Experimental[4]

2-Methylamino-4,5-dimethylthiazole.—A mixture of methylamine hydrochloride (27 g., 0.4 mole), water (100 ml.) and I (51.6 g., 0.4 mole) was heated at reflux temperature (103°) for 8 hr. The immiscible layer of I disappeared. After cooling the mixture to room temperature the solution was extracted three times with 50-ml. portions of ether to remove unreacted I. After treating with decolorizing carbon the solution was concentrated to one-fourth its volume. White crystals of the hydrochloride were obtained (8.4 g.—11.8%) which melted at 284–287° after recrystallization from ethanol. *Anal.* Calcd. for $C_6H_{11}ClN_2S$: Cl, 19.84; S, 17.94. Found: Cl, 20.00; S, 18.10. The rest of the product was isolated by neutralization to give the free base (37 g.—65.1%). The white crystalline solid melted at 125–128° after recrystallization from benzene and ethanol. *Anal.* (See Table I).

2-Anilino-4,5-dimethylthiazole. **(a) From I and Aniline.**—A solution of aniline (93 g., 1 mole), aniline hydrochloride (2.8 g.) and I (64.5 g., 0.5 mole) in benzene (200 ml.) was placed in a flask which was equipped with a 1 × 12-inch column, packed with berl saddles, and an esterification head. The esterification head was designed to separate the water removed by azeotropic distillation with benzene and to continuously return the benzene to the reaction flask. The solution was heated until 8.5 ml. (94.4% of theory) of water was isolated. The benzene and excess aniline (96% recovery) were removed by distillation at 30–50 mm. The residue was distilled at 0.1–0.4 mm. to give 72 g. (71% yield) of a crystalline solid; m.p. 101–105.5°. Recrystallization from ethanol–benzene and ethanol gave large crystals melting at 107–109.5°. *Anal.* (See Table I).

(b) From 3-Chloro-2-butanone and Phenylthiourea.—The reaction of these materials in water gave, after neutralization, a 77% yield of white crystals melting at 94.5–106°. After recrystallization from benzene the product melted at 107.5–109.8° and the mixture melting point with the product obtained in (a) showed no depression.

N,N'-[(2)-4,5-Dimethylthiazolyl]-ethylenediamine.—A solution of ethylenediamine (30 g., 0.5 mole), I (65 g., 0.5 mole), concd. hydrochloric acid (84 ml., 1 mole), water (200 ml.) and ethanol (100 ml.) was heated at the reflux temperature (87°) for 6 hours. After the ethanol was removed by distillation the solution was treated with decolorizing carbon and neutralized with sodium carbonate. The tan precipitate that formed weighed 27.7 g. (39%) and melted at 213–216°. After several recrystallizations from ethanol the white crystalline solid melted at 216–219°. *Anal.* Calcd. for $C_{12}H_{18}N_4S_2$: C, 51.03; H, 6.43; N, 19.84; S, 22.70; mol. wt., 282.4. Found: C, 50.97; H, 6.48; N, 19.77; S, 22.66; mol. wt., 288 (ebullioscopic—acetic acid). When the ethylenediamine and I reacted in a molar ratio of 1:2 this yield is increased to 88.5%.

Acknowledgment.—The analyses of all compounds were made by James R. Kubik, Arthur K. Kuder, and Huffman Microanalytical Laboratories. Sincere appreciation is expressed to Martin Smilek and James A. Early for their assistance with some of the experimental work reported here.

Brecksville, Ohio

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[4] All melting points are uncorrected.

[Contribution from the Laboratory of Pharmaceutical Chemistry, University of Kansas School of Pharmacy]

Proof of Structures Derived from the Hydroxy- and Aminomethylation of Benzotriazole

By J. H. Burckhalter, Verlin C. Stephens and Luther A. R. Hall

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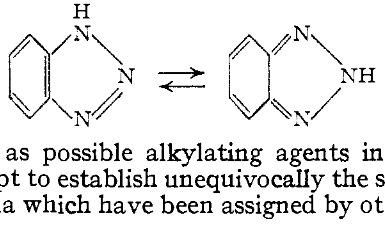
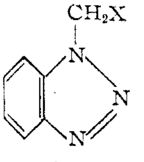
The products isolated from reactions involving benzotriazole and formaldehyde have been shown unequivocally to be substituted at position 1.

Although substitution reactions with benzotriazole are assumed to occur mainly at position 1, this assumption is not always justified.[1] Further, appreciable yields of both isomers, derivable from the following tautomeric forms, are often obtained.[2] Interest in the use of 1-dialkylaminomethylbenzotriazoles as possible alkylating agents induced us to attempt to establish unequivocally the structures Ia and IIa which have been assigned by others.[3,4]





X	X
Ia, NC_5H_{10}	IIa, OH
b, $N(CH_3)_2$	b, Cl
c, NC_4H_8O	

Since the structures of 1- and 2-methylbenzotriazole have been definitely established,[5] attempts were made to confirm the structure of 1-hydroxymethylbenzotriazole (IIa) by its reduction to the methyl compound. With Raney nickel at high pressures and at 150°, hydrogen was absorbed but the only identifiable product was benzotriazole. At room temperature, 90% of IIa was recovered unchanged. Employing 5% palladium-on-charcoal as a catalyst at low pressure, a method used by others to effect reduction of benzyl alcohols to methyl derivatives,[6] the results were also negative. However, IIa was readily converted by means of thionyl chloride to the corresponding chloride (IIb) in yields exceeding 90%, and it was found that IIb could then be reduced by lithium aluminum hydride to 1-methylbenzotriazole, thus establishing unequivocally the structures IIa and IIb. The identity of the 1-methylbenzotriazole was confirmed by boiling point, mixed melting point with an authentic sample and preparation of a picrate.

1-Dimethylaminomethylbenzotriazole (Ib) and 1-(4-morpholinylmethyl)-benzotriazole (Ic), with

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[1] N. O. Cappel and W. C. Fernelius, *J. Org. Chem.*, **5**, 40 (1940).

[2] F. R. Benson and W. L. Savell, *Chem. Revs.*, **46**, 59 (1950).

[3] G. B. Bachman and L. V. Heisey, This Journal, **68**, 2496 (1946).

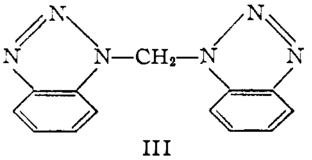
[4] K. Fries, H. Guterback and H. Kuhn, *Ann.*, **511**, 218 (1934).

[5] (a) F. Krollpfeiffer, A. Rosenberg and C. Mühlhausen, *ibid.*, **515**, 124 (1935); (b) A. Reissert, *Ber.*, **47**, 676 (1914).

[6] W. G. Dauben, C. F. Hiskey and A. H. Markhart, This Journal, **73**, 1398 (1951); R. Baltzly and J. S. Buck, *ibid.*, **65**, 1984 (1943); R. Baltzly and P. B. Russell, *ibid.*, **72**, 3410 (1950).

tentative structural assignments, were prepared in excellent yield by the usual conditions of the Mannich reaction.[3] Treatment of Ib with dilute acetic acid gave IIa in 80% yield. Further, Ic was obtained from morpholine and IIb. These experiments confirm the structures represented by I.

Using benzotriazole, formalin and dimethylamine with glacial acetic acid as a solvent in an early attempt to prepare Ib, a product was obtained which was first considered to be a hydrate of 1,1′-methylene-bisbenzotriazole (III). Support for this structure was suggested by analogous studies wherein the same conditions gave a methylene-bisphenol instead of the desired Mannich base.[7] Surprisingly, however, the substance isolated from the acidic medium proved to be identical with 1-hydroxymethylbenzotriazole (IIa). When dimethylamine was omitted from the reaction, the same compound IIa was still obtained in excellent yield. IIa has been prepared by others from benzotriazole and formalin in the presence of sodium acetate,[4] which provided the basic medium more often used for hydroxymethylations.



III

A derivative of IIa, 1-(β-dimethylaminoethoxymethyl)-benzotriazole, was made by treatment of the sodium salt of IIa with β-dimethylaminoethyl chloride.

It was found that 1,1′-methylenebisbenzotriazole (III) could readily be obtained in 88% yield from 1-chloromethylbenzotriazole (IIb) and the sodium salt of benzotriazole. In addition a 4% yield of an isomer of III was isolated. It was assumed to be the unsymmetrical 1,2′-methylenebisbenzotriazole, because of a lower melting point and a much greater solubility in benzene than III.[8]

Experimental[9]

1-Dimethylaminomethylbenzotriazole (Ib).—Using the procedure of Bachman and Heisey,[3] from 11.9 g. (0.1 mole) of benzotriazole, 5 g. (0.11 mole) of dimethylamine in alcohol solution, 9.6 ml. (0.12 mole) of 40% formalin and 150 ml. of methyl alcohol, 16.1 g. (92% yield) of product was obtained, m.p. 95–100°. Recrystallization from Skelly B gave m.p. 99–100.5°.

Anal. Calcd. for $C_9H_{12}N_4$: C, 61.34; H, 6.87. Found: C, 61.41; H, 6.98.

The use of aqueous dimethylamine gave the same product but in a yield of only 63%.

1-(4-Morpholinylmethyl)-benzotriazole (Ic) (a).—Replacing dimethylamine in the foregoing experiment with 9.6 g. of morpholine yielded 21 g. (96%) of product. Recrystallization first from Skelly B and then from alcohol gave m.p. 104–105°.

Anal. Calcd. for $C_{11}H_{14}N_4O$: C, 60.53; H, 6.46. Found: C, 60.74; H, 6.53.

(b).—By gentle warming 8.4 g. (0.05 mole) of 1-chloromethylbenzotriazole (IIb) was dissolved in 300 ml. of benzene. To this solution there was added 8.7 ml. (0.1 mole) of morpholine. After the mixture was allowed to stand overnight, 4.5 g. of hygroscopic solid was collected on a filter and put aside. Concentration of the filtrate and extraction of the resulting residue with hot Skelly B led to the isolation of 9.6 g. (88% yield) of Ic, m.p. 93–104°. Two recrystallizations from benzene–Skelly B and one from Skelly B raised the m.p. to 103.5–105°. A mixed melting point with a sample made by method (a) indicated no depression.

1-Hydroxymethylbenzotriazole (IIa) (a).—A mixture of 60 g. (0.5 mole) of benzotriazole, 40 ml. (0.5 mole) of 40% formalin, 50 ml. of acetic acid and 100 ml. of water was allowed to stand for over two hours at room temperature. The product which had precipitated was dried and recrystallized from hot (not boiling) water to give 66 g. (88% yield) of IIa; m.p. 148–151°. A portion was recrystallized from ethyl acetate with no change in melting point.[10]

Anal. Calcd. for $C_7H_7N_3O$: C, 56.35; H, 4.73. Found: C, 56.45; H, 4.70.

(b).—A mixture of 8.8 g. (0.05 mole) of 1-dimethylaminomethylbenzotriazole (Ib) and 20 ml. of 1:1 acetic acid was allowed to stand at room temperature. The solid dissolved with the evolution of heat, and after an hour a white precipitate which had appeared was collected on a filter and washed well with water; yield 6 g. (80%); m.p. 148–150°.

1-Chloromethylbenzotriazole (IIb).—To 59.6 g. (0.4 mole) of 1-hydroxymethylbenzotriazole kept at ice-bath temperature, 175 ml. of thionyl chloride was added dropwise as long as a vigorous reaction continued. The remainder was added more rapidly. The mixture was then stirred and refluxed for 90 minutes. Excess thionyl chloride was removed by distillation, last traces by heating for a short time with 200 ml. of methanol. After cooling and collecting on a funnel, the product weighed 62 g. (93%), m.p. 136–138°. Recrystallization first from benzene and then from methanol did not change the melting point. This compound is a skin irritant.

Anal. Calcd. for $C_7H_6ClN_3$: C, 50.16; H, 3.61. Found: C, 50.35; H, 3.80.

Conversion of IIb to 1-Methylbenzotriazole.—An ether solution containing 4 g. of lithium aluminum hydride was heated at reflux temperature beneath a soxhlet extractor containing a thimble of 16.7 g. (0.1 mole) of IIb. After four hours much of the ether which had been lost was replaced with dry tetrahydrofuran. Refluxing was continued overnight. The solution was cooled in ice, and water was added dropwise. After treatment with 200 ml. of 10% sodium hydroxide solution, the oily layer which formed was extracted with benzene only with difficulty because of the formation of an emulsion. The benzene solution was washed twice with water and then extracted with a total of 100 ml. of 10% hydrochloric acid. The acid layer was neutralized with ammonia solution and then extracted with 200 ml. of benzene in three portions. The extracts were washed, dried and concentrated to a brown oil which was distilled at 270–275° to give 6.6 g. (50% yield) of 1-methylbenzotriazole which solidified readily; m.p. 57–62°. Recrystallized from a mixture of benzene and Skelly B, it melted at 64–65.5°. Its picrate melted at 148.5–150°.[11] Mixed melting point of the 1-methylbenzotriazole with an authentic sample (m.p. 64–66°) prepared by another method[5a] showed no depression.

1-(β-Dimethylaminoethoxymethyl)-benzotriazole.—A vigorously stirred mixture of 27.7 g. (0.186 mole) of 1-hydroxybenzotriazole (IIa) and 5 g. (0.13 mole) of sodamide in 200 ml. of dry benzene was heated at reflux temperature for four hours, whereupon 17 g. (0.12 mole) of β-dimethylaminoethyl chloride[12] was added and heating continued overnight. The mixture was filtered, and a stream of dry hydrogen chloride was passed into the filtrate to precipitate an oil. After decantation of the solution, treatment of the oil with a small volume of alcohol gave 20 g. of a solid; m.p. 126–133°. Two recrystallizations from absolute alcohol and one from alcohol-benzene left 4 g. (13% yield) of product, m.p. 176–178°.

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[7] J. H. Burckhalter and W. H. Edgerton, unpublished results.

[8] F. Krollpfeiffer, H. Pötz and A. Rosenberg, *Ber.*, **71**, 596 (1938), prepared the related ethylenebisbenzotriazoles and found the melting point of the symmetrical 1,1′-ethylene compound to be 161.1°, while that of the 1,2,-ethylene isomer was 136–137°.

[9] C and H analyses by Mr. Charles Beazley, Skokie, Illinois.

[10] Reference 4 gives m.p. 148°.

[11] A. Reissert, ref. 5b, reported b.p. 270–271°, m.p. 64–65°; picrate, m.p. 149°.

[12] J. H. Burckhalter, V. C. Stephens and L. A. R. Hall, *J. Am. Pharm. Assoc.*, **39**, 271 (1950).

Anal. Calcd. for $C_{11}H_{17}ClN_4O$: Cl, 13.81. Found: Cl, 13.79.

1,1′-Methylenebisbenzotriazole (III) and 1,2′-Methylenebisbenzotriazole.—A vigorously stirred mixture of 11.9 g. (0.1 mole) of benzotriazole and 4 g. (0.1 mole) of sodamide in 200 ml. of dry toluene was heated at reflux temperature for 4 hours. To the hot suspension, 16.7 g. (0.1 mole) of 1-chloromethylbenzotriazole (IIb) was added, and stirring and heating were continued for 19 hours. Cooling gave a solid product which was collected on a filter, washed with benzene and triturated with water to remove sodium chloride. There remained 22.5 g. of dry material, m.p. 188–191°. Concentration of the toluene and benzene solutions gave 4 g. of additional product, m.p. 180–185°. Recrystallization from toluene gave 22 g. (88%) of III, m.p. 191–192.5°. A portion was recrystallized twice from dilute alcohol, m.p. 192–193°.

Anal. Calcd. for $C_{13}H_{10}N_6$: C, 62.39; H, 4.03. Found: C, 62.20; H, 4.02.

Concentration of the original toluene filtrate to complete dryness gave a brown solid which, after recrystallization from a small volume of absolute alcohol, gave 1 g. (4% yield) of a solid; m.p. 142–145°. Two recrystallizations from alcohol and one from Skelly B produced an off-white solid, m.p. 142–146.5°.

Anal. Calcd. for $C_{13}H_{10}N_6$: C, 62.39; H, 4.03; N, 33.59. Found: C, 62.26; H, 3.89; N, 33.81.

This product has been designated as 1,2′-methylene-bis-benzotriazole. A mixed melting point with 1-hydroxybenzotriazole (IIa) was 118–145°, while one with its isomer (III) was 144–175°. It was much more soluble in benzene than III.

LAWRENCE, KANSAS

[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

Synthesis of Arylindenones and a Stereoisomer of Diisohomogenol[1]

BY E. C. HORNING[2] AND JOHN A. PARKER[3]

RECEIVED JANUARY 10, 1952

An investigation of the reactions of β,β-diaryl-β-hydroxypropionic esters, obtained by the Reformatsky reaction from diaryl ketones and α-halogen esters, indicates that certain substituent groups in the aromatic ring and in the side chain determine the course of dehydration under acidic conditions. The normal product is formed in some cases; in others an indenone results. From one of these indenones, IIIA, a synthetic diisohomogenol has been prepared.

The structure of diisohomogenol has been established as IVA by degradation studies; the stereochemical arrangement of the substituents on the indane ring is not known. Studies conducted by Cartwright and Haworth[4] and Müller, Toldy, Halmi and Mészáros[5] on the synthesis of IVA indicate that the synthesized product has the same melting point as the material derived from dimerization of isohomogenol, but the two are not identical and therefore must differ in stereochemical configuration.

The key compound in these studies has been 2-methyl - 3 - (3′,4′ - dimethoxyphenyl) - 5,6 - dimethoxyindenone-1, IIIA, a ketone obtained by oxidative degradation of diisohomogenol, and from which synthetic diisohomogenol has been prepared. Arylindenones of this kind have generally been almost completely inaccessible compounds, although IIIA has been identified by synthesis.[6] Since no satisfactory method has existed for the preparation by synthesis of such compounds, when IIIA is desired it is usually obtained by oxidative degradation of diisohomogenol.[4–7] In another application, difficulties in synthesis have been detailed by Feeman and Amstutz[8] who were interested in the preparation of 3-(3′,4′-dimethoxyphenyl)-5,6-dimethoxyindenone-1. The reported difficulty in finding cyclization conditions for the corresponding indanone and the failure to obtain the indenone by direct cyclization or from the indanone by dehydrogenation or bromination–dehydrobromination indicates the nature of the problem.

An examination of the reactions shown in the chart brought several rather striking facts to light. The usual Reformatsky reaction between diaryl ketones (I) and an α-bromoester results in the formation of hydroxyesters (II) of expected structure. When the hydroxyesters are subjected to dehydration under acidic conditions, the product to be expected is the corresponding β,β-diarylacrylic ester (V). While not all of the possible combinations have been explored, this normal sequence holds in the simple cases which have been investigated. When the ketone I includes an aryl group as 3,4-dimethoxyphenyl, or 3,4,5-trimethoxyphenyl, and the ester is ethyl α-bromopropionate rather than ethyl bromoacetate, the intermediate hydroxyester II is formed normally but, under apparently normal dehydration conditions, the elimination of water is accompanied by cyclization and the product observed is an indenone (III). This cyclization occurs with ease under mild acidic dehydration conditions.

The fact that there are no known conditions for the cyclization of β,β-di-(3,4-dimethoxyphenyl)-acrylic acid or the corresponding β-hydroxyester to the indenone[8] is in sharp contrast to the behavior of the β-hydroxyesters IIA and IIB found here. The substitution of a methyl group in the structure now makes cyclization the exclusive reaction under the conditions indicated. The effect of polyphosphoric acid, a reagent recently introduced by Snyder and Werber[9] in cyclizations, is evidently nonspecific, since phosphorous oxychloride in boiling

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[2] National Heart Institute, Bethesda, Maryland.

[3] National Institutes of Health Predoctorate Fellow, 1950–1951. This paper is from the doctoral thesis of J. A. Parker, submitted to the Graduate School of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(4) N. J. Cartwright and R. D. Haworth, *J. Chem. Soc.*, 948 (1947).

(5) A. Müller, L. Toldy, G. Halmi and M. Mészáros, *J. Org. Chem.*, **16**, 481 (1951).

(6) A. Müller and E. Gal, *Ber.*, **77**, 343 (1944).

(7) W. Doering and J. A. Berson, THIS JOURNAL, **72**, 1118 (1950).

(8) J. F. Feeman and E. D. Amstutz, *ibid.*, **72**, 1526 (1950).

(9) H. R. Snyder and F. X. Werber, *ibid.*, **72**, 2962, 2965 (1950).