Synthesis of 5-Substituted 1-(1-Adamantyl)tetrazoles and Related Compounds

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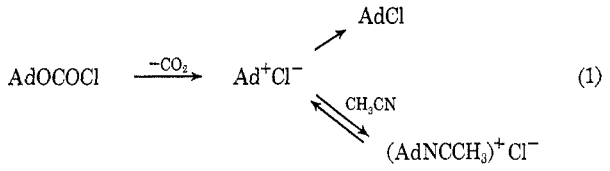
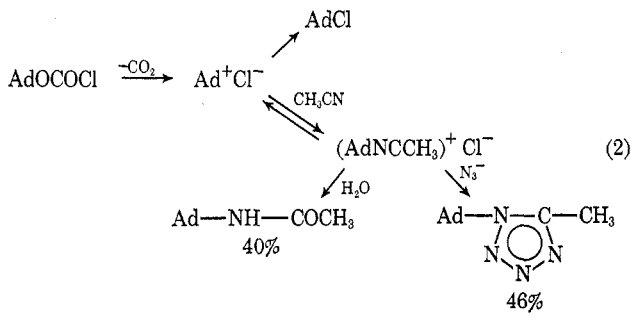
The preparation of 5-substituted 1-(1-adamantyl)tetrazoles has been carried out under neutral conditions, at ambient temperatures, by the reaction of 1-adamantyl iodide with silver hexafluoroantimonate in the appropriate nitrile, followed by addition of a solution of tetraethylammonium azide; the substituents which have been incorporated are methyl, ethyl, propyl, isopropyl, phenyl, vinyl, α-methylvinyl, and *trans*-β-phenylvinyl. By addition of water, rather than azide ion, N-(1-adamantyl)acrylamide and its α-methyl and *trans*-β-phenyl derivatives were prepared. 1-Adamantyl azidoformate and 1-adamantyl azide have also been prepared and characterized.

During a recent investigation of the decomposition of 1-adamantyl chloroformate in a variety of solvents,[1] it was found that the decomposition in dry acetonitrile was accompanied by a competing solvolysis (eq 1). In



(1)

fairly concentrated solution, a precipitate was formed and, upon addition of water, a mixture of 1-adamantyl chloride and N-(1-adamantyl)acetamide was obtained (eq 2). It has been found that precipitation does not



(2)

occur in more dilute solution and titration of the acid developed at 25.0°, after hydrolysis of aliquots of solution, shows that the concentration of the acetonitrilium chloride[2] reaches a maximum after about 8 min and then, over a period of about 4 hr, irreversible conversion to 1-adamantyl chloride takes place.

Trapping the acetonitrilium chloride with azide ion leads to 1-(1-adamantyl)-5-methyltetrazole and, by use of other nitriles as the solvent, the method can be adapted to yield 5-substituted 1-(1-adamantyl)tetrazoles in general. The technique was used to give 1-(1-adamantyl)-5-methyltetrazole in 46% yield by addition of 1-adamantyl chloroformate to sodium azide in acetonitrile. Neither 1-adamantyl azide nor 1-adamantyl azidoformate was observed as products of this reaction. The tetrazole yield is similar to the 40% N-(1-adamantyl)acetamide formed when hydrolysis follows upon solvolysis–decomposition.[1]

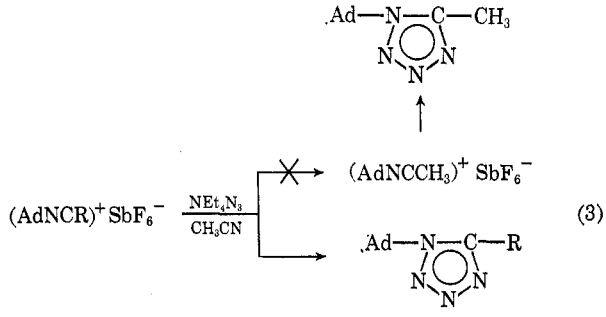
Yields by this technique are limited by the concurrent irreversible decomposition to 1-adamantyl chloride. This competition can be circumvented by use of silver hexafluoroantimonate which removes the nucleophilic chloride ions from solution and replaces them by non-nucleophilic hexafluoroantimonate ions.

$$AdOCOCl + AgSbF_6 \xrightarrow{RCN} (AdNCR)^+SbF_6^- + CO_2 + AgCl\downarrow$$

1-Adamantyl iodide reacts extremely rapidly with silver hexafluoroantimonate and this precursor can be prepared in better than 90% yields by a modification of the one-step reaction of 1-adamantanol with hydriodic acid which was reported by Schleyer and Nicholas.[3] Accordingly, we substituted, as our means of generating the intermediate nitrilium salt, the following reaction.

$$AdI + AgSbF_6 \xrightarrow{RCN} (AdNCR)^+SbF_6^- + AgI\downarrow$$

Sodium azide was found to be of very limited solubility in nitriles other than acetonitrile, and tetraethylammonium azide was substituted in the general scheme. Tetraethylammonium azide was synthesized by interaction of aqueous solutions of barium azide and tetraethylammonium sulfate. For convenience, the tetraethylammonium azide was added as its solution in acetonitrile rather than as a solution in each individual nitrile. This was on the assumption that interaction of the N-(1-adamantyl)nitrilium hexafluoroantimonate with the dissolved azide would be considerably faster than nitrile exchange reactions (eq 3). This assumption was normally a good one, but in a few instances, notably in the formation of vinyl tetrazoles, the pmr spectrum of the crude reaction product showed a low intensity singlet methyl peak at τ 7.28, indicating the presence of small amounts of 1-(1-adamantyl)-5-



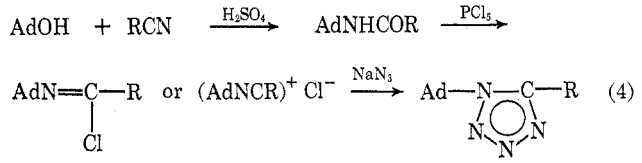
(3)

(1) D. N. Kevill and F. L. Weitl, *J. Amer. Chem. Soc.*, **90**, 6416 (1968).

(2) Although formulated as ionic, this could be fully or partially in the imide chloride form, Ad—N=C(Cl)R.

(3) P. von. R. Schleyer and R. D. Nicholas, *J. Amer. Chem. Soc.*, **83**, 2700 (1961).

methyltetrazole. This contamination could be removed by recrystallization, but, for large-scale preparation of a single tetrazole, it would be desirable to dissolve the tetraethylammonium azide in the same nitrile as that participating in the prior solvolytic reaction. This silver ion assisted synthesis presents an alternative to the usually proposed pathway which would proceed *via* the amide[4] (eq 4).



(4)

The silver ion assisted formation from 1-adamantyl iodide has the advantage of by-passing the isolation of intermediates. It presents a very simple two-step sequence involving only the mixing of ingredients at room temperature over a period of minutes, followed by evaporation, partitioning between an organic solvent and water, and recrystallization. In particular, the mild conditions lead to reasonable yields of 5-vinyltetrazoles, incorporating readily polymerized acrylonitrile and substituted acrylonitriles.[5]

By treatment of the N-(1-adamantyl)nitrilium hexafluoroantimonate solution with water rather than with azide solution, good yields of N-(1-adamantyl)acrylamide and its α-methyl- and *trans*-β-phenyl-substituted derivatives were obtained. By reaction of 1-adamantyl chloroformate with sodium azide, in the absence of nitriles, 1-adamantyl azidoformate and 1-adamantyl azide have been prepared and characterized.

With the exception of 1-adamantyl azide, the pmr spectra in chloroform-*d* include, for the 15 adamantyl protons, a broad peak corresponding to 9 unresolved $\beta + \gamma$ protons and a second upfield broad peak corresponding to 6 unresolved δ protons. The 1-adamantyl azide shows separated signals for each of the three types of protons with a $J_{\beta\gamma}$ coupling constant of 2.6 Hz. The pmr spectral data fit into the general picture previously reported for other 1-substituted adamantanes.[6]

Certain 1-adamantyl and 1,5-substituted tetrazole derivatives have previously been found to exhibit useful biological activity. For example, 1-aminoadamantane (amantadine) and 1-hydrazoadamantane[7] possess antiviral activity, and pentamethylene-1,5-tetrazole (leptazole, "Cardiazole") has been used as a stimulant drug. There could well be examples of 5-substituted 1-(1-adamantyl)tetrazoles which possess appreciable biological activity.

(4) (a) For a brief discussion of the preparation and reactions of tetrazoles, see, for example, M. H. Palmer, "The Structure and Reactions of Heterocyclic Compounds," St. Martins Press, New York, N. Y., 1967, pp 399–403. (b) For preparations involving a more direct route to certain nitrilium salts, see L. A. Lee, E. V. Crabtree, J. U. Lowe, Jr., M. J. Czlesla, and R. Evans, *Tetrahedron, Lett.*, 2885 (1965).

(5) For relatively complex preparations leading to mixtures of 1-methyl-5-vinyltetrazole and 2-methyl-5-vinyltetrazole, see W. G. Finnegan, R. A. Henry, and S. Skolnik, (a) U. S. Patent 3,004,959 (1961) [*Chem. Abstr.*, **56** 15518 (1962)]; (b) U. S. Patent 3,062,880 (1962) [*Chem Abstr.*, **58**, 5705 (1963)]. Also, R. A. Henry, U. S. Patent 3,351,627 (1967) [*Chem. Abstr.*, **68**, 114605 (1968)]. These preparations involve introduction of the exocyclic double bond *after* construction of the tetrazole ring system.

(6) R. C. Fort, Jr., and P. von R. Schleyer, *J. Org. Chem.*, **30**, 789 (1965).

(7) French Patent 1,491,581 (1967); *Chem. Abstr.*, **69**, 96074 (1968). See, also, H. U. Daeniker, *Helv. Chim. Acta*, **50**, 2008 (1967).

Experimental Section[8]

1-Adamantyl Iodide.—This compound was prepared from 1-adamantanol (Aldrich) by a modification of the method reported by Schleyer and Nicholas.[3] Hexane was found to be considerably superior to ether as a solvent for the extraction of the 1-adamantyl iodide. Carrying out the 1-adamantanol–hydriodic acid reaction,[3] decanting the aqueous layer, dissolving the residue in hexane, washing several times with water, drying over anhydrous magnesium sulfate, filtering, and evaporating gave approximately 95% yields of white crystals of 1-adamantyl iodide, mp 75–77° (lit.[3] mp 75.3–76.4°).

Stock Solution of Tetraethylammonium Azide.—A 100-ml portion of 10% aqueous solution of tetraethylammonium hydroxide (Eastman) was neutralized (litmus paper) with concentrated H_2SO_4. A solution of 13 g of barium azide (Alfa Inorganics 15% alcohol) in 50 ml of water was then slowly added until precipitation of barium sulfate ceased. After filtration the solution was concentrated at 50° with application of vacuum to a semisolid residue. A 400-ml portion of acetonitrile (Mallinckrodt "Nanograde") was added and the solution was azeotropically dried and concentrated by distillation to give a 50-ml stock solution.

1-(1-Adamantyl)-5-methyltetrazole. Procedure A.—A mixture of 1.0 g of sodium azide and 25 ml of acetonitrile was added to 2.0 g of 1-adamantyl chloroformate[1,9] and the mixture stirred for 30 min. The mixture was briefly heated to boiling and then allowed to stand at room temperature for a further 20 hr. The acetonitrile was evaporated under reduced pressure and the residue was extracted with benzene. The benzene solution was added to a silicic acid–Celite[10] column and successively eluted with hexane, benzene–hexane mixtures, and chloroform. The chloroform fraction gave 0.93 g (46%) of white solid: mp 127.5–129.0°; ir (KBr) 3.43, 3.50, 6.95, 7.26, 7.39, 7.45, 9.65, 12.00, 14.77 μ; pmr τ 7.28 (S, 3, CH_3), 7.68 (S, 9), 8.19 (S, 6).

Anal. Calcd for $C_{12}H_{18}N_4$: C, 66.03; H, 8.31; N, 25.67. Found: C, 66.11; H, 8.31; N, 25.52.

Procedure B.—A 2.20-g portion of silver hexafluoroantimonate (K and K Laboratories) was dissolved in 75 ml of acetonitrile and dried by azeotropic distillation; distillation was continued to give a residue of ~15 ml. To this residue was added, in a single portion, 1.50 g of 1-adamantyl iodide. An exothermic reaction occurred with precipitation of silver iodide. After about 2 min, 8 ml of the stock solution of NEt_4N_3 in CH_3CN was added and the solution adopted an orange-yellow color. After 30 min of shaking, Celite[10] was added, the mixture was filtered, the cake was washed well with CH_3CN, and the filtrate was evaporated to dryness under aspirator vacuum. The orange residue was partitioned between benzene and water, and the benzene layer was washed with water, dried with anhydrous $MgSO_4$, and evaporated under aspirator vacuum to give 1.25 g of a tan-colored residue. Recrystallization from petroleum ether (bp 60–100°) gave 0.89 g (71%) of white needles, mp 115–116°, followed by resolidification and second mp 126–127°; ir and pmr spectra were identical with those of the product from procedure A.

Anal. Found: C, 66.15; H, 8.35; N, 25.54.

Use of Procedure B to Prepare Other Tetrazoles.—With use of 1.50 g of 1-adamantyl iodide and with substitution of an appropriate nitrile as the solvent for the silver hexafluoroantimonate, several other 5-substituted 1-(1-adamantyl)tetrazoles were prepared. With the higher boiling nitriles, the azeotropic removal of water and concurrent concentration of the $AgSbF_6$ solution was achieved at reduced pressure. In each case, the NEt_4N_3 was added as its stock solution in acetonitrile.

1-(1-Adamantyl)-5-ethyltetrazole.—Nitrile was propionitrile (Eastman). The pmr spectrum of the crude product indicated it to be ~12% 1-(1-adamantyl)-5-methyltetrazole. A recrystallized yield of 0.38 g (29%) of white flakes gave mp 133.5–

(8) Melting points were taken in closed capillary tubes by use of calibrated Anschütz thermometers and a Büchi apparatus. Infrared spectra were obtained on a Beckman IR-8 using Styrofoam–KBr disks. Pmr spectra were recorded with a Varian A-60A spectrometer system, using chloroform-*d* as solvent. Microanalyses were by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Yields are based upon the appropriate 1-adamantyl reactant. Infrared spectra are outlined for three of the tetrazoles and one of the amides.

(9) W. L. Haas, E. V. Krumkalns, and K. Gerzon, *J. Amer. Chem. Soc.*, **88**, 1988 (1966).

(10) Celite is a kieselguhr supplied by the Johns–Manville International Corp., New York, N. Y.

134.5°; pmr τ 6.96 (q, 2, J = 7.5 Hz, CH_3CH_2–), 7.68 (S, 9), 8.20 (S, 6), 8.53 (t, 3, J = 7.5 Hz, CH_3CH_2–).

Anal. Calcd for $C_{13}H_{20}N_4$: C, 67.21; H, 8.68; N, 24.12. Found: C, 67.13; H, 8.79; N, 24.07.

Also, a second crop of 0.26 g (20%) gave mp 130–132°.

1-(1-Adamantyl)-5-propyltetrazole.—Nitrile was butyronitrile (Eastman). The crude residue (1.40 g), gave on recrystallization 0.90 g of white flakes (64%): mp 99–100.5°; pmr τ 7.02 (t, 2, J = 7 Hz, $CH_3CH_2CH_2$–), 7.69 (S, 9), 8.19 (broad, 6 + 2), 8.98 (t, 3, J = 7 Hz, $CH_3CH_2CH_2$–).

Anal. Calcd. for $C_{14}H_{22}N_4$: C, 68.26; H, 9.00; N, 22.74. Found: C, 68.07; H, 9.30; N, 22.69.

1-(1-Adamantyl)-5-isopropyltetrazole.—Nitrile was isobutyronitrile (Eastman). The crude residue (1.34 g) gave on recrystallization 0.87 g of white crystals, mp 156–170° (despite the wide melting point range, the pmr spectrum did not indicate any impurities). Two further recrystallizations from petroleum ether (bp 60–110°) and one from a petroleum ether (8 vol)–benzene (1 vol) mixture gave 0.61 g of white crystals (43%): mp 169–172°; pmr τ 6.52 [m, 1, J = 7 Hz, $(CH_3)_2CH$–], 7.69 (S, 9), 8.19 (S, 6), 8.57 (d, 6, J = 7 Hz, $(CH_3)_2CH$–).

Anal. Calcd for $C_{14}H_{22}N_4$: C, 68.26; H, 9.00; N, 22.74. Found: C, 68.08; H, 8.98; N, 22.82.

1-(1-Adamantyl)-5-phenyltetrazole.—Nitrile was benzonitrile (Velsicol Chemical Corp.). The 1.60 g of residue was recrystallized (0.22 g of tan solid: insoluble) to give 0.49 g of leafy white crystals, mp 154–157°. Two further recrystallizations from a mixture of petroleum ether (8 vol)–benzene (1 vol) gave 0.33 g (21%), mp 158–161°; ir 3.44, 3.51, 6.94, 7.38, 7.41, 7.46, 7.68, 8.44, 9.18, 9.32, 9.93, 12.08, 12.95, 13.48, 14.34, 14.51, 14.70 μ; pmr τ 2.55 (S with fine structure, 5, C_6H_5–), 7.82 (S, 9), 8.33 (S, 6).

Anal. Calcd for $C_{17}H_{20}N_4$: C, 72.82; H, 7.19; N, 19.98. Found: C, 72.81; H, 7.15; N, 20.02.

1-(1-Adamantyl)-5-vinyltetrazole.—Nitrile was acrylonitrile (Eastman). The 1.25 g of residue was recrystallized (some yellow insoluble material) to give 0.62 g of white flakes, mp 97–100° [pmr spectrum indicated presence of about 25% 1-(1-adamantyl)-5-methyltetrazole]. Three further recrystallizations from petroleum ether (bp 60–110°) gave 0.26 g (20%): mp 104–108°; ir 3.43, 3.51, 6.76, 6.96, 7.12, 7.32, 7.41, 7.69, 8.41, 9.11, 9.62, 10.19, 10.58, 12.01, 13.00, 14.36, 15.01 μ; pmr τ 3.07 + 3.59 + 4.21 (AMX vinylic system, 3, J_{AM} = 17.0 Hz, J_{AX} = 10.5 Hz, J_{MX} = 2.1 Hz, respectively the α-H, *trans*[11]-β-H, *cis*[11]-β-H), 7.68 (S, 9), 8.19 (S, 6).

Anal. Calcd for $C_{13}H_{18}N_4$: C, 67.79; H, 7.88; N, 24.33. Found: C, 67.69; H, 7.82; N, 24.23.

1-(1-Adamantyl)-5-(α-methylvinyl)tetrazole.—Nitrile was methacrylonitrile (Eastman). The pmr spectrum of the 1.34 g of crude brown residue indicated the presence of about 10% 1-(1-adamantyl)-5-methyltetrazole. Recrystallization (some insoluble black tar) gave 0.59 g of tan crystals, mp 135–150°. Three further recrystallizations from petroleum ether (bp 60–110°) gave 0.20 g of tan crystals (14%): mp 148–151°; pmr τ 4.41 + 4.72 (MX system with fine structure, 2, respectively *trans*[11]-β-H and *cis*[11]-β-H), 7.68 (S, 9), 7.83 (S with fine structure, 3, CH_3–), 8.24 (S, 6).

Anal. Calcd for $C_{14}H_{20}N_4$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.83; H, 8.25; N, 23.00.

1-(1-Adamantyl)-5-(*trans*-β-phenylvinyl)tetrazole.—Nitrile was cinnamonitrile (Eastman). An additional step was a treatment, prior to evaporation, of the dried benzene solution with carbon black (Norite). The crude tetrazole was recrystallized not from petroleum ether but from a petroleum ether (bp 60–110°) (10 vol)–benzene (1 vol) mixture. Obtained was 0.88 g of tan crystals (49%): mp 163.5–164.5°; pmr τ 2.15 (d, 1, J = 15.8 Hz, vinylic), *ca.* 2.54 (complex overlapping series, 5, C_6H_5–), 2.89 (d, 1, J = 15.8 Hz, vinylic), 7.62 (S, 9), 8.17 (S, 6).

Anal. Calcd for $C_{19}H_{22}N_4$: C, 74.47; H, 7.24; N, 18.28. Found: C, 74.85; H, 7.09; N, 18.17.

N-(1-Adamantyl)acrylamide.—A 2.3-g portion of $AgSbF_6$ was dissolved in 75 ml of acrylonitrile and the solution was distilled until a residue of 10 ml remained. To this residue at room temperature was added 1.5 g of 1-adamantyl iodide followed, after shaking for 5 min, by 10 ml of an acetonitrile (4 vol)–water (1 vol) mixture. After addition of Celite[10] and filtration, the cake was washed with CH_3CN, and the total solution was evaporated to dryness to leave a white residue which was partitioned between benzene and water. The benzene layer was washed several times with water, dried with anhydrous $MgSO_4$, and evaporated to give 1.11 g of white residue. Recrystallization from petroleum ether (60–110°) gave 0.88 g of white needles (75%): mp 148–148.5°; ir 3.08, 3.26, 3.43, 3.51, 6.10, 6.22, 6.51, 6.94, 7.15, 7.40, 7.48, 7.70, 7.91, 8.08, 8.46, 8.92, 9.18, 9.42, 10.12, 10.59, 11.08, 12.41, 13.72 μ; pmr τ 3.81 + 3.91 + 4.44 (3 vinylic protons,[12] respectively *trans*[11]-β-H, α-H, and *cis*[11]-β-H), *ca.* 4.5 (broad, 1, –NH–), 7.94 (S, 9), 8.30 (S, 6).

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.03; H, 9.33; N, 6.82. Found: C, 76.17; H, 9.54; N, 6.63.

N-(1-Adamantyl)methacrylamide.—Prepared as was N-(1-adamantyl)acrylamide with substitution of methacrylonitrile for acrylonitrile. A minor modification was the addition of 1 ml of pyridine concurrent with the 10 ml of aqueous acetonitrile. A crude residue of 1.18 g gave on recrystallization 0.51 g of white crystals (41%): mp 102–104°; pmr τ 4.44 (S with fine structure, 1, *trans*[11]-β-H), *ca.* 4.57 (broad, 1, –NH–), 4.77 (S with fine structure, 1, *cis*[11]-β-H), 7.94 (S, 9), 8.09 (S with fine structure, 3, CH_3–), 8.30 (S, 6).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.56; H, 9.74; N, 6.40.

A second crop of 0.55 g (44%) was recovered from the recrystallization mother liquor, mp 98–102°.

N-(1-Adamantyl)-*trans*-cinnamamide.—Prepared as was N-(1-adamantyl)methacrylamide but with substitution of 25 ml of cinnamonitrile for 75 ml of methacrylonitrile. Recrystallization was from a (bp 60–110°) petroleum ether (4 vol)–benzene (1 vol) mixture rather than from petroleum ether (bp 60–110°). Obtained was 0.25 g of white crystals (16%), mp 196–199° dec. Addition of petroleum ether to the mother liquor gave a further 0.90 g of white crystals (56%), mp 196–198° dec, for a total yield of 72%: pmr τ 2.44 (d, 1, J = 15.7 Hz, *trans*[11]-β-H), *ca.* 2.62 (complex overlapping series, 5, C_6H_5–), 3.66 (d, 1, J = 15.7 Hz, α-H), 7.91 (S, 9), 8.28 (S, 6).

Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.96; H, 8.52; N, 4.91.

1-Adamantyl Azidoformate.[13] **Procedure A.**—To 0.5 g of sodium azide in a mixture of 3.5 g of water and 7.5 g of acetone was added 1.0 g of 1-adamantyl chloroformate. The mixture was stirred for 48 hr at room temperature and 50 ml of water was then added. A colorless oil separated and this was combined with four 25-ml ether extracts of the aqueous soluton. The ether solution was dried with anhydrous Na_2SO_4 and evaporated to dryness. The residue was dissolved in benzene and eluted from a silicic acid–Celite[10] column. Using hexane, a small amount of 1-adamantyl chloride was obtained, followed by a trace of 1-adamantyl azide (ir included 4.80 μ ($-N_3$), no C=O or OH peaks present). A benzene (1 vol)–hexane (1 vol) mixture was then used to elute 0.54 g (52%) of white, crystalline 1-adamantyl azidoformate: mp 43–44° (lit.[15] pale yellow oily liquid); ir 3.44, 3.51, 4.59, 4.70, 5.86, 6.92, 8.24, 9.10, 9.61, 10.42, 10.56, 11.31, 12.32, 13.15, 13.33 μ; pmr τ 7.85 (S, 9), 8.32 (S, 6).

Anal. Calcd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.80; H, 6.78; N, 19.18.

Procedure B.—A 0.5-g portion of 1-adamantyl chloroformate was dissolved in 15 ml of methanol containing 0.33 g of sodium azide. Precipitation of sodium chloride was accompanied by an evolution of gas. After standing overnight, the methanol was removed by evaporation under aspirator vacuum and the residue was extracted with hexane. Column chromatography, as in procedure A, yielded 0.25 g (48%) of white crystalline 1-adamantyl azidoformate, mp 42–43°.

1-Adamantyl Azide.—A 4.0-g portion of 1-adamantyl chloroformate was added to a mixture of 20 ml of ether, 20 ml of water, and 8.0 g of sodium azide. The mixture was stirred for 2 weeks and then the ether layer was separated, dried with anhydrous

(11) In describing the pmr spectra of vinylic compounds, *cis* and *trans* are relative to the α hydrogen or, for α-methyl derivatives, the α-methyl group.

(12) Splitting pattern of vinyl protons identical with that illustrated for N-isopropylacrylamide: N. S. Bhacca, L. F. Johnson, and J. L. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, spectrum 468.

(13) Although there are two references to 1-adamantyl azidoformate in the literature,[14,15] it does not appear to have been prepared in pure form and characterized.

(14) W. V. Curran and R. B. Angier, *Chem. Commun.*, 563 (1967); *J. Org. Chem.*, **34**, 3669 (1969).

(15) K. Gerzon and E. V. Krumkalns, U. S. Patent 3,369,041 (1968).

Na_2SO_4, and evaporated under reduced pressure. The residue was extracted with hexane and the hexane solution was eluted from a silicic acid–Celite[10] column by use of a hexane (3 vol)–benzene (7 vol) mixture. Evaporation of the second fraction gave 0.20 g (6%) of white crystalline 1-adamantyl azide: mp 82–83°; ir 3.43, 3.51, 4.80, 6.92, 8.02, 9.49, 11.32, 12.33, 13.67, 14.82 μ; pmr τ 7.84 (S, 3, γ-H), 8.19 (d, 6, J = 2.6 Hz, β-H), 8.30 (6, δ-H).

Anal. Calcd for $C_{10}H_{15}N_3$: C, 67.76; H, 8.53; N, 23.59. Found: C, 67.56; H, 8.42; N, 23.62.

Evaporation of the first and third fractions gave a trace of 1-adamantyl chloride (identified by infrared spectrum) and 0.3 g of 1-adamantyl azidoformate, mp 42–43°, respectively. A large fourth fraction had an infrared spectrum indicating that it was 1-adamantanol.

Registry No.—1-(1-Adamantyl)-5-methyltetrazole, 24886-62-2; 1-(1-adamantyl)-5-ethyltetrazole, 24940-56-5; 1-(1-adamantyl)-5-propyltetrazole, 24886-63-3; 1-(1-adamantyl)-5-isopropyltetrazole, 24886-64-4; 1-(1-adamantyl)-5-phenyltetrazole, 24886-65-5; 1-(1-adamantyl)-5-vinyltetrazole, 24886-66-6; 1-(1-adamantyl)-5-(α-methylvinyl)tetrazole, 24886-67-7; 1-(1-adamantyl)-5-(*trans*-β-phenylvinyl)tetrazole, 24886-68-8; N-(1-adamantyl)acrylamide, 19026-83-6; N-(1-adamantyl)methacrylamide, 24886-70-2; N-(1-adamantyl)-*trans*-cinnamamide, 24886-71-3; 1-adamantyl azidoformate, 19386-43-7; 1-adamantyl azide, 24886-73-5.

A Reinvestigation of the Mannich Reaction of 4-Nitrophenylacetic Acid and 2,4-Dinitrophenylacetic Acid[1]

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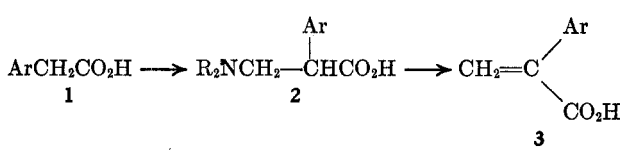
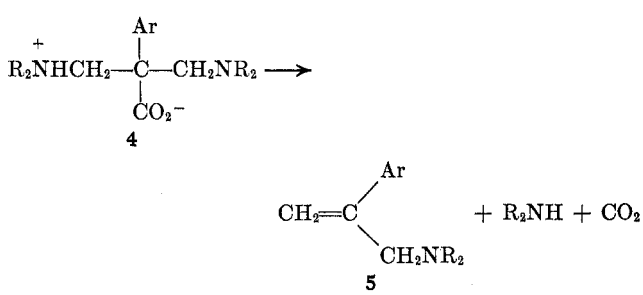
The reaction of 4-nitrophenylacetic acid with piperidine and formaldehyde gives rise to α-(N-piperidinomethyl)-4-nitrostyrene (**5**) *via* a slow second Mannich condensation of the intermediate α-(4-nitrophenyl)-β-(N-piperidino)propionic acid (**2**) and subsequent decarboxylative deamination of **4**. 2,4-Dinitrophenylacetic acid also undergoes mono- and bisaminomethylation under Mannich conditions; however, the intermediate amino acids **6** and **7** spontaneously decarboxylate to yield the monoamine **8** and diamine **9**. The elimination reactions of **2** have been studied over the pH range of 1–11. In acidic medium, deamination occurs to yield theacrylic acid **3**; under basic conditions, decarboxylative deamination predominates to yield 4-nitrostyrene. Above pH 6, **2** also undergoes the retro Mannich reaction.

Although reports due to Mannich and a few later workers indicate that α-methylene functions of certain activated carboxylic acids can undergo condensation to incorporate two $-CH_2NR_2$ groups,[3] a detailed study of these reactions has not been made. Our interest in this topic arose from an attempt to repeat Mannich's synthesis of α-(4-nitrophenyl)acrylic acid. This procedure involves reaction of the piperidinium salt of 4-nitrophenylacetic acid with formaldehyde in aqueous solution to yield α-(4-nitrophenyl)-β-(N-piperidino)-propionic acid (**2**) which is deaminated by heating in aqueous solution kept neutral by periodic addition of dilute hydrochloric acid.[4]



Ar– = 4-nitrophenyl; R_2N– = piperidyl

In the first step of this sequence, we have isolated a 29% yield of α-(N-piperidinomethyl)-4-nitrostyrene (**5**) in addition to the β-amino acid **2** (65% yield). This styrene apparently arises by aminomethylation of **2** to yield **4**, which then undergoes decarboxylative deamination as shown in the following reaction scheme.



Ar– = 4-nitrophenyl; R_2N– = piperidyl

This conclusion is supported by observation of the β-amino acid **2** as an intermediate in the formation of **5**.[5] Stepwise loss of carbon dioxide and piperidine[6] is ruled out since 2-(4-nitrophenyl)-1,3-di(N-piperidino)propane was inert under the reaction conditions.

In contrast to the reaction of 4-nitrophenylacetic acid, Mannich and Stein reported that 2,4-dinitrophenylacetic acid reacts with piperidine and formaldehyde to yield only 2-(2,4-dinitrophenyl)-1,3-di(N-piperidino)-propane (**9**).[4] However, repetition of this reaction in dilute aqueous ethanol solution at 31° resulted in appreciable amounts of the monoamine **8** and 2,4-dinitrotoluene in addition to the diamine **9**. Decarboxylation of the piperidinium salt of 2,4-dinitrophenylacetic acid occurred readily under these conditions. Since Kermack and Muir had reported formation of both

(1) Presented at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969.

(2) Abstracted in part from the M. S. Thesis of E. Hertz, presented to the Department of Chemistry, Villanova University, April 1968.

(3) F. F. Blick, *Org. React.*, **1**, 310 (1942); B. Reichert, "Die Mannich Reaktion," Springer-Verlag, Berlin, 1959, p 41.

(4) C. Mannich and L. Stein, *Ber.*, **58B**, 2659 (1925).

(5) It should be noted that decarboxylative deamination of postulated β-amino acid intermediates under Mannich conditions has been invoked previously, *e.g.*, (a) C. A. Grob and P. W. Schiess, *Angew. Chem. Int. Ed. Engl.*, **6**, 1(1967), and references cited therein; (b) H. Ulrich and A. A. R. Sayigh, *J. Org. Chem.*, **31**, 4146 (1966).

(6) B. B. Thompson, "Some Studies in the Mannich Reaction," Ph.D. Thesis, The University of Mississippi, 1963.