Ball, Official Investigator under Division 9 of the National Defense Research Committee, for facilitating the carrying out of this work, and to Professor A. B. Hastings, Dr. J. M. Buchanan, and Mr. Robert Wolf for aid in determining the oxygen dissociation curves.

Summary

Crystalline horse oxyhemoglobin and serum albumin were treated with mustard gas under controlled *p*H conditions. It was found that:

1. The number of sulfur atoms introduced per molecule of protein is a function of the amount of mustard gas used.
2. The isoelectric points of the treated proteins are shifted in the direction of increasing alkalinity with increase in the number of sulfur atoms introduced.
3. The greatest reduction in titratable groups occurs in the region *p*H 2 to 5.5 where the carboxyl groups are normally titrated. It is concluded that some of the free carboxyl groups of the proteins have been esterified.
4. Further loss in titratable groups occurs in the region *p*H 5.5 to 8.5 where imidazole groups are normally titrated. The results of a study of the reaction of mustard gas with imidazole substantiate the conclusion that at physiological *p*H values mustard gas may react with the imidazole groups of these proteins.
5. With the proportions of mustard gas employed very little reduction in titratable groups in the region *p*H 8 to 11 takes place.
6. The oxygen dissociation curves of mustard gas-treated hemoglobins are shifted in a direction indicating that the modified proteins have a greater affinity for oxygen. It is suggested that this effect is due to the reaction of mustard gas with the imidazole groups of the hemoglobin molecule.

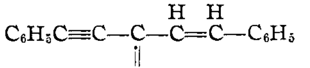
CAMBRIDGE, MASSACHUSETTS RECEIVED OCTOBER 9, 1946

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MISSOURI]

The Action of Sodium, Lithium and Potassium Phenylacetylene on Acid Derivatives

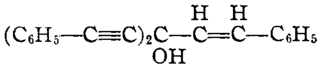
BY DOROTHY NIGHTINGALE AND FRANCIS T. WADSWORTH[1]

In a preceding paper[2] we have noted that the properties of cinnamoylphenylacetylene I prepared from cinnamic anhydride and sodium phenylacetylene differ markedly from those of the compound which Worrall[3] reported as cinnamoylphenylacetylene.



$C_6H_5C{\equiv}C-\underset{\underset{O}{\|}}{C}-\overset{H}{C}=\overset{H}{C}-C_6H_5$

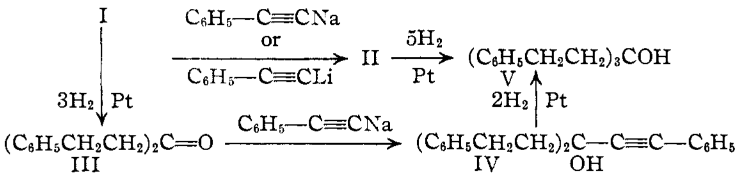
I



$(C_6H_5-C{\equiv}C)_2\underset{OH}{C}-\overset{H}{C}=\overset{H}{C}-C_6H_5$

II

The identity of Worrall's compound has now been established as bis-phenylethynylstyrylcarbinol II by the reactions



Ketone III, obtained by the hydrogenation of I, was identified as dibenzylacetone through its oxime which did not depress the melting point of an authentic specimen. In the Grignard machine, I added one mole of methylmagnesium iodide while II and V liberated one mole of methane. Most of the properties which Worrall described for his compound are those to be expected of a tertiary carbinol.

The tertiary carbinol II was readily obtained from the reaction of either cinnamic anhydride or ethyl cinnamate with lithium phenylacetylene in yields of 54 and 90%, respectively. This fact led us to compare the action of lithium, potassium, and sodium phenylacetylene with the acid derivatives listed in Table I.

In all cases except ethyl formate, lithium phenylacetylene yielded tertiary carbinols, while sodium phenylacetylene yielded ketones with the acid chlorides, tertiary carbinols with ethyl cinnamate and ethyl phenylpropiolate, and only traces of viscous oil with the aliphatic esters. The isolation of phenylpropargyl aldehyde from ethyl formate and lithium phenylacetylene rather than bis-phenylethynylcarbinol was surprising.

Potassium phenylacetylene formed small amounts of acetylphenylacetylene with acetic anhydride and acetyl chloride and a 50% yield of cinnamic acid with ethylcinnamate, but only a trace of viscous oil with all of the other acid derivatives.

The formation of tertiary carbinols rather than ketones from lithium phenylacetylene and the acid derivatives may be due to a greater solubility of the lithium addition product in ether, which may

---

[1] Abstract of a portion of the dissertation to be submitted by Francis T. Wadsworth in partial fulfillment of the requirement for the degree of Doctor of Philosophy at the University of Missouri. Present address: Pan American Refining Company, Texas City, Texas.

[2] Nightingale and Wadsworth, THIS JOURNAL, **67**, 416 (1945).

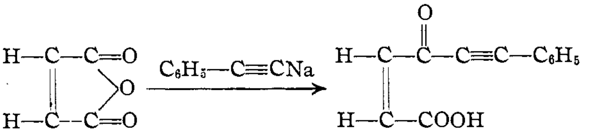
[3] Worrall, *ibid.*, **60**, 1266 (1938).

facilitate the intermediate formation of a ketone and its subsequent reaction with a second molecule of lithium phenylacetylene to form the tertiary carbinol. The formation of a ketone intermediate has been suggested by Gilman and Van Ess[4] to explain the formation of carbinols as well as ketones by the carbonation of organolithium compounds. We were unable to obtain bis-phenylethynyl ketone or tris-phenylethynylcarbinol from lithium phenylacetylene by the procedures used by Gilman and Van Ess for the carbonation of phenyllithium.

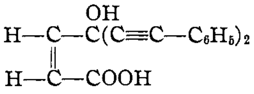
Sodium and lithium phenylacetylene added 1,2 to the carbonyl group of cinnamoylphenylacetylene, but only dark viscous oils or resins were obtained from this ketone with phenylethynylmagnesium bromide, phenylmagnesium bromide, and ethylmagnesium bromide. No identifiable products could be obtained from crotonylphenylacetylene.

Sodium malonic ester reacts with benzoylphenylacetylene to form an α-pyrone ester[5] in 70–95% yields but cinnamoylphenylacetylene formed only an intractable oil under the same conditions.

Sodium phenylacetylene reacted readily with maleic anhydride to form the keto acid VI



VI



VII

but lithium phenylacetylene yielded a mixture of acids, presumably VI and VII, which could not be separated. Similar results were obtained with succinic anhydride.

Acknowledgment.—The special chemicals for this problem were purchased with a grant from the University Research Council.

Experimental

Cinnamoylphenylacetylene.—The following procedure gives a higher yield of easily purified ketone than the one previously described.[2] Phenylacetylene (7.1 g., 0.07 mole) was added to 1.61 g. (0.07 mole) of sodium in 150 cc. of dry ether. When the reaction was complete, the ether was removed and replaced by 150 cc. of dry thiophene-free benzene, and this suspension of sodium phenylacetylene was siphoned slowly with stirring to 19.4 g. (0.07 mole) of cinnamic anhydride in 200 cc. of dry benzene at room temperature. After the reaction was well started, the mixture was stirred successively for four hours in an ice-bath and two hours at room temperature. The complex was decomposed with water, the ether layer washed thoroughly and dried briefly, and the ether removed on a steam-bath. The oily residue solidified when cooled in ice water and was crystallized from petroleum ether (b. p. 60–80°); yield, 9.4 g. (58%), m. p. 69–70°.

The cinnamoylphenylacetylene was reduced catalytically with Adams catalyst to dibenzylacetone III, the oxime of which melted at 92° and did not depress the melting point of an authentic sample of dibenzylacetone oxime.[6]

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.60; H, 7.55. Found: C, 80.37; H, 7.69.

bis-Phenylethynylstyrylcarbinol (II).—Cinnamoylphenylacetylene (0.5 g.) was dissolved in 15 cc. of ether and an ether suspension of lithium phenylacetylene or sodium phenylacetylene was added at room temperature; yields of carbinol 95 and 77%, respectively, m. p. 140–141°.

Anal. Calcd. for $C_{25}H_{18}O$: C, 89.80; H, 5.41. Found: C, 89.59; H, 5.48.

The carbinol II was obtained in yields of 84 and 90% from the condensation of sodium or lithium phenylacetylene, respectively, with ethyl cinnamate by Worrall's procedure. The reactions were carried out at temperatures as low as −30° in an effort to stop the reaction at the ketone stage, but only the tertiary carbinol II was isolated.

tris-β-Phenylethylcarbinol (V).—The carbinol II absorbed five moles of hydrogen to yield tris-β-phenylethylcarbinol V, m. p. 64°.

Anal. Calcd. for $C_{25}H_{28}O$: C, 87.21; H, 8.14. Found: C, 86.92; H, 8.20.

The carbinol V was also obtained as follows: sodium phenylacetylene (0.01 mole) was added to 0.01 mole of dibenzylacetone III in 150 cc. of ether. The carbinol IV was isolated as a viscous oil which did not crystallize. This carbinol absorbed two moles of hydrogen to yield tris-β-phenylcarbinol V, m. p. and mixed melting point with the above sample, 64°.

Reactions of Lithium, Sodium and Potassium Phenylacetylene with Acid Derivatives.—These reactions were all carried out by the following general procedure. The organometallic compound, prepared according to Gilman and Young,[7] was added slowly to 0.01 mole of ester, anhydride, or acid chloride in 200 cc. of dry ether. After stirring several hours at room temperature, the reaction mixture was treated with water, the ether layer washed thoroughly and dried over magnesium sulfate. After removal of the solvent, the liquid products were distilled at 6 mm. and the solids crystallized from a 10% solution of benzene in petroleum ether (60–80°) or from petroleum ether alone. The products, listed in Table I, were identified by their physical constants, solid derivatives, or by analysis. The oils were viscous and untractable. Yields are calculated on the basis of the phenylacetylene used.

Phenylpropargyl aldehyde, prepared from 0.12 molar quantities of lithium phenylacetylene and ethyl formate, distilled at 114–115° (17 mm.); yield, 31%.[8]

Anal. Calcd. for C_9H_6O: C, 83.07; H, 4.51. Found: C, 82.78; H, 4.55.

tris-Phenylethynylcarbinol.—This compound was obtained in yields of 11 and 53%, respectively, by the reaction of 0.06 mole of sodium phenylacetylene or lithium phenylacetylene and 0.06 mole of ethyl phenylpropiolate. The product was crystallized from petroleum ether (60–80°) and melted at 129–130°, the recorded melting point.[9]

Anal. Calcd. for $C_{25}H_{16}O$: C, 90.39; H, 4.81. Found: C, 90.10; H, 4.90.

This carbinol was also isolated from the reaction of lithium phenylacetylene and diethyl carbonate in 20% yield, m. p. and mixed melting point with the above sample, 129–130°.

---

[4] Gilman and Van Ess, *ibid.*, **55**, 1258 (1933).

[5] Kohler, *ibid.*, **44**, 379 (1922).

[6] Melting points of 91° (Ipatieff and Orloff, *J. Russ. Phys.-Chem. Soc.*, **59**, 537 (1927)); 92° (Dunschmann and von Pechmann, *Ann.*, **261** (1891)), and 95–96° (Borsche, *Ber.*, **45**, 49 (1912)); Wedekind, *Ann.*, **378**, 285 (1911) have been reported for dibenzylacetone oxime.

[7] Gilman and Young, *J. Org. Chem.*, **1**, 315 (1936).

[8] A 50% yield of phenylpropargyl aldehyde was reported by Moureu and Delange (*Bull. soc. chim.*, [3] **31**, 1392 (1904)) from sodium phenylacetylene and ethyl formate.

[9] Jozitsch and Seklawin, *J. Russ. Phys.-Chem. Soc.*, **42**, 1491 (1910).

TABLE I

REACTION PRODUCTS OF $C_6H_5C\equiv C$—M WITH ACID DERIVATIVES

R = $C_6H_5C\equiv C$—	Na	Yield, %	Li	Yield, %
Ethyl formate	RCHO	50[b]	RCHO	31
Ethyl acetate	Oil	Trace	R_2COHCH_3[d]	64
Acetyl chloride	$RCOCH_3$	25[a]	R_2COHCH_3[d]	65
Acetic anhydride	$RCOCH_3$	55[a]	R_2COHCH_3[d]	75
Ethyl butyrate	Oil	Trace	$R_2COHC_3H_7$	25
Butyric anhydride	$RCOC_3H_7$	53[a]	$R_2COHC_3H_7$	17
Ethyl crotonate	Oil	. . .	Oil	. .
Crotonic anhydride	$RCOC_3H_5$	49[a]	Oil	. .
Maleic anhydride	$\begin{array}{l}HCCOR\\ \ \ \|\\ HCCOOH\end{array}$	62	$\begin{array}{l}HCCOHR_2\\ \ \ \| \qquad ?\\ HCCOOH\end{array}$	
Succinic anhydride	$\begin{array}{l}H_2CCOR\\ \ \ \ \ |\\ H_2CCOOH\end{array}$	21[a]	$\begin{array}{l}H_2CCOHR_2\\ \ \ \ \ | \qquad ?\\ H_2CCOOH\end{array}$	
Cinnamic anhydride	$RCOCH=CHC_6H_5$	28[a]	$R_2COHCH=CHC_6H_5$	54
Ethyl cinnamate	$R_2COHCH=CHC_6H_5$	30[c]	$R_2COHCH=CHC_6H_5$	90
Hydrocinnamic anhydride	Oil	. . .	Oil	. .
Ethyl hydrocinnamate	Oil	. . .	Oil	. .
Ethyl phenylpropiolate	R_3COH	11	R_3COH	53
Diethyl carbonate	Oil	. . .	R_3COH	20

[a] Ref. 2. [b] Footnote 8. [c] Ref. 3. [d] M. p. and mixed m. p. with an authentic sample of bis-phenylethynylmethylcarbinol 109–110°.

Keto Acids VI and VII.—Sodium phenylacetylene (0.23 mole) in 100 cc. of ether was added slowly to 0.23 mole of maleic anhydride in 200 cc. of ether. The solution was stirred twenty-four hours, then water was added and the separated ether layer was extracted with 10% sodium carbonate solution. The alkaline layer was washed with ether, acidified with acetic acid and the oily layer extracted with ether. After removal of the solvent on a water-bath, the oily product solidified and was crystallized from petroleum ether; yield, 62%, m. p. 122–124°.

Anal. Calcd. for $C_{12}H_8O_3$: C, 72.00; H, 4.00; neut. equiv., 200.2. Found: C, 72.00; H, 4.28; neut. equiv., 206.

Substitution of lithium phenylacetylene gave a mixture of acids the composition of which approximated that of the hydroxy acid VII, but the product, like that (m. p. 95–96°) obtained from succinic anhydride and lithium phenylacetylene, could not be purified. The analytical data did not conform to the requirements for the lactones which might be expected from these acids. Possibly the keto acids contaminated the products, both of which, with concentrated acid, produced a purple color seemingly characteristic of the group $(C_6H_5C\equiv C)_2\underset{|}{C}OH$.

bis-Phenylethynylpropylcarbinol.—This carbinol melted at 71–71.5°.

Anal. Calcd. for $C_{20}H_{18}O$: C, 87.58; H, 6.61. Found: C, 87.48; H, 6.82.

Summary

The product from the reaction of ethyl cinnamate and sodium phenylacetylene is bis-phenylethynylstyrylcarbinol rather than cinnamoylphenylacetylene as previously reported.

With a few exceptions, sodium phenylacetylene yields ketones with acid derivatives while lithium phenylacetylene yields tertiary carbinols. Potassium phenylacetylene reacted less readily if at all with the acid derivatives under investigation.

COLUMBIA, MISSOURI RECEIVED DECEMBER 24, 1946