(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.

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

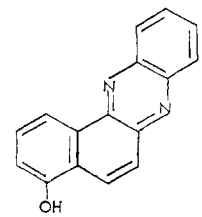
Forrest A. Richey, Jr.,* William J. Bartley, John T. Fitzpatrick, and A. Peter Kurtz

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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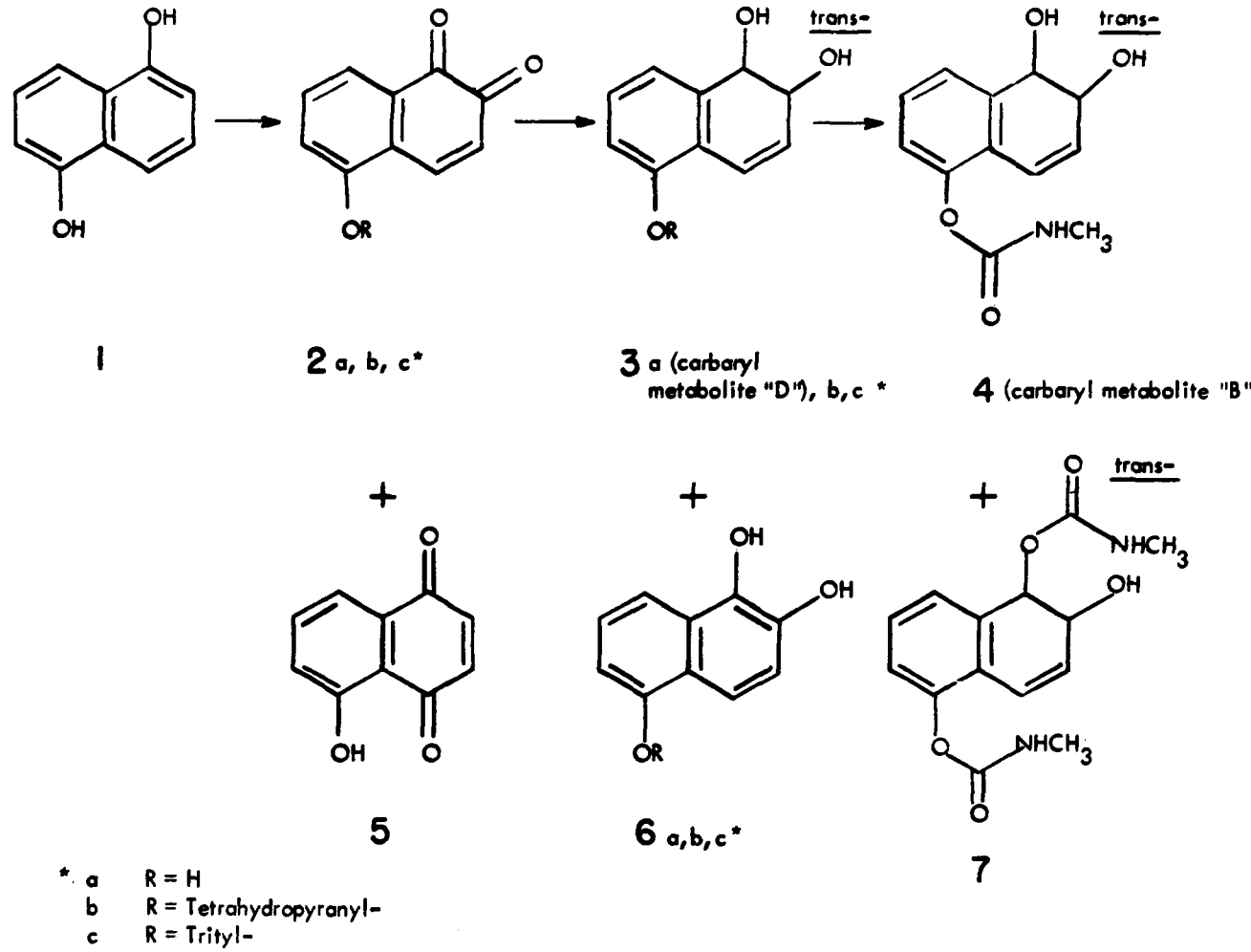


Figure 1. Synthesis of *trans*-5,6-dihydro-5,6-dihydroxy-1-naphthyl methylcarbamate

naphthoquinone (**2a**) was placed in the cup of a Soxhlet extractor fitted to a flask containing 6.0 g (160 mmol) of lithium aluminum hydride (LAH). The apparatus was thoroughly flushed with dry nitrogen and 2.4 l. of anhydrous tetrahydrofuran (THF) was added to the flask. The solvent was refluxed until no further color was extracted (11 g, 64 mmol extracted). The resulting greenish-gray suspension was rapidly stirred and cooled by application of an ice bath to the flask and treated successively with 12 ml of water, 180 ml of diethyl ether, and then 30 ml of glacial acetic acid, the water and acid additions being made dropwise as rapidly as possible without exceeding gentle reflux.

The resulting suspension was filtered and the residue washed with 150 ml of diethyl ether. The combined filtrate and wash were freed of volatile materials under vacuum ($\leq 50°C$) and the residue was deposited directly on 15 g of silica gel. "Dry-column" chromatography (Loev and Goodman, 1967) on silica gel (1800 g of Baker No. 3405 containing 15% water and divided equally among three 7.6 × 69 cm nylon columns) using diethyl ether as the developing solvent provided the initial separation of the crude product. The band containing dihydrotriol **3a** was excised from each column and eluted with diethyl ether. The combined solutions were reduced in volume and subjected to elution chromatography on 150 g of silica gel (prepared as above) packed in and eluted with diethyl ether. Evaporation of solvent from the fractions shown by thin-layer chromatography (tlc, silica gel plates developed with 1:1 benzene–ethyl acetate) to contain *trans*-1,2-dihydro-1,2,5-trihydroxynaphthalene (**3a**) gave 1.7 g (15%) of dark gray solid.

The combined products from three such runs were taken up in 1 l. of diethyl ether, treated with 7 g of activated carbon (Nuchar C-190N), and the mixture was briefly refluxed. The resulting suspension was filtered and the solvent was partially removed in a nitrogen stream, leaving 25 ml of solution. Overnight refrigeration of this solution caused it to deposit 3.0 g (9%) of tiny, pink-tan needles of *trans*-1,2-dihydro-1,2,5-trihydroxynaphthalene (**3a**), melting 151–152.5°C.

This procedure was repeated many times giving **3a** in average yield of 8.3%.

The chemical proof of structure of material prepared as above is based on the following physical data: mass spectrum, parent ion at 178.06335, theoretical for $C_{10}H_{10}O_3$ = 178.062989 (Beynon and Williams, 1963) and *m/e* 160 from loss of water; infrared spectrum (sample suspended in potassium bromide) very similar to that reported by Baron *et al.* (1969), for a sample prepared by saponification of metabolite "B" isolated from cow's urine; ultraviolet spectrum (95% ethanol) λ_{max} ϵ 218 mμ (2.9×10^4), 265 (5.9×10^3), 306 (4.5×10^3), 315 (4.1×10^3) with added base 210–220 off-scale, 245 (2.4×10^4), 342 (1.2×10^4); nmr spectrum (acetone-d_6) (see Figure 2 for spectrum and assignments).

The major product from this reduction, 1,2,5-trihydroxynaphthalene (**6a**), migrated ahead of **3a** on dry column chromatography. Its structural assignment is based on the method of synthesis and mass and infrared spectra consistent with the

structures postulated for compound **6a** and its trimethyl ether derivative prepared from **6a** with dimethyl sulfate and aqueous sodium hydroxide.

***trans*-5,6-Dihydro-5,6-dihydroxy-1-naphthyl Methylcarbamate (4) by Treatment of 3a with Methyl Isocyanate.** A 3.0-g (17 mmol) sample of dihydrotriol **3a** was treated with 200 ml of acetone, 15 μl of triethylamine, and 2.0 ml (36 mmol) of methyl isocyanate under a nitrogen atmosphere in a 250-ml flask sealed by a septum stopper. The resulting solution was kept at room temperature for 3 days and concentrated under vacuum, leaving 4.7 g of tan, semisolid residue. The products from many such runs (16.6 g, 72% average yield) were combined and recrystallized from 360 ml (the minimum amount) of acetonitrile, giving 13.6 g (58% based on **3a**) of *trans*-5,6-dihydro-5,6-dihydroxy-1-naphthyl methylcarbamate (**4**) as grayish-white needles, melting 148.5–150°C. The mother liquor from this recrystallization was concentrated to 25 ml under vacuum and refrigerated to give 0.85 g of grayish-white needles which, upon two recrystallizations from acetonitrile, gave 0.20 g of tiny, white needles, melting 185.5–187°C. The structure of this substance was assigned as *trans*-1,2-dihydro-1,5-bis(*N*-methylcarbamoyl)-2-hydroxynaphthalene (**7**) based on the method of synthesis and the following physical data: infrared spectrum (sample suspended in potassium bromide) 2.98 (NH and OH), 5.81, and 5.85 (C=O); ultraviolet spectrum (methanol solvent) λ_{max} 261 mμ (ϵ 7.0 × 10^3); nmr spectrum (DMSO-d_6) consistent with the proposed structure.

The sample of **4**, melting 148.5–150°C, was shown by tlc (silica gel; 1:1 benzene–acetonitrile) to contain **7** and another impurity. Dry-column chromatography on ten 1.2 × 19 in. columns of silica gel (196 g each) developed with 1:1 benzene–acetonitrile and repeated recrystallization from acetonitrile separated 10.4 g of **4**, melting 162–4°C from this material. A small sample was recrystallized from acetonitrile to constant melting point (166.5–168°C; Baron *et al.*, 1969, give 173–6°C; Leeling and Casida, 1966, give 159°C). The following physical data confirm the structure of our synthetic carbaryl metabolite "B"; infrared spectrum (sample suspended in potassium bromide) nearly identical to that published by Leeling and Casida (1966) for **4** of natural origin; ultraviolet spectrum (95% ethanol solution) λ_{max} ϵ 265 mμ (7.8 × 10^3); nmr spectrum (DMSO-d_6) nearly identical to the published spectrum (Baron *et al.*, 1969) obtained from a sample isolated from cow's urine; mass spectrum, parent ion = 235.084460 (compare 235.084451 given by Beynon and Williams, 1963 for $C_{12}H_{13}NO_4$) and the fragmentation pattern was nearly identical with that from a sample isolated from cow's urine and analyzed under the same conditions.

DISCUSSION

We set out to prepare synthetic carbaryl metabolite "B" (**4**) by the scheme outlined in Figure 1 on the basis of the following precedents. Fremy's Salt reacts with 1,5-dihydroxynaphthalene (**1**), giving 48% of 5-hydroxy-1,2-naphthoquinone (**2a**) (Teuber and Gotz, 1954); LAH reduction of 1,2-naphthoquinone (**9**) gives *trans*-1,2-dihydro-1,2-dihydroxynaphthalene (**10**) (Booth *et al.*, 1950); and it is possible to form a carbamate selectively from a phenol in the presence of an aliphatic alcohol using a tertiary amine catalyst and an isocyanate (Baker and Holdsworth, 1947; Tarbell *et al.*, 1942).

We found that commercial samples of Fremy's Salt were partly decomposed on delivery and chose to prepare this material ourselves. A recently reported preparation (Moser and Howie, 1968) in our hands proved very time-consuming and was modified as follows. Vacuum filtration through a filter

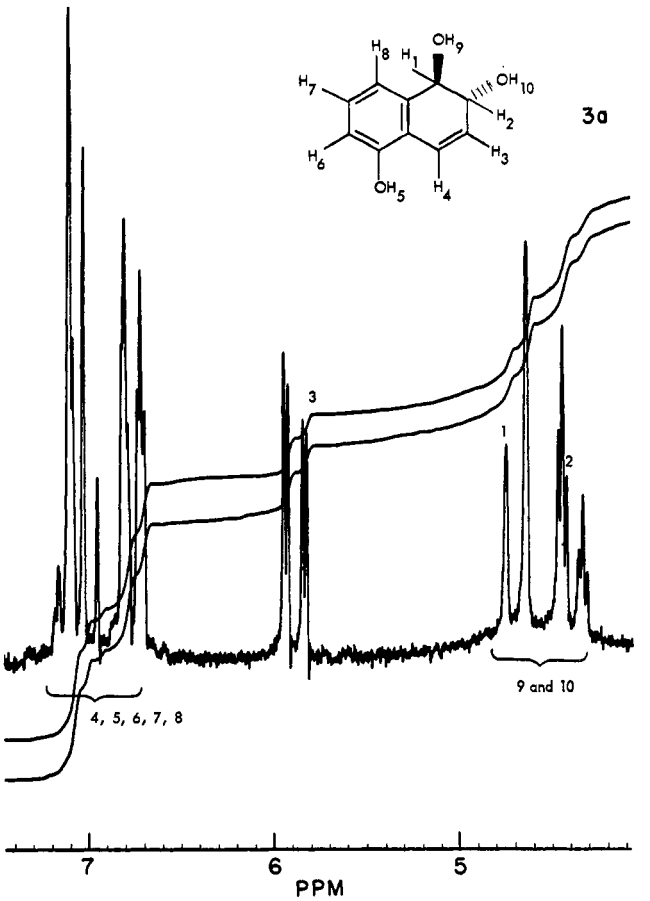
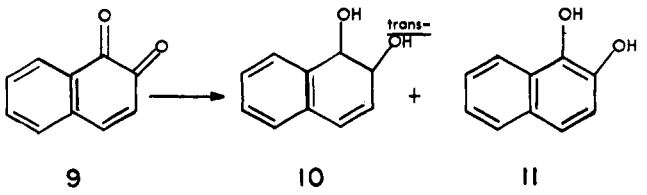


Figure 2. Nmr spectrum of *trans*-5,6-dihydro-5,6-dihydroxy-1-naphthol

paper-supported pad of HyFlo Super Cel (Johns-Manville Products Corp.) was used in place of the reported gravity filtration through filter paper to remove the manganese dioxide side product. This change reduced by one-half the total time required for a preparation on a 2.5-mol scale. When we tried to speed drying of the product using a vacuum desiccator we were troubled by several vigorous decompositions (Note: Possible Hazard!). Accordingly we used all subsequently prepared batches on the day of preparation and while still damp. No further decompositions were noted.

The preparation of 5-hydroxy-1,2-naphthoquinone (**2a**) was scaled up 60-fold and carried out at a lower pH (2.5) than that of the original work, pH 5.0 (Teuber and Gotz, 1954). We found that the use of a substantial excess of Fremy's Salt gave a product mixture from which the 1,2-quinone (**2a**) was more easily separated than it was from a mixture prepared with only a slight excess of the oxidant.

Before reducing 5-hydroxy-1,2-naphthoquinone (**2a**) we undertook a study of the reduction of 1,2-naphthoquinone (**9**) with LAH varying time, temperature, solvent, ratio of reactants, and order of addition. We had hoped to increase the ratio of dihydrodiol **10** to diol **11**. However, our efforts gave no marked improvement over the original procedure of Booth *et al.* (1950). Several other reducing agents were applied to 1,2-naphthoquinone (**9**). BH_3/THF, AlH_3/THF, aluminum isopropoxide/isopropyl alcohol, and $NaBH_4$ in various solvents each gave none of the desired dihydrodiol **10**. Lithium borohydride/THF and sodium dihydrobis(2-methoxyethoxy)-aluminate/benzene each gave a small amount of the desired product **10** but appeared much inferior to LAH for this purpose.



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The products expected (and obtained in addition to unidentified ones) from LAH reduction of 5-hydroxy-1,2-naphthoquinone (**2a**) are *trans*-1,2-dihydro-1,2,5-trihydroxynaphthalene (**3a**) and 1,2,5-trihydroxynaphthalene (**6a**) (Figure 1). An nmr study of a crude reduction mixture showed approximately 20% of dihydrotriol **3a**. Purification by dry-column chromatography (Loev and Goodman, 1967), followed by elution chromatography, activated carbon treatment and recrystallization gave 8% of **3a** based on starting quinone **2a**. The low recovery from this laborious purification scheme severely limited our ability to produce carbaryl metabolite "B" in quantity. Accordingly we sought alternate isolation procedures in the hope that they would be less time-consuming and/or more efficient. Attempted selective oxidation of **6a** in mixtures containing it and **3a** using air or cerium(IV) sulfate gave discouraging results, as did partitioning of reduction mixtures between methylene chloride and aqueous solutions of nickel(II) chloride, boric acid, sodium molybdate, and thorium(IV) nitrate in attempts to remove **6a** by complexation. Since both **3a** and **6a** are phenolic, a basic extraction procedure would be expected to fail to separate them. We have tried to modify the hydroxyl of the quinone **2a** with groups such as tetrahydropyranyl (as in **2b**) or trityl (as in **2c**) so that only one of the expected reduced products (**6b** or **c**) would be phenolic. Several attempts (in which solvent, acidic catalyst, temperature, and time were varied) to prepare **2b** were unsuccessful. Preliminary results suggest that we may be able to prepare the trityloxyquinone **2c**, and we are continuing to follow this lead.

In the search for conditions suitable for selective formation of only the phenolic carbamate from methyl isocyanate and dihydrotriol **3a**, we chose to investigate the more readily available model system of equal parts of α-naphthol and *trans*-1,2-dihydro-1,2-dihydroxynaphthalene (**10**). We discovered that *N,N*-dimethylaniline caused no carbamate formation but that triethylamine seemed to cause formation only of carbaryl in this model system. Similar reaction conditions applied to dihydrotriol **3a** enabled us to isolate 44% of carbaryl metabolite "B" after extensive purification. The method of synthesis coupled with infrared, nmr, ultraviolet, and mass spectral data confirm that we have synthesized the compound having the structure proposed by Leeling and Casida (1966) for carbaryl metabolite "B." Samples of our synthetic material and radioactive metabolite "B" isolated from cow's urine were mixed and recrystallized until the level of radioactivity remained constant within experimental error. The final level was 97% of the value calculated, assuming no separation of the two samples, thus strongly indicating that they were of the same chemical species. The differences in the reported melting points (Leeling and Casida, 1966, 159°C from rabbit urine; Baron *et al.*, 1969, 173–6°C from cow urine) and that of our synthetic material (166.5–168°C) probably arise from differences in chemical and/or optical purity of the various samples.

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