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Received for review January 27, 1972. Accepted March 10, 1972. Supported in part by grants from the Rockefeller Foundation and Herman Frasch Foundation.

Synthesis of 2-Acyl-3-amino-1,2,4-triazoles and 2-Acetyl-3-amino-1,2,4-triazole-5-^{14}C

Melvin Look* and Larry R. White

Acylation of 3-amino-1,2,4-triazole (amitrole) with *N*-acylimidazoles gave 2-acyl-3-amino-1,2,4-triazoles exclusively, whereas previous methods using acyl halides or anhydrides have yielded mixtures of acylated and diacylated derivatives. The new method was used to synthesize 2-acetyl-3-amino-1,2,4-triazole-5-^{14}C.

The acylation of 3-amino-1,2,4-triazole (amitrole, I) with acetyl chloride or acetic anhydride yields mixtures of acetylated and diacetylated derivatives (Staab and Seel, 1959; Van Den Bos, 1960; Coburn *et al.*, 1970). In studies of systemic pesticides at the Pacific Southwest Forest and Range Experiment Station, we needed pure, acylated carbon-14-labeled amitrole. Previous methods were unsatisfactory because of low yields and difficulties in the separation of products. We found that *N*-acetylimidazole (II) acylates amitrole to 2-acetyl-3-amino-1,2,4-triazole (III) without the formation of other isomers, even with a large excess of acetylating agent (Figure 1).

By using 3-amino-1,2,4-triazole-5-^{14}C, radiopurity was maintained. The imidazole method was extended to the synthesis of higher acylated amitroles (Table I).

EXPERIMENTAL

N-Acetylimidazole was purchased from Pierce Chemical Co., Rockford, Ill. The higher analogs were synthesized from acyl halide and imidazole by using the procedure of Staab (1962). Amitrole was obtained from the American Cyanamid Co., Wayne, N.Y. 3-Amino-1,2,4-triazole-5-^{14}C was purchased from New England Nuclear, Boston, Mass., and was used without further purification. Microanalyses were performed by the Microchemical Laboratory of the University of California, Berkeley. Nmr spectra were made in dimethyl sulfoxide-d_6 solvent with an internally locked (TMS) Varian HR-100.

2-Acetyl-3-amino-1,2,4-triazole and Higher Analogs. Amitrole (0.50 g, 5.94 mmol) and 2.60 g (23.61 mmol) of acetylimidazole in 25 ml of acetonitrile were heated under reflux for 2 hr. Dilution with 100 ml of water, extraction of the resulting solution with methylene chloride, and evaporation of the solvent gave, after recrystallization from toluene, 0.45 g (60%) of 2-acetyl-3-amino-1,2,4-triazole, mp 153° C (Van Den Bos had reported mp at 151–154° C). The nmr chemical shift of carbon-5 (3) proton agrees with that in the literature (Coburn *et al.*, 1970). Procedures for higher analogs were also identical, except that stoichiometric amounts of reagents were used to preclude large amounts of difficult-to-remove higher fatty acids.

2-Acetyl-3-amino-1,2,4-triazole-5-^{14}C. 3-Amino-1,2,4-triazole-5-^{14}C (6.9 mg, 98.4 μCi at 1.2 mCi/mmol) was heated under reflux with 36.1 mg (0.33 mmol) of acetylimidazole in 5 ml of acetonitrile for 3 hr. The reaction mixture was concentrated in a nitrogen stream and was purified by preparative thin-layer chromatography on silica gel G by using ethyl acetate–acetone (1:2) solvent (R_f = 0.77). The band detected by X-ray autoradiogram was removed and extracted with acetone. Evaporation gave a solid containing 6.9 mg, 65.3 μCi at 1.2 mCi/mmol (66% radioactive yield), of acetylamitrole.

Table I. Synthesis of 2-Acyl-3-amino-1,2,4-triazoles

Compound	Melting point, °C	Chemical shifts of carbon-3 proton δ C–H (ppm)	Analysis calcd: found, %
2-Acetyl-3-amino-1,2,4-triazole	153	7.53[a]	Known
2-Hexanoyl-3-amino-1,2,4-triazole	80–81	7.47	C, 52.73; C, 52.54 H, 7.74; H, 7.87
2-Nonanoyl-3-amino-1,2,4-triazole	74–75	7.48	C, 58.90; C, 58.56 H, 8.99; H, 8.93
2-Decanoyl-3-amino-1,2,4-triazole	82–83	7.48	C, 60.48; C, 61.00 H, 9.30; H, 9.47
2-Dodecanoyl-3-amino-1,2,4-triazole	87–88	7.45	C, 63.13; C, 63.37 m, 9.84; H, 10.09

[a] 7.57 according to Coburn *et al.* (1970).

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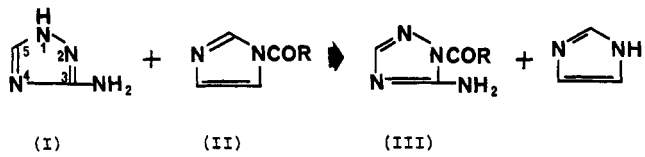

(I) (II) (III)

Figure 1. Synthesis of 2-acyl-3-amino-1,2,4-triazole

The 2-acetyl-3-amino-1,2,4-triazole-5-^{14}C was identical to the unlabeled acetyl amitrole, as was determined by thin-layer chromatography on silica gel G using these three solvent systems: ethyl acetate–acetone–acetic acid (7:13:1) at R_f 0.61; chloroform–ethanol–acetic acid (10:10:1) at R_f 0.55; and benzene–acetone (1:1) at R_f 0.38. Radiopurity determined by tlc and measured with a Tracerlab 4 π scanner was at least 95% on the basis of peak area data.

ACKNOWLEDGMENT

We thank Robert Lundin (USDA Western Regional Research Laboratory, Agricultural Research Service, Albany, Calif.) for running the nmr spectra and for his interpretations, and M. D. Coburn (Univ. of Calif., Los Alamos Scientific Laboratory, Los Alamos, N.M.) for supplying us with experimental data before publication of his article.

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Received for review December 10, 1971. Accepted March 20, 1972. Mention of proprietary products is for identification only and does not imply endorsement of these products by the U.S. Department of Agriculture.

Chemical Synthesis of the Carbaryl Metabolite *trans*-5,6-Dihydro-5,6-dihydroxy-1-naphthyl Methylcarbamate

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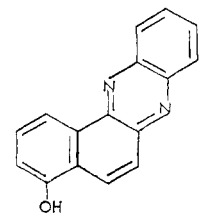
Multigram quantities of *trans*-5,6-dihydro-5,6-dihydroxy-1-naphthyl methylcarbamate (**4**) have been prepared from 1,5-dihydroxynaphthalene in three steps. The synthetic material was shown to have structure **4** by interpretation of its mass, infrared, nmr, and ultraviolet spectra and was shown to cocrystallize with a radioactive sample of carbaryl metabolite "B" isolated from cow's urine. *trans*-5,6-Dihydro-5,6-dihydroxy-1-naphthol (carbaryl metabolite "D") has also been prepared.

We wish to report the first chemical synthesis of *trans*-5,6-dihydro-5,6-dihydroxy-1-naphthyl methylcarbamate (**4**, carbaryl metabolite "B") as outlined in Figure 1. The detection of this substance as a product of carbaryl metabolism in many plant and animal systems has been recorded (Andrawes and Dorough, 1967; Baron *et al.*, 1969; Baron and Locke, 1970; Dorough, 1967; Dorough and Bartley, 1970; Dorough and Casida, 1964; Kuhr and Casida, 1967; Leeling and Casida, 1966; Oonnithan and Casida, 1968; Price and Kuhr, 1969; Sullivan *et al.*, 1970). Since the metabolite may find its way into man's diet, it is necessary that a safe level be determined. The synthesis reported provides material for toxicological evaluation and constitutes chemical proof of the structure **4** first proposed by Leeling and Casida (1966). In addition, this synthetic scheme makes available *trans*-5,6-dihydro-5,6-dihydroxy-1-naphthol (**3a**, carbaryl metabolite "D") as its penultimate product.

EXPERIMENTAL

Preparation of 5-Hydroxy-1,2-naphthoquinone (2a). (Teuber and Gotz, 1954). To a stirred solution of 24 g of potassium hydrogen sulfate and 51 g of potassium dihydrogen phosphate in 9.6 l. of water was added 165 g (approximately 140 g dry weight) of moist potassium nitrosodisulfonate (Fremy's Salt). Immediately after this had dissolved, 24 g of 1,5-dihydroxynaphthalene (**1**) in 1.5 l. of methanol was added and stirring was continued for 1.5 hr. The solid product (red-orange needles) was isolated by filtration and vacuum dried, leaving 18 g (69%) of crude quinone. The mixture was extracted continuously with pentane in a Soxhlet apparatus until no more yellow color was removed. The desired product remaining in the cup as red needles (9.8 g, 37%) had no distinct melting point. This material was identified as 5-hydroxy-1,2-naphthoquinone (**2a**) by its nuclear magnetic resonance (nmr) spectrum in DMSO-d_6 and by conversion to the known 7-hydroxynaphthophenazine (**8**) melting 267–8°C



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[Teuber and Gotz (1954) report mp 267–8°C]. The pentane solution was freed of volatiles in a vacuum, leaving 8.2 g, (32% yield) of 5-hydroxy-1,4-naphthoquinone (**5**) as orange needles and powder. Identity was confirmed by comparison with an authentic sample (Aldrich).

1,2-Dihydro-1,2,5-trihydroxynaphthalene (3a) by LAH Reduction of 2a. A 12-g (69 mmol) sample of 5-hydroxy-1,2-

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