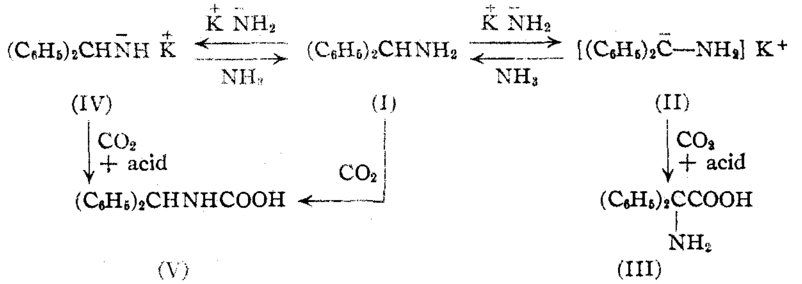
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Metalation and Carbonation of Benzohydrylamine and Derivatives Using Potassium Amide[1]

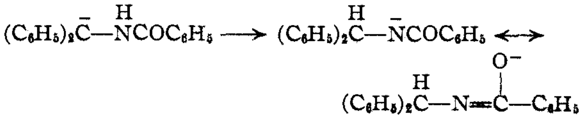
BY CHARLES R. HAUSER, INA C. FLUR AND SIMON W. KANTOR

Because nitrogen is more negative than carbon, the amino hydrogens of methylamine are more acidic than the methyl hydrogens and, with a sufficiently strong base, the amino hydrogens would presumably be ionized preferentially. However, because of the well-known activating effect of the phenyl group, the methylene hydrogens of benzylamine and especially the methinyl hydrogen of benzohydrylamine might be expected to approach or even surpass the amino hydrogens in acidity. Actually, both of these amines produce red colored solutions with potassium amide in liquid ammonia indicating the formation of the corresponding carbanions. Confirmation of the presence of the carbanion (II) from benzohydrylamine (I) has been obtained by carbonation of the potassium salt to form the amino acid (III). However, similar carbonation of the salt from benzylamine has yielded no carboxylic acid. Even with the potassium salt of benzohydrylamine, carbonation has produced the amino acid (III) only under special conditions; frequently the corresponding carbamic acid (V) is obtained. The formation of (V) indicates that the anion of the potassium salt is partly the amide ion (IV), although (V) may also be formed from the free amine. The interconversion of anions (II) and (IV) is considered to involve reaction with the solvent and amide ion, although it might conceivably occur intramolecularly involving the shift of a proton.



The conditions required for the formation of the amino acid (III) are somewhat difficult to define. This product has been obtained twice in yields of 33% and 42% by evaporating the liquid ammonia in the presence of ether and treating the resulting ether suspension with Dry Ice; these are the conditions employed previously in the carbonation of potassium diphenylmethide.[2] However, attempts to duplicate these results have failed; instead of the amino acid, the carbamic acid (V) was obtained. A more certain way of obtaining the amino acid is to evaporate the liquid ammonia rapidly and then to carbonate an ether suspension of the residue. Apparently, as the liquid ammonia is evaporated, salt (II) is converted to salt (IV): this conversion appears to be minimized by the rapid evaporation of the solvent. However, even with some liquid ammonia present, carbonation has given only the carbamic acid. Similarly, carbethoxylation with diethyl carbonate in liquid ammonia has given only the carbamic acid ethyl ester. With these reactions in liquid ammonia solution, especially with the relatively slow carbethoxylation, a steric factor may be important in that the less-hindered amide ion (IV) may react faster than the carbanion (II), the equilibrium shifting in favor of the former.

The two derivatives of benzohydrylamine, N-isopropylbenzohydrylamine[3] and N-phenylbenzohydrylamine,[4] produce red colored solutions with potassium amide in liquid ammonia but, rather surprisingly carbonation of the ether suspension of the residue, obtained on the evaporation of the ammonia, yielded neither the amino acid nor the carbamic acid, most of the amine being recovered. N-Benzoylbenzohydrylamine[5] reacts with potassium amide in liquid ammonia to produce a red colored solution which gradually lightens to pink and finally becomes colorless after four to five minutes. Apparently some of the carbanion is formed but it is soon converted to the amide ion, thus



$$(C_6H_5)_2\bar{C}—\overset{H}{N}COC_6H_5 \longrightarrow (C_6H_5)_2\overset{H}{C}—\bar{N}COC_6H_5 \longleftrightarrow (C_6H_5)_2\overset{H}{C}—N{=}\overset{O^-}{\overset{|}{C}}—C_6H_5$$

It is obvious that derivatives of benzohydrylamine in which both of the hydrogens are substituted can produce only the carbanion. An interesting derivative of this type is benzalbenzohydrylamine (VI) the carbanion of which reacts on carbonation as if it had resonance form (VIIB) rather than (VIIA) since (VIII) is produced apparently exclusively. The acid corresponding to (VIII)

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(1) Part of the work reported in this paper was carried out in connection with a contract with the Office of Naval Research.

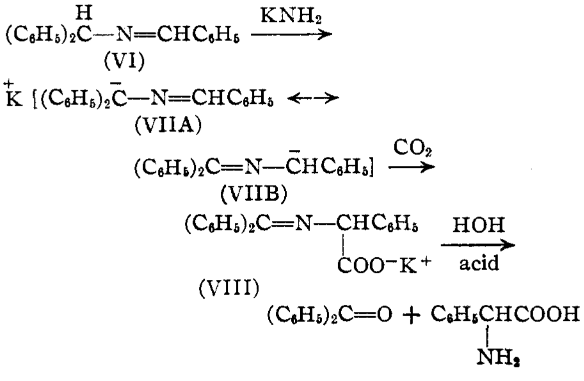
(2) Yost and Hauser, THIS JOURNAL, **69**, 2325 (1947).

(3) This compound (b. p. 170-171° at 19 mm.) was prepared in 72% yield from benzohydrylamine and isopropyl iodide by the method of Leeuw, *Rec. trav. chim.*, **30**, 250 (1911).

(4) This compound was obtained as its hydrochloride as described by Busch and Rinck, *Ber.*, **38** [2], 1767 (1905).

(5) This compound was prepared in 97% yield by the Schotten–Baumann method; see Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 88.

was not isolated but its hydrolysis products, benzophenone and *dl*-α-aminophenylacetic acid, were obtained in good yields on acidification of the reaction mixture.



$$\overset{H}{(C_6H_5)_2C}—N=CHC_6H_5 \xrightarrow{KNH_2} \quad \text{(VI)}$$

$$\overset{+}{K}\,[(C_6H_5)_2\overset{-}{C}—N=CHC_6H_5 \longleftrightarrow \quad \text{(VIIA)}$$

$$(C_6H_5)_2C=N—\overset{-}{C}HC_6H_5] \xrightarrow{CO_2} \quad \text{(VIIB)}$$

$$(C_6H_5)_2C=N—\underset{COO^-K^+}{CHC_6H_5} \xrightarrow[\text{acid}]{HOH} \quad \text{(VIII)}$$

$$(C_6H_5)_2C=O + C_6H_5\underset{NH_2}{C}HCOOH$$

Benzohydrylidenebenzohydrylamine[6] produces a red colored solution with potassium amide in liquid ammonia but the color disappears on replacing the ammonia with ether and the carbonation fails.[7]

It should be pointed out that also certain important syntheses involve metalations of the system, CHNH. One of these consists in the metalation of benzoyl[8] or acetyl[9] aminomalonic ester, followed by alkylation and hydrolysis to form α-amino acids. Application of certain of the ideas discussed above to such syntheses is contemplated.

Experimental[10]

Benzohydrylamine.—This amine has been prepared on a half mole scale from benzophenoneoxime both by reduction with sodium in ethanol and by hydrogenation over Raney nickel. The former method in which the very small scale procedure of Jones and Hurd[11] was adapted gave a satisfactory yield (85%) but the process was somewhat difficult to carry out on the large scale. The hydrogenation in which the general procedure of Adkins[12] was adapted gave equally good yields (85–92%) and it was more convenient.

The oxime (109 g., 0.55 mole) in 600 ml. of 95% ethanol was hydrogenated over Raney nickel at 1000–1300 pounds pressure at 75°. After removal of the catalyst and alcohol, the residue was dissolved in ether. The ether solution was washed with dilute sodium hydroxide, then with water and dried over solid sodium hydroxide. The amine, after removal of the solvent, distilled at 134–135° at 3.5 mm. and at 125–127° at 1 mm.

Carbonation of Benzohydrylamine.—To a stirred solution of 0.075 mole of potassium amide in about 200 ml. of liquid ammonia[13] was added 9.15 g. (0.05 mole) of benzohydrylamine. The solution became red immediately. The ammonia was evaporated rapidly using a steam-bath. When all the liquid ammonia was gone, the black residue was heated on the steam-bath for fifteen minutes. The bath was removed and 200 ml. of anhydrous ether was added with constant stirring. An excess of powdered Dry Ice was then added and the mixture stirred for two hours. When the excess Dry Ice was gone, 200 ml. of water was added and after shaking, the aqueous layer was filtered. Carbon dioxide was then bubbled into the aqueous alkaline solution until neutral to *p*H paper. The precipitate was filtered off and washed with methanol or ethanol to dissolve carbamic acid leaving the amino acid, α,α-diphenylglycine, m. p. 238°, in 31% yield. After several washings with ether and alcohol the melting point was raised to 243–245° dec. (reported m. p. 245–246° dec.).[14] The amino acid was further identified by conversion to benzilic acid, m. p. 150°.[15] In two other runs the pure amino acid, m. p. 243–245°, was obtained in 10% yield. Evaporation of the original ether extract of the mixture generally yielded a considerable amount of recovered benzohydrylamine. The recovered amine plus the carbonated product usually accounted for 80–90% of the starting material.

When the residue obtained on the evaporation of the liquid ammonia was suspended in anhydrous dioxane, a red color was produced but, on carbonation, only a 5% yield of the amino acid (m. p. 238°) was obtained. There was obtained a 50% yield of the carbamic acid, m. p. 89–91° (reported m. p. 91°).[16]

When the liquid ammonia solution was evaporated on a steam-bath as anhydrous ether was added at such a rate as to maintain a constant volume, the amino acid (m. p. 238°) was obtained in 42% yield on immediate carbonation and in 34% yield when the ether suspension was refluxed for two hours before carbonation. However, two attempts to duplicate the first result and one attempt to duplicate the latter have failed; instead of the amino acid the carbamic acid was obtained in yields up to 40%.

When the liquid ammonia solution of the potassium salt of benzohydrylamine was allowed to evaporate to a volume of 50 ml. and the contents of the flask then poured on an excess of powdered Dry Ice, only the carbamic acid (26%) was obtained.

When a mixture of 0.05 mole each of benzohydrylamine and diethylaminomagnesium bromide in ether[17] was refluxed for six hours and powdered Dry Ice then added, no carbonation product could be isolated. Most of the amine was recovered. The amine was similarly recovered when equivalent amounts of methylmagnesium iodide and benzohydrylamine were refluxed for one hour and then carbonated.

Carbonation of Benzalbenzohydrylamine.—To a stirred solution of 0.2 mole of potassium amide in 200 ml. of liquid ammonia was added 27.1 g. (0.1 mole) of benzalbenzohydrylamine (m. p. 100°).[18] The solution became red immediately. The liquid ammonia was evaporated as sufficient ether was added to maintain constant volume and the resulting red suspension was carbonated in the usual manner. After stirring with water, the aqueous layer was acidified with dilute acetic acid. The solid was filtered off and washed with water; it weighed 22.7 g. and melted over a considerable range. This solid was stirred thoroughly with 50 ml. of ether and the mixture filtered. The precipitate was identified as *dl*-α-aminophenylacetic

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[6] This compound was prepared by the method of Ingold and Wilson, *J. Chem. Soc.*, 1502 (1933).

[7] The destruction of the red colored carbanion presumably involves reversion to benzohydrylidenebenzohydrylamine and potassium amide. Similar reversions on replacement of the liquid ammonia by an inert solvent have been observed with sodium triphenylmethide (Kraus and Rosen, THIS JOURNAL, **47**, 2739 (1925)) and with sodium diphenylmethide (see ref. 2) but not with potassium triphenylmethide or potassium diphenylmethide. We have observed the reversion with potassium sym-tetraphenylethide. The tendency for the reversion appears to be dependent both on the metallic cation and on the carbanion. The tendency is greater with sodium ion than with potassium ion and apparently with carbanions which have a greater capacity for resonance.

[8] Redeman and Dunn, *J. Biol. Chem.*, **130**, 341 (1939).

[9] Dakin, *ibid.*, **154**, 549 (1944); Snyder, Shekleton and Lewis, THIS JOURNAL, **67**, 310 (1945); Albertson and Archer, *ibid.*, **67**, 308 (1945).

[10] All melting points are uncorrected.

[11] Jones and Hurd, THIS JOURNAL, **43**, 2438 (1921).

[12] Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937, p. 92.

[13] Hauser, Shivers and Skell, THIS JOURNAL, **67**, 409 (1945); Shivers, Hudson and Hauser, *ibid.*, **65**, 2051 (1943).

[14] Biltz and Seydel, *Ann.*, **391**, 226 (1912).

[15] Jena, *ibid.*, **155**, 80 (1870).

[16] Leuckart and Bach, *Ber.*, **19**, 2130 (1886).

[17] Hauser and Walker, THIS JOURNAL, **69**, 295 (1947).

[18] Michaelis and Linow, *Ber.*, **26**, 2169 (1893).

acid, m. p. 255–257° (after sublimation *in vacuo*) (reported m. p. 255–256°, subl.);[19] the yield was 10.7 g. (71%). The acetyl derivative melted at 197.5–198.5° (reported 198.5).[20] The ether filtrate was evaporated yielding 12 g. (66%) of benzophenone. The semicarbazone melted at 163–164° (reported m. p. 164°).[21]

Summary

1. Benzohydrylamine and certain of its derivatives react with potassium amide in liquid ammonia to form red colored solutions indicating the formation of the corresponding carbanions.

2. Carbonation of the potassium salt of benzohydrylamine has given the corresponding α-amino acid.

3. Carbonation of the carbanion of benzalbenzohydrylamine gives the N-benzohydrylidene α phenylglycine instead of N-benzal α,α-diphenylglycine.

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(19) Zelinsky and Stadnikoff, *Ber.*, **39**, 1726 (1906).

(20) Heilbron, "Dictionary of Organic Compounds," Vol. I, Oxford University Press, New York, N. Y., 1943, p. 112.

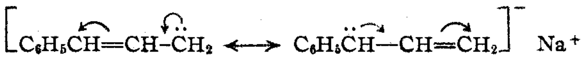
(21) See ref. 5, p. 264.

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

Allylic Rearrangements. XXV. Reaction of the Sodium Derivative of Allylbenzene with α-Haloacetic Acids

BY TOD W. CAMPBELL AND WILLIAM G. YOUNG

The sodium derivative of allylbenzene, which has been the subject of recent investigations[1] undergoes reactions which can best be expressed[1c] as nucleophilic attacks by the resonating anion

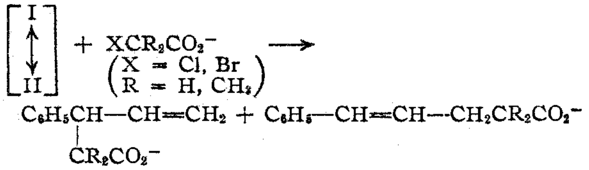


$$\left[C_6H_5CH{=}CH{-}\ddot{C}H_2 \longleftrightarrow C_6H_5\ddot{C}H{-}CH{=}CH_2\right]^- \; Na^+$$

I II

Since most reactions studied in which steric effects are not serious lead to mixtures of products derived from both of the principal resonance forms of the allylbenzene anion, it seemed odd that the reaction with simple halides[1a] gave, at least principally, products derived from form II above.

In an attempt to clarify the issue, the reaction of sodium allylbenzene with a series of α-haloacetate ions was examined. This particular series was chosen since it should be possible to determine the effect of (a) steric hindrance, (b) polarization and (c) the nature of the ion being displaced, on the manner in which the resonating allylbenzene carbanion reacts in displacement reactions. When the chosen reactants were mixed, a rapid reaction ensued. From the reacaction product was isolated a mixture of carboxylic acids, whose formation can be represented by the equation



$$\begin{bmatrix} \text{I} \\ \updownarrow \\ \text{II} \end{bmatrix} + \underset{\left(\begin{smallmatrix} X = Cl,\ Br \\ R = H,\ CH_3 \end{smallmatrix}\right)}{XCR_2CO_2^-} \longrightarrow$$

$$\underset{\displaystyle CR_2CO_2^-}{C_6H_5CH}{-}CH{=}CH_2 + C_6H_5{-}CH{=}CH{-}CH_2CR_2CO_2^-$$

All possible combinations of X and R were examined. The individual acids produced were separated and carefully characterized, principally as benzylamine salts.[2] The composition of the original mixtures was estimated to about ± 2% from the characteristic absorption spectrum[3] for the conjugated system.

From the results listed in Table IV, it will be seen that the polarizing effect of the carboxylate ion adjacent to the carbon atom being attacked is probably more important than simple steric hindrance, since the unsubstituted α-haloacetate ions are certainly less hindered than a compound such as α-methallyl chloride.[1a] It will be noted that the addition of methyl groups on the α-haloacetate ions leads to an increasing amount of the product arising from the primary form of the carbanion, as might be predicted from steric effects.[1c] It is also interesting to note that in this series the nature of the halogen being displaced definitely affects the composition of the mixture obtained from the resonating carbanion, the effect becoming more apparent as the number of methyl groups is increased. This effect of the halogen being displaced on the products has not been noted before in any of the reactions of sodium allylbenzene.

Experimental Part

All melting points are uncorrected.

Reaction of the Sodium Derivatives of Allylbenzene with α-Haloacetic Acids—General Method.—The sodium derivative was prepared in 300 ml. of liquid ammonia in the usual manner[1] from 0.1 *M* of allylbenzene. The solution was forced over as rapidly as possible (by the vapor pressure of the liquid ammonia solvent) into a two-liter three-necked flask containing 0.05 mole of the appropriate α-haloacetic acid dissolved in 20 ml. of ether (anhydrous). The flask was equipped with a stirring device and a wide outlet tube to provide for escape of the ammonia vapors. The characteristic red color of the sodium derivative was discharged rapidly. After evaporation of the solvent, water was added, and the carboxylic acids were separated from the non-acidic material. Table I is a résumé of results obtained by this method. Data are averages of several experiments.

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(1) (a) Levy and Cope, THIS JOURNAL, **66**, 1684 (1944); (b) Campbell and Young, *ibid.*, **69**, 688 (1947); (c) *ibid.*, **69**, 3066 (1947).

(2) Buehler, Carson and Edds, *ibid.*, **57**, 2181 (1935).

(3) Campbell, Linden, Godshalk and Young, *ibid.*, **69**, 880 (1947).