

tions on the enzyme surface which it would have to occupy were the reactions to result in the formation of racemic ethanol-1-*d*. In other words, perhaps the methyl group is forced, by steric repulsions, out of all possible positions except that in which it is actually attracted to the enzyme surface. An interpretation requiring both attractive and repulsive forces between enzyme and substrate is consistent with the fact that the higher aliphatic alcohols,<sup>17</sup> as well as isopropyl alcohol<sup>18</sup> and meth-

anol,<sup>17</sup> react only very slowly with DPN<sup>+</sup> in the presence of yeast alcohol dehydrogenase.

The data of Table II unequivocally demonstrate that the reaction sequence (equations 9 and 10) has accomplished a stereochemical inversion about the asymmetric carbon atom of ethanol-1-*d*. Since the displacement reactions of primary alcohols, halides, tosylates, etc., show second order kinetics,<sup>8</sup> it had often been assumed that these compounds react with stereochemical inversion about the primary carbon atom. The results here presented prove, in one particular instance, that this assumption is correct. The assumption has similarly been substantiated by the independent investigations of A. Streitwieser,<sup>19</sup> who has synthesized butanol-1-*d* by chemical means, and has established the stereochemical inversion of the corresponding bromide.

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TABLE II  
IDENTIFICATION OF THE ENANTIOMORPHS OF ETHANOL-1-*d*  
BEFORE AND AFTER INVERSION

Sequence	Source of monodeuteroethanol	Products of oxidation of monodeuteroethanol atoms D per molecule <sup>a</sup>		
		Acetaldehyde	Direct	Transferred to lactate
I	CH <sub>3</sub> CHO + DPND	0.00	0.8	0.61
		.00	1.1	.88
II	CH <sub>3</sub> CDO + DPNH	.81	0.00	
Inversion	Inverted product from Sequence II	.00	1	.7

<sup>a</sup> Atoms D per molecule/atoms D per molecule of monodeuteroethanol, *i.e.*, atoms D per molecule based on the monodeuteroethanol used.

(17) E. S. G. Barron and S. Levine, *Arch. Biochem. Biophys.*, **41**, 175 (1952).

(18) K. Burton and T. H. Wilson, *Biochem. J.*, **54**, 86 (1953).

(19) A. Streitwieser, *THIS JOURNAL* **75**, 5014 (1953).

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

## Alkylation of Cyclopropyl Phenyl Ketone

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Evidence bearing on the lability of ring hydrogens in cyclopropyl ketones and esters is discussed. It is shown that cyclopropyl phenyl ketone, with sodamide or sodium triphenylmethyl as condensing agent, undergoes normal replacement of the  $\alpha$ -hydrogen atoms in benzylation and carbethoxylation. However, ethyl cyclopropanecarboxylate reacts with these condensing agents by replacement of ethoxy groups, *i.e.*, in a manner characteristic of esters having no  $\alpha$ -hydrogen atoms. It is concluded that the cyclopropyl-type anion can be formed when no alternative mode of reaction is possible and is stable with respect to isomerization to an acyclic anion except in bifunctional types. It is suggested that the base-induced transformations of the nitrocyclopropyl ketones and likewise the rearrangements of epoxyketones represent processes in which ring opening and proton removal are concerted.

The alkylation of cyclopropyl phenyl ketone, reported by Haller and Benoist<sup>1</sup> is one of the few known cases in which a cyclopropyl hydrogen atom exhibits the prototropic activation normally shown by hydrogen atoms alpha to an electron-accepting group. Theoretically the activation of a cyclopropyl hydrogen should be markedly suppressed because of the additional strain in exocyclic double-bonded forms.<sup>2</sup> This effect is strikingly exemplified by the observations of Hass and Shechter<sup>3</sup> on nitrocyclopropane, which is inert toward aqueous bases and which fails to give the characteristic pseudonitrole test.

There are numerous examples among the nitrocyclopropyl esters and ketones, studied by Kohler<sup>4</sup> and by Smith,<sup>5</sup> of facile base-induced transformations which, according to Smith and Engelhardt,<sup>6</sup> are initiated by abstraction of a proton from the ring carbon atom which carries the nitro group. In their mechanism the cyclopropyl anion thus formed undergoes an electronic shift whereby it is transformed to an open-chain anion.

Since with rare exceptions these reactions result in open-chain products the question arises as to whether the alkylation products of cyclopropyl phenyl ketone actually possess the cyclic structures assigned to them by Haller and Benoist with-

(1) A. Haller and E. Benoist, *Ann. chim.*, **IX**, 17, 25 (1923).

(2) The theory has been discussed in terms of I-strain by H. C. Brown, R. S. Fletcher and R. B. Johannesen, *THIS JOURNAL*, **73**, 212 (1951).

(3) H. B. Hass and H. Shechter, *ibid.*, **75**, 1382 (1953). The authors are indebted to Dr. Shechter for the opportunity of seeing the manuscript of the paper in advance of publication.

(4) E. P. Kohler and S. F. Darling, *ibid.*, **52**, 1174 (1930); and earlier papers by Kohler and co-workers.

(5) L. I. Smith and J. S. Showell, *J. Org. Chem.*, **17**, 829 (1952); and earlier papers by Smith and co-workers.

(6) L. I. Smith and V. A. Engelhardt, *THIS JOURNAL*, **71**, 2676 (1949).



(b) **Using Sodium Triphenylmethyl.**—To a solution of sodium triphenylmethyl (0.0356 mole) in ethyl ether (215 ml.). 5.3 g. of cyclopropyl phenyl ketone (0.0363 mole) was added. After one minute the solution had decolorized to a faint yellow. After five minutes, 9.0 g. of benzyl chloride (0.0715 mole) was added and the mixture was allowed to stand overnight. The product, obtained as a distillate after working up the material in the usual way, was an oil which deposited triphenylmethane upon standing. The mother liquor was fractionated by molecular distillation furnishing additional triphenylmethane and 6.2 g. of 1-benzylcyclopropyl phenyl ketone (74%,  $n_D^{20}$  1.5810). The ketone still contained triphenylmethane, but gave a 2,4-dinitrophenylhydrazone, m.p. 125.5–126.5°, which did not depress the melting point of the derivative described above.

**Cleavage of Benzylated Product by Sodamide.**—A mixture of 3.0 g. of 1-benzylcyclopropyl phenyl ketone (0.0127 mole) and 0.55 g. of sodamide in 25 ml. of moist benzene was refluxed for seven hours. The product, impure 1-benzylcyclopropanecarboxamide, m.p. 75–85° (lit.<sup>1</sup> m.p. 84°), was not purified, but was hydrolyzed directly, in methanolic potassium hydroxide, to furnish 1.25 g. of 1-benzylcyclopropanecarboxylic acid, m.p. 106.5–108° (lit.<sup>1</sup> m.p. 104°), after two crystallizations from ligroin.

To confirm the identity of this acid an independent synthesis, based upon the Clemmensen reduction of 1-benzoylcyclopropanecarboxylic acid, was carried out. The procedure was patterned after that described by Martin<sup>10</sup> for the reduction of  $\beta$ -benzoylpropionic acid. The product, obtained in 4% yield, melted at 105–107° after two recrystallizations from ligroin; mixed m.p. with the above-described cleavage product, 106–108°.

**Attempted Carbonation of Cyclopropyl Phenyl Ketone.**—In an attempt to convert the sodium derivative of cyclopropyl phenyl ketone to the known compound, 1-benzoylcyclopropanecarboxylic acid, the sodium derivative was formed from 14.6 g. of cyclopropyl phenyl ketone (0.100 mole) and 4.30 g. of sodamide (0.110 mole) in dry benzene, and a slow stream of carbon dioxide was passed through the solution for three days. The resulting gel was decomposed with water. From the benzene layer, after washing with 5% aqueous sodium hydroxide, 12.2 g. of cyclopropyl phenyl ketone was recovered. The recovered ketone was shown to be identical with the starting material by their identical infrared spectra. The basic washes on acidification gave a small amount of gum from which a trace of benzoic acid was isolated by sublimation.

**Cleavage of Cyclopropyl Phenyl Ketone by Sodamide.**—In an attempted carbethoxylation reaction, a mixture of 14.6 g. of cyclopropyl phenyl ketone (0.100 mole) and 4.87 g. of sodamide (0.125 mole) in 50 ml. of dry benzene was heated under reflux. After one hour the mixture had set to a solid mass. After three hours, 23.6 g. of ethyl carbonate (0.200 mole) dissolved in 100 ml. of anhydrous ethyl ether was added and the heating was continued for two hours. The mixture was treated with ice and hydrochloric acid and the organic layer, after distillation of the benzene, furnished a solid product (8.2 g.) N-carbethoxycyclopropanecarboxamide, m.p. 116–117.5° after one crystallization from ethanol, three from ligroin and sublimation.

*Anal.* Calcd. for  $C_7H_{11}NO_3$ : C, 53.49; H, 7.06; N, 8.91. Found: C, 53.56; H, 7.18; N, 8.63.

The formation of this product pointed toward cleavage of the ketone to cyclopropanecarboxamide and benzene followed by carbethoxylation of the former. Although Haller and Benoist<sup>1</sup> reported that cleavage of cyclopropyl phenyl ketone with sodamide (in moist benzene) gave benzamide, our subsequent experiments showed that cleavage occurs in both directions. In our case the occurrence of a cleavage reaction was not attributable to the presence of moisture, but was characteristic of the particular sample of cyclopropyl phenyl ketone.<sup>11</sup>

(10) E. L. Martin, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 161.

(11) This sample of cyclopropyl phenyl ketone was indistinguishable otherwise from other preparations. The ketone was prepared from  $\gamma$ -chlorobutyrophenone by treatment with alcoholic potassium hydroxide by a procedure similar to that of Conant, Segur and Kirner, *THIS JOURNAL*, **46**, 1882 (1924). The physical constants though disagreeing with those of Haller and Benoist were in close agreement with those given by R. P. Mariella and R. R. Raube, *ibid.*, **74**, 521 (1952).

Repeated attempts to form the sodium derivative from this material by reaction with sodamide resulted only in cleavage, the occurrence of which becomes evident when the mixture sets to a solid mass. In one, a mixture of 7.3 g. of cyclopropyl phenyl ketone (0.050 mole) and 2.44 g. of sodamide (0.062 mole) in 25 ml. of benzene set to a solid mass after one hour on the steam-bath. After decomposition by hydrochloric acid, the aqueous layer, upon extraction with ether, furnished 0.13 g. of benzamide, m.p. 126–127°, mixed m.p. with cyclopropanecarboxamide 86–95°. The combined aqueous solutions were subjected to continuous ether extraction for 96 hours, a procedure necessitated by the high solubility of cyclopropanecarboxamide in water. The ether extract furnished 1.8 g. of cyclopropanecarboxamide (42%), m.p. 123.5–126.5°. The melting point was not depressed by authentic cyclopropanecarboxamide, whereas the mixed melting point with benzamide was 102–111°.

**Carbethoxylation of Cyclopropyl Phenyl Ketone Using Sodium Triphenylmethyl.**—The sodium derivative of cyclopropyl phenyl ketone was prepared from 12.0 g. of ketone (0.082 mole) and sodium triphenylmethyl (0.079 mole) in ethyl ether. After one minute, 24 ml. of ethyl carbonate (0.20 mole) was added and the mixture was allowed to stand overnight. The product, 7.9 g. (44%) of ethyl 1-benzoylcyclopropanecarboxylate, b.p. 104–150° (9 mm.),  $n_D^{20}$  1.5373 (lit.<sup>1</sup>  $n_D^{20}$  1.5353), was hydrolyzed in methanolic potassium hydroxide to furnish 1-benzoylcyclopropanecarboxylic acid, m.p. 146.5–148.5° dec., not depressed by admixture of an authentic sample.

The 2,4-dinitrophenylhydrazone of authentic 1-benzoylcyclopropanecarboxylic acid crystallized in two forms which were separated mechanically and recrystallized from alcohol. One was yellow-orange, m.p. 177.5–179.0° dec. *Anal.* Calcd. for  $C_{17}H_{14}N_4O_6$ : C, 55.14; H, 3.81. Found: C, 55.23; H, 4.04. The second form was brick-red, m.p. 187–188° dec. *Anal.* Found: C, 54.99; H, 4.13. A sample of the red form had changed to an orange-yellow color after standing for six months but its melting point had not changed. The keto-acid obtained by way of the carbethoxylation process formed the identical two modifications of the 2,4-dinitrophenylhydrazone.

**Reaction of Ethyl Cyclopropanecarboxylate with Sodium Triphenylmethyl.**—To a solution of sodium triphenylmethyl (0.119 mole) in ethyl ether, 13.6 g. of ethyl cyclopropanecarboxylate (0.119 mole) was added rapidly in one portion. One minute after addition of the ester, the red color had discharged to a faint yellow and a colorless precipitate separated. After ten minutes, 7 ml. of glacial acetic acid was added. The suspended solid was filtered, washed with ether and with hot water. The filtrate and the ether washings furnished additional solid residues which were combined (29.9 g., m.p. 120–140°) and separated into two components by fractional crystallization from alcohol containing 5% benzene.

The main product, more soluble in the solvent, was a colorless solid (11.6 g., 31%), m.p. 153.5–154°, eventually identified as cyclopropyl triphenylmethyl ketone. *Anal.* Calcd. for  $C_{23}H_{20}O$ : C, 88.42; H, 6.45. Found: C, 88.45; H, 6.52. It did not react with bromine in carbon tetrachloride or with potassium permanganate in acetone. The ultraviolet absorption spectrum in *n*-heptane showed maxima at 292  $m\mu$  ( $\epsilon_{max}$  347) and at 261.5  $m\mu$  ( $\epsilon_{max}$  918). The compound was unaffected by sodamide in refluxing toluene, but with methanolic potassium hydroxide in a sealed tube at 150° for five hours formed triphenylmethane and cyclopropanecarboxylic acid, the latter identified as the *p*-bromophenacyl ester. The identity of the compound was confirmed by the synthesis of an identical product by the action of sodium triphenylmethyl on cyclopropanecarboxyl chloride. The second, less soluble, product (0.6 g., 2%) from the reaction of sodium triphenylmethyl on ethyl cyclopropanecarboxylate was a solid, m.p. 202–203°, believed to be 1,1,1,6,6,6-hexaphenylhexan-2-one. *Anal.* Calcd. for  $C_{42}H_{36}O$ : C, 90.82; H, 6.52. Found: C, 90.55; H, 6.73. The compound was inert toward bromine and potassium permanganate and no product could be obtained with either hydroxylamine or 2,4-dinitrophenylhydrazine. Reaction with methanolic potassium hydroxide in a sealed tube at 165° for five hours formed triphenylmethane and an acid, m.p. 222–223°, believed to be  $\delta$ , $\delta$ , $\delta$ -triphenylvaleric acid. *Anal.* Calcd. for  $C_{23}H_{22}O_2$ : C, 83.69; H, 6.90. Found: C, 83.60; H, 6.71. An attempted synthesis of the acid

through the reaction of 3,3,3-triphenyl-1-iodopropane<sup>12</sup> with the sodium salt of malonic ester failed because of the remarkably low reactivity of the iodo compound. After refluxing the mixture for seven days 55% of the iodo compound was recovered and no other product was isolated. In another experiment the iodo compound, with a fourfold quantity of sodium malonic ester, was refluxed in butyl ether for two days and recovered in 78% yield. The iodo compound undergoes dehydrohalogenation rather than hydrolysis upon refluxing for two days in 2 *N* potassium hydroxide in 80% methanol; the product, m.p. 78.0–78.8°, is assumed to be 3,3,3-triphenylpropene. *Anal.* Calcd. for C<sub>21</sub>H<sub>18</sub>: C, 93.29; H, 6.71. Found: C, 93.34; H, 6.93.

**Reaction of Ethyl Isobutyrate with Sodium Triphenylmethyl.**—Under conditions generally similar to those employed by Hauser and Renfrow,<sup>13</sup> 2.2 g. of ethyl isobutyrate (0.0189 mole) was added to a solution of sodium triphenylmethyl (0.0165 mole) in ethyl ether. After five minutes, 4 ml. of glacial acetic acid was added. Chromatography of the mother liquor from the crystallization of triphenylmethane failed to disclose the presence of any other non-volatile product.

**Reaction of Ethyl Cyclopropanecarboxylate with Sodamide.**—A mixture of 5 ml. of ethyl cyclopropanecarboxylate (0.042 mole) and 3.4 g. of sodamide<sup>14</sup> in 20 ml. of dry toluene was refluxed for four hours in which time it had set to an almost solid mass. The solid was separated and washed with toluene. After treatment of the solid with ice-water and two crystallizations from ethanol a product (0.5 g.) was obtained as colorless needles, m.p. 219–220° (sealed capillary). Hydrolysis of this compound in aqueous methanolic potassium hydroxide liberated ammonia and cyclopropanecarboxylic acid, identified as the *p*-bromophenacyl ester, m.p. 71.9–72.7°. The compound was shown by comparison with an independently synthesized sample to be dicyclopropanecarboxamide, but repeated crystallizations failed to bring the analyses within the allowable range. *Anal.* Calcd. for C<sub>8</sub>H<sub>11</sub>NO<sub>2</sub>: C, 62.71; H, 7.24; N, 9.14. Found: C, 63.14; H, 7.52; N, 8.18. The compound obtained in 33% yield by adding cyclopropanecarboxylic chloride to the suspension resulting from the reaction of cyclopropanecarboxamide with sodamide in dry toluene melted, after three crystallizations from ethanol, at 220–220.5°. *Anal.* Calcd. for C<sub>8</sub>H<sub>11</sub>NO<sub>2</sub>: C, 62.71; H, 7.24; N, 9.14. Found: C, 62.73; H, 7.42; N, 9.13. A mixed melting point of the two products was unchanged.

**Infrared Characterization of Compounds Containing the Cyclopropane Ring.**—The infrared absorption peaks at 9.9, 10.9 and 11.7  $\mu$  have been used to characterize the cyclo-

propane ring.<sup>15</sup> The observed absorption peaks in these regions for a series of compounds in carbon disulfide solution (except 1-benzoylcyclopropanecarboxylic acid, taken as a mull in paraffin oil) are listed in Table I. Similar observations on other cyclopropyl ketones and nitriles have been reported by Wiberley and Bunce<sup>16</sup> who also find that the absorptions in these regions are too variable to be reliable for diagnostic purposes. They found that the two absorptions at 3.23 and 3.32  $\mu$  are more characteristic for the cyclopropane ring. Cyclopropyl phenyl ketone and 1-benzoylcyclopropyl phenyl ketone were investigated in this region, using lithium fluoride optics, and were found to exhibit peaks at 3.240 and 3.322  $\mu$  for the former compound and 3.245 and 3.327  $\mu$  for the latter.

TABLE I  
INFRARED ABSORPTION MAXIMA<sup>a</sup>

Substance	9.9 $\mu$ region	10.9 $\mu$ region	11.7 $\mu$ region
Ethyl cyclopropane-carboxylate	9.67 s	10.59 m <sup>b</sup> 11.14 w	11.69 s 12.13 m
Diethyl cyclopropane-1,1-dicarboxylate	9.67 s	10.30 m	11.66 m
Cyclopropyl phenyl ketone	9.64 s 9.72 s 9.98 s <sup>c</sup> 10.07 vs	10.76 w	11.50 s
1-Benzoylcyclopropyl phenyl ketone	9.68 m <sup>e</sup> 9.74 m 9.98 s 10.00 m <sup>e</sup>	10.28 s 10.84 m	11.80 vw 12.13 w
1-Benzoylcyclopropane-carboxylic acid	9.68 m 10.05 m	10.22 s 10.41 s 10.70 m <sup>e</sup>	11.62 s
1-Benzoylcyclopropane-carboxylic acid	9.58 w 9.69 vw 9.92 s	10.23 m 10.77 s	11.59 w 11.80 w

<sup>a</sup> Intensities are indicated as very weak (vw), weak (w), moderate (m), strong (s) or very strong (vs). <sup>b</sup> Doublet. <sup>c</sup> Appearing as a shoulder at high resolution and slow scanning speed.

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(15) J. M. Derfer, E. E. Pickett and C. E. Boord, *THIS JOURNAL*, **71**, 2482 (1949).

(16) S. E. Wiberley and S. C. Bunce, *Anal. Chem.*, **24**, 623 (1952).

(12) This compound, described by W. D. McPhee and E. G. Lindstrom, *THIS JOURNAL*, **65**, 2177 (1943), was prepared, by the method of these authors, from 3,3,3-triphenylpropanol which in turn was prepared in 61% yield by the lithium aluminum hydride reduction of  $\beta,\beta,\beta$ -triphenylpropionic acid under conditions similar to those employed in similar cases by R. H. Baker, *ibid.*, **70**, 3858 (1948).

(13) C. R. Hauser and R. B. Renfrow, *ibid.*, **59**, 1823 (1937).

(14) The sodamide used throughout this work was the commercial product supplied by Farchan Research Laboratory.