A New Method for Preparing 5-Aryl-2,3-dihydro-1*H*-1,4-benzodiazepines

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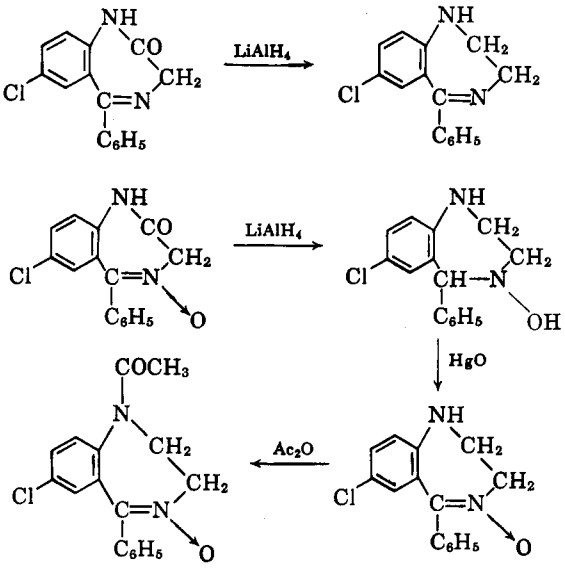
A recent publication[1] has described the preparation of 7-nitro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine from 2-chloro-5-nitrobenzophenone and ethylenediamine. We have had occasion to prepare benzodiazepines of this type, but have found this method to be of limited use. Nitro activation of the aryl chloride appears to be necessary since treatment of 2-bromo-5-chlorobenzophenone with ethylenediamine afforded no benzodiazepine. A more versatile method is the lithium aluminum hydride reduction of 5-aryl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones.



Reduction of 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one with lithium aluminum hydride in ether has afforded 7-chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine in good yield. 7-Chloro-5-phenyl-3,3-tetramethylene-2,3-dihydro-1*H*-1,4-benzodiazepine was prepared similarly.

Lithium aluminum hydride reduction of 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide gave 7-chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine which could be oxidized by mercuric oxide to afford 7-chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine 4-oxide. The 5-*o*-chlorophenyl analog was made by the same route.

Since a large variety of 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones with differing substituents in positions 3,5,6,7,8, and 9 has been disclosed,[2,3] this method can afford a varied group of 2,3-dihydro-1*H*-1,4-benzodiazepines.

The 5-aryl-2,3-dihydro-1*H*-1,4-benzodiazepines were potent central nervous system depressants in animal tests.

(1) J. A. Hill, A. W. Johnson, and T. J. King, *J. Chem. Soc.*, 4430 (1961).
(2) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).
(3) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *ibid.*, **27**, 562 (1962).

Experimental[4]

7-Chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine.—7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (7 g.) was added in portions to a stirred suspension of lithium aluminum hydride (1.6 g.) in anhydrous ether (200 ml.). The mixture was heated under reflux for an hour and the excess hydride was decomposed by careful addition of water. The ether layer was separated, dried over magnesium sulfate, and evaporated to dryness. Recrystallization of the residue from ethanol afforded 3.5 g. of product, m.p. 174–176°.

Anal. Calcd. for $C_{15}H_{13}ClN_2$: C, 70.17; H, 5.11; Cl, 13.81; N, 10.91. Found: C, 70.32; H, 5.07; Cl, 13.6; N, 10.98.

7-Chloro-5-phenyl-3,3-tetramethylene-2,3-dihydro-1*H*-1,4-benzodiazepine, m.p. 180–181° (from ethanol), was similarly prepared in 42% yield.

Anal. Calcd. for $C_{19}H_{19}ClN_2$: C, 73.46; H, 6.16; Cl, 11.41; N, 9.01. Found: C, 73.16; H, 5.92; Cl, 11.20; N, 8.71.

7-Chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine.—7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (10 g.) was treated with lithium aluminum hydride (2.8 g.) in anhydrous ether (250 ml.) as in the preceding example. There was obtained 7 g. of product, m.p. 170–172°.

Anal. Calcd. for $C_{15}H_{15}ClN_2O$: C, 65.57; H, 5.50; Cl, 12.90; N, 10.20. Found: C, 65.87; H, 5.26; Cl, 13.0; N, 10.32.

7-Chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine 4-Oxide.—A suspension of the previous solid (12 g.), mercuric oxide (20 g.), acetone (250 ml.), and water (25 ml.) was stirred for 3 hr. at room temperature. The mixture was filtered and the filtrate was evaporated to dryness *in vacuo*. Recrystallization of the residue from 95% ethanol afforded 8 g. of product, m.p. 247–248°.

Anal. Calcd. for $C_{15}H_{13}ClN_2O$: C, 66.05; H, 4.81; Cl, 13.00; N, 10.27. Found: C, 66.20; H, 4.92; Cl, 13.3; N, 9.92.

7-Chloro-5-*o*-chlorophenyl-2,3-dihydro-1*H*-1,4-benzodiazepine 4-Oxide, m.p. 215–217° (from ethanol), was prepared similarly (45%) from 7-chloro-5-*o*-chlorophenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide,[5] but without the isolation of the intermediate 7-chloro-5-*o*-chlorophenyl-4-hydroxy-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine.

Anal. Calcd. for $C_{15}H_{12}Cl_2N_2O$: C, 58.65; H, 3.94; Cl, 23.09; N, 9.12. Found: C, 58.94; H, 4.04; Cl, 23.50; N, 8.87.

1-Acetyl-7-chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine 4-Oxide.—A solution of 7-chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine 4-oxide (4 g.) in acetic anhydride (20 ml.) was warmed on a steam bath for 0.5 hr. The solution was evaporated to dryness *in vacuo*. The residue was recrystallized from ethanol to afford 1.5 g. of product, m.p. 222–224°. The carbonyl absorption band was at 6.02 μ.

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; Cl, 11.27; N, 8.90. Found: C, 64.90; H, 4.76; Cl, 11.2; N, 9.13.

(4) Melting points are uncorrected.
(5) This compound, m.p. 249–250° dec., was prepared by C. Gochman following method A of ref. 3.

The Decomposition of Methylethylphenylbenzylphosphonium Acetate

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A few examples of thermal decomposition of phosphonium carboxylate salts have been studied.[2] These

(1) Petroleum Research Fund Scholar, 1961–1962.
(2) (a) E. A. Letts and N. Collie, *Phil. Mag.*, **22**, 183 (1886); (b) N. Collie, *J. Chem. Soc.*, **53**, 636 (1888); (c) D. B. Denney and L. C. Smith, *Chem. Ind.* (London), 290 (1961); (d) D. B. Denney and L. C. Smith, *J. Org. Chem.*, **27**, 3404 (1962).

include the acetate, benzoate, and oxalate salts of the tetraethylphosphonium ion,[2a] tetramethylphosphonium benzoate,[2b] and the phosphobetaines, $(C_6H_5)_3\overset{+}{P}(CH_2)_n$-$CO_2^-$ where n = 1,2,3.[2c]

It was the purpose of this research to investigate the thermal decomposition of the unsymmetrical phosphonium salt, methylethylphenylbenzylphosphonium acetate. This compound was chosen because of the possible information it might provide concerning the comparative ease of elimination of the groups bonded to the phosphorus atom in a nucleophilic attack by the acetate ion.[3] More importantly, the system seemed well suited for subsequent stereochemical studies of the type conducted by McEwen, VanderWerf, and coworkers[4] who have investigated other nucleophilic reactions involving the enantiomers[5] of this phosphonium ion.

The outcome of the reaction differed substantially from that of decomposition reactions reported for the symmetrical phosphonium ions.[2a,b,d] The analytical data are summarized in Table I.

TABLE I

ANALYSIS OF REACTION PRODUCTS

Product	Method of analysis	Yield,[a] %
Toluene	V.p.c.[b]	22
Acetic acid	Titration	40
Methyl acetate	V.p.c.	16
Ethyl acetate	V.p.c.	Trace
Phenylacetone	V.p.c.	5
Methylethylphenylphosphine oxide	Infrared	69
cis-2-Methyl-1,3-diphenyl-1-propene	V.p.c.	12
trans-2-Methyl-1,3-diphenyl-1-propene	V.p.c.	16
Ethylphenylbenzylphosphine (as the oxide)	Product isolation	16

[a] 100 × moles product/moles reactant. [b] Vapor phase chromatography.

A mechanistic accounting for the reaction products is somewhat speculative at this point; however, it seems reasonable that the acetate ion may be involved in a nucleophilic attack on a pentacovalent intermediate.

$$(CH_3)(C_2H_5)(C_6H_5)(C_6H_5CH_2)\overset{+}{P} + \tilde{O}\text{—}\overset{O}{\overset{\|}{C}}CH_3 \rightleftharpoons$$

$$(CH_3)(C_2H_5)(C_6H_5)(C_6H_5CH_2)P\text{—}O\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{OAc^-}$$

$$(CH_3)(C_2H_5)(C_6H_5)P{=}O + (CH_3CO)_2O + C_6H_5CH_2{:}^-$$

This proposal has some support in work of others[4b,6] where it has been noted that ethers are produced from the decomposition of certain phosphonium alkoxides at lower temperatures.

$$R_4\overset{+}{P}OR' \xrightarrow{OR'^-} R_3P{=}O + R_2'O + R{:}^-$$

It is likely that phenylacetone is formed by reaction of the benzyl anion with acetic anhydride, and that the isomeric olefins are produced either by a Wittig reaction of the ylid of the methylethylphenylbenzylphosphonium ion with phenylacetone, or by an alternate or competing reaction involving addition of the benzyl anion to phenylacetone with subsequent dehydration of the tertiary alcohol thus formed. That the yields of the olefins from the pyrolysis reaction are nearly equal does not rule out the Wittig pathway to the olefins, since at the elevated temperature of the pyrolysis low stereospecificity would be expected. The appearance of methyl acetate and ethylphenylbenzylphosphine among the reaction products is probably the result of a nucleophilic displacement by acetate ion on the phosphonium ion, and has its analogy in the work of Denney.[2c,d]

Stereochemical assignments for the olefins were made on the basis of the positions of the higher wave-length bands in the near ultraviolet which are usually shifted to higher frequencies for olefins with sterically interacting *cis* substituents[7] (benzyl–phenyl interaction in this case), and comparison of these olefins with those isolated from the isomer mixture obtained from sulfuric acid dehydration of methyldibenzylcarbinol[8] in which *trans*-2-methyl-1,3-diphenyl-1-propene (phenyl and benzyl groups *trans* to each other) should predominate.[9]

Experimental[10]

Methylethylphenylbenzylphosphonium Iodide (I).—This compound was prepared by the method of Bailey[11] and melted at 162–164°.

Methylethylphenylbenzylphosphonium Acetate Hydrate (II).—To a solution of 24.5 g. (0.066 mole) of I in 350 dry methanol was added with stirring at room temperature 12.12 g. (0.0726 mole) of dry, powdered silver acetate. The reaction mixture was protected from atmospheric moisture and heated at 40° with stirring for 6.5 hr. The brown precipitate (16.22 g.) was removed by filtration in a drybox and the methanol distilled under reduced pressure. The viscous liquid was placed in a vacuum desiccator over phosphorus pentoxide and after 5 days it crystallized into a mass of light gray crystals. Two recrystallizations from anhydrous ethyl acetate yielded extremely hygroscopic, fluffy white crystals which were dried *in vacuo* over phosphorus pentoxide at 56° for several days. This treatment produced a substance of m.p. 104.2–105.3° (with softening).

Anal.[12] Calcd. for $C_{18}H_{23}O_2P\cdot{}^2/_3H_2O$: C, 68.77; H, 7.80; P, 9.86. Found: C, 68.52; H, 7.83; P, 10.23.

Pyrolysis of II.—II (14.36 g., 0.0457 mole) was placed in a 25-ml. round-bottomed flask attached to a 44-cm. vacuum jacketed Vigreux column equipped for vacuum distillation. Air was swept out of the system with dry nitrogen. The flask and contents were immersed in an oil bath at 85° and the temperature of the oil bath raised steadily 280° over a period of 22 min. where it was maintained for an hour. First evidence of reaction occurred at a bath temperature of 200° and the reaction became vigorous at 230°. The first fraction (1), 2.93 g., was collected to approximately 120° at atmospheric pressure. The pot was then cooled to 80°, the system placed under vacuum, heating resumed, and a second fraction (2) consisting of 7.95 g. was collected to 165° (9 mm.). A third fraction (3) of 1.68 g. was ob-

(3) G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, 2342 (1929).

(4) (a) K. F. Kumli, W. E. McEwen, and C. A. VanderWerf, *J. Am. Chem. Soc.*, **81**, 3805 (1959); (b) C. B. Parisek, W. E. McEwen, and C. A. VanderWerf, *ibid.*, **82**, 5503 (1960); A. Bladé-Font, C. A. VanderWerf, and W. E. McEwen, *ibid.*, **82**, 2396 (1960); W. E. McEwen, A. Bladé-Font, and C. A. VanderWert, *ibid.*, **84**, 677 (1962).

(5) K. F. Kumli, W. E. McEwen, and C. A. VanderWerf, *ibid.*, **81**, 248 (1959).

(6) M. Grayson and P. T. Keough, *ibid.*, **82**, 3919 (1960).

(7) A. E. Gillam and E. S. Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," 2nd Ed., Edward Arnold Ltd., London, 1957, pp. 267–275.

(8) R. M. Caves, R. L. McLaughlin, and R. H. Wise, *J. Am. Chem. Soc.*, **76**, 522 (1954).

(9) H. C. Brown and M. Nakagawa, *ibid.*, **77**, 3614 (1955).

(10) All melting points and boiling points are uncorrected.

(11) W. J. Bailey, S. A. Buckler, and F. Marktscheffel, *J. Org. Chem.*, **25**, 1996 (1960).

(12) Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

tained at 172–230° (9 mm.) and solidified to a yellow solid on cooling.

Analysis of Fraction 1.—Vapor phase chromatographic separation and examination of infrared spectra indicated the presence of acetic acid, toluene, methyl acetate, and ethyl acetate (trace). Toluene and methyl acetate were determined quantitatively on a 10-ft. Ucon column, and acetic acid by titration with standard base. The fraction contained 31% toluene, 19% methyl acetate, and 38% acetic acid by weight. Water was not determined in this fraction but would theoretically amount to 13.6%.

Analysis of Fraction 2.—A small portion of fraction 2 was extracted with water, the water evaporated, and the infrared spectrum of the residue in chloroform shown to be identical in every respect with that of the authentic material prepared from methylethylphenylbenzylphosphonium iodide by treatment with sodium hydroxide.[4a] The methylethylphenylphosphine oxide was analyzed spectrophotometrically in chloroform solution with a Baird Atomic double beam infrared spectrophotometer using the absorption peak at 8.95 mμ and was shown to represent 67% by weight of fraction 2. Another portion of fraction 2 when treated with 2,4-dinitrophenylhydrazine reagent[13] yielded the 2,4-dinitrophenylhydrazone of phenylacetone, m.p. 152–154°; reported[14] m.p. 152.5–153.5°, m.m.p. 152–154°. Vapor phase chromatographic analysis of fraction 2 on a 10-ft. Ucon column gave the following results: 4% phenylacetone, 19% *trans*-2-methyl-1,3-diphenyl-1-propene, and 14% *cis*-2-methyl-1,3-diphenyl-1-propene by weight. The latter two compounds displayed retention times and ultraviolet spectra identical with the authentic materials prepared by dehydration of methyldibenzylcarbinol.[8] The isomers were separated on a 10-ft. Ucon column from the fraction boiling at 162–164° (9 mm.).[15] The *cis* and *trans* isomers absorbed at 218, 245 and 218, and 249 mμ, respectively.

Fraction 3.—Fraction 3 was recrystallized twice from ethyl acetate–ligroin to yield a compound of m.p. 112–113°; reported[16] m.p. for ethylphenylbenzylphosphine oxide, 110–111°. This compound melted undepressed with purified ethylphenylbenzylphosphine oxide prepared by air oxidation of ethylphenylbenzylphosphine.[16]

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(13) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1960, p. 111.

(14) R. T. Gilsdorf and F. F. Nord, *J. Am. Chem. Soc.*, **74**, 1837 (1952).

(15) Although the mixture of isomers has been reported (ref. 8) this is apparently the first account of their separation. This fraction was shown to consist of 61% *trans* and 39% *cis* isomer.

(16) J. Meisenheimer, J. Casper, M. Horing, W. Lauter, L. Lichtenstadt, and W. Samuel, *Ann.*, **449**, 213 (1926).

Mechanism Study of a Benzilic Acid-Type Rearrangement[1]

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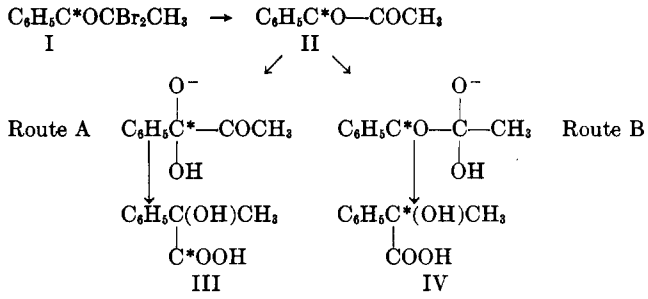
α,α-Dibromopropiophenone (I) rearranges to atrolactic acid (III or IV) during treatment with concentrated sodium hydroxide solution. It has been suggested[4] that the reaction proceeds by way of the intermediate, methyl phenyl diketone (II), which then undergoes a benzilic acid rearrangement.



When these authors subjected dibromo compound I to dilute alkali, no atrolactic acid was recovered; the sole product was 2,5-diphenyl-1,4-benzoquinone, formed in 13% yield by an aldol condensation of two molecules of the diketone. The action of concentrated sodium hydroxide on II produced atrolactic acid in low yield, whereas dilute alkali produced only tar.[4]

The use of carbon-14 as a tracer has been applied here in following the mechanism in the rearrangements starting with both the dibromo compound and the diketone. These two compounds (I and II) were prepared, labeled in the α-position. The atrolactic acid produced by rearrangement of these compounds was degraded by oxidation to acetophenone and carbon dioxide. In both cases essentially all of the original carbon-14 was found in the carbon dioxide. Since this labeled carbon atom was originally adjacent to the phenyl group, 100% phenyl migration must have occurred in both alkaline-catalyzed rearrangements, thereby eliminating route B as a possible mechanism. It is possible that the carbonyl group of II, α to the phenyl group, may be the preferred one for hydroxyl ion attack. However, if hydroxyl ion attack were rapid and reversible, the observed preference of route A also could be explained as due to a tendency of the phenyl group to migrate in preference to the methyl group.

If methyl phenyl diketone is the intermediate in the rearrangement of α,α-dibromopropiophenone, it is obvious that the rearrangement of the diketone must be much faster than the rate of formation. Any appreciable concentration of the diketone would lead to the aldol condensation mentioned previously.

Experimental

(α,α-Dibromopropio-1-C^{14})-phenone (I).—To 9.7 g. (0.4 mole) of magnesium turnings contained in a 250-ml., round-bottomed, three-necked flask was added slowly a solution of 53.6 g. (0.5 mole) of ethyl bromide in 95 ml. of ether. While the flask was cooled in ice, 12.1 g. (0.1 mole) of carbonyl-labeled benzamide was slowly added under dry nitrogen. After a reflux period of 24 hr. the reaction mixture was hydrolyzed with ice and sulfuric acid and extracted with ether. From the extract was obtained 7.5 g. (56% yield) of propiophenone.

One gram of the unpurified propiophenone was treated with a solution of 2.50 g. of bromine in 7.5 ml. of chloroform and allowed to stand at 25.5° for 0.5 hr. before it was refluxed for 4 hr. The solvent was carefully removed to give 2.13 g. (97% theoretical yield) of crude α,α-dibromopropiophenone (I).

Hydrolysis and Rearrangement of α,α-Dibromopropiophenone.—The crude dibromide (I) was stirred vigorously with 42.6 g. of 20% aqueous sodium hydroxide for 3.5 hr. The aqueous phase was extracted with ether and acidified with concentrated hydro-

(1) This paper is based upon work performed at Oak Ridge National Laboratory, which is operated for the Atomic Energy Commission by Union Carbide Corp.

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(4) R. Levine and J. R. Stephens, *J. Am. Chem. Soc.*, **72**, 1642 (1950).