[Contribution from Research and Development Laboratory, Socony Mobil Oil Co., Inc.]

The Aminomethylation of Styrene. A New Synthesis of 3-Amino-1-phenylpropanol[1]

By S. L. Meisel, J. J. Dickert, Jr., and H. D. Hartough

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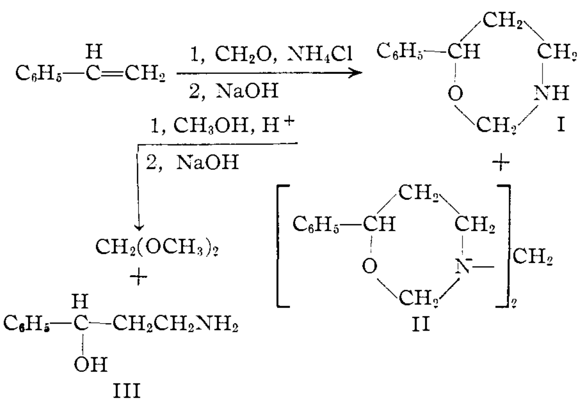
Styrene condenses with formaldehyde and ammonium chloride to form 6-phenyltetrahydro-1,3-oxazine (I) and bis-(N-6-phenyltetrahydro-1,3-oxazino)-methane (II). Reaction of I or II with methanol and hydrochloric acid yields 3-amino-1-phenylpropanol (III), while reaction with acetic anhydride leads to the N-acetyl derivative of I.

The Prins reaction, which involves the acid-catalyzed addition of formaldehyde to olefins to form unsaturated alcohols, glycols, dioxanes and other oxygenated derivatives, is well known.[2] Recently, this reaction has been extended to include the preparation of amino compounds by adding either ammonium or amine salts to the standard mixture.[3–5] This paper discusses the reactions of styrene, formaldehyde and ammonium chloride to form 6-phenyltetrahydro-1,3-oxazine (I), its N-bis-methylene derivative II and the conversion of I and II to 3-amino-1-phenylpropanol (III) and N-acetyltetrahydro-1,3-oxazine.



Davies and Powell have prepared III previously by the reduction of β-aminopropiophenone and have compared its activity with epinephrine.[6]

The reaction of I or II with acetic anhydride leads to N-acetyltetrahydro-1,3-oxazine.

Experimental

Bis-(N-6-phenyltetrahydro-1,3-oxazino)-methane.—To 104 g. (1 mole) of styrene were added 340 g. (4 moles) of 36% formaldehyde solution and 108 g. (2 moles) of ammonium chloride. The well-stirred mixture was warmed to 75–80° for 40 minutes and cooled. An oily layer of about 60 g. separated. This layer contains unreacted styrene, formaldehyde, 4-phenyl-1,3-dioxane and possibly minor amounts of other products formed in the normal Prins reaction. The aqueous layer was extracted three times with diethyl ether to remove additional oily material and then reacted with 2 moles of sodium hydroxide (as a 40% solution). This caused a separation of an amine and aqueous layer. The aqueous layer was extracted with ether and this extract was combined with the amine layer. Removal of the solvent yielded 88 g. of a light yellow viscous oil. About 70 g. (43% based on styrene charged) of this material crystallized on standing to form bis-(N-6-phenyltetrahydro-1,3-oxazino)-methane. The remaining oil (11%) contained impure 6-phenyltetrahydro-1,3-oxazine. The N-bis-methylene derivative was recrystallized from ethanol to yield a product melting at 125.5–126°.

Anal. Calcd. for $C_{21}H_{26}N_2O_2$: C, 74.56; H, 7.69; N, 8.28; mol. wt., 338. Found: C, 74.11; H, 7.75; N, 8.31; mol. wt. (b.p.), 376.

N-Acetyl-6-phenyltetrahydro-1,3-oxazine.—To 161 g. of a mixture of I and II were added 250 ml. of benzene and 214 g. of acetic anhydride. The reaction mixture was cooled during the addition and then refluxed for 3 hr. Removal of the benzene yielded 164 g. of crude product. Distillation yielded a center cut, 133 g. (65%), b.p. 145–146° (0.5 mm.). This material crystallized on standing and was recrystallized from *n*-heptane; m.p. 84–85°.

Anal. Calcd. for $C_{12}H_{15}NO_2$; C, 70.24; H, 7.32; N, 6.83. Found: C, 70.35; H, 7.51; N, 6.87.

3-Amino-1-phenylpropanol.—To 85 g. (0.25 mole) of bis-(N-6-phenyltetrahydro-1,3-oxazino)-methane were added 50 g. of concd. hydrochloric acid, 150 ml. of water and 300 ml. of methanol. The mixture was stirred for 1 hr. at room temperature and then allowed to stand for 16 hr. The reaction mixture was refluxed (69–72°) for 1 hr. and distilled to a reaction temperature of 100° to remove the methylal and excess methanol. After cooling, the reaction mixture was treated with 55 g. of 40% sodium hydroxide. A water-insoluble layer formed and was separated from the reaction mixture. The oil layer was then distilled *in vacuo*. A center cut of 53 g. (70% yield), b.p. 117–119° (1.0 mm.), crystallized on standing. A foreshot of 9 g. and a residue of 13 g. also produced some crystalline material when seeded. The center cut was recrystallized twice from benzene; m.p. 61–62°; lit.[6] 63.5–64°.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.52; H, 8.61; N, 9.27. Found: C, 70.82; H, 8.54; N, 9.16.

A phenylthiourea derivative of this material was prepared and recrystallized three times from absolute ethanol; m.p. 135–135.5°.

Anal. Calcd. for $C_{16}H_{18}N_2OS$: C, 67.13; H, 6.29; N, 9.79. Found: C, 67.28; H, 6.51; N, 10.29.

Discussion

The mechanism of this reaction is probably similar to those proposed for the Prins reaction[7] and for the aminomethylation of olefins with secondary amines.[4,5] However, they are not entirely comparable reactions. Extremely reactive olefins, such as α-methylstyrene, are needed for the latter reaction. Both our work and that of Hennion, Price and Wolff[4] have shown that styrene condenses readily with ammonia but not with secondary amines. This difference may be related to either the ease of formation or the reactivity of the carbonium ion intermediates, $CH_2NH_2^+$ from ammonia and $R_2NCH_2^+$ from secondary amines.

The condensation of formaldehyde with 3-

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[1] Presented at the Delaware Valley Regional Meeting, Philadelphia, February 16, 1956.

[2] (a) H. J. Prins, *Proc. Acad. Sci. Amsterdam*, **22**, 51 (1919); (b) C. C. Price, F. L. Benton and C. J. Schmidle, This Journal, **71**, 2860 (1949).

[3] H. D. Hartough, J. J. Dickert, Jr., and S. L. Meisel, U. S. Patent 2,647,117, 2,647,118 (*C.A.*, **48**, 8265 (1954)).

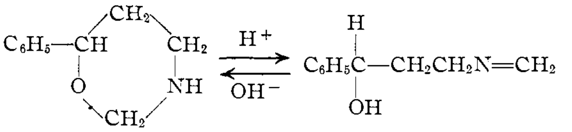
[4] G. F. Hennion, C. C. Price and V. C. Wolff, Jr., This Journal **77**, 4633 (1955).

[5] C. J. Schmidle and R. C. Mansfield, *ibid.*, **77**, 4636 (1955)

[6] R. E. Davies and G. Powell, *ibid.*, **67**, 1466 (1945).

[7] C. C. Price, "Mechanisms of Reactions at the Carbon–Carbon Double Bond," Interscience Publishers, Inc., New York, N. Y., 1946, p. 45.

amino-1-phenylpropanol to form the oxazine derivatives probably involves a formaldimine intermediate. It is possible that a tautomeric equilibrium exists between oxazine and formaldimine.



Some evidence for this is derived from the reaction of oxazine derivatives with methanol and acid to form 3-amino-1-phenylpropanol. This reaction is actually a reversal of the last steps in the aminomethylation reaction. Based on work in the thiophene series,[8] it seems likely that this reaction of the oxazines goes through a formaldimine intermediate. Treatment of the oxazines with sulfuric acid or urea and hydrochloric acid also produces the primary amine. Similar reactions were observed with the formaldimines of the thiophene series. However, in both the oxazine and thiophene series, the primary amines are synthesized best by the methanol procedure.

Styrene can also be condensed with methylamine hydrochloride. However, this reaction goes less readily than the one with ammonium chloride. Improved yields can be obtained with paraformaldehyde and acetic acid as the solvent. The identity of the nitrogen compounds was not investigated.

A series of olefins, other than styrene, which can be condensed with formaldehyde and ammonium chloride include α-methylstyrene, isobutylene, 2-ethyl-1-butene, 2-methyl-1-pentene, α-pinene and β-pinene and butadiene.[3] Olefins such as 1-octene and 1-hexene did not react. Reaction conditions were generally similar to those used for styrene. Exceptions were with isobutylene, where a pressure vessel was used, and with the very reactive olefins, α-methylstyrene and β-pinene, where lower reaction temperatures were used.

The structures of these amines were not determined. On the basis of our work and that of Schmidle and Mansfield,[9] it seems likely that they are mixtures which contain the 6-substituted tetrahydro-1,3-oxazine and 4-substituted-4-piperidinol systems. The latter systems cannot form with olefins of the $RCH{=}CH_2$ type, such as styrene.

[8] H. D. Hartough and S. L. Meisel, THIS JOURNAL, **70**, 4018 (1948).

[9] C. J. Schmidle and R. C. Mansfield, *ibid.*, **77**, 5698 (1955); **78**, 1702 (1956).

PAULSBORO, NEW JERSEY

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

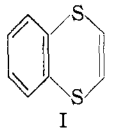
Heterocyclic Vinyl Ethers. XII. The Synthesis of Arylmercaptoacetylenes and a New Cleavage Reaction of Benzo-1,4-dithiadiene[1,2]

BY WILLIAM E. PARHAM AND PAUL L. STRIGHT[3]

RECEIVED APRIL 5, 1956

This paper describes comparative studies of the reaction of *cis* and *trans*-bis-(phenylmercapto)-ethylene (II) and benzo-1,4-dithiadiene (I), with butyllithium. Both *cis* and *trans* II react with butyllithium in ethyl ether at 0° to give phenylmercaptoacetylene (III). The ease of preparation of ethylenes of type II and the high yield of products suggest that this reaction will serve as a convenient source for terminal mercaptoacetylenes. Benzo-1,4-dithiadiene, the cyclic analog of *cis*-II, does not undergo appreciable metalation by reaction with butyllithium in ethyl ether at 0°; however, when such reaction mixtures are treated with dimethyl sulfate, a substitution–elimination (SN-ε) reaction occurs, leading to the formation of 1-(*n*-butylthio)-2-methylthiobenzene (XIII) and acetylene. Possible mechanisms for these reactions are discussed.

In paper IX[4] of this series, attention was called to the fact that open chain analogs of benzo-1,4-dithiadiene (I), such as II, also undergo certain electrophilic substitution reactions at the ethylenic double bond.



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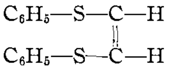

$$\begin{array}{l} C_6H_5{-}S{-}C{-}H \\ \qquad\quad \| \\ C_6H_5{-}S{-}C{-}H \end{array}$$

II

This report describes comparative studies of the reaction of I, and *cis* and *trans* II, with butyllithium.

cis-Bis-(phenylmercapto)-ethylene (II) was treated with *n*-butyllithium in ethyl ether at 0°, and the product was separated into a water-soluble and an ether-soluble fraction. The water-soluble fraction contained the lithium salt of thiophenol, which was characterized by its oxidation to the known diphenyl disulfide. Distillation of the ether solution afforded an orange-yellow oil (60%),[5] which rapidly changed in color to red-brown. The composition of this product (C_8H_6S) suggested that it was phenylmercaptoacetylene,[6] and the infrared spectrum showed absorption typical of terminal acetylene (3290 and 2040 cm.$^{-1}$). The terminal acetylenic group was confirmed by the conversion of the product into the corresponding mercury derivative IV (m.p. 137°). The reaction sequence can thus be formulated as shown in the equation

$$\text{II} + C_4H_9Li \xrightarrow[H_2O]{\text{then}} \underset{>50\%}{C_6H_5SLi} +$$

$$\underset{\text{III }(60\%)}{C_6H_5S{-}C{\equiv}CH} \xrightarrow{Hg^{++}} \underset{\text{IV }(82\%)}{(C_6H_5S{-}C{\equiv}C)_2Hg}$$

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[1] This work was supported by the Office of Ordnance Research, U. S. Army, Contract No. DA-11-022-ORD-1716.

[2] Presented before the 129th Meeting of the American Chemical Society in Dallas, 1956.

[3] From the Ph.D. thesis of P. L. Stright, University of Minnesota, 1955.

[4] W. E. Parham and J. Heberling, THIS JOURNAL, **77**, 1175 (1955).

[5] The yield of undistilled product was estimated to be 80%.

[6] W. E. Truce, J. A. Simms and M. Boudakian, THIS JOURNAL, **78**, 695 (1956), report the first instance of substituted acetylenes of this type.