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The Degradative Benzoylation of 5-Phenyltetrazole

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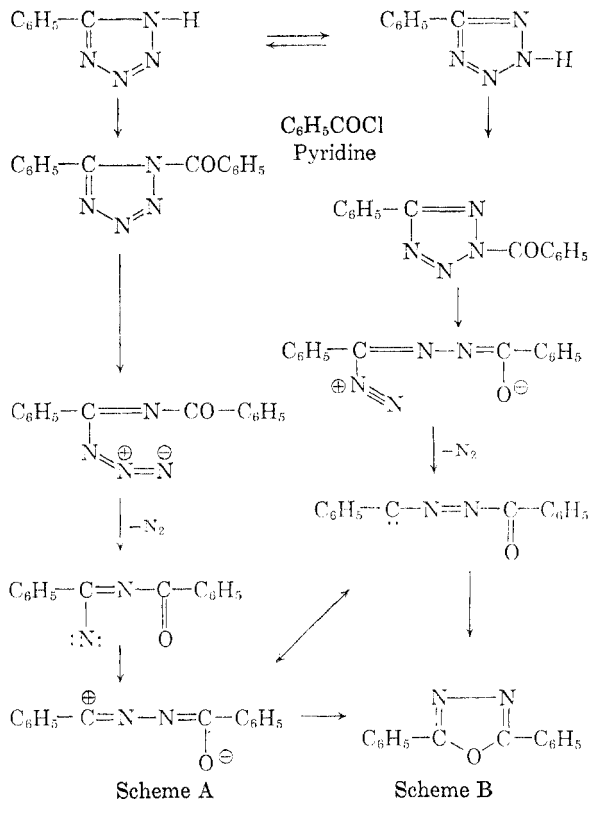
Received November 21, 1960

The degradative benzoylation of 5-phenyltetrazole labeled with N^{15} in the 1- (or 4)position has been investigated. Half of the isotope is recovered in the 2,5-diphenyl-1,3,4-oxidazole formed in the reaction, indicating that nitrogen in the 3,4- (or 1,2) positions of the tetrazole ring is eliminated. These results support the mechanism proposed by Huisgen for the reaction.

Recently Huisgen, Sauer and Sturm[1,2] described a degradative acylation of 5-substituted tetrazoles during which nitrogen is eliminated from the tetrazole ring and a 2,5-disubstituted 1,3,4-oxadiazole is formed. The reaction provides an elegant, controlled degradation of the tetrazole ring. These authors suggested a mechanism that involves attack by the acylating agent at position 2 (or 3) of the tetrazole ring, breaking of the ring at the 2,3-position, elimination of nitrogen, and recyclization through the acyl oxygen to form the oxadiazole (Scheme B).

A similar degradation of 1-*p*-nitrophenyl-5-aminotetrazole during acylation with acetic anhydride was observed in this laboratory.[3] The formation of 2-methyl-5-*p*-nitrophenylamino-1,3,4-oxadiazole under these conditions could be explained most easily by a pathway suggested by Stollé[4] for the degradation of 5-aminotetrazole on prolonged heating with acetic anhydride to 2-acetamido-5-methyl-1,3,4-oxadiazole. It was also suggested[3] that the degradative acylation of 5-substituted tetrazoles could be explained by assumption of attack by the acyl group at the 1- (or 4)position of the tetrazole ring followed by ring opening at the 1,2- (or 3,4)position, elimination of nitrogen from the resulting azido group, migration of the acylimido group from carbon to nitrogen, and recyclization to the oxadiazole (Scheme A).

Scheme B involves elimination of the nitrogen at the 3,4-(or 1,2)positions of the tetrazole ring, while Scheme A requires elimination of nitrogen at the 2,3-positions. A choice between the two courses should be possible by use of suitably labeled tetrazole derivatives. Because of tautomerism inherent in the 5-substituted tetrazole structure, or resonance phenomena of the tetrazolyl anion, it is not possible to distinguish between the 1- and 4-positions on the one hand or the 2- and 3-positions on the other. However, inability to distinguish between the 1- and 4-positions is not critical. Labeling of the tetrazole ring in the 1- (or 4-) position with N^{15} could be accomplished by unequivocal reactions. If the acylation reaction with the 5-substituted tetrazole followed Scheme A, the labeled position would be unaffected and all of the isotope would appear in the oxadiazole. As half of the tetrazole nitrogen is eliminated during the degradation, the isotope content of the oxadiazole should be double that of the starting tetrazole. On the other hand, if Scheme B is involved, the 3,4- (or 1,2)nitrogens would be eliminated. Half of the isotope and half of the tetrazole nitrogen would be lost; the oxadiazole and the original tetrazole should have the same isotope content.



Scheme A Scheme B

Nitrogen labeled benzamide (16.8 at. per cent N^{15}) was prepared by interaction of N^{15} enriched ammonium salts with benzoyl chloride in presence of aqueous sodium hydroxide. The benzamide was dehydrated with thionyl chloride and the labeled benzonitrile was allowed to react without purification with sodium azide and acetic acid in *n*-butyl

(1) R. Huisgen, J. Sauer, and H. J. Sturm, *Angew. Chem.*, 70, 272 (1958).

(2) R. Huisgen, J. Sauer, H. J. Sturm, and J. H. Markgraf, *Chem. Ber.*, **93**, 2106 (1960).

(3) R. M. Herbst and J. K. Klingbeil, *J. Org. Chem.* **23**, 1912 (1958).

(4) R. Stollé, *Ber.*, **62**, 1118 (1929).

alcohol[5] to form 5-phenyltetrazole labeled in the 1-(or 4)-position. The isotope content of 5-phenyltetrazole could not be determined directly. No mass was observed below 240°; at this temperature complete decomposition occurred. Although no peak corresponding to mass 146 was apparent peaks at masses comparable to nitrogen and benzonitrile could be identified along with peaks associated with unidentified decomposition products. The isotope content of the identifiable fragments was not consistent in different runs. Methylation of 5-phenyltetrazole gave a mixture of 1-methyl- and 2-methyl-5-phenyltetrazole[6] both of which gave mass spectra indicating isotope contents of 4.4 and 4.5 at. percent N^{15}, respectively. Treatment of the 5-phenyltetrazole with benzoyl chloride in pyridine[2] gave 2,5-diphenyl-1,3,4-oxidiazole containing 4.4 at. percent N^{15}.

Since half of the isotope was lost during acylation of the tetrazole, it must be concluded that nitrogen was eliminated from the 3,4- (or 1,2)positions and that Scheme B represents the course of the reaction correctly. The *N*-acyl 5-substituted tetrazoles described by Huisgen and co-workers[2] must be the 2-acyl derivatives as suggested by these authors.

EXPERIMENTAL[7]

Benzamide (N^{15}). The interaction of 1.66 g. (0.02 mole) of ammonium nitrate (NH_4^+, 34.7 at. % N^{15}), 1.32 g. (0.01 mole) of ammonium sulfate (normal N distribution), 8.43 g. (0.06 mole) of benzoyl chloride, and 5.6 g. (0.14 mole) of sodium hydroxide in 28 ml. of cold water gave 4.19 g. (86.4%) of benzamide. Recrystallization of 350 mg. of this material from water gave pure benzamide, m.p. and mixture m.p. 128–129°. Found: N^{15}, 16.8 at. %.

5-Phenyltetrazole [1 (or 4) N^{15}]. Dehydration of 3.84 g. (0.032 mole) of benzamide (N^{15}, 16.8 at. %) was accomplished by heating on a steam bath with 7.62 g. (0.064 mole) of thionyl chloride for 1 hr. Excess thionyl chloride was decomposed by addition of 0.6 ml. of water to the cold reaction mixture. Hydrogen chloride and sulfur dioxide were removed as completely as possible at room temperature and atmospheric pressure. The crude benzonitrile was dissolved in 40 ml. of *n*-butyl alcohol. Sodium azide (8.3 g., 0.13 mole) and 11.5 g. (0.19 mole) of glacial acetic acid were added and the mixture boiled under reflux for 4 days. After dilution of the reaction mixture with 80 ml. of water, butyl alcohol and butyl acetate were removed by distillation until 80 ml. of distillate had collected. The residual aqueous solution was made distinctly alkaline to litmus with sodium hydroxide, warmed with charcoal, and the hot, colorless filtrate acidified to Congo Red with concentrated hydrochloric acid. (Care: hydrazoic acid!) 5-Phenyltetrazole crystallized from the hot solution during acidification, yield 3.85 g. (83%). Recrystallization of 2.85 g. of this material from 20% ethanol gave pure 5-phenyltetrazole, m.p. and mixture m.p. 215° with decomposition.[5]

1-Methyl-5-phenyltetrazole and 2-methyl-5-phenyltetrazole [1 (or 4) N^{15}] Methylation of 1 g. of 5-phenyltetrazole [1 (or 4) N^{15}] following the procedure of Henry[6] gave 0.14 g. (13%) of pure 1-methyl-5-phenyltetrazole, m.p. 103–104°, recrystallized from water. Found: 4.4 at. % N^{15}; 0.58 g. (53%) of pure 2-methyl-5-phenyltetrazole, recrystallized from cyclohexane, m.p. 49–50°. Found: 4.5 at. % N^{15}.

2,5-Diphenyl-1,3,4-oxadiazole [3 (or 4) N^{15}]. A solution of 1 g. (0.0068 mole) of 5-phenyltetrazole [1 (or 4) N^{15}] and 0.98 g. (0.007 mole) of benzoyl chloride in 10 ml. of pyridine was heated under reflux on a steam bath for 1 hr. The solution was poured into 75 ml. of ice and water to precipitate the product, yield 1.25 g. (83%). Recrystallization of the crude material from 70% ethanol gave 1.12 g. of pure product, m.p. and mixture m.p. 139–140°, (found: 4.4 at. % N^{15}). Stollé[8] reported m.p. 138°.

Mass spectra of all the labeled compounds were obtained with a magnetic scanning, 90° sector type mass spectrometer at 200°. Temperature of the ion source was 260°, of the leak line 230°, and energy of the ionizing beam was 75 ev. Isotope concentrations were determined by comparison of spectra of similar compounds with normal and enriched N^{15} distribution. 5-Phenyltetrazole alone failed to give a mass spectrum at 200–235°. When the temperature was raised to 240°, a complex spectrum was obtained with no peak at mass 146, but peaks corresponding to the mass of numerous decomposition products including nitrogen (4.1 and 4.3 at. % N^{15}) and benzonitrile (4.7 and 7.4 at. % N^{15}).

Acknowledgment. Our sincere thanks are due Mr. Roland S. Gohlke of the Chemical Physics Research Laboratories of the Dow Chemical Company, Midland, Mich., for determination and interpretation of mass spectra for all compounds.

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(5) R. M. Herbst and K. R. Wilson, *J. Org. Chem.*, **22**, 1142 (1957).

(6) R. A. Henry, *J. Am. Chem. Soc.*, **73**, 4470 (1951).

(7) Melting points were done in open capillaries and are not corrected.

(8) R. Stollé, *J. prakt. Chem.*, (2) **69**, 145 (1904).