ing material, only diene dimer as condensation product, b.p. 87.5–88° (15.0 mm.).

CONTRIBUTION NO. 175 FROM
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Confirmation of the *ortho* Substitution Rearrangement of the Benzhydryltrimethylammonium Ion by Sodium Amide

BY WALLACE R. BRASEN[1] AND CHARLES R. HAUSER

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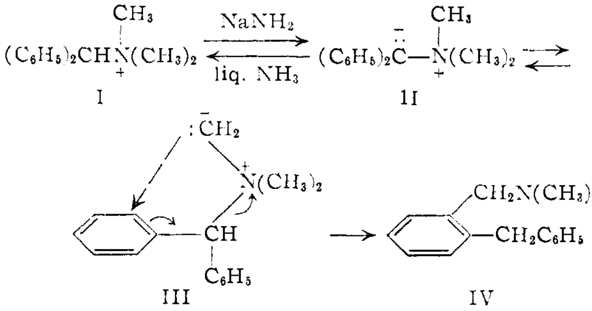
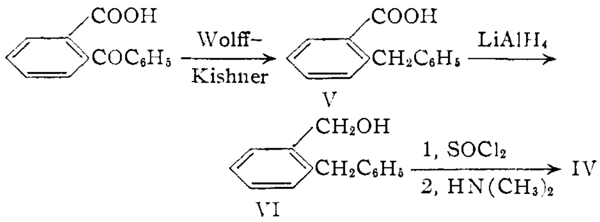
One of the *ortho* substitution rearrangements of benzyl type quaternary ammonium ions by sodium amide in liquid ammonia reported recently,[2] is that of the benzhydryltrimethylammonium ion (I) to form tertiary amine IV (88%). This example is particularly remarkable[3] since the reactive intermediate is carbanion III (an ylide),[4] not carbanion II which is presumably present in much higher concentration.



The product was assigned structure IV because, on oxidation, it produced *o*-benzyl- and *o*-benzoylbenzoic acids. We have confirmed this assignment of structure by unequivocally synthesizing tertiary amine IV from *o*-benzoylbenzoic acid, passing through intermediates V and VI, and showing that it was identical with the tertiary amine obtained from the rearrangement of I.



Experimental[5]

o-Benzylbenzoic acid (V), m.p. 114–115° (lit. m.p. 111–113°,[6] 117°[7]), was prepared in 50% yield by the reduction of *o*-benzoylbenzoic acid by the Wolff–Kishner method according to the general procedure described in "Organic Reactions."[8]

o-**Benzylbenzyl Alcohol (VI).**—To a stirred suspension of 2.1 g. (0.058 mole) of lithium aluminum hydride in 100 ml. of anhydrous ether was added a solution of 14 g. (0.066 mole) of *o*-benzylbenzoic acid in 50 ml. of anhydrous ether. The resulting mixture was stirred and refluxed for one hour, and the excess hydride destroyed by addition of 5 ml. of ethyl acetate. The ether solution, after washing with 10% sulfuric acid and 10% sodium bicarbonate, was dried over potassium carbonate and the solvent removed. The oily residue was crystallized from 30–60° petroleum ether to give 10.6 g. (81%) of *o*-benzylbenzyl alcohol (VI), m.p. 40–41°.

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.93; H, 7.05.

o-**Benzylbenzyl-N,N-dimethylamine (IV).**—A solution of 9.6 g. (0.049 mole) of *o*-benzylbenzyl alcohol in 10 ml. of benzene and 12 g. (0.1 mole) of thionyl chloride was boiled (after the first vigorous reaction had subsided) until the volume of the solution was 15 ml. An additional 10 ml. of benzene was added, and the volume of the solution again reduced to 15 ml. To this material was added an ice-cold solution of 14 g. (0.31 mole, 500% excess) of dimethylamine in 100 ml. of methanol, and the resulting solution allowed to stand for 30 hours. Methanol and excess dimethylamine were removed at the water aspirator and the residue taken up in water. After washing with ether, the aqueous solution was made basic with 10% sodium hydroxide and the liberated amine taken up in ether. The ether solution was dried over solid potassium hydroxide and the solvent removed. The residue was distilled under reduced pressure to yield 7.1 g. (70%) of *o*-benzylbenzyl-N,N-dimethylamine (IV), b.p. 129.5–130° at 2.3 mm., n^{25}_{D} 1.5598.

Anal. Calcd. for $C_{16}H_{19}N$: C, 85.31; H, 8.46; N, 6.22. Found: C, 85.52; H, 8.50; N, 6.33.

The picrate melted at 151–152°; reported m.p. 156–156.6°.[3]

Anal. Calcd. for $C_{22}H_{22}N_4O_7$: N, 12.33. Found: N, 12.03.

Amine IV, obtained from the rearrangement of quaternary ion I as described previously,[2] boiled at 133–135° at 2.5 mm.; n^{25}_{D} 1.5600. It gave a picrate, m.p. 151–152°, which was not depressed on admixture with the picrate (m.p. 151–152°)[2] of the amine prepared from *o*-benzoylbenzoic acid.

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[1] Carbide and Carbon Chemicals Company Fellow, 1954.

[2] S. W. Kantor and C. R. Hauser, THIS JOURNAL, **73**, 4122 (1951).

[3] The rearrangement of I to IV was first observed by M. Sommelet (*Compt. rend.*, **205**, 56 (1937)) who allowed an aqueous solution of the hydroxide of I to evaporate in sunlight. G. Wittig, R. Mangold, and G. Felletschin (*Ann.*, **560**, 116 (1948)) confirmed this result, and showed that the rearrangement may be effected, along with the Stevens 1,2-shift, by means of lithium phenyl.

[4] See G. Wittig and M. Wetterling, *Ann.*, **557**, 193 (1947).

[5] Melting points and boiling points are uncorrected. Analyses are by Clark Microanalytical Laboratory, Urbana, Ill.

[6] E. C. Horning and D. B. Reisner, THIS JOURNAL, **71**, 1036 (1949).

[7] P. H. Dirstine and F. W. Bergstrom, *J. Org. Chem.*, **11**, 55 (1946).

[8] D. Todd, "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 385.

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The Synthesis of N$^{\alpha}$-Acetyl-L-kynurenine[1]

BY R. R. BROWN AND J. M. PRICE[2]

RECEIVED FEBRUARY 12, 1955

This communication presents a convenient method for the synthesis of crystalline N$^{\alpha}$-acetyl-L-, -DL- or -D-kynurenine. Previous methods yielded only racemic non-crystalline material,[3] or depended on isolation from biological material.[4] In this method, ozonolysis of N-acetyltryptophan[5] yielded an intermediate (probably N′-formyl-N$^{\alpha}$-acetylkynurenine)[6] which was converted by mild hydrolysis to N$^{\alpha}$-acetylkynurenine as anticipated

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[1] This research supported by the Wisconsin Division of the American Cancer Society, the Elsa U. Pardee Foundation, and the American Cancer Society upon recommendation of the Committee on Growth of the National Research Council.

[2] Scholar in Cancer Research of the American Cancer Society.

[3] C. E. Dalgleish, *J. Chem. Soc.*, 137 (1952).

[4] C. Yanofsky and D. M. Bonner, *Proc. Natl. Acad. Sci. U. S.*, **36**, 167 (1950).

[5] J. L. Warnell and C. P. Berg, THIS JOURNAL, **76**, 1708 (1954).

[6] A. H. Mehler and W. E. Knox, *J. Biol. Chem.*, **187**, 431 (1950).

on the basis of the easy hydrolysis of N-formylanthranilic acid[7] and N′-formylkynurenine.[6] The product, N$^{\alpha}$-acetylkynurenine, was then purified by ion-exchange chromatography and isolated in crystalline form.

Experimental

N-Acetyl-L-, -DL- and -D-tryptophan were prepared by acetylation of the corresponding optical isomers with acetic anhydride in sodium hydroxide.[8] Ozonolysis was carried out by the procedure of Warnell and Berg[5] with the ozone introduced through a coarse sintered glass disc, the ozone stream providing efficient stirring. One equivalent of ozone was thus passed into a suspension of 7.5 g. of finely powdered acetyltryptophan in 250 ml. of glacial acetic acid at room temperature. Hydrolysis to N$^{\alpha}$-acetylkynurenine was effected by the addition of 30 ml. of concentrated hydrochloric acid to the reaction mixture which was then allowed to stand overnight at room temperature.

The hydrolyzed solution was concentrated to a thick sirup by vacuum distillation on a warm water-bath. The sirup was dissolved in 500 ml. of 0.1 *N* hydrochloric acid and applied to a column of Dowex-50 (Hydrogen form) 7 cm. in diameter and 12 cm. long. The column was then washed with 1.5 l. of 0.1 *N* HCl, 2.0 l. of 1.0 *N* HCl and 700 ml. of 2.4 *N* HCl at which time elution of the product began as indicated by the presence of a high concentration of diazotizable amine.[9] Elution with 2.4 *N* HCl was continued until the diazotizable amine concentration was negligible (about 4.0 l.). The amine fraction was cooled in an ice-bath and strong NaOH solution was added slowly with rapid stirring to adjust the *p*H to 2.5. The solution was saturated with sodium chloride and extracted with a total of 3 l. of ethyl acetate in six equal portions. The extract was vacuum distilled to dryness and the residue taken up in 150 ml. of warm absolute ethanol, treated with a small amount of decolorizing charcoal and filtered. Four volumes of petroleum ether (Skellysolve B) were added to the light yellow filtrate. Light golden-yellow crystals of acetylkynurenine appeared on standing overnight at −20°. The product was filtered, washed with a small volume of ether, and dried *in vacuo* (yield 20–50% of theoretical). The product was not hygroscopic and was quite stable. The acetyl-L- and acetyl-D-kynurenines were pale golden needles which crystallized readily from absolute ethanol-petroleum ether, whereas the acetyl-DL-kynurenine appeared as tiny rosettes which crystallized more slowly.

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.20. Found[10] for N$^{\alpha}$-acetyl-L-kynurenine: C, 57.46, 57.49; H, 5.14, 5.29; N, 11.02, 11.20. Found for N$^{\alpha}$-acetyl-DL-kynurenine: N, 10.96, 11.08. Found for N$^{\alpha}$-acetyl-D-kynurenine: N, 11.09, 11.11.

The specific rotations and melting points are listed in Table I. The materials melted with foaming and decomposition at the indicated temperatures when the sample was inserted in the block at a temperature 15° below the melting point and then heated at the rate of 2° per minute.

TABLE I

Optical form	Sp. rotn. $[\alpha]^{25}D$ 0.5% in 95% ethanol	M.p. with dec., °C.
L	136.5°	188–188.5
DL	−0.3	171–171.5
D	−138.0	188–188.5

Paper chromatography revealed a single spot (bluish-green ultraviolet fluorescence) having an R_f of 0.82 (descending) in the organic phase of butanol, acetic acid, water 4:1:5, and R_f of 0.68 (ascending) in butanol, water, benzene, methanol 1:1:1:2. Hydrolysis in hydrochloric acid produced a different spot corresponding in R_f and ultraviolet fluorescence to kynurenine. N$^{\alpha}$-Acetyl-DL-kynurenine did not resolve on paper whereas the hydrolysis product, DL-kynurenine resolved into spots of D- and L-kynurenine as described by Mason and Berg.[11] N$^{\alpha}$-Acetyl-DL-kynurenine prepared by the procedure of Dalgleish[3] was a non-crystalline glass; however, this material crystallized readily from ethanol-petroleum ether as described above. The crystalline product was identical in melting point, chromatography on paper or Dowex-50 columns, and did not depress the melting point of N$^{\alpha}$-acetyl-DL-kynurenine made from N-acetyl-DL-tryptophan as described above.

The ultraviolet absorption spectra of N$^{\alpha}$-acetyl-L-kynurenine in acid, alkali and at neutrality were similar to those of kynurenine. At *p*H 7.4 in phosphate buffer, maxima were observed at wave lengths of 225 mμ (log ϵ 4.334), 258 mμ (log ϵ 3.823), and 360 mμ (log ϵ 3.632); minima appeared at 248 and 285 mμ.

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[7] W. B. Jacoby and D. M. Bonner, *J. Biol. Chem.*, **295**, 699 (1953).

[8] V. du Vigneaud and R. R. Sealock, *ibid.*, **96**, 511 (1932).

[9] A. C. Bratton and E. K. Marshall, *ibid.*, **128**, 537 (1939).

[10] Analyses by Clark Microanalytical Laboratory, Urbana, Illinois.

[11] M. Mason and C. P. Berg, *J. Biol. Chem.*, **195**, 515 (1952).

Benzoylvinyl Quaternary Ammonium Salts

BY CHESTER J. CAVALLITO[1]

RECEIVED APRIL 8, 1955

Acetylenes, RC≡CH, react with tertiary amine salts to yield vinyl quaternary ammonium salts, $RCH{=}CHN(R')_3X$.[2] It has been found that phenylethynyl ketone reacts readily with tertiary amine salts to form benzoylvinyl quaternary ammonium salts I in good yield. These compounds might be considered as vinylogs of tertiary amine salts of acid chlorides II.

$C_6H_5COCH{=}CH{-}NR_3X$ I

$RCO{-}NR_3X$ II

Derivatives of I were prepared from pyridine hydrochloride and from trimethylamine hydrochloride, as white crystalline salts, the former derivative being rather unstable upon standing for several weeks.

Experimental

To a solution of 9.6 g. (0.1 mole) of trimethylamine hydrochloride in 50 ml. of 95% ethanol was added enough trimethylamine to make the solution alkaline. With cooling and shaking, 13 g. (0.1 mole) of phenyl ethynyl ketone[3] was added. The solution was kept at 25 to 30° and, within a few minutes, crystals began to separate. After 30 minutes, the solution was diluted with an equal volume of ether to complete precipitation of the 2-benzoylvinyltrimethylammonium chloride. The product was recrystallized from ethanol. The yield was 88% of the white crystalline salt, cor. m.p. 159° dec.

Anal. Calcd. for $C_{12}H_{16}ONCl$: C, 63.85; H, 7.15; Cl, 15.70. Found: C, 64.16; H, 6.87; Cl, 15.57.

The pyridinium analog was prepared in a similar manner. Two ml. of pyridine base was added to 0.1 mole of pyridine hydrochloride and 0.1 mole of phenyl ethynyl ketone in alcohol. After keeping the mixture at 25 to 30° for 30 minutes (no precipitate formed) an equal volume of ether was added and the oil which separated crystallized upon cooling. The product was recrystallized from dioxane by addition of ethyl acetate or ether; 87%, cor. m.p. 176° dec.

Anal. Calcd. for $C_{14}H_{12}ONCl$: N, 5.70; Cl, 14.43. Found: N, 5.71; Cl, 14.25.

Addition of alkali to aqueous solutions of these quaternaries leads to rapid liberation of the tertiary amine, R_3N. Ultraviolet absorption spectra measurements of the trimethylammonium salt in water show a maximum of ϵ_{268} 7,700 and a minimum of ϵ_{242} 3,200, with no change apparent

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[1] Irwin, Neisler & Co., Decatur, Ill.

[2] W. Reppe, *Experientia*, **5**, 97 (1949); also p. 65 of "Acetylene and Carbon Monoxide Chemistry," by J. W. Copenhaver and M. H. Bigelow, Reinhold Publishing Corp., New York, N. Y., 1949.

[3] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).