carbostyril, 4,6,8-trimethylcarbostyril, 5,8-dimethoxy-4-methylcarbostyril, 2-chloro-8-methyllepidine, 2-chloro-6-methyllepidine, 2-chloro-5,8-dimethyllepidine, 2-chloro-6,8-dimethyllepidine and 2-chloro-5,8-dimethoxylepidine.

BLOOMINGTON, INDIANA RECEIVED DECEMBER 5, 1945

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF COLORADO AND COLORADO A. AND M. COLLEGE]

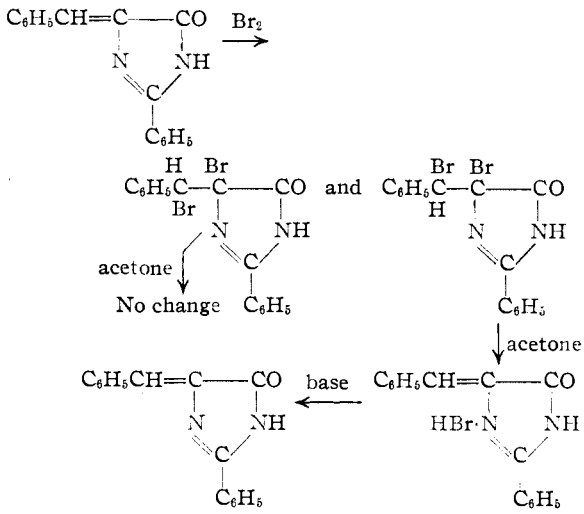
The Glyoxalines. V. The Bromination of 2-Phenyl-4-benzal-5-glyoxalidone

BY DAVID LLOYD WILLIAMS[1] AND ANTHONY R. RONZIO[2]

The synthesis of 2-phenyl-4-benzal-5-glyoxalidone by a number of methods gives varying melting points.[3] The theory has been proposed that this variation of melting points may be due to the *cis-trans* isomerism introduced into the compound by the double bond between the benzal group and the glyoxaline ring.

A study of the bromination of the compound was undertaken with a view of studying this structure and is here reported.

Bromination of the compound in glacial acetic acid by the method of Minovici,[4] yielded a finely divided, crystalline orange precipitate. Attempts at recrystallization from the common organic solvents brought about decomposition of the compound with the formation of a red solution. However, upon placing the product in acetone, partial solution took place leaving a small amount of an insoluble, pale yellow compound. After quickly filtering off the precipitate, the filtrate began to deposit small yellow needles and the acetone acquired the strong lachrymatory power of bromoacetone. The soluble fraction spontaneously lost bromine. Analyses confirmed this observation. The bromination of the glyoxalidone thus leads to two products. The bromination product of one form is unstable and loses bromine. The acetone used as solvent behaves as acceptor for the bromine forming bromoacetone and hydrogen bromide. The hydrogen bromide then, in turn, adds to the debrominated glyoxalidone which precipitates as the insoluble hydrobromide. These reactions are shown in Equation 1.



Equation 1

That a hydrobromide of 2-phenyl-4-benzal-5-glyoxalidone had formed was easily shown by removing the hydrobromic acid with dilute base. The melting point of the compound thus obtained was 280°. The pale yellow compound insoluble in acetone was found by analysis to be a dibromo glyoxalidone. The designation of α-2-phenyl-4-(α - bromobenzyl) - 4 - bromo - 5 - glyoxalidone has been assigned to the compound. The mixture of the two forms of the dibromo glyoxalidone has been designated as ω-2-phenyl-4-(α-bromobenzyl)-4-bromo-5-glyoxalidone.

Two possible explanations can be offered for this unusual phenomenon. Either the benzal glyoxalidone exists as a mixture of *cis* and *trans* forms, thus leading to two dibromo derivatives, having different properties; or, the loading of the carbon atom between the benzene and the glyoxaline ring brought about by the bromination leads to two forms of dibromo derivatives because of steric hindrance. When the bromine atoms are adjacent (*cis*) to one another they are easily removed. When they are opposite from each other (*trans*) they are stable.

The amount of bromine used in the bromination exerted an important influence upon the amount of brominated derivative crystallizing out of the acetic acid solution. When an excess of bromine over the calculated amount was used, no precipitate formed. Upon allowing the solution to stand twenty-four to forty-eight hours, however, glistening orange crystals separated. Analyses indicated that the tribromo derivative of the glyoxalidone had formed. This compound dissolved in acetone completely, then reprecipitated slowly as yellow crystals in a manner analogous to the dibromo derivative. The lachrymatory action of bromoacetone was again noticed. The yellow compound, a hydrobromide, was then treated with dilute sodium hydroxide. Analyses indicated that the free base thus formed was 2-

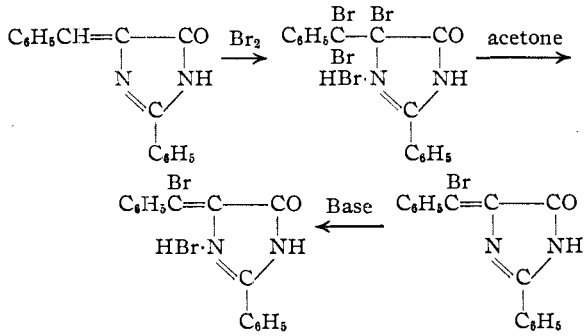
(1) Now engaged in war work at Massachusetts Institute of Technology.

(2) Now at Colorado A. and M. College, Ft. Collins, Colorado.

(3) Williams, Symonds, Ekeley and Ronzio, THIS JOURNAL, **67**, 1157 (1945).

(4) Minovici, *Ber.*, **32**, 2206 (1899).

phenyl-4-(α-bromobenzal)-5-glyoxalidone. The course of this reaction is shown in Equation 2.



Equation 2

Since in this experiment the hydrogen on the alpha carbon has been substituted, two forms of the brominated compound are not possible and the product easily loses bromine.

All attempts to isolate two forms of the monobromo glyoxalidone were unsuccessful. Several experiments which were made in an attempt to debrominate the stable dibromo-glyoxalidone in order to obtain the 2-phenyl-4-benzal-5-glyoxalidone having a different melting point were also unsuccessful.

Experimental

The following procedure is a modification of the directions given by Erlenmeyer[5] for the synthesis of 2-phenyl-4-benzal-5-glyoxalidone. A higher yield and a more easily purified product is obtained.

2-Phenyl-4-benzal-5-glyoxalidone.—A mixture of 9 g. (0.05 mole) of hippuric acid and 4.9 g. (0.05 mole) of fused potassium acetate was placed in a 500-ml., 3-necked flask fitted with a reflux condenser and mechanical stirrer. To this was added 15.3 g. (0.15 mole) of acetic anhydride and 10.6 g. (0.10 mole) of freshly purified benzaldehyde. The mixture was heated slowly on the water-bath while being stirred. The temperature of the bath was allowed to rise to boiling in thirty minutes. A yellow color appeared in the mixture which after about fifteen minutes, set to a solid crystalline mass. At this time the stirring was stopped. After heating at the temperature of boiling water for thirty minutes, the contents of the flask were removed, broken up and filtered. The mass of crystals was washed on the funnel three times with hot water, then with alcohol. The yield of 2-phenyl-4-benzal-5-oxazolone (azlactone) was 11.1 g. (95.1%); m. p. 165–166°.

Forty grams (0.16 mole) of the oxazolone, prepared in this manner, were mixed with 100 ml. of water, 200 ml. of 95% alcohol, and 20 ml. of concentrated ammonium hydroxide and poured in a liter flask fitted with a reflux condenser. The mixture was heated to boiling. The oxazolone dissolved completely within about twenty minutes. Another portion of 20–30 ml. of concentrated ammonium hydroxide and 20 g. of potassium carbonate were added at this time. The refluxing was continued and ammonium hydroxide was added in small portions sufficient to maintain small quantities of ammonia gas always present at the top of the reflux condenser. After heating about an hour, the golden yellow glyoxalidone began to precipitate. When the mixture began to bump, heating was stopped and the crystals of the glyoxalidone were filtered off. The filtrate was returned to the filter flask, a small quantity of ammonium hydroxide added, and heating continued. This procedure was repeated as often as necessary until the glyoxalidone no longer precipitated. The solution deposited an additional quantity of precipitate upon cooling. The precipitates were collected, washed with water, then with alcohol and dried. The weight was 38 g. (95.4%). After recrystallization from either 2-pentanol or butyl acetate the product melted at 280°.

ω-2-Phenyl-4-(α-bromobenzyl)-4-bromo-5-glyoxalidone.—A suspension of 8 g. (0.032 mole) of the purified glyoxalidone in 175 ml. of glacial acetic acid was heated to 60° and 5.2 g. (0.032 mole) of bromine dissolved in 10 ml. of glacial acetic acid was slowly added with stirring. (The reaction proceeds more rapidly in sunlight.) The glyoxalidone dissolved completely. The brominated product began to crystallize in fine orange needles after five to ten minutes. The product was washed several times with glacial acetic acid and dried. The product, weighing 9.49 g. (72%) melted at 165–168° with decomposition. The compound cannot be recrystallized without decomposition. A positive test for bromine was obtained after fusion with sodium.

Anal. Calcd. for $C_{16}H_{12}N_2OBr_2$: N, 6.86. Found: N, 6.59, 6.50.

2-Phenyl-4-benzal-5-glyoxalidone Hydrobromide.—Two tenths of a gram of the dibromo-glyoxalidone was added to 25 cc. of acetone, quickly stirred, and filtered. The filtrate, after standing one and one half to two minutes, quickly deposited a yellow crystalline product. The sharp odor and lachrymatory action of bromoacetone was noticeable. The precipitate was washed with acetone and dried in the desiccator. The product weighing about 0.16 g. (80%) melted at 254–256°. Due to the ease of hydrolysis and instability of this hydrobromide, all attempts at recrystallization were unsuccessful. The compound gave a positive test for bromide ion.

Anal. Calcd. for $C_{16}H_{12}N_2O\cdot HBr$: C, 58.37; H, 3.98; N, 8.51. Found: C, 58.17; H, 3.79; N, 8.35.

When the glyoxalidone hydrobromide was treated with 2 *N* sodium hydroxide in water solution, the free base formed which, recrystallized from 2-pentanol, melted at 280°. A test for bromine (sodium fusion) was negative.

Anal. Calcd. for $C_{16}H_{12}N_2O$: N, 11.29. Found: N, 11.31, 11.35.

α-2-Phenyl-4-(α-bromobenzyl)-4-bromo-5-glyoxalidone.—The portion of the dibromoglyoxalidone insoluble in acetone was washed with acetone and dried. The yellow compound, about 8–10% of the original amount, melted at 245–246° with decomposition. A positive test for bromine was obtained after fusion with sodium.

Anal. Calcd. for $C_{16}H_{12}N_2OBr_2$: C, 47.09; H, 2.96; N, 6.86. Found: C, 47.61, 47.86; H, 3.11, 3.35; N, 6.73, 6.79.

2-Phenyl-4-(α,α-dibromobenzyl)-4-bromo-5-glyoxalidone Hydrobromide.—When the mother liquor from the bromination of the glyoxalidone was allowed to stand several days, an orange crystalline precipitate formed slowly. The product could be recrystallized unchanged from glacial acetic acid; m. p. 260–263°. The amount of the precipitate varies with the amount of bromine used in the bromination. A positive test for bromine was obtained after fusion with sodium.

Anal. Calcd. for $C_{16}H_{12}N_2OBr_4$: C, 33.84; H, 2.12; N, 4.93. Found: C, 34.43, 34.26; H, 2.27, 2.18; N, 4.82, 4.73.

A sealed ampoule of the compound exploded after three months. The explosion was due probably to spontaneous evolution of hydrogen bromide and/or bromine.

2-Phenyl-4-(α-bromobenzal)-5-glyoxalidone Hydrobromide.—When the above described tribromoglyoxalidone hydrobromide was placed in acetone, complete solution took place. In the course of a few minutes, a yellow compound slowly crystallized. The color and form of the crystals were different from glyoxalidone hydrobromide described above. Washed with acetone and dried, the compound melted at 265–266° with decomposition. A

(5) Erlenmeyer, Jr., *Ber.*, **33**, 3036 (1900).

test for bromine ion was positive. The compound could not be purified without decomposition.

Anal. Calcd. for $C_{16}H_{12}N_2OBr_2$: C, 47.09; H, 2.96; N, 6.86. Found: C, 47.65, 47.30; H, 3.20, 3.15; N, 6.98, 6.98.

2-Phenyl-4-(α-bromobenzal)-5-glyoxalidone.—The hydrobromide described above dissolves completely in 2 *N* sodium hydroxide solution. Neutralization with dilute acetic acid precipitated the free glyoxalidone. The compound crystallized from 2-pentanol as long yellow needles melting at 230°. The compound gave a positive test for bromine after fusion with sodium.

Anal. Calcd. for $C_{16}H_{11}N_2OBr$: C, 58.73; H, 3.39; N, 8.56. Found: C, 58.77, 58.74; H, 3.36, 3.40; N, 8.57, 8.42.

Because of damage to the spectrograph at the University of Colorado and lack of repairs due to war conditions, the absorption spectra of these compounds cannot be reported. It is hoped that complete absorption spectra data may be reported later.

Summary

1. Improved procedure for the preparation of 2-phenyl-4-benzal-5-oxazolone (azlactone) and of 2-phenyl-4-benzal-5-glyoxalidone are described.
2. The synthesis and properties of ω-2-phenyl-4-(α-bromobenzyl)-4-bromo-5-glyoxalidone are reported.
3. The isolation and properties of α-2-phenyl-4-(α-bromobenzyl)-4-bromo-5-glyoxalidone are reported.
4. The synthesis and properties of 2-phenyl-4-(α,α-dibromobenzyl)-4-bromo-5-glyoxalidone hydrobromide are reported.
5. The synthesis and properties of 2-phenyl-4-(α-bromobenzal)-5-glyoxalidone and hydrobromide are reported.

FT. COLLINS, COLORADO RECEIVED DECEMBER 13, 1945

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

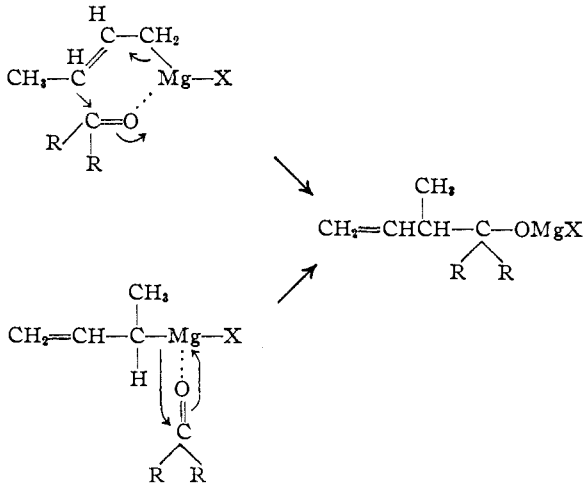
Allylic Rearrangements. XX. Some Addition Reactions of Butenylmagnesium Bromide

BY WILLIAM G. YOUNG AND JOHN D. ROBERTS[1]

Preceding studies of the butenyl Grignard reagent have indicated a striking tendency on the part of the reagent to introduce an α-methylallyl group in coupling reactions with allylic chlorides[2] and in addition reactions to aldehydes,[3,4] ketones[4] and carbon dioxide.[5] Even with highly-hindered ketones as diisopropyl ketone and acetomesitylene[6] the reaction products are predominantly α-methylallyl derivatives.

We have now turned to the investigation of other types of addition reactions of butenylmagnesium bromide and find that with phenyl isocyanate, ethyl formate and ethyl orthoformate the reaction products correspond almost exclusively to the secondary form of the Grignard reagent. With ethyl orthoformate some (<4%) of the diethyl acetal of 3-pentenal was obtained but in the other reactions none of the products resulting from the introduction of the primary butenyl group by the Grignard reagent was detected.

As one of several possible working hypotheses it is possible to account for the results of the addition and coupling reactions by considering the butenyl Grignard reagent (formulated as RMgBr) as being almost exclusively either crotyl or α-methylallylmagnesium bromide depending on the mechanism of the transfer of the butenyl radical to give a α-methylallyl derivative as the reaction product. Choosing a carbonyl addition reaction as an example we have



Similar mechanisms have been suggested for other Grignard reactions.[7,8]

Assuming that butenylmagnesium bromide is a single substance, it appears likely that a possible choice between consideration of the reagent as a crotyl or α-methylallyl derivative might be afforded by a study of the products from the 1,4-addition of the reagent to an α,β-unsaturated

(1) Abbott Laboratories Research Fellow, 1943–1944.
(2) Young, Roberts and Wax, THIS JOURNAL, **67**, 841 (1945).
(3) Ou Kuin-Houo, *Ann. chim.*, [11] **13**, 175 (1940).
(4) Roberts and Young, THIS JOURNAL, **67**, 148 (1945).
(5) Lane, Roberts and Young, *ibid.*, **66**, 543 (1944).
(6) Young and Roberts, *ibid.*, **66**, 2131 (1944); **67**, 319 (1945).
(7) Johnson in Gilman, "Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, Chap. XXV, pp. 1879–1883.
(8) Whitmore and George, paper presented before the Division of Organic Chemistry at the Atlantic City Meeting of the American Chemical Society, September, 1941.