

on a mechanistic basis, and presumably derive part of their driving force from the relief of ring strain. It is interesting, however, that under many other conditions the cyclopropene system in these compounds is remarkably stable. Thus, refluxing an ester of the monoacid with potassium *t*-butoxide in *t*-butyl alcohol for 60 hr. leaves the cyclopropene system intact,⁶ and even in acid, to which it is more sensitive, the compound is unaffected by 40% sulfuric acid in methanol at room temperature or by refluxing *N* methanolic sulfuric acid, although more vigorous conditions cause rearrangement to III. The stability of these compounds, which results from the heavy conjugating substitution, suggests that related cyclopropene derivatives should also be readily preparable.⁷

EXPERIMENTAL

Diphenylcyclopropenedicarboxylic acid (I). A mixture of 17 g. of diphenylacetylene with 1 g. of electrolytic copper dust was heated at 125° with stirring. Diazomalonic ester⁸ (9.3 g.) was added over 1.5 hrs. and the reaction was continued until N₂ evolution had ceased. After solution in ether and filtering, the solvent was removed and the mixture directly hydrolyzed by refluxing for 90 min. with 30 g. KOH in 200 ml. of methanol. After dilution and recovery of the diphenylacetylene by extraction the solution was acidified and the product collected with chloroform. Percolation of the extract through Florex and removal of the solvent yielded 1.5 g. of the acid after crystallization from ether/petroleum ether; m.p. 205° (dec.).

Anal. Calcd. for C₁₇H₁₂O₄: C, 72.85; H, 4.32. Found: C, 73.32; H, 4.37.

In the infrared the compound showed carbonyl absorption at 5.98 μ. In the ultraviolet spectrum it showed maxima at 306, 315, and 225 mμ (log ε 4.48, 4.38, and 4.30, respectively).

The dimethyl ester of (I) was prepared with diazomethane. Crystallized from ether/petroleum ether it had m.p. 143–143.5°.

Anal. Calcd. for C₁₉H₁₆O₄: C, 74.04; H, 5.23; mol. wt., 308. Found: C, 74.26; H, 5.30; mol. wt. (Rast, camphor), 297, 290.

In the infrared the compound absorbs at 5.90 and 5.98 μ. The ultraviolet spectrum shows maxima at 306, 322, 225, and 230 mμ (log ε 4.48, 4.40, 4.11, and 4.08 respectively).

The diester dibromide was prepared from the above compound by Darling's procedure,³ m.p. 197–198°.

Anal. Calcd. for C₁₉H₁₆O₄Br₂: Br, 34.2. Found: Br, 34.19.

The compound showed absorption in the ultraviolet at 220 mμ, (log ε_{max} 3.9). The dibromide was not affected by treatment with potassium permanganate solution in acetone at room temperature.

The neutral lactone (III). This compound, prepared by melting (I) according to Darling,³ had m.p. 149–151°; in the infrared it had a strong band at 5.77 μ, and in the ultraviolet it absorbed at 272 mμ (log ε 4.26), and had strong end absorption.

α,β-Diphenylcrotonolactone was prepared by the method of Thiele.⁴ The m.p. of 150–152° (reported 152°) was undepressed on mixture with the above lactone, and their infrared and ultraviolet spectra were identical in all respects.

1,2-Diphenylcyclopropene-3-carboxylic acid was prepared in a similar manner to that of the dicarboxylic acid, but the

ethyl diazoacetate was added dropwise to the diphenylacetylene at 135–140° over 2.5 hr. The product, crystallized from acetone, had m.p. 209–211° (dec.) (23% yield).

Anal. Calcd. for C₁₆H₁₂O₂: C, 81.33; H, 5.12. Found: C, 81.29; H, 5.27.

The ultraviolet spectrum of the compound had maxima at 306, 323, 225, and 232 mμ (log ε 4.52, 4.42, 4.34, and 4.28 respectively). On heating at 220–230°, the acid was converted to (III), m.p. 149–152° (20% yield), as evidenced by identity of spectra.

The methyl ester, m.p. 83–85°, had maxima in the ultraviolet at 306, 323, 224, and 232 mμ (log ε 4.53, 4.42, 4.34, and 4.29 respectively). This spectrum was unaffected by refluxing with 1 *N* sulfuric acid in methanol for 24 hr. or by standing with 40% methanolic sulfuric acid for 12 hr., although on refluxing of this latter solution for 19 hr the compound was converted into (III), m.p. 152–154°, in 40% yield. Both the monoacid and its methyl ester show the expected carbonyl absorption in the infrared.

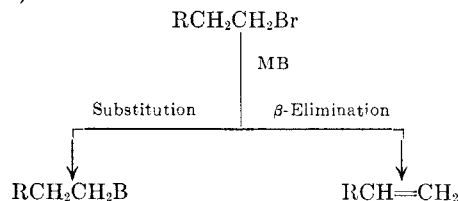
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Influence of Metallic Cation on Substitution versus Elimination Reactions of Alkyl Halides with Alkali Bases¹

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An alkyl halide may undergo with an alkali base (MB) the substitution and β-elimination reactions,



Although variations in the basic strength of the anion B⁻ are known to influence the relative extents of these two courses of reaction,³ variations in the metallic cation associated with the basic anion in alcohol appears to have no appreciable effect on the two courses. Thus, no significant difference in the ratio of the substitution and elimination products was observed by Newman and Evans⁴ on treatment of 2-ethylhexyl bromide with lithium, sodium, and potassium ethoxides in ethanol solution.

However, differences in the ratio of the two types of products have been observed on varying the alkali cation associated with certain stronger

(1) Supported by a grant from the Duke University Research Council.

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(3) See C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, pp. 451–452; E. E. Royals, *Advanced Organic Chemistry*, Prentice-Hall, Inc., New York, N. Y., 1954, p. 299.

(4) M. S. Newman and F. J. Evans, Jr., *J. Am. Chem. Soc.*, **76**, 4187 (1954).

(6) R. Breslow and M. Battiste, *Chem. & Ind. (London)*, 1143 (1958).

(7) For one example, cf. R. Breslow, *J. Am. Chem. Soc.*, **79**, 5318 (1957).

(8) H. Lindemann, A. Wolter, and R. Groger, *Ber.*, **63**, 702 (1930).

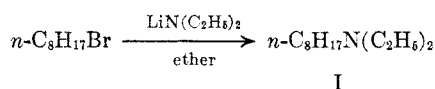
TABLE I
TERTIARY AMINES AND OLEFINS FROM ALKYL BROMIDES WITH EQUIVALENTS OF ALKALI DIETHYLAMIDES

| Alkyl Bromide | Alkali Diethylamide | Solvent at 35–40°C. | Time, Hours | Amine Yield, % | Olefin Yield, % | Recovered Alkyl Bromide, % | Residue, Grams |
|-----------------|----------------------|---------------------|-------------|----------------|--------------------|----------------------------|----------------|
| <i>n</i> -Octyl | Lithium | Ether | 2.5 | 47 | 0 | 42 | 6 ^a |
| <i>n</i> -Octyl | Lithium ^b | Ether | 17.0 | 89 | Trace ^c | 0 | 2 |
| <i>n</i> -Octyl | Sodium | Benzene | 7.0 | 30 | 5 ^d | 4 | 9 |
| <i>n</i> -Octyl | Sodium | Benzene | 6.5 | 22 | 19 ^e | 29 | 13 |
| 2-Ethylhexyl | Lithium | Ether | 5.0 | 45 | Trace ^c | 45 | 5 ^a |
| 2-Ethylhexyl | Sodium | Benzene | 6.5 | 24 | 16 ^f | 2 | 14 |

^a This residue is presumably diphenyl incurred in the preparation of the lithiumphenyl. ^b In this experiment two equivalents of the base were treated with one equivalent of the alkyl bromide. ^c A small amount of material giving a positive test for unsaturation with potassium permanganate was found in the neutral fraction. ^d Estimated by titration with bromine in carbon tetrachloride of an aliquot of neutral material, b.p. 95–116° (760 mm.), consisting of a mixture of recovered heptane (dispersant for sodium) and olefin. ^e Estimated by refractive index of neutral material, b.p. 109–122° (760 mm.), consisting of a mixture of recovered toluene (dispersant for sodium) and olefin. ^f Estimated by titration with bromine in carbon tetrachloride of an aliquot of neutral material, b.p. 107–116° (760), consisting of a mixture of recovered toluene and olefin.

bases in less dissociating solvents. Shreve and Rothenberger⁵ obtained relatively less olefin from certain alkyl halides with sodium amide in liquid ammonia than with potassium amide.⁶ Newman and co-workers⁷ realized better yields of the substitution product from 1-bromo-3-chloropropane with the lithium derivative of 1-hexyne than with the sodium or potassium derivative.

We have found that *n*-octyl and 2-ethylhexyl bromides undergo relatively more of the substitution reaction and relatively less β -elimination with lithium diethylamide in refluxing ether than with sodium diethylamide in benzene at about the same temperature (Table I). For example, *n*-octyl bromide underwent largely the substitution reaction with the lithium reagent to form tertiary amine I, whereas this halide evidently exhibited mainly β -elimination with the sodium reagent.



It can be seen from Table I that the yield of tertiary amine I was 89% with two equivalents of the lithium reagent. A lower yield (47%) of this amine was realized with an equivalent of this reagent, but much of the halide was recovered and none of the olefin was detected. A similar result was obtained with 2-ethylhexyl bromide and the lithium reagent. On the other hand, the sodium reagent not only produced lower yields of the tertiary amine, but it also gave considerable amounts

(5) R. N. Shreve and L. W. Rothenberger, *Ind. Eng. Chem.*, **29**, 1361 (1937).

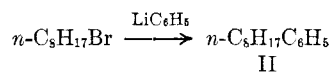
(6) We have observed that, in contrast to sodium or potassium amide in liquid ammonia, lithium amide failed to react appreciably with *n*-octyl bromide in liquid ammonia during 2 hr., and 89% of the unchanged bromide was recovered. Similarly, 73% of this halide was recovered after refluxing with lithium amide in triethylamine for 7 hr.

(7) M. S. Newman, M. W. Renoll, and I. Auerbach, *J. Am. Chem. Soc.*, **70**, 1023 (1948).

of the olefin or residue that may be assumed to have arisen from the olefin. In a blank experiment with octene-1 and sodium diethylamide, similar residuous material was obtained and only about half of the olefin was recovered.⁸

It should be pointed out that the sodium diethylamide employed in the two experiments with *n*-octyl bromide was prepared with sodium phenyl that had been obtained from sodium dispersions in *n*-heptane and toluene respectively (see notes *d* and *e*, Table I). Nevertheless, the yield of the tertiary amine I based on the halide used minus that recovered was about 31% in both experiments. The differences in the yields of the olefin may be attributable to the use of different detection methods and to different degrees of polymerization.

Similarly, lithiumphenyl reacted with *n*-octyl bromide to give a better yield of *n*-octylbenzene (II) than sodiumphenyl. The yields of this substitution product based on the halide that reacted were 78% and 51% respectively. Moreover, much less residue was obtained with the lithium reagent.



The use of ether with the lithium reagent and benzene with the sodium reagent in these experiments may have had some effect on the two courses of reaction.

These results (as well as the earlier ones)⁷ indicate that when a substitution type of reaction is desired with a nitrogen or carbon base, the lithium reagent would, in general, be chosen over the sodium reagent.

(8) This experiment was performed by A. Theodore Stewart in this laboratory. Since the sodium diethylamide was prepared from sodium and chlorobenzene, the polymerization of the olefin might possibly have been effected by unused metal as well as by the sodium diethylamide.

EXPERIMENTAL⁹

Lithiumphenyl solutions (*M*) were prepared and standardized according to the method described by Jones and Gilman.¹⁰

Sodiumphenyl. In a flame-dried flask under a nitrogen atmosphere was placed 0.5 mole of sodium as a 45% dispersion in toluene¹¹ or a 50% dispersion in *n*-heptane.¹¹ The dispersion was immediately covered with dry benzene, and about 5 ml. of a solution of 28.7 g. (0.255 mole) of chlorobenzene in 25 ml. of benzene was added. As soon as formation of the sodiumphenyl commenced, as evidenced by a rise in temperature and the formation of black granular particles in the grey mixture, the stirrer was started and the flask immersed in a Dry Ice-methanol bath. The remainder of the chlorobenzene solution was then added during 30 min. to 1 hr., while maintaining the temperature of the reaction between 25–40° by proper adjustment of the cooling bath. After conclusion of the addition, the reaction mixture was stirred an additional 30 min. at room temperature to insure completion of the reaction. At the end of this time, the reaction mixture consisted of a black suspension of sodiumphenyl granules. This material was used immediately for further reaction (see below) without storage.

Reaction of alkyl halides with metallo diethylamides. (Table I). (A) *With lithium diethylamide.* To 200 ml. (0.2 mole) of a *M* lithiumphenyl solution was added dropwise with stirring over 20 min. 16.1 g. (0.22 mole) of diethylamine in 25 ml. of dry ether. After stirring for an additional 10–20 min., a solution of an equivalent of the alkyl halide in an equal volume of ether was added during 0.5 hr., and the reaction completed by refluxing for the time indicated. The reaction mixture was cooled and decomposed by the addition of 50 ml. of water, and the ether layer, to which was added an ether extract of the aqueous layer, was extracted with several portions of 5*N* hydrochloric acid solution, washed with water and dried over CaCl₂. The acidic extracts were combined, made strongly basic with 5*N* sodium hydroxide solution, salted out with sodium chloride, and extracted with several portions of ether. The ether layer containing the basic fraction was then dried over potassium hydroxide. The solvents were removed from both fractions and the residues distilled to yield recovered halide and amine. Material from the neutral fraction boiling in the range 80–103° (760 mm.) was tested with potassium permanganate solution to determine the presence of olefin. Only traces of material giving a positive test for unsaturation were obtained.

(B) *With sodium diethylamide.* To 0.25 mole of sodiumphenyl, prepared as described above, was added during 30 min., 20.5 g. (0.28 mole) of diethylamine in 25 ml. of benzene and the black, sirupy mixture stirred an additional 30–60 min. to insure formation of the sodium diethylamide. To the stirred liquid was added during 30 min. an equivalent of the alkali halide in an equal volume of benzene, and the reaction then completed as indicated in Table I. The reaction mixture was cooled, and 20 ml. of ethanol added cautiously to decompose any unreacted sodium followed by water. The reaction mixture was then worked up as described above for lithium diethylamide. Since the olefins formed in these reactions boil close to that of the toluene or heptane used as dispersant for the sodium, the neutral material was carefully fractionated and the various frac-

tions tested with potassium permanganate solution to determine the presence of olefin. If olefin was indicated present in the fraction, the amount present was estimated by the methods indicated in Table I.

The following new amines were prepared by these methods. From *n*-octyl bromide there was obtained *N,N*-diethyl-*n*-octylamine, b.p. 221–224° (760 mm.), 93–95° (10 mm.).

Anal. Calcd. for C₁₂H₂₇N: C, 77.75; H, 14.69. Found: C, 77.70; H, 14.67.

From 2-ethylhexyl bromide there was obtained *N,N*-diethyl-2-ethylhexylamine, b.p. 205–208° (760 mm.).

Anal. Calcd. for C₁₂H₂₇N: C, 77.75; H, 14.69; N, 7.56. Found: C, 77.75; H, 14.34; N, 7.56.

Reaction of *n*-octyl bromide with metallo phenyls. (A) *With lithiumphenyl.* To 250 ml. (0.25 mole) of a *M* solution of lithiumphenyl in ether was added dropwise during 2.5 hours, 48.3 g. (0.25 mole) of *n*-octyl bromide in 50 ml. of ether. The reaction mixture was stirred for 30 min. at room temperature, then stirred and refluxed for 1.5 hr., cooled and decomposed with water. The ether layer was washed with dilute hydrochloric acid, saturated sodium bicarbonate solution and water, and, after combining with an ether extract of the aqueous layers, dried over calcium chloride. The solvent was removed and the residue distilled *in vacuo* to give 5.7 g. (12%) of recovered *n*-octyl bromide, b.p. 77–81° (10 mm.), 32.8 g. (69%) of *n*-octyl benzene, b.p. 125–127° (10 mm.) (reported¹² b.p. 264–265° (760 mm.), and 2.8 g. of gummy residue. A small low-boiling forerun gave a negative test with potassium permanganate solution.

(B) *With sodiumphenyl.* To 0.25 mole of sodiumphenyl was added during 45 min., 48.3 g. (0.25 mole) of *n*-octyl bromide in 50 ml. of benzene. The reaction mixture was stirred at room temperature for 1 hr., then stirred and refluxed for 1 hr. After cooling and decomposing with methanol followed by water, the benzene layer was worked up as described above for lithium phenyl. There was obtained 15.3 g. (32%) of recovered *n*-octyl bromide, b.p. 79–82° (10 mm.), 16.3 g. (35%) of *n*-octyl benzene, b.p. 129–134° (12 mm.), and 14.9 g. of high boiling residue. A small low-boiling forerun gave only a weak positive test with potassium permanganate solution.

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(12) F. Eisenlohr and L. Schulz, *Ber.*, **57**, 1815 (1924).

Microbiological Synthesis of 2-Hydroxyandrost-1,4-diene-3,17-dione¹

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The recent publication on the synthesis of 2-hydroxy- $\Delta^{1,4}$ -3-keto steroids by Baran³ prompts us to report, as part of a study on possible precursors to the aromatic ring A, the microbiological conversion of 2 α -hydroxytestosterone to 2-hydroxy-

(9) Analyses by Clark Microanalytical Laboratories, Urbana, Ill. Melting points and boiling points are uncorrected. Distillations described herein were performed on a 30 cm. Vigreux column.

(10) R. G. Jones and H. Gilman, *Org. Reactions*, Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 353.

(11) Generous samples of these materials were obtained from the National Distillers Corporation through the courtesy of Dr. V. L. Hansley.

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(2) Present address: Radiobiological Research Unit, A.E.R.E., Harwell, Didcot, Berkshire, England.

(3) J. S. Baran, *J. Am. Chem. Soc.*, **80**, 1687 (1958).