Found: C, 59.42; H, 5.75.

**Benzoic Anhydride.**—The isolation and identification of benzoic anhydride as an intermediate was achieved in the following manner. The reaction was monitored by ir and when the absorbance of the peaks at 1735 and 1790 $cm^{-1}$ reached a maximum the reaction was quenched. Solvent and excess TSST were stripped off under vacuum, leaving a very viscous oil. This oil was soluble in $CCl_4$, and upon the addition of methyl alcohol white needlelike crystals were obtained. The material was recrystallized and gave a sharp melting point at 42°. The ir and nmr spectra were identical with literature values for benzoic anhydride. *Anal.* Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.26 H, 4.58.

**Benzoic Acid.**—The isolation and identification of benzoic acid as the final product in the reaction of BPO and TSST was achieved in the following manner. The reaction was monitored by ir and when the peak at 1700 $cm^{-1}$ reached a maximum (accompanied by the disappearance of the peaks at 1735 and 1790 $cm^{-1}$) the reaction was quenched. The $CCl_4$ and excess sulfur compound were stripped off and the remaining material was twice recrystallized from $CCl_4$ and gave a sharp melting point at 121–122°. The ir and nmr spectra were identical with the literature values.

**Procedure for Kinetic Runs.**—The kinetic runs were carried out in sealed 1-cc glass ampoules in a constant-temperature bath. Reaction volumes were 0.6 cc and less than 1% of the $CCl_4$ solvent is in the vapor phase at 80°. Concentrations of reactants measured at room temperature differ negligibly from those present at 80°. Samples were removed at preselected times, thermally quenched, and stored in the refrigerator. After all samples had been removed, including infinity samples run to 10 half-lives, the concentration of the components of the reaction mixture was determined.

The disappearance of BPO was followed by ir on a Beckman IR-7 using the peak at 1770 $cm^{-1}$. Also the concentrations of benzoic anhydride and benzoic acid were monitored by ir using the peaks at 1735 and 1790 $cm^{-1}$ for the anhydride and 1700 $cm^{-1}$ for benzoic acid. All other products were determined by gc. The raw data were treated by a computer program to obtain a linear least squares fit of the data using the equation

$$\log (A - A_\infty) = -kt/2.303 + \log (A_0 - A_\infty)$$

where $A$ is the optical density. A typical kinetic run consists of 14 points and two infinity readings, since the infinity reading has a strong influence on the calculated rate constant. The kinetics were studied over about 70% of the reaction. The correlation coefficient is generally 0.99 or better with the probable error in the slope about 1%.

**Registry No.**—Benzoyl peroxide, 94-36-0; BOMS, 19207-88-6; benzoic anhydride, 93-97-0; benzoic acid, 65-85-0; methyl sulfide, 75-18-3; propyl sulfide, 111-47-7; isobutyl sulfide, 592-65-4; *sec*-butyl sulfide, 626-26-6; *tert*-butyl sulfide, 107-47-1; *tert*-butyl disulfide, 110-06-5; methyl disulfide, 624-92-0; ethyl disulfide, 110-81-6; isobutyl disulfide, 1518-72-5; propyl disulfide, 629-19-6; isopropyl disulfide, 4253-89-8; *sec*-butyl disulfide, 5943-30-6; phenyl sulfide, 139-66-2; *tert*-amyl disulfide, 34965-30-5; styrene, 100-42-5; lauroyl peroxide, 105-74-8; azobisisobutyronitrile, 78-67-1; *tert*-butyl perbenzoate, 614-45-9; di-*tert*-butyl peroxylate, 110-05-4; propionyl peroxide, 3248-28-0; *p*-nitrophenylazotriphenylmethane, 16186-97-3.

**Acknowledgment.**—We wish to acknowledge discussion of this manuscript with Professors Eric Block, Ennio Cuiffarin, Richard Hiatt, Carl Johnson, John Kice, and J. C. Martin. We also thank Dr. James P. Stanley for helpful suggestions and Mr. J. W. Allen, an undergraduate at LSU, for assistance. Dr. Pryor wishes to express thanks to Dr. W. F. Libby and the UCLA Department and to Professor Melvin Calvin and Dr. Richard Lemmon for hospitality during a sabbatical year spent at UCLA and UC—Berkeley, to the Guggenheim Foundation for a Fellowship, 1970–1971, and to NIH for a special Postdoctoral Fellowship, Summer, 1971.

# Notes

## The Synthesis and Configuration of *cis*-2,6-Dimethyl-1,4-cyclohexanedione, *r*-2,*c*-6-Dimethyl-*c*-4-hydroxycyclohexanone, and Two Related Diols[1]

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In conformational studies of 4-hydroxycyclohexanones,[2] a key compound needed for comparison was *r*-2,*c*-6-dimethyl-*c*-4-hydroxycyclohexanone[3] (**1**), mp 66°. We wish to report the preparation and configuration of this hydroxy ketone (**1**) and some related compounds shown in Scheme I.

Catalytic hydrogenation of 2,6-dimethylhydroquinone (**2**) with $Rh/Al_2O_3$ catalyst gave a mixture from which two diols were isolated: diol A, mp 139–140°, and diol B, mp 118–119°. The total hydrogenation product mixture contained *ca.* 60% of diol A and *ca.* 30% of diol B (gas chromatographic analysis). The assignment of configuration to diols A and B is based upon a comparison of their nmr spectra with those predicted for each of the four possible meso (**3**–**6**) and two possible *dl* (**7** and **8**) 2,6-dimethyl-1,4-cyclohexanediols (Chart I and Table I).

The very narrow CHOH proton nmr band widths, $W = 5 \pm 1$ Hz, observed for diols A and B are sufficient evidence to eliminate structures **5**–**8**; only the equatorial C-1 protons of diols **3** and **4** would be expected to exhibit such narrow band widths (Chart I and Table I). Structures **3** and **4** may be differentiated by comparison of their C-4 proton band widths. Thus, diol A, with a C-4 proton band width of 31 ± 1 Hz, must be assigned the all-cis diol structure **3** (C-4 proton axial). Diol B, with a C-4 proton band width of 11 ± 1 Hz, must be assigned diol structure **4** (C-4 proton equatorial). In addition to the C-1 and C-4 proton band width data, the number of methyl doublets observed adds further evidence tending to rule out structures **7** and **8** as possibilities (Table I).

The ir spectra of diols A and B, 0.004 *M* in carbon tetrachloride solution, are consistent with the assigned structures. Free hydroxyl OH stretching peaks were observed at 3643 and 3624 $cm^{-1}$ for diol A and at 3642 and 3631 $cm^{-1}$ for diol B. The higher frequency peaks (3642, 3643 $cm^{-1}$) may be attributed to the OH stretch-

SCHEME I

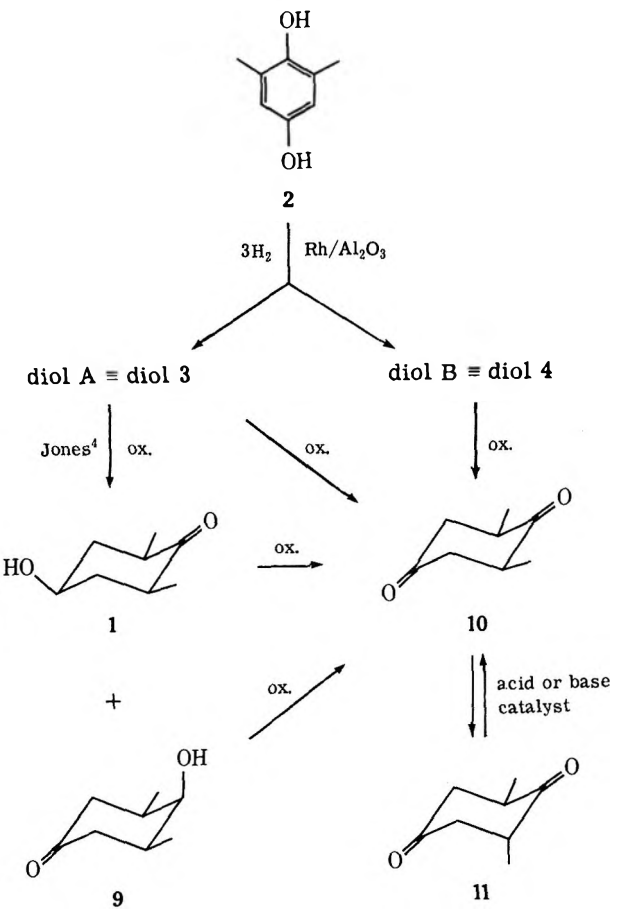
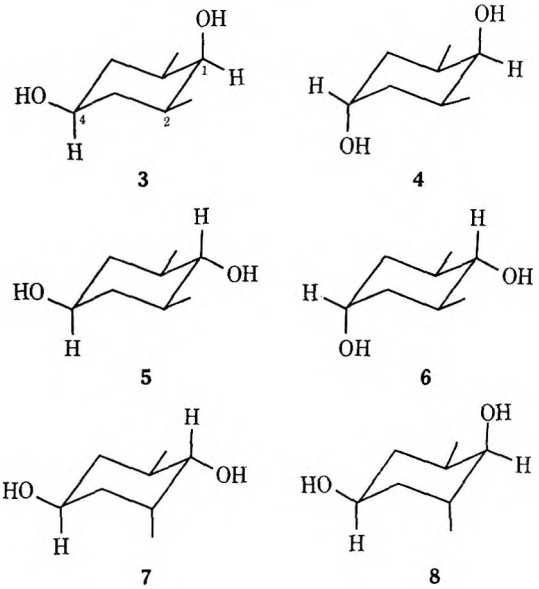



CHART I

THE 2,6-DIMETHYL-1,4-CYCLOHEXANEDIOLS




(1) Taken in part from the Doctoral Dissertation of T. W. Giants, Tufts University, June 1971. This work was supported in part by Public Health Service Research Grant GM-08813 from the National Institutes of Health and in part by the National Science Foundation.

(2) R. D. Stolow, T. Groom, and M. Gerace, *J. Amer. Chem. Soc.*, **90**, 3290 (1968); T. Groom, Ph.D. Dissertation, Tufts University, 1969.

(3) Stereochemistry nomenclature rule E-3.3, *J. Org. Chem.*, **35**, 2849 (1970).

(4) J. Meinwald, J. Crandall, and W. E. Hymans, *Org. Syn.*, **45**, 77 (1965); R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953).

TABLE I
COMPARISON OF THE OBSERVED NMR OF DIOLS A AND B WITH THE PREDICTED NMR OF DIOLS 3–8

| Diol[a] | Number of $CH_3$ doublets | C-1 proton band width,[b] Hz | C-4 proton band width,[c] Hz |
|---|---|---|---|
| A | 1 | 5 ± 1 | 31 ± 1 |
| B | 1 | 5 ± 1 | 11 ± 1 |
| **3** | 1 | 5 ± 1 | 30 ± 2 |
| **4** | 1 | 5 ± 1 | 12 ± 2 |
| **5** | 1 | 20 ± 2 | 30 ± 2 |
| **6** | 1 | 20 ± 2 | 12 ± 2 |
| **7** | 2 | 14 ± 2 | 30 ± 2 |
| **8** | 2 | 8 ± 2 | 26 ± 3 |

[a] The population of the conformer shown in Chart I is expected to be >99% for diols **3–6**, *ca.* 98% for diol **7**, and *ca.* 80% for diol **8**. [b] The sum of the two vicinal coupling constants involving the C-1 proton should equal the C-1 proton band width. The C-1 proton band widths predicted for diols **3–8** assumed $J_{1a,2a}$ = 10, $J_{1a,2e}$ = 4, $J_{1e,2a}$ = 2.5, and $J_{1e,2e}$ = 3.5 Hz.[d] [c] The sum of the four vicinal coupling constants involving the C-4 proton should equal the C-4 proton band width. The C-4 proton band widths predicted for diols **3–8** assume $J_{3a,4a}$ = 11, $J_{3e,4a}$ = 4, $J_{3a,4e}$ = 2.5, and $J_{3e,4e}$ = 3.5 Hz.[d] [d] These coupling constants are based in part upon values for analogous compounds determined by James L. Marini, Ph.D. Dissertation, Tufts University, 1969.[5,6]

ing vibration of a hindered axial C-1 hydroxyl group.[7] As found for 4-*tert*-butylcyclohexanol and related compounds,[8] one would expect the OH stretching frequency of the C-4 axial hydroxyl group to be greater than that of the C-4 equatorial hydroxyl group in diols A and B. Therefore, diol A (**3**) has an equatorial C-4 hydroxyl group (3624 $cm^{-1}$) while diol B (**4**) has an axial C-4 hydroxyl group (3631 $cm^{-1}$).

Chemical evidence also supports these assignments. Under the catalytic hydrogenation conditions used, the major product is expected to be the all-cis diol (**3**).[9] The result of the hydrogenation, formation of 60% of diol A, is consistent with the assignment of structure **3** to diol A. Furthermore, diols A and B yield the same dione upon Jones oxidation.[4] Therefore, diols A and B must have the same configuration at C-2 and C-6. Upon limited Jones oxidation,[4] diols A and B each give a different stereoisomeric 2,6-dimethyl-4-hydroxycyclohexanone. Therefore, diols A and B must differ in configuration at C-4 (as clearly shown by the C-4 proton band widths, Table I, and the ir frequencies given above). Taken together, the nmr, ir, and chemical results provide conclusive evidence supporting the assignment of structure **3** to diol A and structure **4** to diol B.

The Jones oxidation[4] of either diol **3** or **4** with excess reagent gave *cis*-2,6-dimethyl-1,4-cyclohexanedione (**10**). When the Jones oxidation of diol **3** was carried out with only enough reagent to convert half of the hydroxyl groups present to carbonyl groups, then in addition to the dione **10**, two hydroxy ketones (**1** and **9**) were also formed. The four-component mixture containing some unreacted diol **3**, dione **10**, and hydroxy ketones **1** and **9** was separated by preparative thin layer chromatography on silica gel. One component, mp 66–66.5°, isolated in 30% yield, was identified as hydroxy ketone **1**. A comparison of nmr spectra shows clearly that in the formation of hydroxy ketone **1**, the C-4 proton of diol **3** was retained while the C-1 proton was lost. The four-component mixture obtained by a similar limited Jones oxidation of diol **4** has not been separated successfully.

The equilibrium mixture of *cis* and *trans* diones (**10** ⇄ **11**), easily prepared by adding a trace of acid catalyst to a solution of cis dione **10**, had been obtained previously by hydrolysis of the lithium–ammonia–ethanol reduction product of the dimethyl ether of **2**.[10] The gas chromatographic peak height ratio for **10**:**11** in the equilibrium mixture was 57:43.[11]

## Experimental Section

Routine nmr spectra were recorded by use of a Varian A-60A spectrometer.[12] Nmr band widths were obtained by use of a Varian HA-100 spectrometer locked on internal tetramethylsilane.

Infrared spectra (OH bands) were recorded as previously reported,[13] by use of 0.004 *M* solutions of the diols in dried Spectr-analyzed carbon tetrachloride in 1.00-cm cells at *ca.* 25°. Routine infrared spectra were recorded by use of a Perkin-Elmer 237B spectrophotometer.[12]

Gas chromatography was carried out at 114° by use of an F and M 5750 flame ionization gas chromatograph with a 90 cm, 0.188 in. o.d. copper column packed with 4% Versamid 900 (General Mills) on 100–120 mesh Gas Chrom P. The column was conditioned before use by heating in an oven at 200° for 2 hr without gas flow and then at 180° for 24 hr with 15 ml/min dried nitrogen gas flow through the column.[11]

Melting points were determined in open Pyrex capillary tubes by use of an oil bath apparatus and are corrected. Microanalyses were performed by Dr. S. M. Nagy and by Spang Microanalytical Laboratory.

**Hydrogenation of 2,6-Dimethylhydroquinone** (**2**).—To a solution of 10.9 g (76.0 mmol) of 2,6-dimethylhydroquinone (**2**), mp 152.5–153°, dissolved in 80 ml of absolute ethanol (reagent quality) in a 500-ml Parr bottle were added 1 ml of acetic acid and 3.0 g of 5% rhodium on alumina catalyst (Engelhard Ind.). Hydrogenation at 30° and 3 atm initial pressure of hydrogen was complete in 29 hr. Removal of catalyst and solvent gave 11 g (100%) of a solid product mixture. Gas chromatographic analysis of the mixture showed the presence of 60% of diol **3**, 30% of diol **4**, and very small amounts of at least two other components (presumably isomeric diols).[14]

***cis,cis*-2,6-Dimethyl-*cis*-1,4-cyclohexanediol** (*c*-2,*c*-6-Dimethyl-*r*-1,*c*-4-cyclohexanediol[3]) (**3**).—Recrystallization of the above product mixture four times from benzene gave 5 g (45%) of white crystals, mp 137.5–139°. Gas chromatography gave a single peak. Further recrystallization gave diol **3**: mp 139–140°; ir (Nujol) 1377, 1118, 1030, 980, 937, and 860 $cm^{-1}$; nmr [$(CD_3)_2SO$ + 2% DCl in $D_2O$] δ 0.88 (d, $J$ = 5.5 Hz, 6, $CH_3$), 1.0–1.6 (m, 6, $CH_2$ and $CH_3CH$), 2.52 (quintet, $CD_3SOCD_2H$), 3.23 (unresolved m, 1, CHCHOH), 3.4 (m, 1, $CH_2CHOH$), and 3.8 (s, 2, OH). **3** is entered in Table I as diol A.

*Anal.* Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.59; H, 11.29.

***cis,cis*-2,6-Dimethyl-*trans*-1,4-cyclohexanediol** (*c*-2,*c*-6-Dimethyl-*r*-1-*t*-4-cyclohexanediol[3]) (**4**).—A sample (0.65 g) of the

(5) R. D. Stolow and J. L. Marini, *Tetrahedron Lett.*, 1449 (1971).

(6) H. Booth in "Progress in Nuclear Magnetic Resonance Spectroscopy," Vol. 5, J. W. Emsley, J. Feeney and L. H. Sutcliffe, Ed., Pergamon Press, Oxford, 1969, p 149.

(7) For a comparison of our result with values for other hindered alcohols, see R. E. Lyle and D. H. McMahon, *Tetrahedron Lett.*, 4885 (1967).

(8) H. S. Aaron, C. P. Ferguson, and C. P. Rader, *J. Amer. Chem. Soc.*, **89**, 1431 (1967), and references cited therein.

(9) P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals," Academic Press, New York, N. Y., 1967.

(10) M. M. Bonaventura, Ph.D. Dissertation, Tufts University, 1965; H.-J. Teuber, D. Cornelius, and U. Wölcke, *Justus Liebigs Ann. Chem.*, **696**, 116 (1966).

(11) A. E. Clements, M.S. Thesis, Tufts University, 1965.

(12) Nmr and infrared spectra of diols **3** and **4** have been reproduced in the Doctoral Dissertation of T. W. Giants, Tufts University, 1971.

(13) R. D. Stolow, P. M. McDonagh, and M. M. Bonaventura, *J. Amer. Chem. Soc.*, **86**, 2165 (1964).

(14) P. F. Wiley and O. Weaver, *J. Org. Chem.*, **25**, 1664 (1960), reported the catalytic hydrogenation of 2,6-dimethyl-*p*-benzoquinone with Raney nickel at 180°, conditions which gave considerable hydrogenolysis and only 14% of liquid diol product mixture.

residue obtained by evaporation of the benzene filtrates above was chromatographed on a column of neutral alumina (Fluka, type 507C, 47.5 g, shaken with 1.5 ml of water for 1 hr). After elutions with hexane and benzene, elution with anhydrous ether gave 0.4 g of solid. Recrystallization from benzene gave 0.25 g of white crystals, mp 118–119°, which showed a single peak upon gas chromatography: ir (Nujol) 1375, 1181, 1145, 1008, 963, 938, and 808 $cm^{-1}$; nmr [$(CD_3)_2SO$ + 2% DCl in $D_2O$] $\delta$ 0.85 (d, $J$ = 6.2 Hz, 6, $CH_3$), 1.2–2.2 (m, 6, $CH_2$ and $CH_3CH$), 2.57 (quintet, $CD_3SOCD_2H$), 3.37 (unresolved m, 1, CHCHOH), 3.88 (quintet, 1, $CH_2CHOH$), and 4.1 (s, 2, OH). **4** is entered in Table I as diol B.

*Anal.* Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found, C, 66.97; H, 11.11.

Continued elution with 19:1 ether–methanol gave a second fraction, 0.25 g, mp 139–141°, identified as diol **3**.

*r*-2,*c*-6-Dimethyl-*c*-4-hydroxycyclohexanone[3] (**1**).—To a solution of 0.40 g (3.4 mmol) of diol **3** in 15 ml of acetone (reagent grade, purified by distillation from $KMnO_4$), stirred vigorously in an ice–salt–water bath at −5°, was added dropwise 0.89 ml (1 equiv) of 2.5 *M* chromic acid solution[4] during 15 min. After stirring for an additional 15 min at −5°, a chilled solution of 1.3 g of $NaHSO_3$ in 40 ml of water was added and the mixture was extracted immediately with 6 × 100 ml of chilled ether. The ether layer was washed with 2 × 15 ml of cold 10% $NaHCO_3$ and then with 15 × 4 ml of cold water. The final washings were neutral. The ether layer was dried over anhydrous $MgSO_4$. Removal of solvent under reduced pressure gave a viscous oil which showed four peaks upon gas chromatography. One peak gave the same retention time as the starting material, diol **3**. The three expected products are hydroxy ketones **1** and **9** and dione **10**. Thin layer chromatography also showed four components.

The product was applied to three preparative thin layer chromatography plates, 20 × 20 cm, coated with a 2-mm layer of silica gel (E. Merck, $PF_{254}$). Double development with 1:1 anhydrous ether–benzene gave separation of the components. Each band was extracted with 10 × 20 ml of anhydrous ether. Filtration, removal of solvent under reduced pressure, and recrystallization from hexane gave from one band 0.12 g (30%) of fluffy white crystals, mp 66–66.5°, assigned structure **1**: nmr[2] ($CD_3OD$) $\delta$ 0.97 (d, $J$ = 5.5 Hz, 6, $CH_3$), 1–3 (m, 6, $CH_3CH$-$CH_2$), 4.2 (nonet, 1, CHOH, band width 30.2 ± 0.2 Hz), and 4.7 (s, 1, OH); nmr[2] (benzene) 4.0 (nonet, 1, CHOH, band width 29.5 ± 0.2 Hz).

*Anal.* Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.72; H, 10.16.

Similarly, a second band yielded an oily residue, which after recrystallization from hexane gave 0.08 g (20%) of white, fluffy crystals, mp 53–54°, not fully characterized, but probably *r*-3,*c*-5-dimethyl-*c*-4-hydroxycyclohexanone (**9**).[14]

*cis*-2,6-Dimethyl-1,4-cyclohexanedione (**10**). A. Jones Oxidation of Diol **3**.—To 2.50 g (0.0173 mol) of diol **3** in 88 ml of acetone (distilled from $KMnO_4$) at 0° was added dropwise with vigorous stirring 18.7 ml (100% excess) of 2.48 *M* chromium oxide solution[4] during 15 min. The temperature was maintained at 0–5° during the addition and for 15 min of further stirring following the addition. Then 3.62 g of $NaHSO_3$ in 88 ml of water at 0° was added. The resulting green solution was immediately extracted with 3 × 290 ml of ether. Each ether extract was washed successively with 110 ml of 10% $NH_4Cl$, 110 ml of 10% $NaHCO_3$, and 66 ml of water. The ether extracts were combined and dried over anhydrous sodium sulfate. The ether was removed under reduced pressure to give 2.2 g (90%) of a white solid, mp 85–87°. Two recrystallizations from hexane gave 1.3 g of cis dione **10**, mp 87.5–88°, containing *ca.* 1% of the trans epimer, detected by gas chromatography.[11]

*Anal.* Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.73; H, 8.64.

B. Jones Oxidation of Diol **4**.—As above, but on a smaller scale, 0.28 g (0.0019 mol) of diol **4** gave 0.24 g (89%) of white solid, mp 86–87.5°. Recrystallization from hexane gave 0.19 g of cis dione **10**, mp 87.5–88.5°. Reaction of **10** with excess 1,2-ethanedithiol and boron trifluoride–ether gave a product, mp 95–96° (from methanol).

**Registry No.**—**1**, 34958-40-2; **3**, 34958-41-3; **4**, 34958-42-4; **10**, 34958-43-5.

## Bicyclo[3.2.1]oct-6-en-2-one. A Convenient Synthesis of Bridged Polycyclic, Homoconjugated Ketones[1,2]

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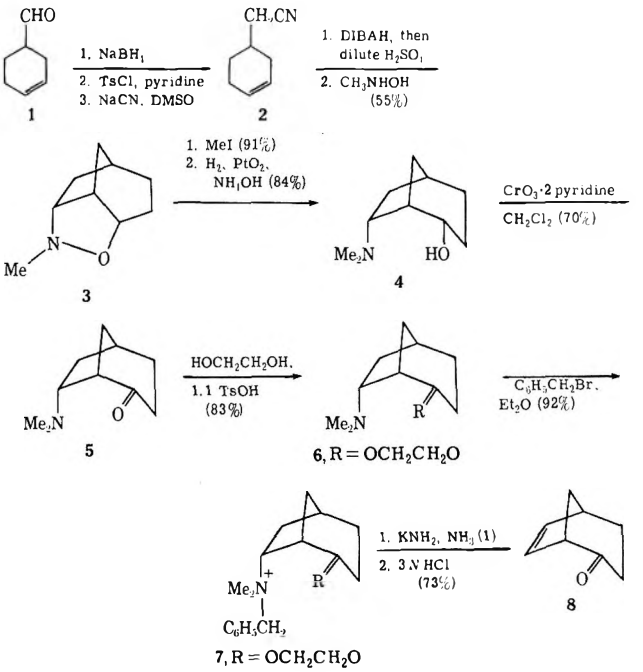
As part of a continuing program of exploration of the mechanistic nuances and the synthetic scope of intramolecular 1,3-dipolar cycloadditions of nitrones, we have prepared a variety of polycyclic isoxazolidines.[3] It is the purpose of this report to describe a simple and efficient degradation scheme which will allow conversion of certain of these products to homoconjugated ($\gamma,\delta$-unsaturated) ketones. These latter are of both theoretical and preparative import.

The key compound of the present example is the tricyclic isoxazolidine **3**, which was prepared by the reaction of 3-cyclohexen-1-acetaldehyde with *N*-methylhydroxylamine. The aldehyde was obtained by diisobutylaluminum hydride reduction of 3-cyclohexen-1-acetonitrile (**2**). Quaternization of **3** with methyl




iodide followed by hydrogenolysis gave the amino alcohol **4**, which was in turn oxidized to the *N*,*N*-dimethylamino ketone **5**.[4] The ethylene ketal **6** was then prepared, and it was benzylated to afford **7**.[5] Reaction with potassium amide in liquid ammonia and

(1) This work was supported by the National Science Foundation under Grant No. GP 14114.

(2) For the previous paper in this series, see N. A. LeBel and E. G. Banucci, *J. Org. Chem.*, **36**, 2440 (1971).

(3) N. A. LeBel, *Trans. N. Y. Acad. Sci.*, **27**, 858 (1965); N. A. LeBel, G. H. J. Slusarczuk, and L. A. Spurlock, *J. Amer. Chem. Soc.*, **84**, 4360 (1962).

(4) The Collins oxidation procedure, ref 9, has proven superior in our hands; however, Jones, Kiliani, and Sarett oxidations were successful in varying degrees.

(5) Benzylation proved superior to methylation because the subsequent elimination reaction generated improved yields of product **8**.

subsequent hydrolysis of the ketal gave bicyclo[3.2.1]-oct-6-en-2-one (**8**) directly. The overall yield of **8** from **2** was 16.3%, under conditions which involved the isolation of pure intermediates at each stage.[6]

The ketone **8** has not been described previously, and its homoconjugated nature is apparent from the ultraviolet spectrum [$\lambda_{max}$ 212 nm ($\epsilon$ 3600) and 299 (180) in isooctane] which clearly shows the enhanced n → $\pi^*$ transition relative to its saturated analog.

The synthetic scheme described in this report is applicable to large-scale work and is quite general.

### Experimental Section

**Methods.**—Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were measured with a Perkin-Elmer Model 237B grating infrared spectrophotometer. Nmr spectra were obtained with a Varian Associates Model T-60. Analyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind.

**3-Cyclohexenyl-1-acetonitrile (2).**—3-Cyclohexenyl-1-methanol was prepared in good yield by reduction of 3-cyclohexene-1-carboxaldehyde (**1**) with $NaBH_4$ in methanol, bp 65–67° (4 Torr), $n^{25}D$ 1.4817 [lit.[7] bp 79–83° (12 Torr), $n^{20}D$ 1.4852]. Reaction of the alcohol with *p*-toluenesulfonyl chloride in pyridine followed by the usual work-up gave a 97% yield of the crude tosylate. The tosylate (500 g, 1.99 mol) was added to a solution of NaCN (1.2 molar equiv) in 600 ml of freshly distilled DMSO at 80°. The addition required 15–20 min, during which time the temperature rose to about 95°. The oil bath was removed and stirring was continued for 3 hr at room temperature followed by the usual aqueous work-up; there was obtained after distillation 218 g (90%) of 3-cyclohexenyl-1-acetonitrile (**2**), bp 61–66° (2.5 Torr), $n^{24.2}D$ 1.4726.

*Anal.* Calcd for $C_8H_{11}N$: C, 79.34; H, 9.09; N, 11.57. Found: C, 79.55; H, 9.09; N, 11.80.

**3-Methyl-2-oxa-3-azatricyclo[4.2.2.0$^{4,9}$]decane (3).**—Diisobutylaluminum hydride (40 g, 0.28 mol) was slowly added to a mechanically stirred solution of 3-cyclohexenyl-1-acetonitrile (27.61 g, 0.23 mol) in 200 ml of hexane under a nitrogen atmosphere while the temperature was maintained at 10–20°. After addition was completed, the solution was stirred for 1 hr, and the excess hydride was destroyed by careful addition of cold 10% $H_2SO_4$. Dropwise addition of the dilute acid was continued, keeping the temperature below 30° until about 200 ml had been added. The white precipitate was removed by filtration and washed thoroughly with ether. The aqueous layer was separated and extracted with ether. The combined ether extract was washed with brine, dried ($MgSO_4$), and concentrated on a rotary evaporator to give 25.25 g of crude 3-cyclohexen-1-acetaldehyde.

Purification of the aldehyde can be effected by distillation; however, because of extensive formation of nonvolatile residues, this is not desirable or necessary. 3-Cyclohexen-1-acetaldehyde shows bp 46–52° (3.7 Torr), $n^{25}D$ 1.4702.

*Anal.* Calcd for $C_8H_{12}O$: C, 77.43; H, 9.67. Found: C, 77.14; H, 9.72.

The 2,4-dinitrophenylhydrazone melted at 120–121° (lit.[8] mp 125–126°). To a refluxing solution of the crude aldehyde in 500 ml of toluene was added dropwise a solution of methylhydroxylamine in 15 ml of methanol. The water produced was collected in a Barrett receiver and the first 20 ml of liquid was readded to the reaction mixture. Refluxing was continued for 16 hr. The cooled reaction mixture was extracted with 10% HCl (4 × 100 ml). The combined aqueous layers were extracted with ether, basified with 20% NaOH, and continuously extracted with ether for 24 hr. The organic layer was dried and concentrated to give a dark residue which was distilled to afford 19.3 g (55.4%) of **3**: bp 50–60° (0.3 Torr), 67–69° (1.25 Torr); $n^{27.5}D$ 1.4995; ir (neat) 2940, 1450, and 1438 cm$^{-1}$; nmr ($CCl_4$) $\delta$ 4.20 (d of t, 1 H), 3.65–3.27 (m, 1 H), 3.10–2.80 (m, 1 H), 2.47 (s, 3 H), and 2.25–1.00 (m, 9 H).

*Anal.* Calcd for $C_9H_{15}NO$: C, 70.58; H, 9.80; N, 9.15. Found: C, 70.40; H, 9.68; N, 9.28.

The methiodide of isoxazolidine **3** was obtained in 91–100% yield by stirring an ether solution of **3** with a threefold excess of methyl iodide. Crystallization from a mixture of ethanol and ether gave the pure salt, mp 151–152°.

*Anal.* Calcd for $C_{10}H_{18}NOI$: C, 40.68; H, 6.10; N, 4.75. Found: C, 40.61; H, 6.15; N, 4.70.

***endo,endo*-7-(*N,N*-Dimethylamino)bicyclo[3.2.1]octan-2-ol (4).**—The methiodide of **3** (9.43 g, 3.2 mmol) was hydrogenated over 0.9 g of prereduced $PtO_2$ in 100 ml of absolute ethanol containing four drops of concentrated $NH_4OH$ at 2 atm for 16 hr. The catalyst was removed and the filtrate was concentrated. The residue was taken up in 10% NaOH and ether, and the aqueous layer was extracted thoroughly with ether. The combined ether extract afforded a viscous liquid, which was distilled to give 4.54 g (84%) of the amino alcohol **4**: bp 66–67° (0.5 Torr); $n^{24}D$ 1.4912; mp 171–173° (crystallized from a mixture of methanol and ether); ir (neat) 3425 cm$^{-1}$ (br); nmr ($CCl_4$) $\delta$ 3.33 (br, 2 H), 2.28 (s, 6 H), 2.6–1.0 (m, 11 H).

*Anal.* Calcd for $C_{10}H_{19}NO$: C, 71.01; H, 11.24; N, 8.28. Found: C, 70.92; H, 11.48; N, 8.27.

***endo*-7-(*N,N*-Dimethylamino)bicyclo[3.2.1]octan-2-one (5).**—To a mixture of pyridine (12.0 g, 0.15 mol) and 75 ml of $CH_2Cl_2$ was added dry $CrO_3$ (7.62 g, 76.2 mmol) in several portions.[9] The mixture was stirred for 15 min, and the amino alcohol **4** (2.15 g, 12.7 mmol) was added in one batch. After 30 min of stirring, the solvent was removed on a rotary evaporator. The residue was taken up in ether and 5% NaOH, and the aqueous layer was continuously extracted with ether for 24 hr. The extract was concentrated to give an oil which was distilled. There was obtained 1.48 g (70%) of amino ketone **5**: bp 67–69° (0.5 Torr); ir (neat) 1710 cm$^{-1}$; nmr ($CCl_4$) $\delta$ 2.10 (s, 6 H), 2.8–1.0 (m, 11 H).

*Anal.* Calcd for $C_{10}H_{17}NO$: C, 71.86; H, 10.18; N, 8.38. Found: C, 71.57; H, 10.35; N, 8.49.

***endo*-7-(*N,N*-Dimethylamino)2-ethylenedioxybicyclo[3.2.1]-octane (6).**—The amino ketone **5** (4.69 g, 28.1 mmol) was refluxed in 100 ml of benzene with 4 ml of ethylene glycol and 1.1 equiv of *p*-toluenesulfonic acid. The cooled solution was basified and continuously extracted with ether for 24 hr. The extract, after concentration and distillation, afforded 4.94 g (83%) of the amino ketal **6**, bp 60–65° (0.5 Torr).

The benzylammonium bromide salt of **6** was prepared by stirring a solution of the amino ketal **6** with benzyl bromide in a mixture of ether and acetone for 3 days. The solid was washed well with ether and recrystallized from a mixture of absolute ethanol and ether to give 92% of **7**, mp 222–224° dec.

*Anal.* Calcd for $C_{19}H_{28}NO_2Br$: C, 59.69; H, 7.38; N, 3.66. Found: C, 59.60; H, 7.40; N, 3.51.

**Bicyclo[3.2.1]oct-6-en-2-one (8).**—To a suspension of 4 equiv of $KNH_2$ in liquid ammonia was added the quaternary ammonium salt **7** (2.00 g, 5.11 mmol) in several portions, and the mixture was stirred for 3.5 hr. A small amount of $NH_4Cl$ was added to destroy excess amide. The ammonia was allowed to distil and was replaced by ether. Water was added, the layers were separated, and the aqueous layer was extracted with ether. The combined ether extract yielded a liquid which was stirred with a two-phase, ether–3 *N* HCl mixture for 16 hr. The layers were separated and the aqueous layer was extracted with ether. The combined organic layer contained 466 mg (73%) of the ketone **8**: mp 65–81° (after sublimation); mass spectrum *m/e* 122 ($M^+$); ir ($CCl_4$) 3065 (w), 2495, 2865, 1720, 1590 (w), 1220, 1085, 727, and 710 cm$^{-1}$; nmr ($CCl_4$) $\delta$ 6.15 (d of q, 2 H), 2.90 (sextet 2 H), 2.7–2.1 (m, 3 H), 2.05–1.55 (m, 3 H). The nmr spectrum of **8** may be contrasted with that of bicyclo[3.2.1]-oct-6-en-3-one,[10] which shows the vinyl protons as a rather narrow, unresolved multiplet at $\delta$ 6.20.

The 2,4-dinitrophenylhydrazone melted at 151–152° after recrystallization from ethanol.

*Anal.* Calcd for $C_{14}H_{14}N_4O_4$: C, 55.63; H, 4.67; N, 18.54. Found: C, 55.36; H, 4.61; N, 18.39.

The ketone **8** was hydrogenated to the known bicyclo[3.2.1]-octan-2-one and it was shown by glpc to be the major ketone from

(6) We have shown that it is quite feasible to introduce a resolution step in the sequence at the amino alcohol stage, allowing for the generation of optically active homoconjugated ketones similar to **8**: M. A. Sciaraffa, unpublished work.

(7) J. Edelson, C. G. Skinner, J. M. Ravel, and W. Shive, *Arch. Biochem. Biophys.*, **80**, 416 (1959).

(8) M. Schwarz, A. Besold, and E. R. Nelson, *J. Org. Chem.*, **30**, 2425 (1965).

(9) J. C. Collins W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968); R. Ratcliffe and R. Rocehorst, *J. Org. Chem.*, **35**, 4000 (1970).

(10) N. A. LeBel and R. N Liesmer, *J. Amer. Chem. Soc.*, **87**, 4301 (1965).

the deaminative ring expansion of 2-aminomethylbicyclo[2.2.1]-oct-5-en-2-ol.

**Registry No.**—**2**, 34956-61-1; **3**, 34956-62-2; **3** MeI, 34956-63-3; **4**, 34956-64-4; **5**, 34956-65-5; **6**, 34956-66-6; **7**, 34956-67-7; **8**, 34956-68-8; **8** 2,4-DNP, 34956-69-9; 3-cyclohexen-1-acetaldehyde, 24480-99-7.

## Reactions of Bicyclo[3.2.1]octan-8-ylidene and Bicyclo[3.2.1]oct-2-en-8-ylidene

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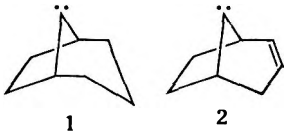
*Received October 29, 1971*

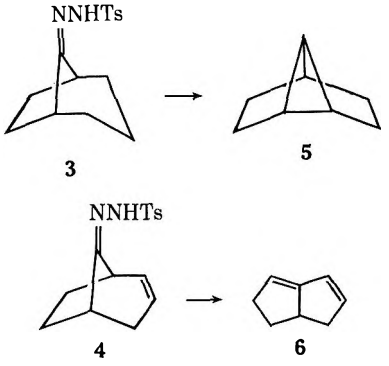
The "nonclassical" stabilization of singlet carbenes by olefinic bonds has been suggested by Hoffmann and Gleiter[1] for systems in which the molecule is constrained in such a way that addition to the double bond cannot occur. This has been termed a "foiled methylene" and is commonly referred to as a nonclassical carbene. Fisch and Pierce[2] and Moss, Dolling, and Whittle[3] have recently described such potential cases with the bicyclo[3.3.1]non-2-en-9-ylidene[2] and 7-norbornenylidene[3] systems. We would like to report work on some related carbenes, bicyclo[3.2.1]-octan-8-ylidene (**1**) and bicyclo[3.2.1]oct-2-en-8-ylidene (**2**), the latter providing an excellent example of the foiled methylene reaction.



**1** **2**

Carbenes **1** and **2** were generated by the sodium methoxide catalyzed decomposition of the corresponding tosylhydrazones **3** and **4** at 150° in dry diglyme. Hydrocarbon products were isolated in 80–90% yield by pentane extraction of the water-diluted reaction mixture and analyzed by capillary gas chromatography (gc). Decompositions were carried out using both 2 and 4 equiv of base with no significant effect on product composition.[4]

The two carbenes follow strikingly different reaction paths. **1** gave a product mixture containing three components in the relative amounts of 1.5, 98, and *ca.* 0.5% (in order of elution from the gc column). The major product was identified as tricyclo[3.3.0.0$^{2,8}$]-octane (**5**), the result of a 1,3-insertion reaction, by a comparison of its gc retention time and ir and nmr spectra with those of an authentic sample of the known hydrocarbon.[5,6] The unsaturated carbene **2** gave two products in the relative amounts of 3 and 97%. The major product is an unstable, colorless liquid and is assigned the structure of the 1,2-rearrangement product, bicyclo[3.3.0]octa-1,7-diene (**6**), on the basis of




**3** **5**

**4** **6**

its hydrogenation to bicyclo[3.3.0]octane and the following spectral data: nmr ($CCl_4$) $\delta$ 5.23 (m, 1 H, vinyl), 6.16 (AB, 2 H, $J$ = 7 Hz, five-membered ring vinyl[7]), 3.0 (m, broad, 1 H, bridgehead), 1.2–2.8 (6 H, envelope of peaks); uv (pentane) $\lambda_{max}$ 247 nm (heteroannular conjugated diene)[8]; ir ($CCl_4$) 3110 and 3050 (vinyl CH), 1648 (C=C), 720 cm$^{-1}$ (out of plane CH bend for cis alkene); mass spectrum (70 eV) M$^+$ 106. No attempt was made to identify the minor products of these reactions.

The contrasting behavior of carbenes **1** and **2**—insertion *vs.* rearrangement—is similar to but far more dramatic than that found for the related $C_7$ and $C_9$ carbenes.[2,9] Apparently the saturated carbene **1** has the carbenoid center well situated for insertion into the axial $C_2$–H bond. It shows a much greater propensity for insertion compared to rearrangement (98%) than the homologous carbenes, norbornan-7-ylidene (12%)[9] and bicyclo[3.3.1]nonan-9-ylidene (80%).[2]

The preference for rearrangement in the unsaturated carbene **2** can be explained in several ways. Since models indicate that the axial hydrogen in **2** is farther away from the carbenoid center than it is in **1**, it is possible that the insertion reaction is simply less favorable than rearrangement in this case. Alternatively, the difference in behavior can be rationalized very nicely in terms of a "foiled methylene." A stabilizing interaction of the carbenoid center with the double bond would further discourage the insertion reaction, because it tends to twist the axial hydrogen even farther away from the reacting center. Since addition to the double bond is also discouraged by the nature of the strained tetracyclic hydrocarbon **7**[10] which would result, the most favorable reaction of the nonclassical carbene becomes the 1,2 rearrangement to the diene **6**. Presumably, double-bond interaction in the stab-

(1) R. Gleiter and R. Hoffmann, *J. Amer. Chem. Soc.*, **90**, 5457 (1968).

(2) M. H. Fisch and H. D. Pierce, Jr., *Chem. Commun.*, 503 (1970).

(3) R. A. Moss, U.-H. Dolling, and J. R. Whittle, *Tetrahedron Lett.*, 931 (1971).

(4) Variation in the number of equivalents of base present has been observed to strongly affect product composition. See R. H. Shapiro, J. H. Duncan, and J. C. Clopton, *J. Amer. Chem. Soc.*, **89**, 1442 (1967).

(5) M. Schwarz, A. Besold, and E. R. Nelson, *J. Org. Chem.*, **30**, 2425 (1965).

(6) The decomposition of **3** serves as an excellent synthetic route to **5**.

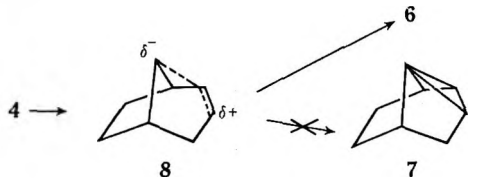
(7) (a) O. L. Chapman, *J. Amer. Chem. Soc.*, **85**, 2014 (1963); (b) G. V. Smith and H. Kriloff, *ibid.*, **85**, 2016 (1963); (c) P. Laszlo and P. v. R. Schleyer, *ibid.*, **85**, 2017 (1963).

(8) The $\lambda_{max}$ calculated for compound **6** using Woodward's rules is 234 nm. The discrepancy between the calculated value and the observed value (bathochromic shift) can be attributed to the strain of the double bond at the ring juncture. Consider, for example, $\Delta^{3,5}$-*B*-norcholestadiene: $\lambda_{max}^{calcd}$ 234 nm, $\lambda_{max}^{obsd}$ 245 nm. L. F. Fieser, *J. Amer. Chem. Soc.*, **75**, 4386 (1953). Bicyclo[3.2.0]hepta-1,6-diene: $\lambda_{max}^{calcd}$ 234 nm, $\lambda_{max}^{obsd}$ 255 nm.[3]

(9) R. A. Moss and J. R. Whittle, *Chem. Commun.*, 341 (1969).

(10) This hydrocarbon would contain a carbon atom having all four bonds on one side of a plane. For the synthesis and properties of such compounds, see, for example, K. B. Wiberg, *et al.*, *J. Amer. Chem. Soc.*, **93**, 246 (1971); **91**, 3372 (1969); *Tetrahedron Lett.*, 5855 (1968); 317 (1969). For theoretical discussions see M. D. Newton and J. M. Schulman, *J. Amer. Chem. Soc.*, **94**, 773 (1972), and W.-D. Stohrer and R. Hoffmann, *ibid.*, **94**, 779 (1972).

ilized carbene would be of the unsymmetrical homoallylic type indicated in **8**, as has been suggested for the




related carbonium ion.[11] Although the nonclassical carbene rationalization is an attractive one for explaining the chemistry of **2**, present results do not allow a decision between it and alternative mechanisms. We plan to pursue experiments which will help to distinguish between possible mechanisms.

### Experimental Section[12]

**Bicyclo[3.2.1]oct-2-en-8-one** was prepared by the method of Foote and Woodward,[13] except that dioxane was used in place of methanol for cleavage of the ethylene ketal. This gave the ketone with only a trace of the ketal (by gc), boiling at 74–75° (8 mm) [lit. bp 130° (25 mm),[13] 69–70° (5 mm)[11]].

**Bicyclo[3.2.1]octan-8-one** was prepared from the bicyclo[3.2.1]oct-2-en-8-one described above by hydrogenation over platinum oxide in methanol.[13] This produced a mixture containing 40% ketone and 60% of a higher boiling material presumed to be the corresponding dimethyl ketal. Treatment of the mixture under the cleavage conditions mentioned above gave the ketone in 73% yield after sublimation (90°, aspirator pressure) as a white, waxy solid melting at 141–144.8° (st, lit.[13] mp 140–141°).

**Bicyclo[3.2.1]octan-8-one Tosylhydrazone (3).**—Bicyclo[3.2.1]octan-8-one (1.24 g, 0.01 mol) in 5 ml of methanol was added all at once to a gently refluxing solution of 1.96 g (0.0105 mol) of *p*-toluenesulfonylhydrazine[14] in 10 ml of methanol. More methanol (5 ml) was added and the solution was allowed to reflux for 20 min. An equal volume of hot water was added and the tosylhydrazone was allowed to crystallize. Collection of the solid and recrystallization from methanol–water gave 2.64 g (90% yield) of white, crystalline **3** melting at 182.5–184° dec.

*Anal.* Calcd for $C_{15}H_{20}N_2O_2S$: C, 61.62; H, 6.90. Found: C, 61.48; H, 6.86.

**Bicyclo[3.2.1]oct-2-en-8-one Tosylhydrazone (4).**—Bicyclo[3.2.1]oct-2-en-8-one was converted to the crystalline tosylhydrazone in 98% yield by the same procedure as described above for **3**, mp 182.5–183.5° dec.

*Anal.* Calcd for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25. Found: C, 62.28; H, 6.13.

**Decomposition of Tosylhydrazone 3.**—**3** (294 mg, 1 mmol) and 112 mg (2 mmol) of sodium methoxide were slurried in 5 ml of dry diglyme in a single-necked flask fitted with a condenser, and the mixture was heated at 145–150° with magnetic stirring for 1 hr. Rapid evolution of nitrogen was over in about 10 min. The reaction mixture was allowed to cool, and then poured into 50 ml of water. The aqueous solution was extracted with five 10-ml portions of pentane and the combined pentane extracts were washed with eight 10-ml portions of water and dried ($MgSO_4$). The pentane solution was concentrated by distillation (glass helicies column) to about 1 ml and analyzed by gas chromatography on a 150 ft × 0.01 in. stainless steel capillary column coated with tris-β-cyanoethoxypropane (TCEP) and operated at 58° and 25 psi nitrogen pressure. The analysis showed peaks at 5.4, 6.4, and 9.2 min in the respective relative amounts of 1.5, 98, and *ca.* 0.5%. A duplicate experiment using 4 equiv of base gave the same product composition within experimental error. The major product has the same gc retention time and ir and nmr spectra as an authentic sample of tricyclo[3.3.0.$0^{2,8}$]-octane (**5**) prepared by the method of Schwarz, *et al.*[5]

(11) N. A. LeBel and L. A. Spurlock, *Tetrahedron*, **20**, 215 (1964).

(12) Melting points and boiling points are uncorrected. Nmr spectra were recorded on a Varian Associates A-60 spectrometer, using tetramethylsilane as an internal standard.

(13) C. S. Foote and R. B. Woodward, *Tetrahedron*, **20**, 687 (1964).

(14) L. Friedman, R. L. Little, and W. R. Reichle, *Org. Syn.*, **40**, 93 (1960).

In a larger scale experiment[15] 3.62 g (0.0124 mol) of **3** was decomposed in 25 ml of diglyme with 2.98 g (0.0552 mol) of sodium methoxide. The crude product (1.20 g, 90% yield) was distilled at 131–136° (647 mm) [lit.[5] bp 68–72° (45 mm)] to give 0.916 g of a colorless oil (69% overall yield). The tricyclooctane was 95% pure by gc analysis.

**Decomposition of Tosylhydrazone 4.**—Decomposition of **4** and analysis of the products were carried out as described above for **3**. With 2 equiv of base, gc analysis showed peaks at 6.3 and 9.1 min in the relative amounts of 2 and 98%, respectively. With 4 equiv of base 4% of the minor component was observed. The major product is a colorless liquid which appears to polymerize readily. Pure compound was isolated by preparative gas chromatography on a 6 ft × 0.25 in. column packed with 10% FFAP[16] on Chromosorb W, operating temperature 72°, helium flow 50 ml/min. Spectral data for the compound are listed in the text above and are consistent with bicyclo[3.3.0]octa-1,7-diene (**6**) as the structure.

Hydrogenation of the decomposition product over platinum oxide in pentane gave a colorless liquid which was shown to be identical with a sample of bicyclo[3.3.0]octane by a comparison of their gc retention times and nmr spectra. The nmr spectrum ($CCl_4$) consists of a broad singlet at δ 2.48 (2 H, bridge) and a highly symmetrical complex multiplet centered at δ 1.5 (12 H). The authentic sample of bicyclo[3.3.0]octane was prepared by the thermal decomposition of bicyclo[3.3.0]octan-2-one[17] semicarbazone, mp 183–184° dec (lit.[18] mp 180° dec), with potassium hydroxide as described by Cook and Linstead.[18] The hydrogenation product was also compared with a sample of bicyclo[4.2.0]octane prepared by hydrogenation over platinum oxide in pentane of the photolysis product of 1,3-cyclooctadiene.[19] The two had different gc retention times on the 150-ft capillary column at 58° and different nmr spectra. The nmr spectrum (neat) of bicyclo[4.2.0]octane consists of a broad singlet at δ 2.28 (2 H, bridge), a complex multiplet centered at δ 1.78 (4 H, $C_7$, $C_8$), and a singlet at δ 1.48 (8 H, $C_2$, $C_3$, $C_4$, $C_5$).

**Registry No.**—**1**, 34952-71-1; **2**, 34952-72-2; **3**, 34956-57-5; **4**, 34956-58-6; **5**, 2401-89-0; **6**, 34956-60-0.

**Acknowledgment.**—We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Graduate School of the University of Nevada, Reno, for support of this research.

(15) Data of Dean Evans, University of Nevada.

(16) FFAP is a modified Carbowax 20M stationary phase available from Varian Aerograph, Walnut Creek, Calif.

(17) A. C. Cope and W. R. Schmitz, *J. Amer. Chem. Soc.*, **72**, 3056 (1950).

(18) A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, 946 (1934).

(19) (a) R. S. H. Liu, *J. Amer. Chem. Soc.*, **89**, 112 (1967); (b) W. J. Nebe and G. J. Fonken, *ibid.*, **91**, 1249 (1969).

## The Dienone–Phenol Rearrangement. The So-Called Medium Effect[1]

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Among the acid-catalyzed rearrangements of dienones to phenols[3–6] are found examples in which the course of

(1) Supported by a grant from the Robert A. Welch Foundation.

(2) Postdoctoral Fellow, 1969–1971.

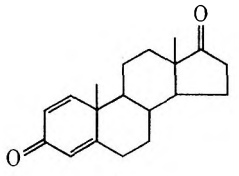
(3) N. L. Wendler in "Molecular Rearrangements," Part 2, P. de Mayo, Ed., Interscience, New York, N. Y., 1964, pp 1028–1034.

(4) A. J. Waring in "Alicyclic Chemistry," Vol. 1, H. Hart and G. J. Karabatsos, Ed., Academic Press, New York, N. Y., 1966, pp 207–215.

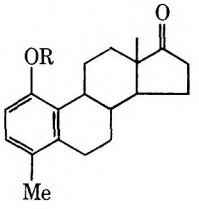
(5) H. J. Shine, "Aromatic Rearrangements," Elsevier, Amsterdam, 1967, pp 55–66.

(6) B. Miller in "Mechanisms of Molecular Migrations," Vol. 1, B. S. Thyagarajan, Ed., Interscience, New York, N. Y., 1968, pp 275–285.

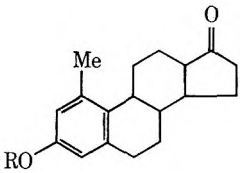
rearrangement is affected by the medium. The rearrangement of 1,4-androstadiene-3,17-dione (**1**) in acetic anhydride–zinc chloride at room temperature gave 1-acetoxy-4-methyl-3-deoxyestrone (**2a**) in 70–92% yield.[7] In contrast, **1** in 48% hydrobromic acid at room temperature gave 55% of 1-methylestrone (**3b**) and only



**1**

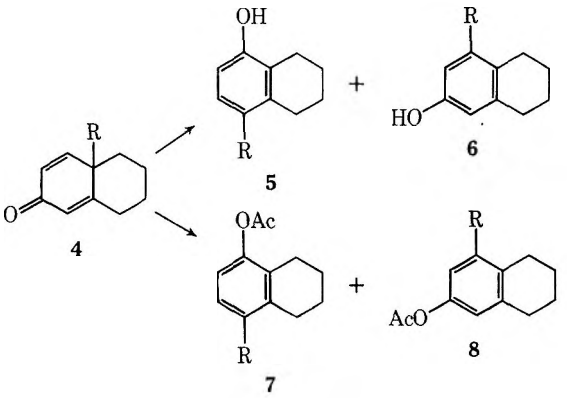


**2a**, R = Ac
**b**, R = H
**c**, R = $F_3CCO$



**3a**, R = Ac
**b**, R = H
**c**, R = $F_3CCO$

11% of 1-hydroxy-4-methyl-3-deoxyestrone (**2b**).[8] Similar results were obtained with **1** and concentrated hydrochloric acid at room temperature (48% of **3b**, 25% of **2b**), and by boiling **1** in a mixture of acetic and hydrochloric acids (35% of **3b**, 10% of **2b**). Furthermore, **1** in trifluoroacetic anhydride at room temperature gave 80% of **2c** and 10% of **3c** (determined after hydrolysis of the esters).[9] Simpler examples are known in the hexahydronaphthalenes. Rearrangement of 10-methyl-2-keto-$\Delta^{1,9:3,4}$-hexahydronaphthalene (**4a**) in concentrated hydrochloric acid at 100° gave 62% of 4-methyl-*ar*-2-tetralol (**6a**) and only 10% of 4-methyl-*ar*-1-tetralol (**5a**).[8] Rearrangement of **4a** in



**4** **5** **6** **7** **8**

**a**, R = Me; **b**, R = Et; **c**, R = Pr; **d**, R = Bu

acetic anhydride–sulfuric acid at room temperature gave 80% of **7a** and 20% of **8a**, while rearrangement in 30–50% aqueous mineral acid gave 80% of **6a** and 20% of **5a**.[10]

These results have given rise to the belief that the medium influences the direction of migration in dienone–phenol rearrangements.[4,5] The reasons behind this influence are not known, although it has been noted that steric and electronic effects are probably responsible.[8]

We have now found that the so-called solvent or medium effect appears to apply only to dienone **4a** and not the higher homologs **4b–d**. That is, the medium effect is not a general phenomenon, and, insofar as compounds **4** are concerned, the difference in types of rearrangement must be sought not in the nature of the medium but in the nature of the migrating groups. The first indication of this situation was provided in fact by Bell, who found that rearrangement of **4b** in acetic anhydride–sulfuric acid gave only **8b**, and not the anticipated **7b**.[11] We have carried out rearrangements of **4a–d** in acetic anhydride–sulfuric acid and in aqueous sulfuric acid. Results are given in Table I. The results with **4a** agree with those of Hopf and Dreiding,[10] while the result with **4b** in acetic anhydride–sulfuric acid confirms Bell's work in that **8b** predominates, although we have found the other isomer **7b** to be formed too.

TABLE I

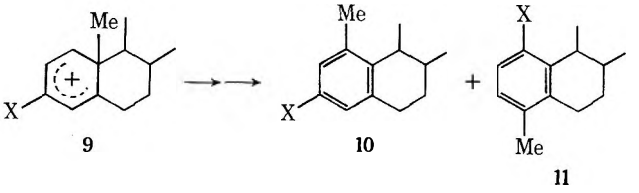
PRODUCTS[a] OF REARRANGEMENT OF **4a–d** IN ACETIC ANHYDRIDE–SULFURIC ACID AND IN AQUEOUS SULFURIC ACID

| | 20.6 *N* $H_2SO_4$[b] | | $Ac_2O$–$H_2SO_4$[c] | |
|---|---|---|---|---|
| Compd | **5**, % | **6**, % | **7**, % | **8**, % |
| **4a** | 14 | 86 | 84 | 16 |
| **4b** | 23 | 77 | 10 | 90 |
| **4c** | 2 | 98 | 7 | 93 |
| **4d** | 8 | 92 | 1 | 99 |

[a] Normalized to 100%. For total yields, see Experimental Section. [b] At 51.5°. [c] At room temperature.

The data in Table I show that **6** predominates in all of the tetralols and that **8** predominates in all of the acetates except the two in which R = Me. Obviously it is not only the medium which affects product distribution but also the nature of the angular group R.

Wolff and Dannenberg[12] have recently surveyed rearrangements to steroidal products which originate from the ion **9** (X = OH, OEt, Br, Cl, Me, *t*-Bu, $C_6H_5$, OAc, $O_2CCF_3$, H), and have concluded that the division in pathways to **10** and **11** is influenced by the resonance



**9** **10** **11**

effect of the substituent X in **9**. The value of $\Delta\sigma$ ($\sigma_p - \sigma_m$) is used as a measure of the effect for each substituent, and it is found that the **11**-type product is obtained when $\Delta\sigma$ is larger than −0.21. The $\Delta\sigma$ values quoted for OH (−0.49) and OAc (−0.08) illustrate Wolff and Dannenberg's relationship insofar as it would concern compounds which appear in our own work (**5a–8a**). The relationship is not valid, however, for rearrangements of our **4b–d** and it is evident that the resonance effect of substituent X in **9** can be only

(7) A. S. Dreiding and A. Voltman, *J. Amer. Chem. Soc.*, **76**, 537 (1954).
(8) A. S. Dreiding, W. J. Pummer, and A. J. Tomasewski, *ibid.*, **76**, 3159 (1953).
(9) E. Hecker and E. Meyer, *Chem. Ber.*, **97**, 1926 (1964).
(10) H. W. Hopf and A. S. Dreiding, *Angew. Chem., Int. Ed. Engl.*, **4**, 690 (1965).
(11) K. H. Bell, *Tetrahedron Lett.*, 397 (1967).
(12) T. Wolff and H. Dannenberg, *Tetrahedron*, **27**, 3417 (1971).

a small part of the several factors which control product formation.

It is evident from the results in Table I that the migratory aptitude of the angular alkyl group plays a dominant role. There still remain to be unravelled, however, those factors which control rearrangement of the angular methyl compound, **4a**.

The data in Table I were obtained from rearrangements at room temperature in acetic anhydride–sulfuric acid and at 51.5° in 20.6 *N* sulfuric acid. The effect of temperature on rearrangement of **4a** was measured. The ratio **7a**:**8a** was 85:15 at 100°. Rearrangement of **4a** in concentrated hydrochloric acid at 100° gave **5a** and **6a** in the ratio 15:85. These data show that temperature does not affect the trend in product formation. We assume that this will apply to rearrangements of **4b–d**, too.

### Experimental Section

**Materials.**—Commercially available 2-methylcyclohexanone (Aldrich Chemical Co.) and 2-propylcyclohexanone (K and K Laboratories) were used. 2-Ethyl- and 2-butylcyclohexanone were prepared by oxidation[13] of the corresponding cyclohexanol (K and K Laboratories). The four cyclohexanones were fractionally distilled before use in the annelation with 2-butyn-3-one (Farchan Research Laboratories). Annelation was carried out as described by Woodward and Singh,[14] and the products **4** were fractionally distilled, giving [yield, boiling point, ir ($cm^{-1}$) in $CHCl_3$] **4a**, 10.3%, 93–98° (2 mm), 1650, 1625; **4b**, 6.8%, 99–105° (1 mm), 1670, 1630; **4c**, 5.1%, 102–111° (1 mm), 1665, 1625; **4d**, 2.9%, 107–117° (1 mm), 1660, 1630.

**Rearrangements. A. In Acetic Anhydride.**—A solution of 500 mg of dienone **4** in 50 ml of acetic anhydride containing 3–4 drops of concentrated sulfuric acid was either allowed to stand 24 hr at room temperature or heated at 100° for 30 min. The solution was diluted with water and extracted with ether, and the ether was pumped off after drying over magnesium sulfate. Portions of the weighed residue were chromatographed quantitatively on a Varian Aerograph Model 700 gas chromatograph using a 10-ft (**4a**) or 20-ft (**4b–d**) 10% Carbowax 60/80 Chromosorb W column at 150°.

Total yields were: from **4a**, 72%; **4b**, 85–90%; **4c**, 79–83%; **4d**, 81–91%. Several runs were made in each case. Unrearranged dienone was obtained with **4b–d** and was separated quantitatively in the chromatograph.

**B. In Aqueous Sulfuric Acid.**—A solution of 500 mg of **4** in 5 ml of 20.6 *N* sulfuric acid was kept in a bath at 51.5° for 2 days. Quantitative work-up was as in A. Total yields were: from **4a**, 90%; **4b**, 83%; **4c**, 80–93%; **4d**, 75–89%. Small amounts of unrearranged **4c** and **4d** were obtained in some runs and were separated as in A.

**C. In Concentrated Hydrochloric Acid.**—A solution of 500 mg of **4a** in 5 ml of the acid was either kept at room temperature for 4 days or boiled for 30 min. Work-up and separation were as in A. Total yields were always close to 90%. Two runs at room temperature gave an average of **5a**:**6a** of 15:85. Five runs at reflux gave the same result.

**Product Identification.**—Products **5a**, mp 86–87°, **6a**, mp 103–105°, **7a**, mp 73–74°, and **8a** (liquid) were identified by comparison with data in the literature. Furthermore, **6a** was acetylated to form **8a**, while **7a** and **8a** were hydrolyzed to **5a** and **6a** by boiling in aqueous 20% KOH. Product **8b** (liquid) was identified by comparison with data in the literature.[11] Hydrolysis of **8b** gave **6b** (liquid) which was shown by pmr to be identical with **6b** obtained from rearrangement of **4b** in 20.6 *N* sulfuric acid. The identities of the two other products from **4b** were assumed to be as shown because they were the only other products obtained in the rearrangements (**5b** in 20.6 *N* sulfuric acid, and **7b** in acetic anhydride). Products **6c**, mp 66.5–68.5°, **6d** (liquid), **8c** (liquid), and **8d** (liquid) were identified by comparison of their pmr and infrared spectra with those of **6a**, **6b**, **8a**, and **8b**. The amounts of products **5c**, **5d**, **7c**, and **7d** were too small to allow identification. Identities were assumed since no other products than these and the major ones (**6**, **8**) were observed in the glc chromatograms.

**Pmr of products (aromatic region)** follows: **6a** (d, 6.4, 6.3), **6b** (d, 6.3, 6.2), **6c** (d, 6.4, 6.35), **6d** (d, 6.4, 6.35); $J$ = 3 cps in all cases; **8a** (s, 6.6), **8b** (s, 6.65), **8c** (s, 6.5), **8d** (s, 6.65); **5a** (q, 6.85, 6.40, 6.45, 6.35, $J$ = 8, 8, and 14 cps), **7a** (q, 7.05, 6.90, 6.75, 6.60, $J$ = 9 cps).

**Registry No.**—**4a**, 703-02-6; **4b**, 13984-73-1; **4c**, 34956-90-6; **4d**, 34956-91-7; **5a**, 4242-05-1; **6a**, 3718-79-4; **6b**, 34956-94-0; **6c**, 34956-95-1; **6d**, 34956-96-2; **7a**, 34956-97-3; **8a**, 34956-98-4; **8b**, 34956-99-5; **8c**, 34957-00-1; **8d**, 34957-01-2.

(13) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1956, p 337.

(14) R. B. Woodward and T. Singh, *J. Amer. Chem. Soc.*, **72**, 494 (1950).

## An Improved Synthesis of 5-Alkylresorcinols

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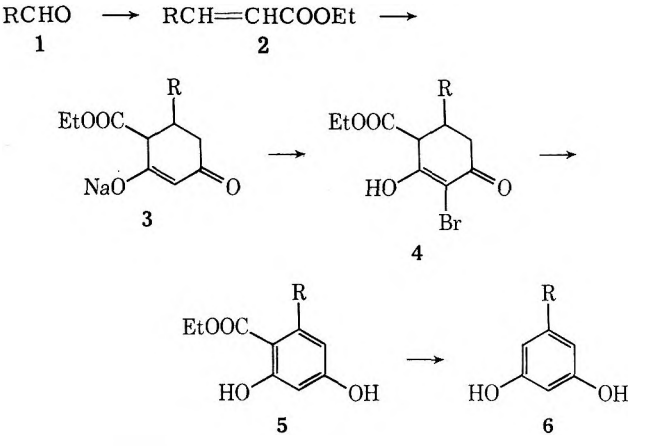
*Received January 4, 1972*

There are at present three general methods for preparing 5-alkylresorcinols;[1-3] however, they are tedious and expensive. I wish to report here an improvement of the last of these methods[3] which should be of convenience to workers requiring 5-alkylresorcinols in pharmaceutical research and, in particular, in the preparation of Cannabis (marijuana) analogs.

The synthetic scheme is outlined as follows.




The aldehyde **1** was converted in high yield to the β-alkylacrylate ester **2** on reaction with the sodium salt of triethyl phosphonoacetate[4] (see Table I). Michael addition of the sodium salt of ethyl acetoacetate to **2** gave **3**. The yield of **3** was dependent on

(1) C. M. Suter and A. W. Weston, *J. Amer. Chem. Soc.*, **61**, 232 (1939). Procedure involves reaction of Grignard reagent with 3,5-dimethoxybenzamide followed by reduction of the ketone product and demethylation. See also applications of their procedure by R. Adams, *et al.*, *ibid.*, **70**, 664 (1948); **71**, 1624 (1949).

(2) J. L. Dever, U. S. Patent 3,278,606 (Monsanto, 1966); *Chem. Abstr.*, **65**, 20062e (1966). Procedure involves conversion of 1,3,5-trichlorobenzene to 1,3-dimethoxy-5-chlorobenzene followed by formation of Grignard reagent, reaction with carbonyl compound, reduction, and demethylation.

(3) (a) R. M. Anker and A. H. Cook, *J. Chem. Soc.*, 311 (1945); (b) F. Korte and H. Sieper, *Justus Liebigs Ann. Chem.*, **630**, 71 (1960); (c) R. Valters and O. Neilands, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, **6**, 710 (1968); *Chem. Abstr.*, **70**, 77495t (1969).

(4) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

TABLE I

RCH=CHCOOEt

| Registry no. | R | Yield RCH=CHCOOEt based on RCHO, % | Bp, °C (mm) |
|---|---|---|---|
| 15790-86-0 | $(CH_3)_2CH$ | 86 | 79–81 (31)[a] |
| 34993-63-0 | $(CH_3)_2CHCH_2$ | 90 | 96 (34–30)[b] |
| 22147-62-2 | $(CH_3)_3C$ | 88 | 92–93 (34)[c] |
| | $CH_3(CH_2)_4$ | 87 | 57–62.5 (1.4)[d] |
| 34993-65-2 | $(CH_3)_3CCH_2$ | 92 | 61 (3.3)[e] |
| | $CH_3(CH_2)_5$ | 89 | 70–75 (0.90)[f] |
| | $CH_3(CH_2)_{10}$ | 82 | 106–110 (0.02)[g] |

[a] Lit.[4] bp 65° (15 mm); nmr for

$$(CH_3)_2CHCH{=}CHCOOCH_2CH_3$$
a b c d e f

δ 1.05 (d, 6, $J_{ab}$ = 7 Hz, a), 1.23 (t, 3, $J_{ef}$ = 7 Hz, f), 2.4 (m, 1, b), 4.07 (q, 2, e), 5.63 (d of d, 1, $J_{cd}$ = 16, $J_{bd}$ = 1.5 Hz, d), 6.80 (d of d, 1, $J_{bc}$ = 7 Hz, c). [b] Lit. bp 106–107° (5 mm) (Japanese patent); *Chem. Abstr.*, **54**, 6551*b* (1960) (literature boiling point seems unreasonably high); nmr for

$$(CH_3)_2CHCH_2CH{=}CHCOOCH_2CH_3$$
a b c d e f g

δ 0.92 (d, 6, $J_{ab}$ = 6 Hz, a), 1.24 (t, 3, $J_{fg}$ = 7 Hz, g), 1.5–2.2 (m, 3, b + c), 4.10 (q, 2, f), 5.69 (d of t, 1, $J_{de}$ = 16, $J_{ce}$ = 1 Hz, e), 6.84 (d of t, 1, $J_{cd}$ = 7 Hz, d). *Anal.* Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.33. Found: C, 69.03; H, 10.39. [c] Lit. bp 54° (12 mm): F. Bohlmann, H. L. Ahrens, and H. Kritzler, *Abh. Braunschweig. Wiss. Ges.*, **9**, 173 (1957); *Chem. Abstr.*, **52**, 10875*a* (1958); nmr for

$$(CH_3)_3CCH{=}CHCOOCH_2CH_3$$
a b c d e

δ 1.05 (s, 9, a), 1.24 (t, 3, $J_{de}$ = 7 Hz, e), 4.13 (quartet, 2, d), 5.63 (d of d, 1, $J_{bc}$ = 16 Hz, c), 6.87 (d of d, 1, b). [d] Lit. bp 70–72° (1.5 mm): M. Jacobson, *J. Amer. Chem. Soc.*, **75**, 2584 (1953). [e] Nmr for

$$(CH_3)_3CCH_2CH{=}CHCOOCH_2CH_3$$
a b c d e f

δ 0.95 (s, 9, a), 1.25 (t, 3, $J_{ef}$ = 7 Hz, f), 2.05 (d of d, 2, $J_{bc}$ = 8, $J_{bd}$ = 1 Hz, b), 4.13 (q, 2, e), 5.71 (d of t, 1, $J_{cd}$ = 16 Hz, d), 6.88 (d of t, 1, c). *Anal.* Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.30; H, 10.69. [f] Lit. bp 99.5–102° (5 mm): J. Cason, N. L. Allinger, G. Sumrell, and D. E. Williams, *J. Org. Chem.*, **16**, 1181 (1951). [g] Lit. bp 165–167° (11 mm): L. P. Kyrides, F. B. Zienty, G. W. Steahly, and H. L. Morrill, *J. Org. Chem.*, **12**, 577 (1947).

the steric hindrance presented by the β-alkyl group of **2** (see Table II). When R = *tert*-butyl, no product had formed after 20 hr, but after 4 weeks some precipitate had formed which did not give rise to 5-*tert*-butylresorcinol. When R = isopropyl, a low yield of the desired product **3** was obtained in 20 hr which gave pure **6** after subsequent steps. Extending the reaction time to 3 days gave more **3** but the **6** obtained from this material was impure (nmr). Yields of **3** were low in the cases R = neopentyl and R = carbethoxymethyl, but were quite good for R = isobutyl and for the linear series R = methyl, *n*-amyl, *n*-hexyl, and *n*-undecyl. The Michael condensation between ethyl tiglate and ethyl acetoacetate did not proceed under these reaction conditions.

Monobromination of **3** to give **4** was accomplished with cupric bromide in 1,2-dimethoxyethane (DME). The published procedures used bromine in acetic acid and obtained ethyl 2,4-dihydroxy-3,5-dibromo-6-alkylbenzoate in fair yields, but poor in the case R = *n*-amyl.[3] Overall yields of **6** from **3** were decreased (30–50% yield in the case R = *n*-amyl) when cupric chloride was substituted for cupric bromide in this step, or when DMF, methanol, or dichloromethane replaced DME as the solvent. In addition, it was necessary to avoid the premature thermal dehydrobromination of **3** during work-up. This decomposition was apparently inhibited by the presence of residual DME. Cuprous bromide was recovered quantitatively.

The unstable bromodione **4** was dehydrobrominated in refluxing DMF to give crude **5**, which presumably underwent partial hydrolysis and decarboxylation to give some **6**. Modest yields of pure **5** were obtained in the cases R = methyl, *n*-undecyl, and carbethoxymethyl where solubility differences made it possible to separate the mixture. A trace of **5**, R = *n*-hexyl, was also isolated. Conversion of crude **5** to **6** was accomplished with aqueous base as per the published procedure.[3] In the case R = carbethoxymethyl, a complex product mixture resulted from which no phenylacetic acid could be isolated. Distillation gave in all cases pure **6** as a pale yellow viscous oil, some of which crystallized (see Table II). Overall yields of **6** from **3** were 75–81%.

## Experimental Section

**General Comments.**—The aldehydes used were purchased from Eastman and Aldrich and were distilled before use with the exception of pivaldehyde and 3,3-dimethylbutyraldehyde, which were prepared by the method of Brown and Tsukamoto.[5] Ethanol was further dried by distillation from calcium ethoxide. 1,2-Dimethoxyethane was distilled from potassium. Cupric bromide was prepared in large scale from cupric oxide and a 5% excess of the calculated amount of concentrated hydrobromic acid, followed by sufficient bromine to remove the milkiness on dilution of a drop of the mixture with water. Concentration gave black cupric bromide which was dried *in vacuo* over potassium hydroxide flakes. Dimethylformamide (B & A) was used as received. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

**Triethyl Phosphonoacetate.**[6]—Ethyl chloroacetate (650 g, 5.3 mol, freshly distilled, bp 143.0–143.5°) and triethyl phosphite [880 g, 5.3 mol, freshly distilled, bp 69° (35 mm)] were thoroughly mixed and placed in a 3-l. flask equipped with an immersed thermometer and condenser, and under an atmosphere of nitrogen. The reaction mixture was heated and stirred and slowly brought to 125°, and then the external heat was discontinued for 30 min as the reaction proceeded. A vigorous but controlled evolution of ethyl chloride occurred. The temperature was then brought to 160° over a 75-min period and held there for 8 hr, after which time ethyl chloride evolution had stopped. The liquid was allowed to cool overnight, and then distilled through a 12-in. Vigreux column, giving, after a small forerun, product at 74–77° (0.03 mm), 1141 g (96%), as a colorless and practically odorless liquid [lit.[6] bp 109° (0.80 mm)].

**Conversion of Aldehyde 1 to Ethyl β-Alkylacrylate (2).**—In a 3-l. flask equipped with a mechanical stirrer, condenser, and dropping funnel was placed 45.3 g of 53% sodium hydride (dispersion in mineral oil, 1.0 mol) and 1 l. of dry ether. The flask was swept with nitrogen and maintained under positive nitrogen pressure. The reaction mixture was stirred in an ice bath while 224.2 g (1.0 mol) of triethyl phosphonoacetate was added dropwise over 75 min. The mixture then was stirred at reflux for 1 hr, at which time hydrogen evolution had completely stopped. The mixture then was thoroughly cooled in a salted ice bath which was frequently renewed during the course of the addition of the aldehyde (1.0 mol), which was done dropwise over about 1 hr at this scale. The reaction mixture occasionally became viscous near the end of the addition, but redissolved

(5) H. C. Brown and A. Tsukamoto, *J. Amer. Chem. Soc.*, **83**, 4549 (1961).

(6) The procedure using ethyl chloroacetate is recorded here because it is generally believed that the more expensive ethyl bromoacetate is required; see L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 1216.

TABLE II

| Registry no. | R | Yield of 3 from 2, % | Yield of 6 from 3, % | Bp (mm) or mp, °C, of 6 | Nmr, δ (solvent) of 6 | Carbon calcd (found), % | Hydrogen calcd (found), % |
|---|---|---|---|---|---|---|---|
| 504-15-4 | $CH_3$ | 77 | 75 | 112 (0.06),[a] 96–97 | ($D_2O$) 2.17 (s, 3, Me), 5.0 (broad, 2, HOD), 6.33 (s, 3, aryl) | | |
| 34993-66-3 | $(CH_3)_2CH$ | 22 | 75 | 121 (0.07)[b] | ($CDCl_3$) 1.00 (d, 6, $J$ = 7 Hz, Me), 2.6 (m, 1, CH), 6.30 (s, 3, aryl), 7.3 (broad, 2, OH) | 71.02 (70.55) | 7.95 (7.93) |
| 34993-67-4 | $(CH_3)_2CHCH_2$ | 84 | 79 | 120 (0.04), 94.5–95.0 from hexane | (Acetone-$d_6$) 0.87 (d, 6, $J$ = 7 Hz, Me), 1.7 (m, 1, CH), 2.30 (d, 2, $J$ = 7 Hz, $CH_2$), 6.10 (s, 3, aryl), 8.0 (broad, 2, OH) | 72.26 (72.00) | 8.49 (8.52) |
| 500-66-3 | $CH_3(CH_2)_4$ | 76 | 80 | 132 (0.05),[c] 44–46 | ($CDCl_3$) 0.7–1.8 (m with max at 0.82 and 1.27, 9), 2.4 (broad, 2, $CH_2$), 6.28 (s, 3, aryl), 7.25 (s, 2, OH) | 73.30 (72.98) | 8.95 (9.14) |
| 34993-68-5 | $(CH_3)_3CCH_2$ | 30 | 78 | 129 (0.05)[d] | ($CDCl_3$) 0.81 (s, 9), 2.27 (s, 2, $CH_2$), 6.23 (s, 3, aryl), 6.4 (broad, 2, OH) | 73.30 (72.81) | 8.95 (8.91) |
| 5465-20-3 | $CH_3(CH_2)_5$ | 76 | 81 | 142 (0.05)[e] | ($CDCl_3$) 0.7–1.8 (m with max at 0.82 and 1.23, 11), 2.3 (broad, 2, $CH_2$), 6.23 (s, 3, aryl), 7.05 (s, 2, OH) | 74.19 (74.10) | 9.34 (9.36) |
| 34155-91-4 | $CH_3(CH_2)_{10}$ | 85 | 78 | 173 (0.03),[f] 75–76 from hexane | ($CDCl_3$) 0.7–1.7 (m with max at 1.27), 2.4 (broad, 2, $CH_2$), 6.2 (broad, 2, OH), 6.27 (s, 3, aryl) | 77.22 (76.99) | 10.67 (10.64) |
| | $EtOOCCH_2$ | 31 | | | | | |

[a] Lit. mp 106–108°, bp 147° (5 mm), ref 3a. Melting point of product was unchanged after repeated recrystallization and distillation; however, when seeded while molten with authentic orcinol, product then had mp and mmp 106–108°. [b] Product did not crystallize: lit. mp 110°, bp 120° (0.15 mm); J. P. Brown, D. H. Johnson, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 2019 (1951). [c] Lit. mp 49° (ref 3a), bp 162–164° (5 mm) (ref 1). [d] Product did not crystallize, but formed a hydrate on recrystallization from water, mp 116–117°. [e] Lit.[1] bp 192–195° (11 mm). [f] Lit. mp 67–71°: M. Asano and K. Yamaguti, *J. Pharm. Soc. Jap.*, 60, 105 (1940); *Chem. Abstr.*, **34**, 5070 (1940).

on continued stirring. The cold mixture was stirred for an additional 10 min, and then was slowly brought to reflux, whereupon a heavy, viscous, oily precipitate of sodium diethyl phosphate separated, rendering further stirring impossible. The reaction mixture was refluxed for 10 min, and then the clear ether layer was decanted from the oil. The remaining oil was dissolved in 500 ml of warm water and the upper organic layer was separated. The aqueous layer was extracted with 200 ml of ether. The combined organic solutions were extracted with 200 ml of saturated sodium bicarbonate solution, dried with magnesium sulfate, filtered, rotary evaporated, and distilled through a Vigreux column. The products were all colorless liquids which gave ir absorptions at 1655 and 1720 $cm^{-1}$ and had nmr spectra which suggested that they were pure trans isomers. See Table I for specific yields, boiling points, and nmr spectra.

**Condensation of Ethyl β-Alkylacrylate with Ethyl Acetoacetate.**—A solution of sodium ethoxide was prepared from 25.3 g (1.1 g-atom) of sodium and 500 ml of dry ethanol in a 2-l. flask equipped with a mechanical stirrer, condenser, and dropping funnel, and under positive nitrogen pressure. To the solution was added 156 g (1.2 mol) of ethyl acetoacetate. The solution was stirred at reflux for 30 min, and then the desired ethyl β-alkylacrylate **2** (1.0 mol) was added dropwise to the refluxing solution over approximately 90 min. The dione sodium salt **3** began to precipitate at or near the end of the addition in the case of the less hindered ethyl β-alkylacrylates, whereas several hours after the addition were required for the more hindered esters. The reaction mixtures were in any case refluxed for about 20 hr, cooled in ice, and filtered. The precipitate was washed with 500 ml of ice-cold absolute ethanol, followed by several portions of ether, then air-dried for 1 hr. The white, powdery product was placed for 1 hr in a 90° oven, then dried overnight *in vacuo*. No difference in yield was observed in the following steps whether the product was used immediately or had been stored for several months at room temperature. See Table II for specific yields.

**5-Alkylresorcinol (6).**—In a 250-ml flask equipped with a powerful magnetic stirring assembly and a condenser were placed the desired dione sodium salt **3** (100 mmol) and 100 ml of DME. The system was flushed with nitrogen and stirred at room temperature while 44.67 g (200 mmol) of cupric bromide was added portionwise over 5 min under a stream of nitrogen. The solution became warm and stirring was continued without external heating for 30 min, and then the solution was stirred for 1 hr at reflux. The solution was cooled and rotary evaporated while care was taken not to heat the warming bath above 50°, and not to remove more than approximately 65 ml of the DME. The remaining solution was diluted with 200 ml of benzene and filtered to remove the mixture of cuprous and sodium bromides. The precipitate was washed with 50 ml of benzene and dried, giving a quantitative yield of inorganic salts. Washing with water and redrying gave a quantitative yield of white cuprous bromide. The combined benzene filtrates were rotary evaporated (50° maximum warming bath) and the crude bromodione was taken up in 100 ml of DMF and placed in a 500-ml flask under nitrogen. The solution was stirred and brought to reflux (the temperature must be raised fairly slowly in larger scale runs to avoid a sudden exotherm). Low boilers were allowed to escape until the liquid temperature reached 150°, and then the mixture was refluxed for 4 hr, allowed to cool, poured into 500 ml of water, and extracted with three 100-ml portions of dichloromethane. (In the orcinol preparation, R = methyl, the DMF solution was not diluted with water but instead the DMF was removed on the rotary evaporator under 1.0 mm vacuum, 90° warming bath.) The combined dichloromethane layers were dried with magnesium sulfate, filtered, and rotary evaporated. The residue then was either converted to the 5-alkylresorcinol **6**, as will be described next, or purified to give ethyl 6-alkyl-2,4-dihydroxybenzoate (**5**). To this residue was added a solution of 24 g (600 ml) of sodium hydroxide in 200 ml of water. The mixture was stirred at reflux under nitrogen in the hood (some dimethylamine evolution) for 3 hr, and then cooled in ice and acidified cautiously (some frothing may occur) with a cold solution of 20 ml (720 mmol) of concentrated sulfuric acid in 80 ml of water while stirring under nitrogen in an ice bath. The solution was then brought to reflux under nitrogen for 5 min, cooled, and extracted with several portions of ether. The combined ether layers were dried with magnesium sulfate, filtered, and rotary evaporated. The crude product, a black, viscous oil, was distilled (short path, air cooling) and product was collected in all cases as a pale yellow, viscous oil. See Table II for yields and physical data.

**Ethyl 6-Methyl-2,4-dihydroxybenzoate (Ethyl Orsellinate).**—The above residue (R = methyl) remaining after DMF removal *in vacuo* was treated with 100 ml of water which dissolved the orcinol and precipitated the ethyl orsellinate. The mixture was filtered and the precipitate was dissolved in 150 ml of hot chloroform. This solution was dried with sodium sulfate, filtered, and diluted with 150 ml of hot hexane. On standing, most of the colored material came out as an oil. The yellow, supernatant liquid was decanted from the oil and boiled down to a volume of 150 ml. On slow cooling, the product separated as pale yellow crystals, 8.2 g (42%), mp 127.5–9.5°. Two recrystallizations from 50% aqueous ethanol, using activated charcoal, gave a pure white product, mp 131.0–131.5° (lit.[3c] mp 130.0–131.5°).

**Ethyl 6-Hexyl-2,4-dihydroxybenzoate.**—Repeated extraction of the residue (R = *n*-hexyl) described in the above 5-alkylresorcinol preparation, with boiling hexane followed by refrigeration, left behind an insoluble black oil. The combined hexane solutions while still warm were extracted with water, dried with magnesium sulfate, filtered, and chilled slowly in a Dry Ice bath with occasional scratching. Crystals finally separated. Three recrystallizations from hexane gave a small amount of the ester, mp 74–75°.

*Anal.* Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.33; H, 8.28.

**Ethyl 6-Undecyl-2,4-dihydroxybenzoate.**—This residue (R = *n*-undecyl) described in the above 5-alkylresorcinol preparation was dissolved in 250 ml of hot hexane. On refrigeration, 10.15 g of crystalline product separated. The mother liquor gave an additional 4.40 g of crystals on concentration, thus giving a yield of 14.55 g (41%). Two recrystallizations from hexane gave an analytical sample, mp 67.5–68.5°.

*Anal.* Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.13; H, 9.67.

**Ethyl 2-Carbethoxy-3,5-dihydroxyphenylbenzoate.**—The residue (R = carbethoxymethyl) as described in the above 5-alkylresorcinol preparation had solidified. It was recrystallized from 175 ml of hot 70:30 hexane–dichloromethane, giving 11.5 g (43%) of tan needles of product. Recrystallization (same solvent system, activated charcoal used) gave 9.5 g of white needles, mp 107.0–107.5°. Another recrystallization gave an analytical sample, mp 107.5–108.0° with prior softening (lit.[7] mp 108°).

*Anal.* Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 58.06; H, 5.98.

**Registry No.**—Triethyl phosphonoacetate, 867-13-0; ethyl 6-hexyl-2,4-dihydroxybenzoate, 34993-70-9; ethyl 6-undecyl-2,4-dihydroxybenzoate, 34991-68-9.

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(7) A. Kamal, A. Robertson, and E. Tittensor, *J. Chem. Soc.*, 3379 (1950).

## A Convenient Synthesis of Barrelene

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Since its initial synthesis in 1960,[1] numerous papers have appeared concerning the spectra, reactivity, and properties of the homoconjugated triene barrelene (**1**). Recent work in this laboratory necessitated the preparation of some of this compound and bicyclo[2.2.2]octa-2,5-diene (**2**). The somewhat tedious synthetic routes to these materials[1-3] prompted a search for a more facile preparative route. The results of Hine and coworkers[4] suggested the opportunity for a three-step synthesis of both **1** and **2** if suitable alterations were made in the free-radical chlorination and dehydrohalogenation steps utilized in their procedure. In this fashion it has been possible to effect such a synthesis.

The first step is the ionic addition of hydrogen bromide to bicyclo[2.2.2]oct-2-ene, which affords 1-bromobicyclo[2.2.2]octane in yields exceeding 94%. Free-radical chlorination of the bromide using controlled excesses of sulfuryl chloride affords mixtures of polychlorobromobicyclo[2.2.2]octanes which may be biased in favor of the monochloro or polychloro derivatives depending on the amount of sulfuryl chloride employed. The final step is the low-temperature dehydrohalogenation of the polyhalobicyclo[2.2.2]octane mixture using potassium *tert*-butoxide in DMSO. Use of this reagent allows the multiple elimination reaction to be conducted at temperatures below the decomposition point of barrelene but still in reasonable yields. Separation and collection of the products by glpc using a temperature-programmed 10 ft × 0.375 in. Carbowax 20M column afforded pure samples of bicyclo[2.2.2]-octa-2,5-diene and barrelene. The yield of barrelene from bicyclo[2.2.2]oct-2-ene was approximately 2%. No attempts to maximize this yield were made, thereby indicating that overall yields in excess of those observed may be realized.

### Experimental Section

**1-Bromobicyclo[2.2.2]octane.**—The procedure of Doering and Farber[5] was used. In a 1-l. three-necked flask was placed a solution of 75 g (0.70 mol) of bicyclo[2.2.2]oct-2-ene in 400 ml of ether. The stirred mixture was cooled to 10° and 65 g (0.80 mol) of hydrogen bromide was bubbled in at a rate such that a temperature of 15° was always maintained. After the addition was complete the stirred mixture was kept at room temperature for 1 day. Then it was poured into 1 l. of ice water. The layers were separated and the aqueous portion was extracted three more times with 100 ml of ether. The combined ether extracts were washed with saturated sodium bicarbonate solution until the washings were basic and then with 200 ml of saturated sodium chloride solution. After drying ($MgSO_4$), evaporation of the solvent afforded 124 g (94%) of white, crystalline 1-bromobicyclo[2.2.2]octane, nmr ($CCl_4$) $\tau$ 5.76 (m, 1 H, HCBr) and 7.3–8.9 (m, 12 H).

**Chlorination of 1-Bromobicyclo[2.2.2]octane.**—A modified method of Hine and coworkers[4] was used. In a 500-ml one-necked flask was placed 124 g (0.66 mol) of bicyclooctyl bromide, 135 g (1.00 mol) of sulfuryl chloride, and 0.24 g of benzoyl peroxide. The reaction vessel was purged with nitrogen and the mixture was heated at reflux until the temperature of the mixture reached 190°. After cooling, the black residue was dissolved in 600 ml of ether. The resulting solution was washed twice with 50 ml of saturated sodium bicarbonate solution and twice with 100 ml of saturated sodium chloride solution. Drying ($MgSO_4$) and solvent removal afforded a residue which upon distillation gave two major fractions: (a) bp <130° (19 mm), 49 g (40%), judged from nmr to be mostly unreacted starting material; (b) bp 130–165°, 60 g, a mixture of polychlorobromobicyclo[2.2.2]octanes. Fraction b was used without further purification in the dehydrohalogenation step.

**Bicyclo[2.2.2]octa-2,5-diene and Bicyclo[2.2.2]octa-2,5,7-triene.**—In a dry nitrogen-flushed 500 ml three-necked flask were placed 56 g (0.50 mol) of potassium *tert*-butoxide and 150 ml of dry dimethyl sulfoxide. Then 25 g of the polychlorobromobicyclo[2.2.2]octane fraction (b) in 50 ml of dimethyl sulfoxide was added dropwise over a 10-hr period while the temperature was maintained at 40°. Upon completion of the addition the mixture was heated at 40° for an additional 1 hr, cooled, and poured into 1 l. of ice water. The aqueous solution was extracted with three 100-ml pentane portions and the combined extracts were washed twice with 50 ml of saturated sodium chloride solution. Drying ($MgSO_4$) and removal of the pentane by distillation through a 30-cm column packed with glass helices gave a 15-g residue which upon distillation afforded 5.0 g of a colorless liquid, bp 90–120°

(1) H. E. Zimmerman and R. M. Paufler, *J. Amer. Chem. Soc.*, **82**, 1514 (1960).

(2) H. E. Zimmerman, G. L. Grunewald, R. M. Paufler, and M. A. Sherwin, *ibid.*, **91**, 2330 (1969).

(3) C. A. Grob, H. Kny, and A. Gagneux, *Helv. Chim. Acta*, **40**, 130 (1957).

(4) J. Hine, J. A. Brown, L. H. Zalkow, W. E. Gardner, and M. Hine, *J. Amer. Chem. Soc.*, **77**, 594 (1955).

(5) W. v. E. Doering and M. Farber, *ibid.* **71**, 1514 (1949).

(155 mm). Glpc analysis using a 10 ft × 0.375 in. Carbowax 20M column programmed at 1°/min from 80 to 105° after a post injection delay of 20 min and at 10°/min from 105 to 160° with an upper limit delay of 20 min revealed 4 major and 12 minor components using a helium flow of 56 ml/min. Nmr spectra of the major components eluting at 27.5 and 42 min showed them to be bicyclo[2.2.2]octa-2,5-diene [nmr ($CCl_4$) $\tau$ 3.30 (p, 4 H, CH=), 6.50 (m, 2 H, bridgehead), and 8.78 (m, 4 H, bridge)][6] and bicyclo[2.2.2]octa-2,5,7-triene [nmr ($CCl_4$) $\tau$ 3.50 (structured pentet, 6 H, CH=) and 5.40 (m, 2 H, bridgehead)],[2] respectively. The two other major eluents had retention times of 54.5 and 60.5 min and were not further characterized. Two of the minor components eluting at 13 and 20 min were identified as benzene and bicyclo[2.2.2]oct-2-ene, respectively. The percentages of 1 and 2 estimated on the basis of total eluted materials were approximately 17 and 32%. Preparative glpc separation of 2.0 g of distillate afforded 0.24 g of barrelene for a yield of 2% based on bicyclo[2.2.2]octene.

**Equipment.**—Nmr spectra were taken using a Jeol C-60HL spectrometer. Analytical and preparative glpc were conducted using a Hewlett-Packard Model 5750 vapor phase chromatograph equipped with a Model 5797 A collection unit.

**Registry No.**—Barrelene, 500-24-3; 1-bromobicyclo-[2.2.2]octane, 7697-09-8.

(6) K. Lori, Y. Hata, R. Muneyuki, Y. Takano, T. Tsuji, and H. Tanida *Can. J. Chem.*, **42**, 926 (1964).

## An Improved Preparation of 1,3-Cyclopentanedione

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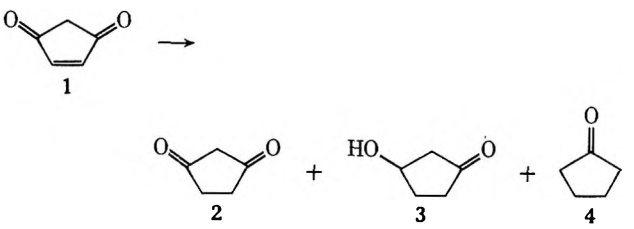
During the course of other investigations, we required a source of relatively large amounts of 1,3-cyclopentanedione (2). Although this compound and its alkylated derivatives have been used in the synthesis of many materials of varying degrees of complexity,[1] methods for its preparation, particularly on a large scale, are limited. The most widely quoted method[2] suffers from large solvent volumes, difficult isolation, and erratic yields. Other methods give unacceptably low yields.[3] Catalytic hydrogenation and zinc–acetic acid reduction of 4-cyclopentene-1,3-dione (1) have been reported.[4] Low yields of 2 were obtained, but the choice of catalyst and reaction conditions for these reactions did not appear to be optimal. Therefore we decided to reinvestigate the reduction of 1 as an attractive route to 2.

It is well established that the selective hydrogenation of olefins in the presence of carbonyl functions occurs best when palladium rather than platinum catalysts are employed.[5] Whereas the use of Adams' catalyst in the hydrogenation of 1 afforded only 2% of 2 in addition to large amounts of 3 and 4,[4] employing a palladium catalyst resulted in the continuous absorption of in excess of 1 equiv of hydrogen and the formation of a 3:2 mixture of 2 and 3, which could be separated by distillation. No cyclopentanone was formed. Variation of the solvent from 95 to 75% ethanol drastically reduced the rate of reduction, but did not change the product distribution substantially.




The reduction of conjugated diketones with zinc in acetic acid is a well-documented process,[6] but the reported yield[4,7] of 2 from the reduction of 1 was low. We verified these results, but found that *the use of activated zinc*[8] afforded 2 *in 75–77% yield* after recrystallization. Purification by sublimation at pressures greater than 0.02 mm reduced the yield to less than 60%. The ready availability of 4-cyclopentene-1,3-dione[9] coupled with the simplicity and high yield of this reduction clearly make this route the method of choice for the preparation of 2. Whether the use of activated zinc in other reductions of this type will result in a similar improvement in yield remains to be investigated.

### Experimental Section

Infrared spectra were taken on a Beckmann IR 12 spectrometer in chloroform solution; nmr spectra were recorded on a JEOLCO C60HL spectrometer in deuteriochloroform and are reported in parts per million from an internal standard (TMS = 0). Melting points are uncorrected. Microanalyses were performed by A. B. Gygli, Toronto, Ontario.

**Catalytic Hydrogenation of 1.**—To a solution of 1 g (0.01 mol) of 4-cyclopentene-1,3-dione[9] (1) in 25 ml of 95% ethanol was added a catalytic amount of 5% palladium on charcoal, and the mixture was hydrogenated at room temperature and pressure. Continuous absorption of hydrogen occurred until 1.6 molar equiv had reacted, at which point the reaction stopped. The solution was filtered free of catalyst, the solvent was evaporated, and the residue was distilled (90° bath temperature, 0.5 mm). Analysis of the distillate (0.37 g) by glc (8 ft × 0.25 in. 20% SE-30, 125°) showed the presence of two compounds, one of which had the same retention time as 2-cyclopentenone. No cyclopentanone was present. The spectra of the distillate identified the material as 3-hydroxycyclopentanone (3) from which the 2-cyclopentenone was formed by dehydration during glc analysis: ir 3610, 3450, 1737 $cm^{-1}$; nmr $\delta$ 4.6 (m, 1, CHOH), 3.58 (s, 1, –OH), 2.5–2.0 (m, 6). The residue from the distillation (0.6 g, 60%) was 1,3-cyclopentanedione (2), mp 151–152° (sublimed sample) (lit.[4] mp 149–150°).

**Zinc Reduction of 1.**—To a mixture of 500 ml of glacial acetic acid and 100 g (1.54 mol) of activated zinc[8] in a 2-l. flask equipped with a mechanical stirrer and maintained at 95° with an oil bath was added a solution of 20 g (0.21 mol) of 1 in 300 ml of glacial acetic acid over a period of 2 hr. The mixture was stirred at 95° for 1 hr, filtered, cooled to room temperature, and filtered again. Evaporation of the solvent at reduced pressure afforded a light yellow residue which gave 2 (15.5 g, 76%) on recrystallization from methanol–ethyl acetate (1:3) at −78°, mp 148–149°.

(1) (a) R. Zurfluh, E. N. Wall, J. B. Siddall, and J. A. Edwards, *J. Amer. Chem. Soc.*, **90**, 6224 (1968); (b) L. Velluz, J. Vallas, and G. Nomine, *Angew. Chem., Int. Ed. Engl.*, **4**, 181 (1965); (c) T. B. Windholz and M. Windholz, *ibid.*, **3**, 353 (1964).

(2) F. Merenyi and M. Nilsson, *Acta, Chem. Scand.*, **17**, 1801 (1963).

(3) J. H. Boothe, R. G. Williams, S. Kushner, and J. H. Williams, *J. Amer. Chem. Soc.*, **75**, 1732 (1953).

(4) C. H. DePuy and E. F. Zaweski, *ibid.*, **81**, 4920 (1959).

(5) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 10.

(6) See, for example, J. Elks, R. M. Evans, A. G. Long, and G. H. Thomas, *J. Chem. Soc.*, 451 (1954).

(7) H. O. House and G. Rasmusson, *J. Org. Chem.*, **28**, 27 (1963).

(8) J. W. Cornforth, R. H. Cornforth, G. Popjak, and I. Y. Gore, *Biochem. J.*, **69**, 146 (1958).

(9) G. H. Rasmusson, H. O. House, E. F. Zaweski, and C. H. DePuy, *Org. Syn.*, **42**, 36 (1962).

*Anal.* Calcd for $C_5H_6O_2$: C, 61.22; H, 6.16. Found: C, 61.25; H, 6.13.

**Registry No.**—**1**, 930-60-9; **2**, 3859-41-4; zinc, 7440-66-6; palladium, 7440-05-3.

**Acknowledgments.**—We would like to express our thanks to the National Research Council of Canada for financial support, to Mr. D. Hill for technical assistance, and to Dr. K. G. Rutherford for helpful discussions.

## Preparation of Acyclic Isoimides and Their Rearrangement Rates to Imides

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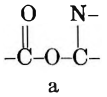
*Received October 26, 1971*

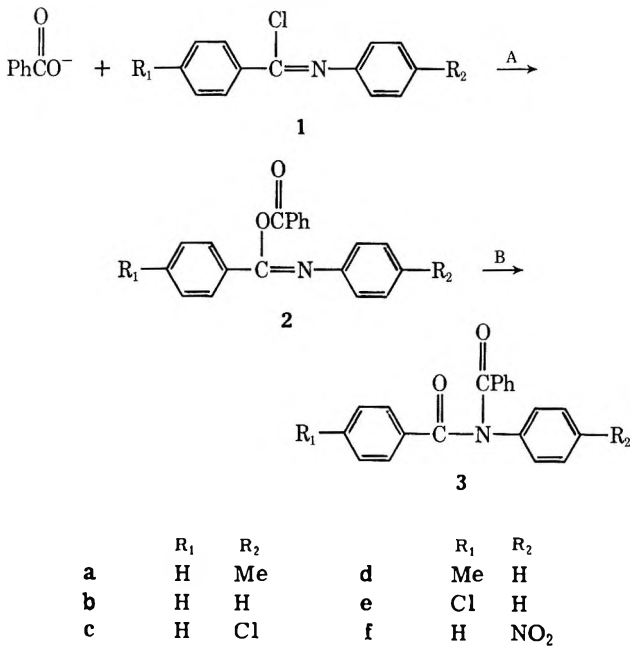
The 1,3(O–N) acyl transfer of the acyl imidate group (a) in a Mumm rearrangement[1-4] (reaction B of Scheme



a

I) proceeds by an intramolecular process. To examine

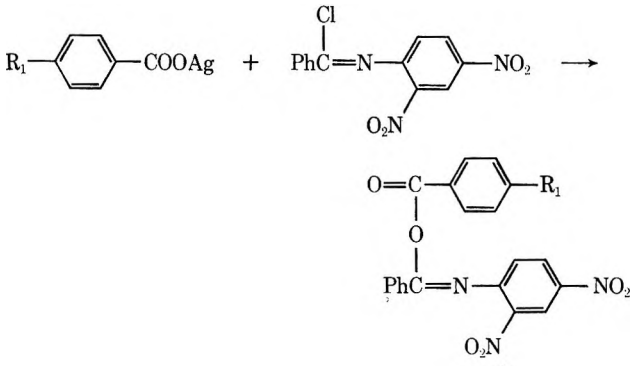
SCHEME I



| | $R_1$ | $R_2$ | | $R_1$ | $R_2$ |
|---|---|---|---|---|---|
| **a** | H | Me | **d** | Me | H |
| **b** | H | H | **e** | Cl | H |
| **c** | H | Cl | **f** | H | $NO_2$ |

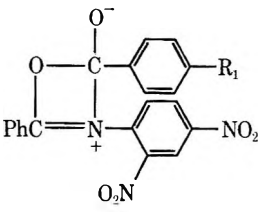
the possibility of carrying out intermolecular acylations with such a structure, a series of isoimides **2** were prepared to study the relative ease of formation and measure the rate of rearrangement to imide **3**. If the intramolecular rearrangement rate could be inhibited, intermolecular acyl transfer might occur. Intramolecular analogies to this have been found many times when an additional acylatable group is present in the isoimide.[5-9]

It has long been known that imidoyl chlorides react with carboxylate anions to form imides. It had been suspected that isoimides were intermediates in this reaction (Mumm rearrangement), but early attempts to prepare these intermediates were unsuccessful due to the rapid rearrangement to imide. Finally, by careful work at room temperature and below, Curtin and Miller[2,3] were able to prepare isoimides stabilized by two nitro groups by the following method.



**4**

They were able to establish that the rearrangement of isoimide **4** to imide was first order in isoimide and that $\rho$-para for the migrating group was about +0.6. From these facts and the fact that more polar solvents increased the rate, they proposed the reaction as proceeding through a four-membered ring transition state (or intermediate)[10] **5**.



**5**

In the present study isoimides were prepared by allowing triethylammonium benzoate to react with the appropriate imidoyl chloride **1** in chloroform solution at about 0°. The reactions were rapid and exothermic except in the case of the nitro-substituted imidoyl chloride, where no significant concentration of isoimide accumulated because it rearranged approximately as fast as it was formed (Table I).

The rates of rearrangement of the isoimides once formed were measured without prior isolation because isolation of compounds this labile would have required very special handling. Instead the half-lives were determined in the solution in which they were formed by an infrared comparison method explained in the Experimental Section. From our data (Table I),

(1) O. Mumm, H. Hesse, and H. Volquartz, *Ber.*, **48**, 379 (1915).
(2) D. Y. Curtin and L. L. Miller, *J. Amer. Chem. Soc.*, **89**, 637 (1967).
(3) D. Y. Curtin and L. L. Miller, *Tetrahedron Lett.*, 1869 (1965).
(4) J. W. Schulenberg and S. Archer, *Org. React.*, **14**, 31 (1965).
(5) E. Taschner, B. Rzeszotarska, and L. Lubienska, *Chem. Ind. (London)*, 402 (1967).
(6) D. S. Kemp and R. B. Woodward, *Tetrahedron*, **21**, 3019 (1965).
(7) R. B. Woodward and R. A. Olofson, *J. Amer. Chem. Soc.*, **83**, 1007 (1961).
(8) R. B. Woodward, R. A. Olofson, and H. Mayer, *ibid.*, **83**, 1010 (1961).
(9) G. Gokel, G. Luedke, and I. Ugi in "Isonitrile Chemistry," I. Ugi, Ed., Academic Press, New York, N. Y., 1971, p 145.
(10) The four-membered ring mechanism had been briefly alluded to but not formally depicted by C. L. Stevens and M. E. Munk, *J. Amer. Chem. Soc.*, **80**, 4069 (1958).

TABLE I

RATES OF FORMATION AND REARRANGEMENT OF ISOIMIDES 2

| Run | Isoimide | $R_1$ | $R_2$ | Formation[a] time, min, *ca.* 0° | Half-life,[b] min, 19.6° |
|---|---|---|---|---|---|
| 1 | 2a | H | Me | 3 | 15.5 ± 1.0 (18) |
| 2 | 2b | H | H | 5 | 22.8 ± 1.4 (12) |
| 3 | 2c | H | Cl | 45 | 45.6 ± 2.7 (19) |
| 4 | 2c | H | Cl | | 44.4 ± 3.0 (3)[c] |
| 5 | 2d | Me | H | 4 | 13.4 ± 1.1 (22) |
| 6 | 2e | Cl | H | 20 | 41.3 ± 2.4 (26) |
| 7 | 2f | H | $NO_2$ | ~36 hr | 3.7 hr[d] |

[a] Measured by time of maximum attainment of enol ester carbonyl band in the ir. [b] Numbers in parentheses refer to number of measurements in the average. [c] Starting isoimide concentration 0.1 *M* with excess triethylammonium benzoate (0.314 *M*). [d] Calculated using data of runs 1 through 3.

the $\rho$-para was $-1.27$ for each ring studied as calculated by the least squares method.

These negative $\rho$ values lend support to the intermediacy of **5**, although the values might have been expected to be higher in view of the great amount of charge developed. A possible explanation for these low $\rho$ values might be that the positive charge in the transition state (or intermediate) can be distributed between both the nitrogen and the oxygen of the four-membered ring.

It is clear that the nucleophilic substitution reaction to form the isoimide is promoted by electron-donating groups ($R_1$, $R_2$) in the imidoyl halide ($\rho$ is clearly negative) with substantial positive charge development on the trigonal carbon. The mechanism of displacement probably bears a strong relationship to that of hydrolysis of imidoyl chlorides, where Ugi, Beck, and Fetzer[11] also find rate enhancement by electron-donating groups. They propose that hydrolysis in acetone–water proceeds by the following pathway.

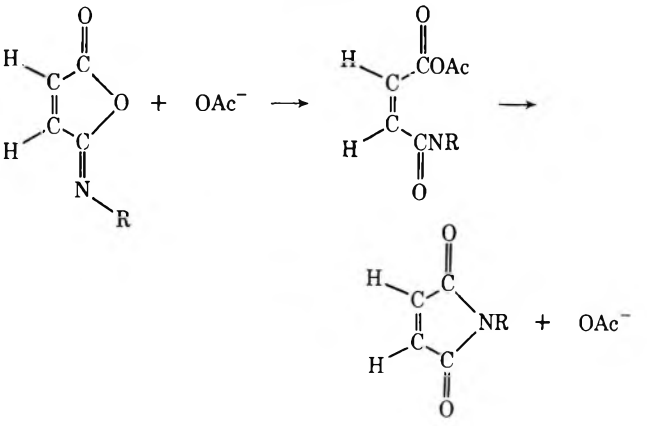
$$RC(Cl)=NR' \rightleftharpoons \underbrace{RC^{+}=NR'\ Cl^{-}}_{\text{ion pair}} \xrightarrow{H_2O} RC(=O)NHR' + HCl$$

In the present case, an ion pair as depicted above would explain the relative rate data for the preparation of isoimides.

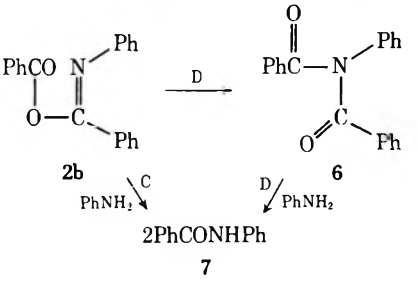
Although carboxylate anions have been implicated in the mechanism of the rearrangement of cyclic isoimides (Scheme II),[12] they do not appear to participate in any measurable way in the rearrangement of acyclic isoimides. This can be seen from the fact that **2c** rearranged at the same rate within experimental error whether benzoate ion was added or not.

To investigate the possibility of intermolecular acylation with one of these isoimides, two experiments were run in which aniline was treated at 0° with a freshly prepared chloroform solution of benzoyl *N*-phenylbenzimidate (**2b**). This particular combination of reactants was chosen since the product of any acylation would be the same as the by-product from the acylating agent. The acylation could then proceed by two possible routes (C and/or D, Scheme III). The progress of the reactions was followed by ir, and it was found

SCHEME II



SCHEME III



that, in the run where an equimolar amount of aniline was used, only dibenzoylaniline (**6**) was isolated. In the second run where ten times the equimolar amount of aniline was used, it appeared (ir monitoring) that the isoimide was consumed by rearrangement in the control experiment as fast as it was consumed in the presence of aniline. After rearrangement to imide was essentially complete at 0°, the reaction mixture with aniline was allowed to stand at room temperature overnight. From this reaction then, benzanilide (**7**) was the only product isolated. From this experiment, it is clear that the predominant pathway to benzanilide is *via* the imide. This is not completely unexpected, since Stevens and Munk[10] have shown that intermolecular acylation of amines with imides can be used preparatively.

The failure to achieve intermolecular acylation with an isoimide in this case may be due to the relative instability of the isoimide used toward rearrangement or the low nucleophilicity of aniline. Further work with more stable isoimides together with more reactive amines is indicated to see whether this failure to achieve acyl transfer is general for this type of potential acylating agent.

### Experimental Section[13]

**Preparation of Imidoyl Chlorides.**—These compounds were prepared by refluxing the appropriate anilide either with an excess of thionyl chloride or with 1 mol of phosphorus pentachloride in a benzene slurry. The volatile constituents were removed under vacuum, and purification was effected by vacuum distillation, vacuum sublimation, or recrystallization. The melting ranges are tabulated in Table II.

(11) I. Ugi, F. Beck, and U. Fetzer, *Chem. Ber.*, **95**, 126 (1962).

(12) C. K. Sauers, *J. Org. Chem.*, **34**, 2275 (1969), and references cited therein.

(13) All infrared spectra were taken on a Perkin-Elmer Model 137. The benzoic acid was sublimed and the triethylamine was passed through an alumina column before use. Chloroform was freed of the ethanol preservative by passing through an alumina column and was found to be quite stable in this condition as long as light was rigorously excluded. All melting ranges are uncorrected. Rates were determined at 19.6 ± 0.1° (corrected).

TABLE II
MELTING RANGES OF IMIDOYL CHLORIDES AND IMIDES

| | 1 | | 3 | |
|---|---|---|---|---|
| Comp | Mp, °C found | Mp, °C reported | Mp, °C found | Mp, °C reported |
| a | 54–57 | 52[a] | 146–146.5 | 142–144[e] |
| b | 42–45 | 39–41[b] | 162.5–164.5 | 163–164[f] |
| c | 62.5–64.5 | 68[c] | 158–159 | 159–160[g] |
| d | 52–54.5 | | 162–163.5 | 159[f] |
| e | 69.5–71.5 | 66–67[d] | 130–132 | |
| f | 114.5–117 | 118–120[b] | 209–210.5 | 203[h] |

[a] F. Just, *Ber.*, **19**, 980 (1886). [b] Reference 11. [c] H. Ley, *Ber.*, **31**, 241 (1898). [d] G. H. Coleman and R. E. Ryle, *J. Amer. Chem. Soc.*, **68**, 2007 (1946). [e] Reference 1. [f] M. P. Freunler, *Bull. Soc. Chim. Fr.*, **31**, 623 (1904). [g] S. Birtwell, *J. Chem. Soc.*, 2561 (1949). [h] O. Mumm, *Ber.*, **43**, 890 (1910).

**Preparation and Determination of Half-Lives of the Substituted Benzoyl *N*-Phenylbenzimidates (Isoimides).**—The isoimides were prepared in the following way. A chloroform solution of triethylammonium benzoate (10 ml, 1 *M*, 0°) was rapidly pipetted into a chloroform solution of the appropriate imidoyl chloride (5 ml, 2 *M*, 0°). The resulting solution was well mixed and kept in an ice bath while the reaction to form isoimide proceeded. With the faster reacting imidoyl chlorides, temperature rises of up to 8° were noted within a minute or two. The developing band in the infrared spectrum (*ca.* 1737 $cm^{-1}$ in $CHCl_3$) was observed during this period to ascertain when the isoimide had completely formed [maximum attainment of this band relative to the adjacent band (*ca.* 1680 $cm^{-1}$) of the C=N]. In all cases except that with *N*-*p*-nitrophenylbenzimidoyl chloride, the isoimide **2** formed completely before any rearrangement could be detected.

The half-lives of the isoimides were determined as follows. The isoimide solution as prepared above was allowed to stand at room temperature for several hours until rearrangement to imide was complete. A 5-ml aliquot was then accurately diluted to 25 ml with chloroform (solution 0.133 *M* in imide).

Now a fresh solution of isoimide was prepared as described above. A 5-ml aliquot of this isoimide solution was diluted accurately to 25 ml with chloroform thermostated at 19.6° (solution about 0.133 *M* in isoimide), and the diluted mixture was thermostated at 19.6° (solution A).

A 10-ml aliquot of the imide solution (thermostated at 19.6°) was mixed ($t = t_0$) with a 10-ml aliquot of the isoimide (solution A), and this mixture was thermostated at 19.6° (solution B). This solution then simulated solution A after rearrangement of half of the isoimide.

The infrared spectrum between 1800 and 1650 $cm^{-1}$ was determined for these two mixtures (A and B) every 1 to 3 min (depending on length of half-life) until the isoimide (*O*-acyl carbonyl) band became only a shoulder on the imide carbonyl band. In practice, the spectra were taken only with solution B at first until the isoimide band became a shoulder; then only solution A spectra were taken for the balance of the run.

The values for the half-lives were determined by measuring the time difference between identical solution A and solution B spectra using as a basis of comparison the distance between the isoimide maximum and the minimum between it and the adjoining carbonyl peak (*ca.* 1680 $cm^{-1}$), linearly interpolating as required. The results are tabulated in Table I.

**Preparation and Rearrangement of Benzoyl *N*-(*p*-Chlorophenyl)benzimidate (2c) in the Presence of Excess Benzoate.**—The general procedure described above was followed except that solution A was prepared in such a way that it was 0.1 *M* in isoimide and 0.314 *M* in triethylammonium benzoate. The results are tabulated in Table I.

**Dibenzoylaniline.**—The chloroform solutions remaining from the experimental measurement of the rate of rearrangement of benzoyl *N*-phenylbenzimidate were combined and evaporated. The residue was extracted with benzene (125 ml). After filtration, the benzene solution was concentrated to about 40 ml. After being cooled to room temperature, the product was isolated by filtration, yield 6.8 g (45%), mp 162.5–164.5° (lit.[14] mp 163–164°).

(14) M. P. Freundler, *Bull. Soc. Chim. Fr.*, **31**, 630 (1904).

**Acylation Tests Using Benzoyl *N*-Phenylbenzimidate.**—Two acylation experiments were run with varying amounts of aniline. The solution of the acylating agent was prepared in each case as follows. A solution of *N*-phenylbenzimidoyl chloride (5 ml of 2 *M* chloroform solution) at 0° was mixed with a solution of triethylammonium benzoate (10 ml of 1 *M* chloroform solution) at 0°. Within a few minutes the reaction to form isoimide was complete (ir) after a temperature rise of 8°. The mixture was cooled to 0° before adding to the aniline.

**Run 1.**—A 10-ml aliquot of the isoimide (*ca.* 6.67 mmol) was pipetted as soon as it had been formed into a tube containing aniline (0.621 g, 6.67 mmol) at 0°. This mixture, together with the remaining 5-ml solution of isoimide, was kept at 0° for the balance of the experiment. After 4 hr, the ir enol ester band was still the same intensity in each sample although a major portion of the isoimide had rearranged. After a total of 17 hr at 0°, the ir enol ester band had disappeared from each sample. The reaction mixture (isoimide–aniline) was treated with enough chloroform to dissolve the product which had precipitated during the last hours of standing. The resulting solution was extracted with water, 6 *N* HCl, water, saturated aqueous $NaHCO_3$, and finally water. The chloroform layer was dried ($Na_2SO_4$). The solution ir was identical with that of dibenzoylaniline. The chloroform was evaporated, and the residue was crystallized from benzene to yield pure dibenzoylaniline, yield 1.24 g (62%), mp 159–161.5°, ir ($CHCl_3$) identical with that of authentic dibenzoylaniline.

**Run 2.**—The procedure was the same as that of run 1 except as noted below. The aniline used was ten times that of run 1. Examination of the ir spectra of the two solutions periodically disclosed that the ir enol ester carbonyl band diminished at about the same rate in each solution and had completely disappeared after 8.5 hr at 0°. At this point the reaction containing aniline was removed from the ice bath and stored at room temperature overnight. Work-up was as in run 1. The chloroform solution was evaporated to dryness to yield benzanilide, yield 2.22 g (85%), mp 162–163.5°, ir ($CHCl_3$) identical with that of authentic benzanilide.

**Preparation of Imides.**—The chloroform solutions from the rate runs for each isoimide were combined after rearrangements were complete. The resulting solution was extracted with water twice, dried with anhydrous sodium sulfate, and taken to dryness. The resulting residue was crystallized from benzene. The melting ranges of the various imides are given in Table II.

**Registry No.**—**1d**, 34916-13-7; **2a**, 34916-14-8; **2b**, 34916-15-9; **2c**, 34934-83-3; **2d**, 34916-16-0; **2e**, 34916-17-1; **2f**, 34916-18-2; **3e**, 34916-19-3; **7**, 93-98-1.

## Orbital Symmetry Control in the Cycloadditions of Ketenes to Norbornadiene

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*Research Laboratories, Eastman Kodak Company, Rochester, New York 14650*

*Received March 28, 1972*

Recent reports of orbital symmetry control in the cycloadditions of ketenes to cyclopentadiene[2] prompt us to communicate our results with cycloadditions of ketenes to norbornadiene. The cycloadducts of dichloroketene with norbornene and norbornadiene have

(1) IAESTE Student, Summer, 1971.

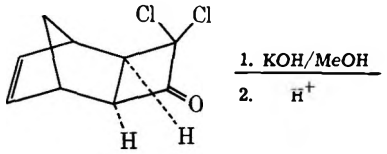
(2) (a) W. T. Brady and R. Roe, Jr., *J. Amer. Chem. Soc.*, **92**, 4618 (1970); W. T. Brady and E. F. Hoff, Jr., *J. Org. Chem.*, **35**, 3733 (1970); (b) M. Rey, S. Roberts, A. Dieffenbacher, and A. S. Dreiding, *Helv. Chim. Acta*, **53**, 417 (1970); (c) P. R. Brook, J. M. Harrison, and A. J. Duke, *Chem. Commun.*, 589 (1970).

TABLE I
ADDITION OF RXC=C=O TO NORBORNADIENE (A) AND NORBORNENE (B)

| Compd | R | X | Yield in cyclohexane, % | *syn*-Halo epimer, %[a] | Yield in MeCN, % | *syn*-Halo epimer, %[c] |
|---|---|---|---|---|---|---|
| 6[b,c] | A Me | Cl | 16.2 | 0 | 7.5 | 60 |
| 7[b,d] | A Et | Cl | 14.3 | 0 | 7.8 | 56 |
| 8[b,e] | A *i*-Pr | Cl | 5.7 | 0 | 1.0 | 0 |
| 9[b,f] | A Me | Br | 16.7 | 0 | 5.2 | 100 |
| 10 | A *t*-Bu | Br | 0 | | 0 | |
| 11[b,g] | B Me | Cl | 12.4 | 0 | 5.4 | 50 |

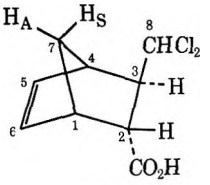
[a] Analyzed by nmr spectroscopy; see text. [b] Satisfactory combustion analytical data (±0.35%) were provided for these compounds. Ed. [c] Bp 53–59° (0.06 mm). [d] Bp 63–64° (0.1 mm). [e] Bp 80–87° (0.3 mm). [f] Bp 88–90° (0.5 mm). [g] Bp 72–74° (0.1 mm).

the exo configuration by nmr inference,[3] which is confirmed by the following degradative scheme.



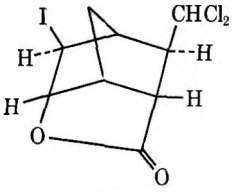

1

1. KOH/MeOH
2. $H^+$




2

$I_2$/KI
$NaHCO_3$

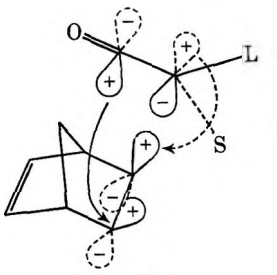



3

Thus, treatment of 1 with methanolic KOH yields the product of Conia-type opening,[4] *endo*-2-carboxy-*exo*-3-dichloromethylbicyclo[2.2.1]hept-5-ene,[2] which has epimerized at C-2, apparently owing to the unfavorable steric interaction of two bulky cis substituents. Conversion of 2 to the iodolactone 3 fixes the endo configuration of the carboxy group and consequently the exo configuration of the dichloromethyl. The nmr spectra of 2 and 3 correlate unambiguously with those of the corresponding monochloro analogs.[5]

That this is a stereospecific exo cycloaddition not involving endo cycloaddition and isomerization[6] is concluded from the observation[7] that the retro Diels–Alder reactions in these norbornadiene cycloadducts do not occur below 450°. Furthermore, the dichloroketene cycloadduct with norbornene (also exo) is not capable of this type of retro Diels–Alder isomerization.

Hence, it is reasonable to consider that the reacting ketene approaches norbornadiene from the exo side. If one assumes an orthogonal approach for a concerted $_{\pi}2_s + {}_{\pi}2_a$ cycloaddition[8] taking into account the steric requirements, it is most probable that the oxo moiety of the ketene should approach first as pictured in **4**. This would lead on closing to the least expected isomer, **5**, with the largest group, L, in the syn configuration.[9]

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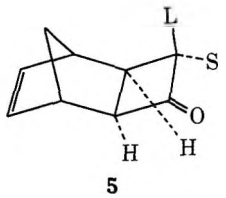


5

The experimental results (Table I) are consistent with this interpretation. Based on the downfield shift of the O-bridge protons with halogen anti, the alkyl substituent is exclusively syn in this series (Me to *i*-Pr) with cyclohexane as solvent. However, using acetonitrile as solvent increases the effective size of the halogen and of the whole ketene by greater solvation, resulting in the appearance of syn halo cycloadduct and diminished yields. In comparison to the results of cycloadditions of haloketenes to cyclopentadiene, norbornadiene has a considerably higher steric requirement, which is reflected in the greater stereoselectivity and much reduced yields. Examination of Dreiding models of **4** indicates that this system approaches the limit of steric interaction that will allow the reaction to proceed. Approach and cycloaddition of ketenes from the endo side of norbornadiene are prohibited by interaction of the nonreacting $\pi$ electrons with the oxo nonbonding and $\pi$ electrons and of norbornene by the severe steric interaction of the ketene substituent with the dimethylene bridge in the rotating and closing step.

## Experimental Section

***endo*-2-Carboxy-*exo*-3-dichloromethylbicyclo[2.2.1]hept-5-ene (2).**—A mixture of 4.06 g (0.02 mol) of 3,3-dichloro-4-oxotricyclo[4.2.1.$0^{2,5}$]non-7-ene (1),[3] 3.6 g (0.06 mol) of KOH, and 100 ml of methanol was heated at reflux for 1 hr, concentrated to dryness, and extracted with ether. The solid residue was taken up in water and acidified with concentrated HCl, depositing 2.10 g (47.6%) of colorless crystalline product, mp 130–134°. Recrystallization from water–methanol raised the melting point to 137–138°.

The 90-MHz nmr had the following absorptions ($CDCl_3$, decoupled): $\delta$ 3.30 ($J_{1,2}$ = 3.5 Hz), 2.85 ($J_{2,1}$ = 3.5, $J_{2,3}$ = 4.5 Hz), 2.60 ($J_{3,2}$ = 4.5, $J_{3,4}$ = 1.0, $J_{3,8}$ = 9.0 Hz), 3.07 ($J_{4,3}$ = 1.0, $J_{4,5}$ = 3 Hz, $J_{4,7}$ small), 6.38 ($J_{5,4}$ = 3, $J_{5,6}$ = 5.5 Hz, $J_{5,1}$ small), 6.14 ($J_{6,5}$ = 5.5, $J_{6,7}$ = 2.5 Hz), 1.59 ($J_{7A,7S}$ = 10.5 Hz, $J_{7,other}$ small), 5.61 ($J_{8,3}$ = 9.0 Hz).

*Anal.* Calcd for $C_9H_{10}Cl_2O_2$: C, 48.9; H, 4.6; Cl, 32.1. Found: C, 48.7; H, 4.7; Cl, 32.1.

The iodolactone **3** was prepared in 64.6% yield, mp 99–100° (ether–ligroin).

*Anal.* Calcd for $C_9H_9Cl_2IO_2$: C, 31.2; H, 2.6; Cl, 20.4; I, 36.6. Found: C, 31.5 H, 2.8; Cl, 20.1; I, 36.6.

**Addition of Haloketenes to Norbornenes (General Procedure).**—To a stirred solution of 50.5 g (0.5 mol) of triethylamine, 125

(3) L. Ghosez, R. Montaigne, A. Roussel, H. Vanlierde, and P. Mollet, *Tetrahedron*, **27**, 615 (1971).

(4) J. M. Conia and J. L. Ripoll, *Bull. Soc. Chim. Fr.*, 763 (1963).

(5) H. Christol, A. Donche, and F. Plénat, *ibid.*, 1315 (1966); H. Christol, J. Coste, and F. Plénat, *ibid.*, 3934, 3939 (1969).

(6) S. Selzer in "Advances in Alicyclic Chemistry," Vol. 2, Academic Press, New York, N. Y., 1968, p 1.

(7) A study of this reaction will be reported elsewhere.

(8) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

(9) M. J. S. Dewar, *Angew. Chem.*, **83**, 859 (1971), utilizing the basis sets of orbitals for the ketene and the alkene, predicts a "skew" approach for maximum orbital interaction in the transition state but the same product stereochemistry as for "orthogonal" approach. The data presented here and in ref 2 do not allow a distinction to be made between the "skew" and "orthogonal" mechanisms.

ml of norbornadiene, and 1 l. of cyclohexane (or acetonitrile) at reflux under nitrogen was added gradually (2 hr) a solution of 0.5 mol of the requisite haloacyl halide in 50 ml of cyclohexane (or acetonitrile). The mixture was refluxed for an additional 1 hr, allowed to stand overnight at room temperature, filtered through Celite, concentrated under vacuum, and distilled. The distillate was freed from halogenated impurities generally present by placing in ten volumes of hexane and treating gradually with one volume of 1,5-diazabicyclo[4.3.0]non-5-ene. After standing for 1 hr, the upper layer was decanted, washed four times with water, dried over anhydrous sodium sulfate, and distilled. The isopropyl derivative was more sensitive and required washing with 10% aqueous NaOH and subsequent chromatography on Florisil. Properties of these products are presented in Table I.

**Registry No.**—**2**, 34922-27-5; **3**, 34922-28-6; *syn*-**6**, 34922-29-7; *anti*-**6**, 34934-85-5; *syn*-**7**, 34934-86-6; *anti*-**7**, 34934-87-7; *syn*-**8**, 34922-30-0; *anti*-**8**, 34922-31-1; *syn*-**9**, 34934-88-8; *anti*-**9**, 34934-89-9; *syn*-**11**, 34922-32-2; *anti*-**11**, 34922-33-3.

## Tautomerism of a Secondary Azo Compound Accompanying Thermal Decomposition[1]

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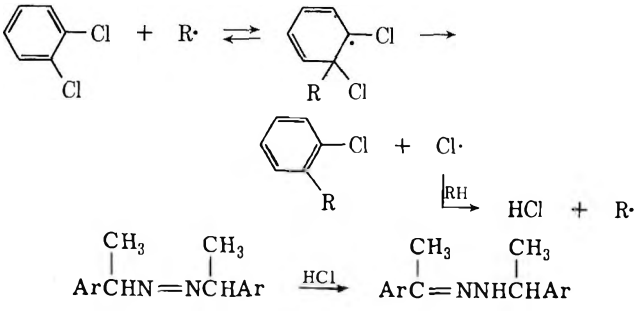
*Received December 22, 1971*

While studying[2] the thermal decomposition of some symmetrical secondary aralkyl azo compounds in solution, we found that in chlorinated solvents and with halogen-substituted azo compound, in addition to radical decomposition products, variable amounts of the starting material were diverted to a material that ultimately yielded the ketone of the initial moieties of the azo compound. α-Phenylazoethane (**1a**), when decomposed in a wide series of solvents (Table I), gave close to 100% yield of radical products (by glpc analysis). In *o*-dichlorobenzene, however, only 80% of the starting azo compound was accounted for when analysis was performed upon opening the sealed ampoule. After the ampoule had stood open for approximately 1 day a peak corresponding to acetophenone appeared. This peak grew with time and after 2 weeks finally accounted for all the α-phenethyl moieties in the starting material. A similar result was found for azo compound **1b** (*p*-chlorophenylazoethane) in benzene.

Addition of pyridine to an *o*-dichlorobenzene solution of **1a** prevented the side reactions; upon thermolysis only normal azo decomposition products were noted. Similarly, **1b** yielded almost theoretical radical products, and no ketone, upon addition of pyridine to the decomposition solution. Addition of dry 0.01 *M* HCl to fresh benzene solutions of **1a** and **1b** resulted in rapid rearrangement of the azo compounds to hydrazones as seen by nmr (*vide infra*). Under the conditions of these studies the hydrazones were stable in the sealed ampoules. Upon opening to air, a rapid oxidation occurred which produced one molecule of ketone for each azo compound originally added. After the ampoules had stood for about 1 week a second molecule of ketone was found, at this point accounting for all the starting material. These data are summarized in Table I. It is interesting to note that the radical–radical reaction rate constant ratio ($k_d/k_c$) remains constant for both compounds independent of the side reaction leading to ketone.

When **1a** was decomposed at 118° in benzene in a degassed and vacuum-sealed nmr tube for 24 hr (*ca.* 8 half-lives), the nmr peaks for the diphenylbutanes (*meso* and *dl*) as well as those for ethylbenzene and for styrene were evident. Glpc analysis showed only these products in close to quantitative yield. A similar experiment using dichlorobenzene as solvent showed, in addition to the peaks noted for the benzene solution, a doublet at $\tau$ 8.56, an equal-sized singlet at $\tau$ 8.25, and a small quartet at $\tau$ 5.5, readily assignable to the corresponding hydrazone. When this nmr tube was opened to air and allowed to stand overnight, the three peaks attributed to hydrazone disappeared and were replaced by a singlet at $\tau$ 8.5 (identical with acetophenone). The *p*-chloroazo compound, **1b**, showed analogous behavior in benzene. In degassed ampoules at room temperature all the secondary aralkyl azo compounds that we have examined in a wide range of solvents including the chlorinated benzenes are indefinitely stable to decomposition and rearrangement.

It is clear that we are observing an acid-catalyzed (by the pyridine experiment) rearrangement of the azo compound to hydrazone accompanying the radical decomposition, and subsequent formation of ketone from hydrazone in two steps, one fast and one slow. We conclude that the acid-catalyzed rearrangement accompanies the radical decomposition, a likely path being




The reversible addition of a radical to the aromatic nucleus probably occurs in benzene as well, but when chlorine is attached to the ring, the reverse reaction must compete with the loss of a stable chlorine atom. A very small amount of this process would produce sufficient acid to catalyze the rearrangement.

Immediately after opening, analysis in all cases showed no trace of acetophenone. The decomposed solution of **1a** in dichlorobenzene was examined by glpc after opening and exposure to anaerobic water in one experiment, and to dry oxygen in another. The oxygenated sample showed 1 mol of acetophenone per mole of hydrazone within 15 min, but the aqueous sample showed only small traces of acetophenone. It thus seems that the first mole of acetophenone arises from the reaction of hydrazone with oxygen. Several in-

(1) Taken in part from the Ph.D. dissertation of R. C. C., University of California, Riverside, 1971. Support by the Air Force Rocket Propulsion Laboratory (R. C. C.) and the Intramural Fund of the University of California is gratefully acknowledged.

(2) M. J. Gibian and R. C. Corley, *J. Amer. Chem. Soc.*, **94**, 4178 (1972).

TABLE I

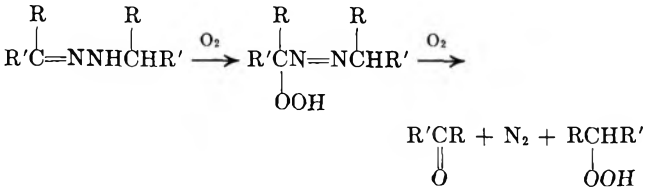
RATE CONSTANT RATIOS AND PRODUCT BALANCES FROM THE DECOMPOSITIONS OF COMPOUNDS 1a AND 1b[a]

| Azo compound ArCHN=NCHAr (CH3, CH3) | Solvent | No. of samples[b] | $k_d/k_c$[c] | Yield[d] of combination + disproportionation products, % | Yield of ketone, % |
|---|---|---|---|---|---|
| Ar = $C_6H_5$ (1a) | $C_6H_6$ | 8 | 0.097 ± 0.002 | 95 ± 2 | 0 |
| 1a | o-$C_6H_4Cl_2$ | 16 | 0.090 ± 0.006 | 80 ± 3 | 21–54[e] |
| 1a | $C_6H_6/C_6H_5N$ | 2 | [f] | [f] | 0[g] |
| Ar = p-$ClC_6H_4$ (1b) | $C_6H_6$ | 8 | 0.176 ± 0.009 | 50 ± 2 | 48.6 ± 2.2[h] |
| 1b | $C_6H_6/C_6H_5N$ | 4 | 0.182 ± 0.008 | 96.9 ± 2.4 | 0 |

[a] From decomposition of the appropriate azo compounds at 118° in sealed ampoules degassed three times. [b] Each sample analyzed in duplicate by glpc. [c] Relative rates of disproportionation to combination as moles α-arylethane/mole 2,3-diarylbutane. [d] From standard plots using 0.1 *M* biphenyl as internal standard. [e] The yield is given as a range since it increases with time up to the value 54%, after which time it remains constant. [f] No values given since pyridine obscured the disproportionation product peak in the glpc trace. [g] Acetophenone was added and the solution rechecked to prove pyridine was not obscuring that peak also, which it was not. [h] The only analysis on this solution was 4 days after opening.

vestigators[3–5] have shown that hydrazones are readily autoxidized to azo hydroperoxides.

The azo hydroperoxide could decompose to ketone, nitrogen, and a secondary alkyl hydroperoxide *via* a homolytic scission and reaction with oxygen. The resultant phenylalkyl hydroperoxide would slowly decompose to a second mole of ketone, with ample precedent.[6]



Chloroazo compound **1b** had been found by Cohen, *et al.*,[7] to yield only about 60% of the theoretical amount of $N_2$, and Peterson and Ross[8] also obtained approximately 60% of the theoretical $N_2$ in their study of induced decomposition of azo compound **1a** in the presence of chloranil. Both groups postulated hydrazone formation.

In both these and the study reported here the abnormal decomposition was found when a reactant or solvent contained chlorine. Ioffe and Stopskii[9] have determined that the hydrazone is the more stable tautomer for a series of alkyl azo compounds, in agreement with the observations here. Care must be exercised in analyzing the results of studies of free radicals in halogenated aromatic solvents.

### Experimental Section

A more detailed description of synthesis, solvent purification, analytical equipment, techniques, and experimental errors has been presented elsewhere.[2] Benzene, *o*-dichlorobenzene, and pyridine were dried and carefully distilled.

The azo decompositions were performed in sealed ampoules after three freeze–thaw degassings at $10^{-6}$ mm. Half-lives of the azo compounds studied were approximately 3 hr[7] at 118° and typical reaction times were 24–48 hr (8–16 half-lives).

For the nmr studies, three nmr tubes connected to 10/30 standard taper joints were degassed, sealed, and thermolyzed as above. Tube A contained 49.1 mg of **1a** and 0.5 ml of benzene, tube B 50 mg of **1a** and 0.5 ml of *o*-dichlorobenzene, and tube C 65 mg of **1b** and 0.5 ml of benzene.

**Registry No.**—**1a**, 5661-68-7; **1b**, 32234-17-6.

(3) A. J. Bellamy and R. D. Guthrie, *J. Chem. Soc.*, 3528 (1965).
(4) H. C. Yao and P. Resnick, *J. Org. Chem.*, **30**, 2832 (1965).
(5) G. J. Karabatsos and R. A. Taller, *J. Amer. Chem. Soc.*, **85**, 3624 (1963).
(6) A. G. Davies, "Organic Peroxides," Butterworths, London, 1961, Chapters 9 and 10.
(7) S. G. Cohen, S. J. Groscos, and D. B. Sparrow, *J. Amer. Chem. Soc.*, **72**, 3947 (1950).
(8) R. Peterson and R. Ross, *Tetrahedron Lett.*, 18 (1960).
(9) B. V. Ioffe and V. S. Stopskii, *ibid.*, 1333 (1968).

## Transannular Alkylations of Cyclooctanones

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*Contribution No. 2109 from the Department of Chemistry, Indiana University, Bloomington, Indiana 47401*

*Received March 8, 1972*

Intramolecular alkylation reactions have recently enjoyed considerable popularity as a method for the synthesis of complex polycyclic compounds.[2] In the present report we examine three suitably substituted cyclooctanones for which transannular effects might be expected to play an important role.

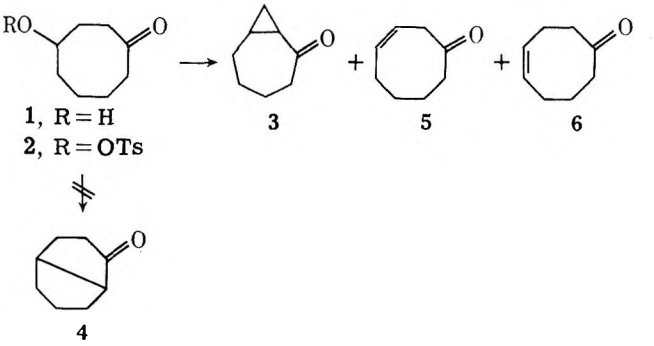
Derivatives of 4-hydroxycyclooctanone (**1**) were examined first. In this instance base treatment should promote enolate formation by proton removal at either side of the carbonyl group with roughly equal facility. The conformational constraints of the carbocyclic system might be expected to enhance the formation of a cyclopentane ring at the expense of the normally favored three-membered ring.[3] In fact, treatment of tosylate **2** with NaH–DMSO, KO-*t*-Bu in ether, or potassium carbonate in DMF all gave bicyclo[5.1.0]cyclooctan-2-one (**3**) cleanly. None of the isomeric ketone **4** was detected. Heating alcohol **1** with dicyclohexylcarbodiimide[4] led to **3** in a more direct synthetic approach.

The acetolysis of certain sulfonate esters has been described as proceeding by participation of a preformed enol derived from a neighboring ketone group.[5] A similar process could occur with **2**. Treatment of **2**

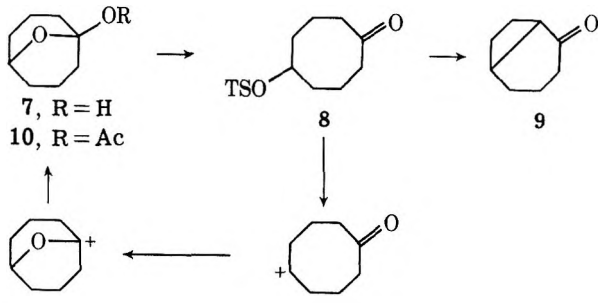
(1) (a) Alfred P. Sloan Fellow, 1968–1970; John Simon Guggenheim Fellow, 1970–1971. (b) NSF Undergraduate Summer Research Participant, 1970–1971. (c) NSF Undergraduate Summer Research Participant, 1967.
(2) See, for example, C. H. Heathcock, *J. Amer. Chem. Soc.*, **88**, 4110 (1966); **89**, 4133 (1967); J. E. McMurry, *ibid.*, **90**, 6821 (1968); H. W. Whitlock, *ibid.*, **84**, 3412 (1962).
(3) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 198.
(4) C. Alexandre and F. Ronessac, *Tetrahedron Lett.*, 1011 (1970).
(5) J. L. Marshall, *Tetrahedron Lett.*, 753 (1971).

with acetic acid containing sodium acetate gave **3** as the major product; but the simple elimination products 3-cyclooctenone (**5**) and 4-cyclooctenone (**6**) were also formed. Interestingly, increasing the concentration of sodium acetate increased the percentage of **3**. Heating **2** in pyridine also gave unsaturated ketones in addition to **3**.

Thus, intramolecular alkylation in **2** proceeds with a kinetic preference for cyclopropane formation. In agreement with these results a model of the enolate precursor of **4** does not indicate an exceptionally favorable stereoelectronic situation despite the enforced proximity of the potentially interacting carbon centers. Transannular bond formation is also observed under the acidic conditions of the acetolysis of **2**.

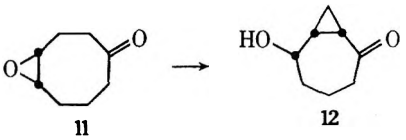



Only one cyclization mode is possible for derivatives of 5-hydroxycyclooctanone (which exists in the hemiketal form **7**), although this process leads to a cyclobutane derivative, normally not a facile cyclization. Nonetheless, reaction of tosylate **8** with either NaH–DMSO or KO-*t*-Bu in ether generated bicyclo[4.2.0]-octan-2-one (**9**) cleanly. Potassium carbonate in DMF




gave no reaction with **8** and heating **7** with dicyclohexylcarbodiimide did not yield a volatile product. Acetolysis of **8** gave mainly 4-cyclooctenone along with small amounts of **10**, probably formed by the indicated cationic cyclization. Thus, intramolecular alkylation of cyclooctanone **8** proceeds readily under strongly basic conditions but not otherwise.

The final ketone examined was 4,5-epoxycyclooctanone (**11**). This compound can react at either of the transannular functional carbons from two possible enolate positions. Furthermore, the fused epoxide ring perturbs the conformational situation. Finally, from a synthetic point of view the generation of a hydroxy group in the potential bicyclic products is of interest. Reaction of **11** with KO-*t*-Bu in ether or potassium carbonate in DMF gave only one of the possible alkylation products, *endo*-6-hydroxybicyclo[5.1.0]octanone (**12**). Thus, three-membered ring cyclization is again favored. The assigned stereochemistry of **12** follows from the presumed SN2 alkylation mechanism.




## Experimental Section

**General.**—Nuclear magnetic resonance (nmr) spectra were taken in carbon tetrachloride solution with Varian A-60 or HR-220 spectrometers. Infrared spectra (ir) were obtained with Perkin-Elmer Model 137 Infracord spectrophotometers on neat samples. Gas chromatography (glpc) was performed on Aerograph A600 (analytical, hydrogen flame detctor), and A700 (preparative) instruments. Analytical columns were 10 ft × 0.125 in. 30% Carbowax 20 M or 10 ft × 0.375 in. SE-30 on Chromosorb W; preparative columns were 10 ft × 0.375 in. 30% Carbowax or 5 ft × 0.375 in. 15% SE-30 on 60–80 Chromosorb W. Percentage composition data were estimated by peak areas and are uncorrected for compound response. Anhydrous magnesium sulfate was used for all drying operations. Microanalyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind.

**4-Hydroxycyclooctanone *p*-Toluenesulfonate.**—To an ice-cold solution of 10 g of **1** in 50 ml of pyridine was added 15 g of *p*-toluenesulfonyl chloride. The mixture was stirred at 0° for 24 hr and then poured into an ice–10% hydrochloric acid mixture. The crystalline mass was collected, washed with a small amount of ether, and recrystallized from hexane to give 10 g (50%) of **2**: mp 83–85°; ir 5.9, 7.5, 8.6, and 11.2 $\mu$; nmr $\delta$ 7.6 (AA'BB' multiplet, 4, aromatic protons), 4.6 (m, 1, CHOTs), 2.45 (s, 3, $CH_3$), and 2.6–1.5 (m, 12).

*Anal.* Calcd for $C_{15}H_{20}O_4S$: C, 60.79; H, 6.80. Found: C, 60.52; H, 6.63.

**5-Hydroxycyclooctanone *p*-Toluenesulfonate.**—To an ice-cold solution of 10 g of **7**[6] in 50 ml of pyridine was added 21 g of *p*-toluenesulfonyl chloride. The mixture was stirred at 0° for 68 hr. The solid material was removed by filtration, water (2 ml) was added, and the solution was stirred for an additional 5 hr before pouring into an ice–10% hydrochloric acid mixture. The crystalline mass was removed by filtration to give 12.8 g (61%) of **8**: mp 77–79°; ir 5.88, 7.4, 8.58, and 11.10 $\mu$; nmr $\delta$ 7.5 (AA'BB' multiplet, 4, aromatic protons), 4.2 (m, 1, CHOTs), 2.4 (s, 3, $CH_3$), and 2.6–1.7 (m, 12). An analytical sample was prepared by recrystallization from hexane.

*Anal.* Calcd for $C_{15}H_{20}O_4S$: C, 60.79; H, 6.80. Found: C, 60.54; H, 6.79.

**Reaction of 2 with Pyridine.**—To 25 ml of pyridine was added 1 g of **2**. The solution was heated on a steam bath for 6 hr, poured into 150 ml of an ice–10% hydrochloric acid solution, and extracted with ether. The ether extracts were washed with 10% hydrochloric acid, saturated sodium carbonate, and water, then dried and concentrated to give 0.32 g (76%) of a crude oil. Glpc showed two products in the ratio 89:11.

The major product was identified as **3** by comparison of its ir spectrum with that of an authentic sample.[7] The minor product was **6**, as shown by comparison.[8]

**Acetolysis of 2.**—To a stirred solution of 1 g of **2** in 40 ml of acetic acid was added 58 mg of anhydrous sodium acetate. The reaction was refluxed for 6 hr, poured into ice–water, and extracted with pentane. The extracts were combined, washed with saturated sodium carbonate solution and water, and then dried and concentrated to give 0.38 g (94%) of a crude oil. Glpc showed two products in the ratio 91:9. The mixture was separated by glpc. The major product was **3**. The second peak was a mixture of **5** (direct comparison[8]) and **6** in the ratio 20:80 as determined from comparison of the nmr integral for the olefin protons of both compounds at $\delta$ 5.65 with the protons characteristic of **5** at $\delta$ 3.05.

(6) Badische Anilin- und Soda-Fabrik Akt.-Ges., British Patent 823,007 (1959); *Chem. Abstr.*, **54**, 8675 (1960).

(7) W. G. Dauben and G. H. Berezin, *J. Amer. Chem. Soc.*, **89**, 3449 (1967). Professor Dauben kindly supplied us with an ir spectrum for comparison purposes.

(8) N. Heap and G. H. Whitham, *J. Chem. Soc. B*, 164 (1966).

To three separate stirred solutions of 0.1 g of **2** in 4 ml of acetic acid were added 2.9, 5.8, and 14.5 mg, respectively, of anhydrous sodium acetate. The reaction mixtures were refluxed for 6 hr, poured into 20 ml of ice–water, and extracted with pentane. Samples were analyzed by glpc. One equivalent of sodium acetate gave a **3**:**5** plus **6** ratio of 81:19; 2 equiv gave 90:10, and 5 equiv gave 92:8.

**Reaction of 1 with Dicyclohexylcarbodiimide.**—To 0.61 g of dicyclohexylcarbodiimide was added 0.42 g of **1**. Stirring was begun and a trace of freshly prepared CuCl was added to the flask. The flask was heated to 150° for 20 min, at which time the material in the flask had solidified. The volatile components were removed by distillation at 150° (10 mm) to give 0.28 g (76%) of **3**.

**Reaction of 2 with NaH–DMSO.**—In a flask was placed 0.3 g of sodium hydride–mineral oil dispersion. After the solution was washed three times with pentane, 10 ml of dimethyl sulfoxide was added by syringe and the mixture was heated under nitrogen at 70–80° for 45 min. After cooling, 1 g of **2** in 10 ml of dimethyl sulfoxide was added and the mixture was allowed to stir at room temperature for 6 hr. The product was extracted with pentane and concentrated to give 0.34 g (78%) of **3**.

**Reaction of 2 with KO-*t*-Bu.**—To 1 g of **2** in 50 ml of anhydrous ether under a nitrogen atmosphere was added 1 g of KO-*t*-Bu. The reaction was stirred for 6 hr at room temperature, at which time the solid material was removed by filtration and washed with ether. The ether extracts were washed with water and concentrated to yield 0.42 g (90%) of **3**.

**Reaction of 2 with $K_2CO_3$–DMF.**—To 1 g of **2** in 30 ml of DMF was added 1.0 g of anhydrous $K_2CO_3$. The mixture was heated to 85° for 4 hr. Water was added and the mixture was extracted with pentane. The extracts were washed with distilled water, dried, and concentrated to give 0.24 g (50%) of **3**.

**Acetolysis of 8.**—Reaction as described above for **2** gave 0.37 g (87%) of an oil containing two products in the ratio 94:6. The major product was **6**; the minor one was **10**.[9]

**Reaction of 7 with Dicyclohexylcarbodiimide.**—To 0.61 g of dicyclohexylcarbodiimide was added 0.42 g of **7**. Stirring was begun and a trace of freshly prepared CuCl was added to the flask. The flask was heated to 150° for 5 hr, at which time it was observed that no precipitate had formed. The reaction was then heated to 200° for 8 hr and cooled to 150°, and the volatile components were removed by distillation. Only small amounts of starting material were recovered.

**Reaction of 8 with $K_2CO_3$–DMF.**—Reaction as described for **2** gave only starting material.

**Reaction of 8 with NaH–DMSO.**—Reaction as described for **2** gave 0.3 g (71%) of an oil identified as **9**:[10] ir 5.85 $\mu$; nmr $\delta$ 2.5–3.2 (m, 2) and 1.2–2.5 (m, 10); 2,4-DNP, mp 178–179.5° (lit.[11] mp 179.5–180°).

**Reaction of 8 with KO-*t*-Bu.**—Reaction as described for **2** gave 0.39 g (90%) of **9**.

**Reaction of 11 with $K_2CO_3$–DMF.**—To 2 g of **11**[12] dissolved in 60 ml of DMF was added 4 g of anhydrous $K_2CO_3$. The mixture was heated to 140° for 72 hr with stirring. The solid materials were removed by filtration and the DMF was removed by distillation at reduced pressure. The solid residue was removed by filtration and washed with ether. The filtrate was concentrated to give 1.8 g (89%) of **12**: ir 3.0, 3.45, 6.0, 8.75, 10.35, and 12.6 $\mu$; nmr $\delta$ 4.1 (s, 1), 3.4 (s, 1), 2.15–1.15 (m, 8), 0.8 (m, 1), and 0.4 (m, 1).

*Anal.* Calcd for $C_9H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.82; H, 8.75.

**Reaction of 11 with KO-*t*-Bu.**—A slurry of 1 g of **11**, 2 g of KO-*t*-Bu, and 30 ml of anhydrous ether was stirred under nitrogen at room temperature for 12 hr, poured into saturated $NH_4Cl$ solution, and extracted with ether. The ether extract was washed with water, dried, and concentrated to give 0.9 g (90%) of **12**.

**Registry No.**—**2**, 34958-36-6; **8**, 34958-37-7; **11**, 34958-38-8; **12**, 34958-39-9.

(9) C. Ganter and J. F. Moser, *Helv. Chim. Acta*, **52** (3), 735 (1969).
(10) A. C. Cope and R. W. Gleason, *J. Amer. Chem. Soc.*, **84**, 1933 (1962).
(11) H. O. House and T. O. Cronin, *J. Org. Chem.*, **30**, 1069 (1965).
(12) J. K. Crandall, J. P. Arrington, and C. F. Mayer, *J. Org. Chem.*, **36**, 1428 (1971).

**Acknowledgment.**—We thank the National Science Foundation for financial support and the Badische Anilin- und Soda-Fabrik Akt.-Ges. for generously providing samples of **1** and **7**.

## 2,3-Annelations on Quinoline and Pyridine 1-Oxides

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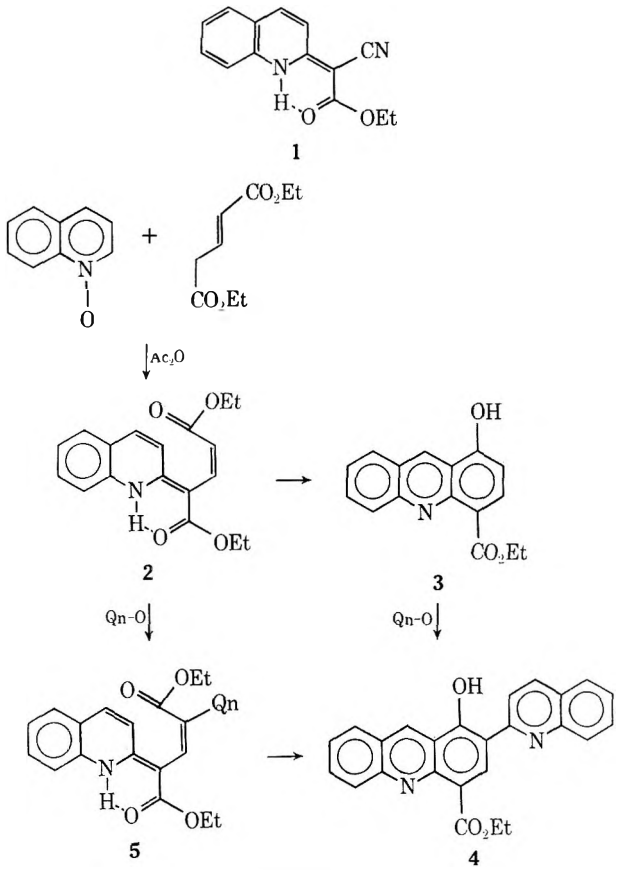
*Received March 14, 1972*

Ethyl $\alpha$-(2-quinolyl)cyanoacetate, the product of the reaction of quinoline 1-oxide with ethyl cyanoacetate in the presence of acetic anhydride,[1] exists exclusively in the tautomeric form **1**.[2] This finding prompted us



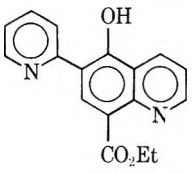

to study the possibilities of achieving 2,3-annelations on the quinoline nucleus *via* intermediates having the salient structural features of **1**. We chose to investigate the reaction of diethyl glutaconate with quinoline 1-oxide, with the idea that if intermediate **2** were formed,[3] its geometry should be such as to permit nucleophilic attack by C-3 on the terminal ester function to yield the acridinol **3**.

The product of the reaction proved to be 4-ethoxycarbonyl-2-(2′-quinolyl)-1-acridinol (**4**) rather than **3**.

(1) M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.*, **11**, 415 (1963).
(2) J. E. Douglass and J. M. Wesolosky, *J. Org. Chem.*, **36**, 1165 (1971).
(3) The cis geometry shown about the terminal carbon–carbon double bond in **2** is not unreasonable in view of the expected rotational lability of this grouping.

The unexpected introduction of a quinolyl group onto the acridine nucleus could have occurred in one of two ways: a second mole of quinoline 1-oxide reacts (i) with 2 to give intermediate **5** which ring closes to **4** or (ii) with **3** to yield **4**. The latter path appears unlikely in view of our failure to detect any reaction of quinoline 1-oxide with several representative phenols. Efforts to isolate either intermediate **2** or **5** have been fruitless.

Pyridine 1-oxide reacts in an analogous manner to afford 8-ethoxycarbonyl-6-(2′-pyridyl)-5-quinolinol (**6**),




**6**

although it could only be isolated from the reaction mixture as its fluoroborate salt and in very low yield.

### Experimental Section[4]

**4-Ethoxycarbonyl-2-(2′-quinolyl)-1-acridinol (4).**—A mixture of 20 mmol of anhydrous quinoline 1-oxide, 20 mmol of diethyl glutaconate (Aldrich Chemical Co.), and 40 mmol of acetic anhydride was stirred at room temperature under nitrogen for 24 hr. The solid which formed was filtered off and recrystallized from chloroform–acetone to yield 2.37 g of very fine, orange needles, mp 204–205°. High-resolution mass spectrometry indicated the composition of the molecular ion (*m/e* 394) to be $C_{25}H_{18}N_2O_3$; ir (KBr) 3550 (OH) and 1735 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 1.43 (t, 3, $CH_3$), 4.38 (q, 2, $OCH_2$), 7.56–7.92 (m, 7), 8.13 (s, 1, 3-H), 8.17 (d, 1, $J$ = 8 Hz, 3′-H), 8.55 (d, 1, $J$ = 8 Hz, 4′-H), 8.86 (d, 1, $J$ = 10 Hz, 5-H), 9.26 (s, 1, 9-H),[5] and 10.46 ppm (s, 1, OH); mass spectrum (60 eV) *m/e* 394 (100, $M^+$), 365 [96, $M^+ - (H + C_2H_4)$], and 128 (35, $C_9H_6N^+$); uv max ($CHCl_3$) 246 nm (log ε 4.52), 288 (4.23), and 438 (4.39).[6]

*Anal.* Calcd for $C_{25}H_{18}N_2O_3$: C, 76.13; H, 4.60; N, 7.10. Found: C, 76.15; H, 4.55; N, 7.04.

When the amounts of quinoline 1-oxide and acetic anhydride were doubled, the yield of **4** was increased to 4.52 g (57%).

**8-Ethoxycarbonyl-6-(2′-pyridyl)-5-quinolinol (6).**—Diethyl glutaconate (9.3 g, 0.050 mol) was added over a period of 30 min to a stirred, ice-cold solution of 9.5 g (0.10 mol) of anhydrous pyridine 1-oxide in 22.4 g (0.22 mol) of acetic anhydride under nitrogen. After the addition was complete, the mixture was allowed to warm to room temperature and stand overnight. Water (100 ml) was added and the water–acetic acid azeotrope was removed on a rotary evaporator until no acetic acid could be detected in the distillate. The reddish-black, viscous residue was triturated with water to remove any unreacted pyridine 1-oxide, taken up in 50 ml of ether, and then treated with 5% fluoroboric acid (to pH 3). The precipitate which formed was filtered off, washed successively with cold water and ether, and recrystallized twice from 80% aqueous ethanol to afford 0.72 g (4%) of yellowish-orange needles: mp 235–240° dec; ir (KBr) 3510 (OH), 1720 (C=O), and 1070 $cm^{-1}$ ($BF_4^-$); nmr (DMSO-$d_6$) δ 1.44 (t, 3, $CH_3$), 4.38 (q, 2, $OCH_2$), 7.6–9.5 (m, 9), and 10.7 ppm (broad s, 1, OH).

*Anal.* Calcd for $C_{17}H_{15}BF_4N_2O_3$: C, 53.43; H, 3.96; N, 7.33. Found: C, 53.12; H, 3.59; N, 7.41.

**Registry No.**—**4**, 34918-49-5; **6**, 34903-57-6.

**Acknowledgment.**—Support for part of this work by a grant from the Marshall University Foundation is gratefully acknowledged.

(4) Melting points were determined on a calibrated Mel-Temp apparatus. Infrared spectra were recorded on a Perkin-Elmer 237 spectrophotometer, nmr spectra on a Varian A-60A spectrometer, and uv spectra on a Beckman DK spectrophotometer. The mass spectrum was kindly provided by the Union Carbide Technical Center, South Charleston, West Virginia.

(5) J. P. Kokko and J. H. Goldstein, *Spectrochim. Acta*, **19**, 1119 (1963).

(6) R. M. Acheson, "Acridines," Interscience, New York, N. Y., 1956, Chapter VII.

## γ-Butyrolactones from the Irradiation of Unsaturated Esters in Alcohols

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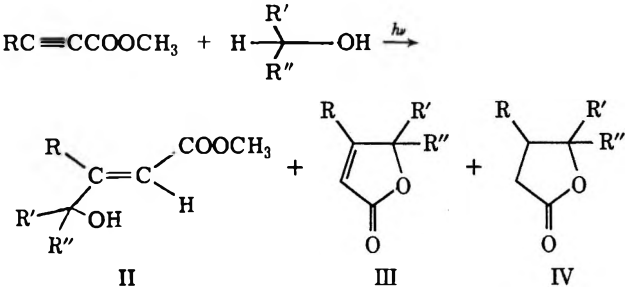
*Received November 29, 1971*

In view of its intrinsic importance in natural product chemistry, γ-lactone synthesis has been a subject of several investigations. A photochemical method first explored by Schenck and coworkers[1] led to the synthesis of some γ-lactones which are not otherwise easily accessible.[2,3] It involves irradiation of an α,β-unsaturated acid in alcohol in the presence of a sensitizer. However, in many instances, particularly when primary alcohols are employed, this method gives poor yields of the lactones. More recently, direct irradiation of α,β-acetylenic esters I (R = $CH_3$, $COOCH_3$, or H) in alcohols has also been shown to yield γ-butyrolactones IV as secondary photolysis products, the primary products being the hydroxy esters II and the unsaturated lactones III.[4,5] The facility with which the adducts II and III are formed prompted us to investigate the possible synthesis of γ-butyrolactones by direct irradiation of olefinic esters.




Photochemical studies with olefinic esters have mainly been concerned with double bond migration *via* γ-hydrogen abstraction[6] and cycloaddition to olefins.[7] The purpose of this communication is to present some synthetic and mechanistic aspects of unsensitized addition of alcohols to olefinic esters.

Irradiation of dilute alcoholic solutions of the ester leads to disappearance of the latter and a concomitant formation of the corresponding lactone. The yields of the lactones were determined by vacuum distillation of the concentrated reaction mixtures (Table I).

The formation of γ-butyrolactones suggests that addition of the alcohol takes place across the double bond of the ester to give an open-chain γ-hydroxy ester which would readily cyclize to form the observed lactone.

(1) G. O. Schenck, G. Koltzenburg, and H. Grossman, *Angew. Chem.*, **69**, 177 (1957).

(2) R. Dulou, M. Vilkas, and M. Pfau, *C. R. Acad. Sci.*, **249**, 429 (1959).

(3) M. Pfau, R. Dulou, and M. Vilkas, *Bull. Soc. Chim. Fr.*, **34**, 3336 (1967).

(4) S. Majeti, Ph.D. Thesis, University of California, Los Angeles, 1969; *Diss. Abstr.*, **30**, 4977b (1970).

(5) B. Büchi and S. H. Fearheller, *J. Org. Chem.*, **34**, 609 (1969).

(6) R. R. Rando and W. v. E. Doering, *ibid.*, **33**, 1671 (1968); M. J. Jorgenson, *Chem. Commun.*, **137** (1965); P. J. Kropp and H. J. Krauss, *J. Org. Chem.*, **32**, 3222 (1967).

(7) A. Cox, P. DeMayo, and R. W. Yip, *J. Amer. Chem. Soc.*, **88**, 1043 (1966); P. DeMayo, S. T. Reid, and R. W. Yip, *Can. J. Chem.*, **42**, 2828 (1966).

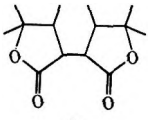
TABLE I

IRRADIATION OF UNSATURATED ESTERS IN ALCOHOLS[a]

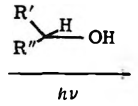
| Starting ester | Alcohol | Time, hr | Unreacted ester, % | γ-Lactone, %[b] |
|---|---|---|---|---|
| 1 | 2-Propanol | 7 | 26 | 64 |
| 2 | 2-Propanol | 14 | 38 | 70 |
| 3 | 2-Propanol | 12 | 58 | 50[d] |
| 1 | Ethanol | 10 | 40 | 68[c] |
| 2 | Ethanol | 10 | 46 | 71[c] |
| 3 | Ethanol | 15 | 68 | 59[c] |

[a] No attempt was made to identify minor volatile products; however, they were taken into account in calculating yields. [b] Based on disappeared starting material. [c] Mixture of cis and trans isomers. [d] The high-boiling material obtained on irradiation of methyl crotonate in 2-propanol has been identified as a dilactone (8) *via* spectroscopic and analytical data.

Since photolyses were carried out in the absence of a sensitizer, the addition reaction most probably took place after hydrogen abstraction from the solvent by the excited ester. Intermolecular hydrogen abstraction by

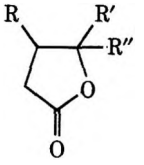


8



$RCH{=}CHCOOCH_3$

1, R = *cis*-$COOCH_3$
2, R = *trans*-$COOCH_3$
3, R = $CH_3$



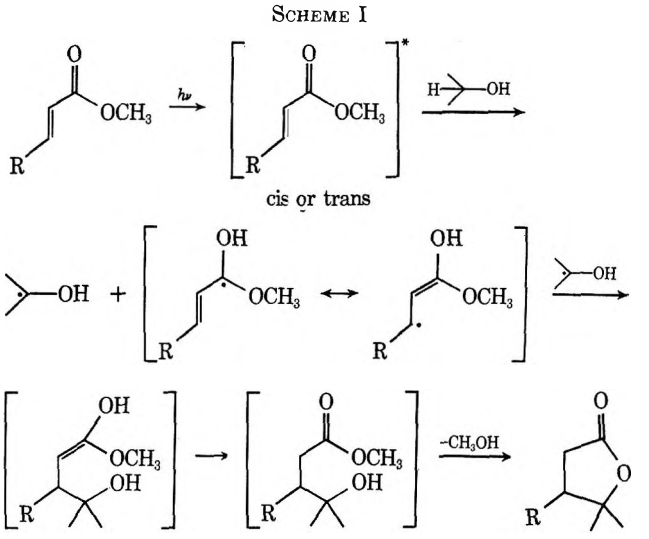
4, R = $COOCH_3$; R′ = R″ = $CH_3$
5, R = $COOCH_3$; R′ = $CH_3$; R″ = H
6, R = $CH_3$; R′ = R″ = $CH_3$
7, R = $CH_3$; R′ = $CH_3$; R″ = H

an excited olefinic ester has not yet been established, although products derived from such a reaction have been observed on several occasions.[3,7] Initial hydrogen abstraction by the excited ester carbonyl leads to α-hydroxyalkyl and allylic radicals, and coupling of the former to the β carbon of the latter followed by tautomerization gives rise to the γ-hydroxy ester, as shown in Scheme I. The hydrogen abstraction step involving the ester carbonyl group is consistent with a mechanism suggested for double bond migration to the β,γ position in the photolyses of α,β-unsaturated esters.[8,9]

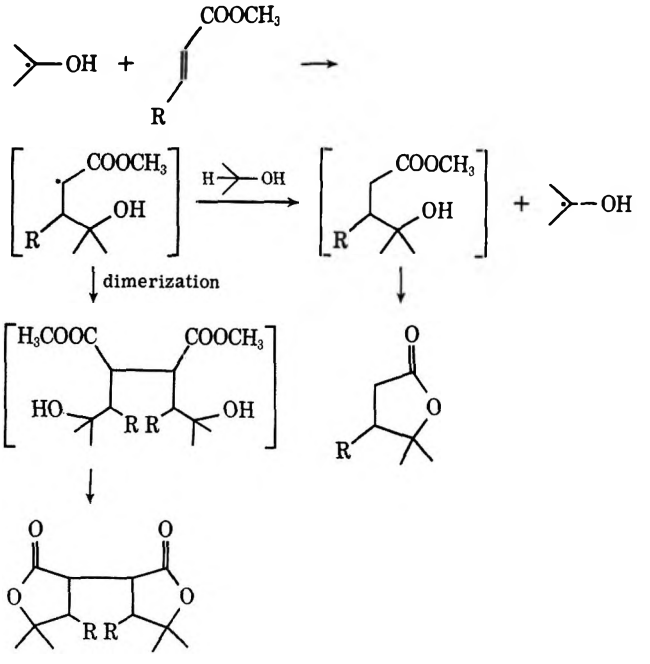
Alternatively, the α-hydroxyalkyl radical could add to the ester in its ground state, and H abstraction by the resulting radical would yield the product and simultaneously initiate chain reaction, as in the case of the benzophenone-sensitized reaction.[3] The isolation of dilactone 8 from the irradiation of methyl

(8) J. A. Barltrop and J. Wills, *Tetrahedron Lett.*, 4987 (1968).
(9) M. J. Jorgenson, *ibid.*, 4991 (1968).

SCHEME I




crotonate in 2-propanol provides support for the proposed radical sequence. However, in the absence of additional evidence it is not possible to ascertain the importance of the radical chain mechanism.




## Experimental Section

**General Irradiation Procedure.**—Irradiations were conducted with 475-ml alcoholic solutions containing 30–50 mmol (5.0 g) of ester using a 450-W Hanovia medium-pressure mercury arc and a water-cooled Vycor immersion well. The solutions were stirred vigorously with a magnet and with a stream of argon introduced through a tube containing an opening at the bottom of the outer jacket. The irradiation mixtures were concentrated and vacuum distilled prior to glpc analysis and spectral characterization of individual components.

**Methyl 2-(1-Hydroxy-1-methylethyl)succinate γ-Lactone (Methyl Terebate) (4).**—Irradiation of 5.0 g of dimethyl maleate in 2-propanol gave 5.7 g of a pale yellow residue which upon distillation yielded 1.2 g of the starting ester, 3.3 g of the lactone 4, bp 111–112° (0.2 mm), and 1.2 g of an undistilled dark residue. Similar irradiation of 5.0 g of dimethyl fumarate in 2-propanol provided after distillation 1.9 g of the starting ester, 2.8 g of lactone 4, and 1.3 g of an undistilled residue. The lactone was

identified from its spectral data[10] and was confirmed by comparison with an authentic sample prepared by a known procedure:[1] ir 1790 (lactone C=O), 1750 (ester C=O), 1380 and 1370 $cm^{-1}$ [$C(CH_3)_2$]; nmr $\delta$ 3.71 (s, 3, $OCH_3$), 2.71 (m, 3, $CH_2$ and CH), 1.55 (s, 3, $\gamma$-$CH_3$), and 1.25 (s, 3, $\gamma$-$CH_3$); mass spectrum *m/e* (rel intensity) 172 (1.7), 157 (48.0), 141 (9.0), 129 (32), 116 (13), 115 (39), 69 (20.5), and 55 (100.0).

**4-Hydroxy-3,4-dimethylpentanoic Acid $\gamma$-Lactone** (6).—Irradiation of 5.0 g of *trans*-methyl crotonate in 2-propanol provided 2.9 g of a mixture of methyl 3-butenoate and cis and trans crotonates, 1.1 g of the lactone 6, bp 74–75° (0.8 mm), and 0.8 g of residue. Lactone 6 was identified from its spectral data and was confirmed by comparison with an authentic sample:[2] ir 1783 (C=O) and 1380 and 1370 $cm^{-1}$ [$C(CH_3)_2$]; nmr $\delta$ 2.35 (m, 2, $\alpha$-$CH_2$), 1.39 (s, 3, $\gamma$-$CH_3$), 1.21 (s, 3, $\gamma$-$CH_3$), and 1.05 (d, 3, $\beta$-$CH_3$, $J$ = 7 Hz). The methine proton resonance was presumed to be submerged under the methyl resonances as a multiplet; mass spectrum *m/e* (rel intensity) 128 (51), 113 (60), 95 (13), 84 (17), 70 (17), 69 (37), and 59 (100). Crystallization of the residue from ether–petroleum ether (bp 30–60°) gave rise to 0.6 g of dilactone 8, mp 161–162°, identified on the basis of its spectral data and mechanistic reasoning:[2] ir 1776 (C=O) and 1380 and 1370 $cm^{-1}$ [$C(CH_3)_2$]; nmr $\delta$ 2.0–3.0 (m, 2, $\alpha$ and $\beta$-CH) 1.5 (s, 3, $\gamma$-$CH_3$), 1.28 (s, 3, $\gamma$-$CH_3$), and 1.02 (d, 3, $\beta$-$CH_3$, $J$ = 6.5 Hz); mass spectrum *m/e* (rel intensity) 254 (12), 239 (55), 221 (7), 193 (5), 128 (32), 127 (12), 113 (55), 109 (17), 95 (20), 74 (17), 70 (32), 69 (30), and 59 (100).

*Anal.* Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 65.89; H, 8.62.

**Methyl 2-(1-Hydroxyethyl)succinate $\gamma$-Lactone ($\gamma$-Methylparaconic Acid Methyl Ester)** (5).—Dimethyl maleate (5.0 g) when irradiated in ethanol gave rise to 2.0 g of the starting material, 2.1 g of a mixture of cis and trans lactones (5) in 34:66 ratio, bp 94–98° (0.2 mm), and 1.0 g of residue. Similar irradiation of dimethyl fumarate yielded 2.3 g of the starting ester, 2.0 g of a mixture of cis and trans lactones 5 in 46:54 ratio, and 0.8 g of residue. The isomeric lactones were separated by glpc analysis and characterized *via* their spectral properties. Stereochemical assignment is only tentative as it is based on glpc retention times and nmr data: ir 1792 (lactone C=O) and 1754 $cm^{-1}$ (ester C=O); nmr $\delta$ (cis) 4.6 (m, 1, OCH), 3.8 (s, 3, $OCH_3$), 2.3–3.0 (m, 3, CH and $CH_2$), and 1.5 (d, 3, $\gamma$-$CH_3$, $J$ = 7 Hz), (trans) 4.8 (m, 1, OCH), 3.8 (s, 3, $OCH_3$), 2.3–3.0 (m, 3, CH and $CH_2$), 1.25 (d, 3, $\gamma$-$CH_3$, $J$ = 7 Hz); mass spectrum *m/e* (rel intensity) 158 (3.8), 143 (10), 130 (19), 127 (22), 116 (32), 115 (26), 114 (49), 111 (6.0), 99 (27), 87 (27), 83 (25), 59 (23), and 55 (100); high-resolution mass data, parent ion, calcd, 158.0579; obsd, 158.0572; (M − 15) ion, calcd, 143.0344; obsd, 143.0343.

**4-Hydroxy-3-methylpentanoic Acid $\gamma$-Lactone** (7).—Irradiation of methyl crotonate (5.0 g) in ethanol gave 2.6 g of a mixture of methyl 3-butenoate and cis and trans crotonates, 0.8 g of a mixture of cis and trans $\gamma$-lactones in 50:50 ratio, bp 80–86° (5 mm), and 0.6 g of residue. The lactones were identified from their spectral data and from a comparison of nmr data with reported values:[11] ir 1783 $cm^{-1}$ (C=O); nmr $\delta$ (cis) 4.15 (m, 1, OCH), 2–2.9 (m, 3, CH and $CH_2$), 1.4 (d, 3, $\gamma$-$CH_3$, $J$ = 7 Hz), and 1.15 (d, 3, $\beta$-$CH_3$, $J$ = 7 Hz); (trans) 4.6 (m, 1, OCH), 3.0–2.0 (m, 3, CH and $CH_2$), 1.25 (d, 3, $\gamma$-$CH_3$ $J$ = 7 Hz), and 1.03 (d, 3, $\beta$-$CH_3$, $J$ = 7 Hz); mass spectrum *m/e* (rel intensity) 114 (69), 99 (88), 86 (18), 71 (92), 70 (100), 56 (35), and 55 (95).

**Registry No.**—**4**, 6934-77-6; **5**, 35096-31-2; **6**, 2981-96-6; **7**, 6971-63-7; **8**, 35096-34-5.

**Acknowledgment.**—The author wishes to acknowledge stimulating discussions with Professor Christopher S. Foote of the University of California at Los Angeles, under whose guidance the initial work was performed.

(10) Infrared spectra were obtained in chloroform solution with a Perkin-Elmer infracord spectrophotometer. Nmr spectra were determined in $CDCl_3$ solution with a Varian HA-100 or T-60 spectrometer using tetramethylsilane as an internal standard. Gas chromatographic analyses were performed on an Aerograph 200 instrument using a 10 × 0.25 in. column packed with 20% SE-30 on 60/80 mesh Chromosorb W. Mass spectra were obtained on an Atlas CH-4 instrument.

(11) J. F. Laporte and R. Rambaud, *C. R. Acad. Sci., Ser. C*, 262, 1095 (1966).

## Catalytic Reduction of Azlactones in Alkaline Media. Synthesis of Amino Acids

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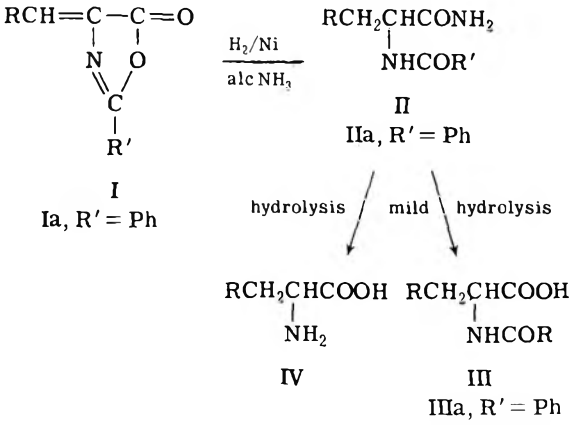
There are three general methods, employing reduction and hydrolysis, for the conversion of azlactones to the corresponding acylamino acids or amino acids. Reduction can be effected with sodium or sodium amalgam in water or ethanol, with hydriodic acid and red phosphorus in acetic acid or acetic anhydride, or catalytically over Pt or Pd in the presence of hydrogen. Though most amino acids, excepting tryptophane, have been synthesized by treatment with hydriodic acid and red phosphorus, the method using sodium or amalgam is not of wide applicability.[1-3] Catalytic reduction has been less favored[4-7] owing, perhaps, to the high cost of Pt and Pd, which becomes a factor in large-scale laboratory preparations, and resistance of azlactones to hydrogenation, which required their initial hydrolysis to the unsaturated acylamino acids.

The present investigations in this direction were undertaken in order to devise a method which combines high yields with few experimental operations. Since catalytic hydrogenation has not received sufficient attention, an attempt has been made to improve this method and make it more economical for large-scale preparations by substituting nickel for the noble metal catalysts which, apart from being expensive, are sensitive to impurities. The sequence of reactions leading to the amino acids generally involves hydrolysis of azlactone to acylaminoacrylic acids, followed by catalytic reduction and finally hydrolysis to the amino acids. It was found that the first two steps could be combined by reductive hydrolysis of a suspension of azlactone (I) in alcoholic ammonia over Raney nickel at elevated hydrogen pressure and room temperature.




(1) H. Fischer and W. Zerweck, *Ber.*, **56**, 519 (1923).
(2) A. Sonn, E. Miller, W. Bulow, and W. Meyer, *ibid.*, **58**, 1103 (1925).
(3) F. Schaaf and A. Labouchers, *Helv. Chim. Acta*, **7**, 357 (1924).
(4) M. Bergmann, F. Stern, and C. Witte, *Justus Liebigs Ann. Chem.*, **449**, 277 (1926).
(5) H. E. Carter, P. Handler, and D. B. Melville, *J. Biol. Chem.*, **129**, 359 (1939).
(6) H. J. Harwood and T. B. Johnson, *J. Amer. Chem. Soc.*, **56**, 468 (1934).
(7) R. N. Herbst and D. Shemin, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 491.

TABLE I

DL-*N*-BENZOYLAMINO ACID AMIDES

| Registry no. | Compd | Hydrogen pressure, psi | Hydrogenation time, hr | Mp, °C | Yield, % |
|---|---|---|---|---|---|
| 24250-72-4 | DL-*N*-Benzoylphenylalanine amide | 50 | 9 | 197–198 | 95 |
| 34996-77-5 | DL-*N*-Benzoyl-*O*-methyltyrosine amide[a,b] | 37.5 | 15 | 215–216 | 77.5 |
| 34996-78-6 | DL-*N*-Benzoyl-3,4-dimethoxyphenylalanine amide[a] | 42 | 3 | 195–196 | 78 |
| 34996-79-7 | DL-*N*-Benzoyltyrosine amide | 40 | 16 | 238–239 | 100 |
| 34996-80-0 | DL-*N*-Benzoyl-3-methoxy-4-hydroxyphenylalanine amide[a] | 55 | 8 | 209–210 | 83.5 |
| 34996-81-1 | DL-*N*-Benzoyl-δ-phenylnorvaline amide[a,c] | 52 | 5 | 160–161 | 75 |
| 34996-82-2 | DL-*N*-Benzoyl-β-furylalanine amide[a,c] | 45 | 5 | 198–199 | 74 |
| 34996-83-3 | DL-*N*-Benzoylvaline amide | 39 | 9 | 220–221 | 84 |
| 34996-84-4 | DL-*N*-Benzoylisoleucine amide | 53 | 4.5 | 215–216 | 72.6 |
| 34996-85-5 | DL-*N*-Benzoylnorleucine amide | 37 | 2 | 143–144 | 76 |
| 24250-71-3 | DL-*N*-Benzoylleucine amide | 32 | 1 | 171–172 | 74 |
| 34996-87-7 | DL-*N*-Benzoylnorvaline amide[c] | 41.5 | 3 | 180–181 | 75 |

[a] Compounds reported for the first time. [b] This was sparingly soluble in hot ethanol and was dissolved in glacial acetic acid for separation from the catalyst and for crystallization. [c] These were soluble in ethanol and no prior heating was required for separation from the catalyst.

TABLE II

DL-*N*-BENZOYLAMINO ACIDS

| Registry no. | Compd | Hydrolyzing agent[a] | Time, hr | Mp, °C | Yield, % |
|---|---|---|---|---|---|
| 2901-76-0 | DL-*N*-Benzoylphenylalanine | A | 18 | 184–185 | 98.8 |
| 34996-89-9 | DL-*N*-Benzoyl-*O*-methyltyrosine | A | 16 | 175–176 | 75 |
| 34996-90-2 | DL-*N*-Benzoyl-3,4-dimethoxyphenylalanine[b] | A | 16 | 180–181 | 95 |
| 34996-91-3 | DL-*N*-Benzoyltyrosine | A | 16 | 194–195 | 89 |
| 2901-78-2 | DL-*N*-Benzoyl-3-methoxy-4-hydroxyphenylalanine | A | 14 | 162–163 | 70 |
| 34996-93-5 | DL-*N*-Benzoyl-δ-phenylnorvaline | A | 12 | 191–192 | 90 |
| 34996-94-6 | DL-*N*-Benzoyl-β-furylalanine | B | | 162–163 | 80 |
| 2901-80-6 | DL-*N*-Benzoylvaline | A | 15 | 147–148 | 89 |
| 2901-99-7 | DL-*N*-Benzoylisoleucine | A | 16 | 135–136 | 95 |
| 34337-14-9 | DL-*N*-Benzoylnorleucine | A | 12 | 135–136 | 80 |
| 17966-67-5 | DL-*N*-Benzoylleucine | A | 16 | 138 | 83 |
| 34337-10-5 | DL-*N*-Benzoylnorvaline | A | 12 | 151–152 | 85 |

[a] A = Hydrochloric acid (36%); B = sodium hydroxide (30%). [b] Compound reported for the first time.

TABLE III

DL-AMINO ACIDS

| Registry no. | Compd | Hydrolyzing agent[a] | Reflux time, hr | Mp, °C | Yield, % |
|---|---|---|---|---|---|
| 150-30-1 | DL-Phenylalanine | A | 5 | 274–275 dec | 90 |
| 7635-29-2 | DL-*O*-Methyltyrosine | A | 4 | 264–265 dec | 76 |
| 33522-62-2 | DL-3,4-Dimethoxyphenylalanine | A | 6 | 241–242 dec | 84 |
| 556-03-6 | DL-Tyrosine | A | 5 | 306–307 dec | 88 |
| 4214-13-5 | DL-3-Methoxy-4-hydroxyphenylalanine | A | 6 | 245–246 dec | 80 |
| 34993-02-7 | DL-δ-Phenylnorvaline[b] | B | 24 | 239–240 dec | 96 |
| 4066-39-1 | DL-β-Furylalanine[c] | C | 24 | 256–257 dec | 73 |
| 516-06-3 | DL-Valine | A | 1.5 | 291–292 dec | 100 |
| 443-79-8 | DL-Isoleucine | A | 2 | 270–271 | 90 |
| 616-06-8 | DL-Norleucine | A | 4 | 284–285 dec | 85 |
| 328-39-2 | DL-Leucine | A | 3 | 286–287 dec | 88 |
| 760-78-1 | DL-Norvaline | A | 2 | 284–285 | 82 |

[a] A = Hydrochloric acid (36%); B = sodium hydroxide (30%); C = barium hydroxide (16%). [b] Obtained from the corresponding *N*-benzoylamino acid amides by refluxing with sodium hydroxide (30%) for 24 hr. [c] Obtained from the corresponding amide by refluxing with barium hydroxide (16%) for 24 hr.

The resulting acylamino acid amide (II) could then be hydrolyzed either to acylamino acid (III) or to the desired amino acid (IV) by mild or stringent treatment with acid or alkali.

In all, 12 amino acids were synthesized and, as evident from the tables given in the Experimental Section, the yields were either comparable to or substantially better than those obtained by existing methods.

### Experimental Section

Satisfactory analyses were obtained for all the reported compounds. Melting points (of the analytically pure compounds whose yields are given in the tables) were taken on a Gallen-Kamp melting point apparatus in open capillaries and are uncorrected. The general procedure reported below was adopted in each case with slight modifications which are indicated as footnotes in the appropriate table. Yields are reported for analytically pure samples. All other similar compounds were prepared more or less by the same general procedure.

**Raney Nickel Catalyst.**—The catalyst was prepared in 5- to 15-g lots using the procedure given in "Organic Syntheses"[8] with the following modifications. Addition of nickel–aluminum alloy (50:50) (BHD) to the sodium hydroxide solution was conducted at room temperature (25–30°) and was completed within 20 min, during which time the temperature rose to 90°. Stirring was continued for another 10 min, and the reaction continued directly at steam bath temperature for another 1–2 hr, when evolution of hydrogen stopped. Catalyst thus obtained could be used for three successive runs without appreciable loss in activity.

**Acylamino Acid Amides.**—Azlactone[9] either in solution or in the form of a suspension (0.025 mol) in ethanol (95%) and ammonia (0.5 mol) catalyst (3 g) was hydrogenated in a Parr hydrogenation apparatus at 32–55 psi for 1–16 hr. Completion of hydrogenation could be read off the gauge provided with the hydrogenation flask and was further marked in most cases either by change in color (*e.g.*, colored to colorless) or by the formation of a flocculent white precipitate. In case of precipitation, which occurred with benzoylphenylalanine amide, benzoyl-3,4-dimethoxyphenylalanine amide, benzoyl-*O*-methyltyrosine amide, benzoyltyrosine amide, and benzoyl-3-methoxy-4-hydroxyphenylalanine amide, the contents were heated to dissolve the amide before filtration of the catalyst. The combined filtrate and washings were evaporated to dryness under reduced pressure and the residue thus obtained was crystallized from ethanol (95%).

Reduction of the azlactones of aliphatic aldehydes and ketones generally required less time (1–9 hr) than that of the aromatic ones. Most amides were purified by recrystallization from ethanol (95%), and some aliphatic amides were crystallized from aqueous ethanol (30–80%) (Table I).

***N*-Benzoylamino Acid.**—The above benzoylamino acid amides were converted into the corresponding *N*-benzoylamino acids by heating on a boiling water bath or a sand bath with hydrochloric acid (36%) till complete dissolution occurred. The required benzoylamino acid crystallized out on keeping the reaction mixture overnight. A single recrystallization from ethanol gave an analytically pure sample (Table II).

**Amino Acid.**—Amino acids were obtained directly from *N*-benzoylamino acid amides by heating them at reflux temperature with hydrochloric acid (36%) for different lengths of time (1.5–6 hr). The amino acid hydrochlorides so obtained were treated with silver oxide, which made isolation of the free amino acids smooth and quantitative (Table III).

**Acknowledgment.**—We are indebted to Dr. S. M. F. Rahman, Head of the Department, for providing research facilities. One of us (A. B.) is thankful to the University Grants Commission, New Delhi, India, for financial aid.

(8) R. Mozingo, *Org. Syn.*, **21**, 15 (1941).
(9) R. Adams, "Organic Reactions," Vol. III, Wiley, New York, N. Y., 1947, pp 198–239.

## C-3 Nucleophilic Substitution of 3-Azetidinyl Tosylates. Alkylation

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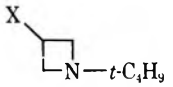
Recently several new 1-*tert*-butylazetidines have been prepared from 1-*tert*-butylazetidines possessing a replaceable functional group at the 3 position. Ohta, *et al.*, reported that 1-*tert*-butyl-3-azetidinyl tosylate reacts with amines and mercaptides to yield 3-aminoazetidines and 3-azetidinyl thioethers, respectively.[2] Gaertner[3] reported that chloroazetidine **2** gives the same results on reaction with these reagents and reacts with alcoholic solutions of alkali metal alkoxides to yield 1-*tert*-butyl-3-alkoxyazetidines. To date, however, the only reported C–C bond forming reaction at C-3 involves the reaction of **1**[2,4] or **2**[3] with cyanide yielding cyanoazetidine **3**. The rate of the reaction



**1**, X = OTs
**2**, X = Cl
**3**, X = CN

of **1** with potassium cyanide in methanol has been shown to be independent of cyanide concentration,[4] which, along with the solvolysis rate data for **1**[4] and the observation that *cis*- and *trans*-1-*tert*-butyl-2-methyl-3-azetidinyl tosylates undergo hydrolysis with stereospecific retention of configuration,[5] seems indicative of an intermediate 1-azabicyclo[1.1.0]butonium ion in the reaction with cyanide and in the solvolysis reactions[4-6] of azetidinyl tosylates.

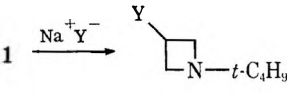
As a continuation of our investigations into the chemistry of functionally substituted azetidines, we have allowed **1** to react with the sodio derivatives of several active methylene compounds. It can be seen from the data in Table I that when the reaction proceeds

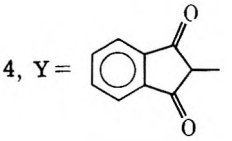
TABLE I
PER CENT YIELDS OF ALKYLATED AZETIDINES OBTAINED FROM THE REACTION OF 1 WITH SODIO DERIVATIVES OF ACTIVE METHYLENE COMPOUNDS

| Compd | Solvent | % Alkylation[a] | Solvent | % Alkylation |
|---|---|---|---|---|
| 4 | MeOH | 0.0 | $Et_2O$ | 0.0 |
| 5 | EtOH | 11 | | |
| 6 | EtOH | 39 | $Et_2O$[b] | ~0[c] |
| 7 | EtOH | 67 | $Et_2O$[b] | 8–9[c] |

[a] Isolated yield. [b] Contains 1 equiv of ethanol. [c] Per cent of crude azetidinyl product by pmr.

in alcoholic solvent, the yield of alkylated product is significantly better than when the reaction is conducted in ether solvent. Since the reactions in the different solvents were conducted for essentially the same period of time, it may be surmised that the reactions in ether





**5**, Y = $CN(CO_2Et)CH$
**6**, Y = $(CO_2Et)_2CH$
**7**, Y = $Ac(CO_2Et)CH$

(1) To whom correspondence should be addressed.
(2) T.-Y. Chen, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jap.*, **41**, 712 (1968).
(3) V. R. Gaertner, *J. Org. Chem.*, **35**, 3952 (1970).
(4) R. H. Higgins, F. M. Behlen, D. F. Eggli, J. H. Kreymborg, and N. H. Cromwell, *ibid.*, **37**, 524 (1972).
(5) R. H. Higgins and N. H. Cromwell, in press.
(6) J. A. Deyrup and C. L. Moyer, *Tetrahedron Lett.*, 6179 (1968).

are considerably less rapid than those in the alcoholic solvent. This is consistent with a cationic intermediate and appears to be inconsistent with the direct displacement mechanism.[7]

The ir and pmr spectra of **5** and **6** are consistent with the expected structures for these compounds. Thus the pmr spectrum of **6** consists of a four-proton quartet[8] centered at $\delta$ 4.20 ppm (methylene protons of ethyl groups), a six-proton multiplet at $\delta$ 2.90–3.75 (ring protons plus the methine proton of the malonate group) which integrates to five protons upon addition of deuterium oxide, a six-proton triplet[8] at $\delta$ 1.28 (methyl protons of the ethyl groups), and a nine-proton singlet[8] at $\delta$ 0.93 (*tert*-butyl protons); the infrared spectrum of **6** contains a typical ester carbonyl stretching frequency at 1740 $cm^{-1}$ in carbon tetrachloride. The spectra of **5** are very similar. The pmr spectrum consists of a two-proton quartet at $\delta$ 4.26 (methylene protons of the ethyl group), a one-proton doublet ($J$ = 7.4 Hz) at $\delta$ 3.77 (methine proton of cyanoacetate group) which disappears on addition of deuterium oxide, a five-proton multiplet at $\delta$ 2.67–3.63 (ring protons), a three-proton triplet at $\delta$ 1.32 (methyl protons of ethyl group), and a nine-proton singlet at $\delta$ 0.95 (*tert*-butyl protons); the infrared spectrum of **5** contains a typical ester carbonyl stretching frequency at 1742 $cm^{-1}$ in deuteriochloroform.

The spectra of **7** are significantly different from those of **5** and **6**. The infrared spectrum ($\nu_{CCl_4}$ 3300, 1690, and 1635 $cm^{-1}$) suggests that the acetoacetate is extensively enolized, a result which was not anticipated since $\alpha$-alkyl substituents generally decrease the amount of enol present.[9] Additional support for an enol structure for **7** can be obtained from the pmr spectrum: a four-proton multiplet (of which the quartet of the methylene protons of the ethyl group can be observed at $\delta$ 4.20) at $\delta$ 4.00–4.52 (one set of the C-2,4 protons of the ring and the methylene protons of the ethyl group), a three-proton multiplet at $\delta$ 2.27–3.50 (remainder of the ring protons), a three-proton absorption of two singlets[10] centered at $\delta$ 2.18 (acetyl protons), a three-proton triplet at $\delta$ 1.29 (methyl protons of the ethyl group), a nine-proton absorption of two singlets at $\delta$ 1.05 and 0.98 (*tert*-butyl protons) in a ratio of *ca.* 9:1, respectively, and a broad one-proton absorption at $\delta$ 0.86 (OH) which disappears on addition of deuterium oxide.

While it is possible that the magnetic nonequivalence of the acetyl and *tert*-butyl protons is the result of the same type of phenomenon observed in the spectrum of **6** (*vide supra*), we are of the opinion that the nonequivalence of these protons in **7** is best described in terms of different enolic structures.[11] The broad absorption at 3300 $cm^{-1}$ seems indicative of predominantly *intermolecular* hydrogen bonding, as upon dilution this absorption is found to have obscured two weaker absorptions at 2285 and 2335 $cm^{-1}$. Consequently, we suggest that the singlet at $\delta$ 1.05 in the pmr spectrum of **7** is due to the *tert*-butyl protons of the intermolecularly hydrogen bonded species, and the singlet at $\delta$ 0.98 is due to one (or both) of the intramolecularly hydrogen bonded forms of **7**.

These interesting new derivatives of azetidine are potential starting points in the synthesis of a variety of other azetidines. Such possibilities are being investigated in this laboratory.

## Experimental Section[12]

**1-*tert*-Butyl-3-azetidinyl Tosylate (1).** This compound, which was first prepared by Ohta, *et al.*,[13] was prepared *via* the sodium hydride method.[14]

**Preparation of Alkylated Azetidines in Alcoholic Solvent. Attempted Preparation of 2-(1-*tert*-Butyl-3-azetidinyl)indane-1,3-dione (4).**—To a solution of 0.525 g (9.73 mmol) of sodium methoxide and 1.42 g (9.72 mmol) of indane-1,3-dione in 100 ml of ether was added 2.75 g (9.72 mmol) of **1**. The solution was stirred for 2 days at room temperature and then evaporated to a viscous yellow-brown oil. Aqueous, saturated sodium carbonate (150 ml) was added, and the solution was extracted twice with equal volumes of ether. The combined ethereal extracts were dried (sodium carbonate). The pmr spectrum of the residue remaining after evaporation of the ether was superimposable on that of 1-*tert*-butyl-3-methoxyazetidine.[4]

**Ethyl (1-*tert*-Butyl-3-azetidinyl)cyanoacetate (5).**—To 100 ml of an ethanolic solution of sodium ethoxide prepared from 0.60 g (0.025 g-atom) of sodium was added 2.83 g (0.0250 mol) of ethyl cyanoacetate. After stirring for a few minutes, 7.00 g (0.0248 mol) of **1** was added and the solution was stirred for 20 hr (allowing a longer reaction time gave no increase in yield). After filtering, the ethanol was removed *in vacuo*. The filtered salts were washed with ether, the filtrate being added to the residue from evaporation of the ethanol. The ethereal solution was again filtered, and the ether was removed *in vacuo*. Distillation, bp 108–114° (0.8 Torr), afforded 0.61 g (11%) of **5** as a colorless oil which rapidly turned red and resinified on standing.

We were unable to obtain the picrate of **5** in pure form.

*Anal.* Calcd for $C_{18}H_{23}N_5O_9$ (picrate, mp 180° dec): C, 47.68; H, 5.11; N, 15.50. Found: C, 46.88; H, 5.05; N, 15.98.

**Ethyl (1-*tert*-Butyl-3-azetidinyl)acetoacetate (7).**—To a solution prepared from 0.60 g (0.025 g-atom) of sodium and 100 ml of ethanol was added 3.35 g (0.025 mol) of ethyl acetoacetate and then 7.00 g (0.0248 mole) of **1**. The solution was stirred at room temperature for 40 hr and then filtered to remove much of the precipitated sodium *p*-toluenesulfonate. The ethanol was removed *in vacuo*. The filtered salt was washed with ether, which was then added to the oily residue obtained after the evaporation of the ethanol; the dry sodium *p*-toluenesulfonate weighed 4.80 g (99%). The ethereal solution of **7** was again filtered, and the ether was removed *in vacuo*. Distillation afforded 4.00 g (67%) of **7** as a nearly colorless liquid, bp 90–95° (0.5 Torr).

*Anal.* Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.81; mol wt, 241. Found: C, 64.63; H, 9.56; N, 5.72; mol wt, 241 (mass spectrometer).

**Diethyl (1-*tert*-Butyl-3-azetidinyl)malonate (6).**—To a solution prepared from 0.60 g (0.025 g-atom) of sodium and 100 ml of ethanol was added 4.00 g (0.025 mol) of ethyl malonate and then 7.00 g (0.0248 mol) of **1**. The solution was stirred at room temperature for 64 hr and worked up exactly as described for the preparation of **7**. Distillation, bp 100–104° (0.6 Torr), afforded 2.60 g (39%) of **6** as a colorless liquid. Much resinous material remained in the distilling flask.

(7) See, for example, K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, pp 388–389.

(8) Each member of this absorption appears as two slightly separated ($\Delta\nu$ = 1–2 Hz) absorptions.

(9) M. S. Newman, "Steric Effects in Organic Chemistry," Wiley, New York, N. Y., 1956, p 446.

(10) Appears as two slightly separated singlets ($\Delta\nu$ = 1 Hz).

(11) We have insufficient data to assign geometrical isomers to any enol other than the chelated one.

(12) Melting points are uncorrected. Microanalyses were determined by Micro-Tech Laboratories, Skokie, Ill., or by Alfred Bernhardt Mikroanalytisches Laboratorium, Hohenweg, West Germany. Pmr spectra were determined on either a Varian A-60 or a Varian A-60D spectrometer in deuteriochloroform solutions containing *ca.* 1% TMS, internal standard. Infrared spectra were determined on a Perkin-Elmer Model 237 spectrophotometer.

(13) T.-Y. Chen, T. Sanjiki, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jap.*, **40**, 2401 (1967).

(14) R. H. Higgins, E. Doomes, and N. H. Cromwell, *J. Heterocycl. Chem.*, **8**, 1063 (1971).

In a subsequent preparation, dry hydrogen chloride gas was passed through the ethereal solution of **6** and ethyl malonate. The ethereal solution of ethyl malonate was carefully decanted from the oily hydrochloride of **6**. The hydrochloride was washed with ether and then liberated to the free amine by the action of an excess of triethylamine in ether. The ethereal solution was then filtered and distilled as before. Compound **6** was again obtained in a 39% yield with slightly less resinification in the distilling flask.

*Anal.* (picrate, mp 85–86.5°). Calcd for $C_{20}H_{28}N_4O_{11}$: C, 48.00; H, 5.64; N, 11.20. Found: C, 47.86; H, 5.46; N, 11.40.

**Attempted Preparation of Alkylated Azetidines in Ether. Attempted Preparation of 2-(1-*tert*-Butyl-3-azetidinyl)indane-1,3-dione (4).**—To a solution of 0.52 g (3.56 mmol) of indane-1,3-dione and 0.085 g (3.54 mmol) of sodium hydride in 25 ml of ether, which had been stirred for 15 min, was added 1.00 g (3.53 mmol) of **1**. The mixture was stirred for 30 hr. Water was added, and the ethereal layer was separated and dried (magnesium sulfate). Evaporation of the ether yielded 0.95 g of white solid identified as **1** by pmr spectroscopy.

**Attempted Preparation of Diethyl (1-*tert*-Butyl-3-azetidinyl)-malonate (6).**—To a solution of sodium ethoxide prepared from 0.57 g (0.0248 g-atom) of sodium and 1.14 g (0.0248 mol) of ethanol in 100 ml of ether was added 4.00 g (0.025 mol) of ethyl malonate. After *ca.* 20 min 7.00 g (0.025 mol) of **1** was added. After 48 hr the mixture was filtered and the ether was removed *in vacuo*. The pmr spectrum of the crude product indicated little if any **6**.

**Preparation of Ethyl (1-*tert*-Butyl-3-azetidinyl)acetoacetate (7).**—To a solution of sodium ethoxide prepared from 0.57 g (0.0248 g-atom) of sodium and 1.14 g (0.0248 mol) of ethanol in 100 ml of ether was added 3.35 g (0.025 mol) of ethyl acetoacetate. After stirring for *ca.* 20 min, 7.00 g (0.025 mol) of **1** was added. After stirring for 48 hr the mixture was filtered, and the ether was removed from the filtrate *in vacuo*. The pmr spectrum indicated 8–9% of the azetidine to be **7**, the remainder unreacted **1**.

**Registry No.**—**1**, 17358-65-5; **5**, 34910-31-1; **5** picrate, 34910-32-2; **6**, 34910-33-3; **6** picrate, 34910-34-4; **7**, 34910-35-5.

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## A Solvolytic Fission of a Carbon–Fluorine Bond Induced by Triethyl Orthoformate in 6β-Fluoro-17α-acetoxyprogesterone[1]

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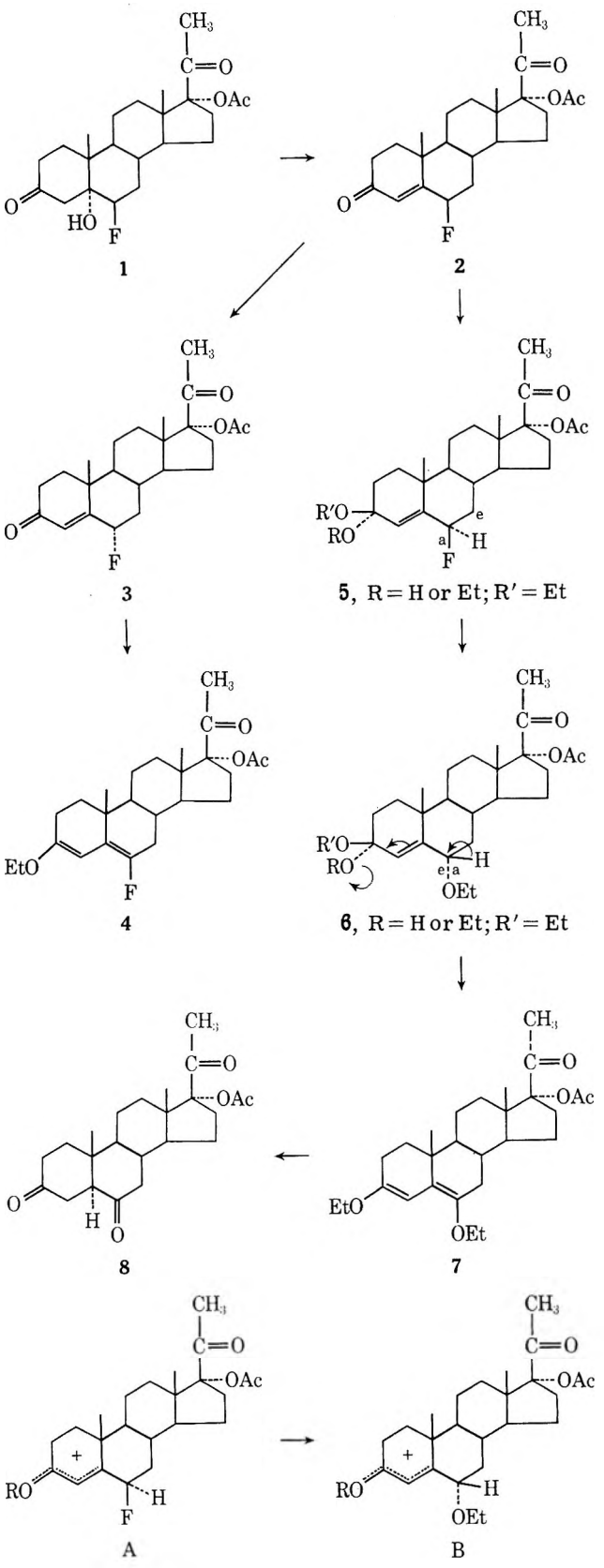
*Received June 29, 1971*

In the course of a series of synthetic transformations, we became interested in the preparation of 3-ethoxy-6-fluoro-17α-acetoxypregna-3,5-dien-20-one (**4**) from 6β-fluoro-17α-acetoxyprogesterone (**2**). Treatment of **2** with triethyl orthoformate in dichloromethane solution in the presence of *p*-toluenesulfonic acid dihydrate at room temperature gave a new compound in 79% yield which differed from the expected dienol ether **4**. The structure of this new compound was established as 3,6-diethoxy-17α-acetoxypregna-3,5-dien-20-one (**7**) based on its physical properties and conversion to the corresponding 3,6-diketone **8** on treatment with acid. Formation of this interesting product may be explained as follows. It is known that 6β-fluoro-3-keto steroids require very severe conditions for epimerization to the corresponding 6α-fluoro isomers, such as treatment with hydrogen chloride in acetic acid for a period of several hours.[2] This indicates that loss of an equatorial




(1) This paper represents Contribution No. 391 from the Institute of Organic Chemistry, Syntex Research, Palo Alto, Calif.

(2) A. Bowers, L. Cuellar Ibañez, and H. J. Ringold, *Tetrahedron*, **7**, 138 (1959).

proton in a cation such as A (R = H) to give a fluorodienol analogous to **4** is slow. In the present experiment, initial formation of A (R = Et) or the ketal or hemiketal **5** is apparently followed by preferential solvolysis of the axial fluorine atom at C-6 to yield the 6α-ethoxy intermediate [6 or B (R = Et)]. This intermediate then collapses to **7** by loss of the axial C-6 proton.

It is noteworthy that the 6α-fluoro isomer **3** yields the enol ether **4** as expected.[3]

### Experimental Section[4]

**6β-Fluoro-17α-acetoxyprogesterone (2).**—A suspension of 900 mg of 5α-hydroxy-6β-fluoro-17α-acetoxyprogesterone[2] (1) in 10 ml of dichloromethane containing 1 ml of pyridine was cooled to 0° and then 900 mg of thionyl chloride was added. The mixture was stirred at 0° for 30 min and then diluted with 100 ml of water. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic phase was washed with water to neutrality and dried with anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The crystalline residue was crystallized once from acetone–hexane and twice from dichloromethane–hexane to yield 650 mg of **2**: mp 184°; $[\alpha]D$ −18°; uv 233 mμ (ε 13,180); nmr 0.78 (18-H), 1.30, 1.32 (19-H, $J$ = 2.5 Hz), 2.08, 2.11 (21-H + 17α AcO), 4.61, 5.02 (6α-H, $J$ = 48 Hz), 5.83, 5.92 ppm (4-H, $J$ = 4 Hz). *Anal.* Calcd for $C_{23}H_{31}O_4F$: C, 70.74; H, 8.00; F, 4.84. Found: C, 70.78; H, 8.32; F, 4.32.

**3,6-Diethoxy-17α-acetoxypregna-3,5-dien-20-one (7).**—A solution of 1 g of 6β-fluoro-17α-acetoxyprogesterone in 10 ml of dichloromethane was treated at room temperature with 30 mg of *p*-toluenesulfonic acid dihydrate and 0.9 ml of triethyl orthoformate. The reaction mixture was stirred for 2 hr at room temperature and then 5 drops of pyridine was added and the mixture was washed with water, dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane and filtered through 15 g of sil ca gel, eluting with the same solvent (500 ml). The solvent was removed under reduced pressure to yield 900 mg of **7**, homogenous on tlc (25% ethyl acetate–75% hexane).

This material was crystallized from dichloromethane–methanol to yield an analytical sample: mp 104–106°; $[\alpha]D$ −119°; uv 322 mμ (ε 716), 246 (19,326); $\nu_{max}$ 1735, 1770, 1250 $cm^{-1}$; nmr 0.68 (18-H), 0.96 (19-H), 2.11 (21-H), quartets centered at 3.75 and 3.85, and triplets centered at 1.26 and 1.32 (C-6 and C-3 EtO groups) and 5.68 ppm (4-H). *Anal.* Calcd for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07; O, 17.99. Found: C, 72.88; H, 9.01; O, 18.24.

This product proved to be unstable on standing. A small sample was dissolved in a mixture of 95% tetrahydrofuran–5% water and treated with a few drops of concentrated hydrochloric acid. After 30 min, no starting material was present and a more polar, nonultraviolet-absorbing compound corresponding to diketone **8** was detected by tlc analysis. Not enough sample was available for full characterization of this compound.

**Registry No.**—**2**, 336-79-8; **7**, 35048-85-2.

**Acknowledgments.**—Thanks are due to Dr. John Fried for very helpful discussions during the preparation of this manuscript.

(3) P. Crabbé and J. Iriarte, unpublished results.

(4) Melting points are corrected. Optical rotations were measured in chloroform solution unless stated otherwise using an O. C. Rudolph and Sons Model 80 polarimeter. Ultraviolet spectra were measured in methanol using a Cary Model 14 spectrometer. Nmr spectra were recorded on a Varian A-60 spectrometer using deuteriochloroform as solvent. Chemical shifts are recorded in parts per million (ppm). Infrared spectra were measured using a Perkin-Elmer Model 137 spectrophotometer. We wish to thank Dr. L. Throop's staff for these measurements.

# Communications

See Editorial, *J. Org. Chem.*, **37**, No. 13, 4A (1972).

## A Total Synthesis of Prostaglandins $F_{1\alpha}$ and $E_1$

*Summary: A synthesis of prostaglandins $F_{1\alpha}$ and $E_1$ has been accomplished starting from the lactone* **1** *by a route in which the carboxylic side chain is added first and the remaining side chain subsequently; key intermediates include the hydroxy acid* **2**, *the aldehyde* **3**, *and the ketone* **4**.

*Sir:* In previous papers we have reported the synthesis of the six primary prostaglandins from a common intermediate by a route in which the seven-carbon carboxyl-bearing side chain was elaborated after the eight-carbon hydroxylic side chain.[1,2] We now describe a modification of this approach in which the side chains are introduced in the reverse order. The modified synthetic scheme can advantageously be applied to the synthesis of a new range of prostanoid structures which are of biological and medical interest.

Conversion of the readily available (−)-hydroxy lactone **1**[2] to the tetrahydropyranyl (THP) derivative and reduction with 1.1 equiv of diisobutylaluminum hydride in toluene at −78° for 1.0 hr yielded the oily lactol **2**[3,4] which was condensed with the Wittig reagent derived from 5-triphenylphosphoniopentanoic acid[5] and sodio methylsulfinylcarbanide[5] in dimethyl sulfoxide to form the hydroxy acid **3**[4,6] (83% from **1** after silica gel column chromatography using ethyl acetate as eluent). Treatment of the hydroxy acid **3** with excess diazomethane in ether afforded the hydroxy ester **4**[3,4] which was acetylated using 2.25 equiv of acetic anhydride in pyridine at 50°. Hydrogenation of the resultant acetoxy ester **5**[3,4] was carried out in 5% acetic acid–absolute ethanol as solvent under 1 atm of hydrogen for 48[7] hr with 5% palladium on carbon

(1) E. J. Corey, R. Noyori, and T. K. Schaaf, *J. Amer. Chem. Soc.*, **92**, 2586 (1970).

(2) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *ibid.*, **93**, 1490 (1971); see also E. J. Corey, T. Ravindranathan, and S. Terashima, *ibid.*, **93**, 4327 (1971).

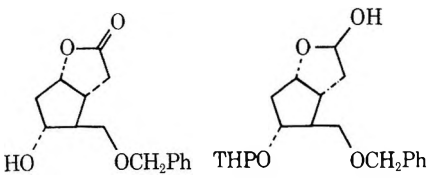
(3) Unless designated, the crude product was used without purification.

(4) Infrared and nmr (at 60 MHz) spectra were in agreement with the assigned structure.

(5) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969).

(6) Satisfactory mass spectral data were obtained on this oily compound.

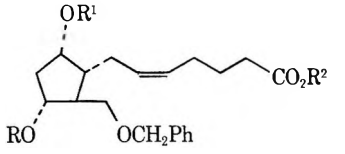
(7) The first equivalent of hydrogen is rapidly consumed (2 hr), whereas the second equivalent is slowly consumed over the remaining 46 hr. Alternatively, the hydrogenation can be monitored by thin layer chromatography using 2:1 benzene–ether as eluent with the ether **5** and alcohol **6** having $R_f$ 0.80 and 0.20, respectively.



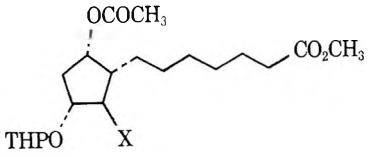
**1** $[\alpha]^{20}D$ −7.2° (*c* 1, $CHCl_3$)



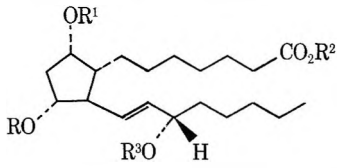
**2** $[\alpha]^{20}D$ +7.2° (*c* 0.8, $CHCl_3$)



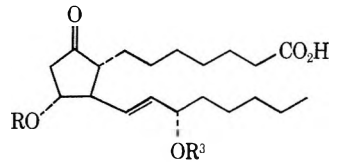
**3**, R = THP; $R^1$ = H; $R^2$ = H
**4**, R = THP; $R^1$ = H; $R^2$ = $CH_3$
**5**, R = THP; $R^1$ = $COCH_3$; $R^2$ = $CH_3$



**6**, X = $CH_2OH$
**7**, X = CHO
**8**, X = CH=CHCO($n$-$C_5H_{11}$)
**9**, X = CH=CHCHOH($n$-$C_5H_{11}$)



**10**, R = $R^3$ = H; $R^1$ = $COCH_3$; $R^2$ = $CH_3$
**11**, R = $R^1$ = $R^2$ = $R^3$ = H
**12**, R = $R^3$ = THP; $R^1$ = $COCH_3$; $R^2$ = $CH_3$
**13**, R = $R^3$ = THP; $R^1$ = $R^2$ = H



**14**, R = $R^3$ = THP
**15**, R = $R^3$ = H

(Engelhard Industries, Inc.) (amount, 0.10 times weight of substrate **5**) to afford the oily alcohol **6**[3,4] (82% from **3**). Oxidation of the alcohol **6** using the Collins reagent generated *in situ*[8] in methylene chloride at 0° produced the unstable oily aldehyde **7** which was immediately treated with the sodio derivative of dimethyl 2-oxoheptylphosphonate[9] in dimethoxyethane at 25° for 2.0 hr to form stereospecifically the oily trans enone **8**[4,6] (83% from **6** after silica gel column chromatography using 1:1 methylene chloride–ethyl acetate as eluent). Treatment of the enone **8** with excess zinc borohydride[5] in dimethoxyethane at 25° for 3.0 hr afforded a mixture of epimeric alcohols **9**[3,4,10] (ratio ~1:1). Hydrolysis of **9** using 2:1 acetic acid–water at 40 ± 2° for 2.5 hr afforded the 11$\alpha$,15$\alpha$-dihydroxy prostanoid **10**[11,12] and its 15$\beta$ epimer (>95% yield from **8**). Separation of the desired 15$\alpha$ epimer **10**[4,6] from the mixture was accomplished by silica gel column chromatography using 4:1 ether–cyclohexane as eluent. Further, the 15$\beta$ epimer of **10** could be used in the synthesis, since it reverts to the precursor **8** upon oxidation with activated manganese dioxide in methylene chloride followed by pyranylation with dihydropyran (1.5 equiv) in methylene chloride containing *p*-toluenesulfonic acid (0.01 equiv) at 25° for 5 min.

Optically active prostaglandins $F_{1\alpha}$ and $E_1$ were obtained from the 11$\alpha$,15$\alpha$-dihydroxy prostanoid **10** in the following manner. Cleavage of **10** with 1.0 *N* aqueous sodium hydroxide (3 equiv) in methanol–tetrahydrofuran at 25° for 1.5 hr afforded crystalline prostaglandin $F_{1\alpha}$ (**11**), >95% yield from **10** which was homogeneous by thin layer chromatographic analysis). Recrystallization from ethyl acetate–cyclohexane afforded prostaglandin $F_{1\alpha}$ (**11**) as colorless needles, $[\alpha]^{20}D$ +25.0° (*c* 1.1, THF), mp and mmp[13] 100–101.5°. The ir and nmr spectra and chromatographic behavior of the two samples of prostaglandin $F_{1\alpha}$ were identical.

The dihydroxy prostanoid **10** was converted to the bistetrahydropyranyl derivative **12**[3,4] using dihydropyran (3 equiv) in methylene chloride containing *p*-toluenesulfonic acid (0.01 equiv) at 25° for 20 min. Cleavage of **12** with 1.0 *N* aqueous sodium hydroxide (3 equiv) in methanol–tetrahydrofuran afforded the bis-THP ether of prostaglandin $F_{1\alpha}$ (**13**)[3,4] which was oxidized by Jones reagent at −20° affording the bis-THP ether of prostaglandin $E_1$ (**14**).[3,4] Hydrolysis of **14** using 2:1 acetic acid–water at 40 ± 2° for 5 hr afforded crystalline prostaglandin $E_1$ (**15**, 55% yield from **10**). Recrystallization from ethyl acetate–cyclohexane afforded colorless microcrystals, $[\alpha]^{20}D$ −57.0° (*c* 0.9, THF), mp and mmp[13] 113.5–114.0°. The spectra and chromatographic properties of the two samples of prostaglandin $E_1$ were identical.

We anticipate that a number of improvements in the synthetic approach described above may be realizable, including the use of other protecting groups which will render many of the intermediates crystalline and the use of modified procedures[14] for the stereoselective introduction of the chiral center at C-15.

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(12) For nomenclature with regard to stereochemical orientation, see B. Samuelsson, *Angew. Chem., Int. Ed. Engl.*, **4**, 410 (1965).
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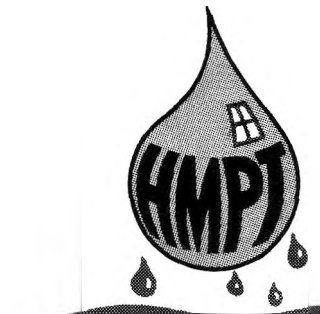


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