way. The triacetate crystallized from light petroleum in needles, m.p. 152–153°.

(*b*) An ice-cooled suspension of 0.75 g. of 5-chloro-1,2-naphthoquinone in 1.5 ml. of acetic anhydride was treated with 2 drops of concentrated sulfuric acid. The quinone dissolved rapidly and the triacetate began to separate after 10 min. It formed needles, m.p. 153° (from light petroleum), identical with those obtained in (*a*).

*Anal.* Calcd. for $C_{16}H_{13}ClO_6$: C, 57.1; H, 3.9; Cl, 10.55. Found: C, 57.3; H, 4.05; Cl, 10.45.

*2,5-Dichloro-1,4-naphthoquinone.* Three grams of chlorine were passed into a suspension of 4 g. of 5-chloro-1,4-naphthoquinone in 80 ml. of glacial acetic acid. The quinone dissolved, the dichloride soon began to separate, and was collected after 1 hr. (5.1 g., m.p. 164–165°). This was refluxed for 10 min. in 100 ml. of glacial acetic acid containing 2.55 g. of anhydrous sodium acetate, and diluted with water. Crystallization of the precipitate from aqueous methanol afforded 2,5-dichloro-1,4-naphthoquinone in yellow plates, m.p. 98–100°. (Yield 70% from the dichloride.)

*Anal.* Calcd. for $C_{10}H_4Cl_2O_2$: C, 52.9; H, 1.8. Found: C, 53.0; H, 1.8. Reductive acetylation afforded 1,4-diacetoxy-2,5-dichloronaphthalene in needles, m.p. 160° (from ethanol).

*Anal.* Calcd. for $C_{14}H_{10}Cl_2O_4$: C, 53.7; H, 3.2. Found: C, 54.0; H, 3.2.

*3-Anilino-2,5-dichloro-1,4-naphthoquinone.* Aniline (1 ml.) was added to a suspension of 0.25 g. of 2,5-dichloro-1,4-naphthoquinone in 3.5 ml. of ethanol, and left overnight. The crystalline product was collected, and recrystallized from benzene in dark red needles, m.p. 220–221°. (Mixed m.p. with 3-anilino-5-chloro-1,4-naphthoquinone, 192–196°). Yield 57%.

*Anal.* Calcd. for $C_{16}H_9Cl_2NO_2$: C, 60.4; H, 2.85; N, 4.4. Found: C, 60.7; H, 2.29; N, 4.8.

*2,5-Dichloro-3-hydroxy-1,4-naphthoquinone.* (*a*) The above anilinodichloroquinone was hydrolyzed by boiling in 50% (v./v.) sulfuric acid for 10–15 min., as before. Crystallization from light petroleum, followed by sublimation *in vacuo* gave orange needles, m.p. 180–181°. Yield 33%.

(*b*) A solution of 0.18 g. of chlorine in 5 ml. of glacial acetic acid was added to 0.35 g. of finely powdered 5-chloro-3-hydroxy-1,4-naphthoquinone. The mixture was warmed for 3 hr. on the water bath and the product then isolated by pouring into water (50 ml.). Purification as above gave orange crystals, m.p. and mixed m.p. 180–181°. Yield 27%.

*Anal.* Calcd. for $C_{10}H_4Cl_2O_3$: C, 49.4; H, 1.65. Found: C, 49.6; H, 1.75.

*5-Chloro-2 and 3-p-tolylthio-1,4-naphthoquinone.* A solution of 0.33 g. of toluene-*p*-thiol in 2 ml. of methanol was added to a suspension of 0.5 g. of 5-chloro-1,4-naphthoquinone in 5 ml. of the same solvent. Next day the dark red solution was poured into an oxidizing solution of 0.6 g. of potassium dichromate, 0.3 ml. of concentrated sulfuric acid, and 5 ml. of ice water. The resulting precipitate was crystallized from methanol to give (*a*) orange-red needles and plates, m.p. 158° (49%), and (*b*) more soluble, pale orange needles, m.p. 175–176° (12%).

*Anal.* Calcd. for $C_{17}H_{11}ClO_2S$: C, 64.9; H, 3.5; Cl, 11.3; S, 10.2. Found: (a), C, 64.7; H, 3.25; Cl, 11.2; S, 9.7. (b), C, 64.6; H, 3.8; Cl, 10.85; S, 9.9.

Compound (*b*) was shown to be 5-chloro-2-*p*-tolylthio-1,4-naphthoquinone as follows: Solutions of 140 mg. of toluene-*p*-thiol in 1 ml. of ethanol, and 45 mg. of sodium hydroxide in 1 ml. of water, were mixed, brought to the boil, and added, all at once, to a boiling solution of 250 mg. of 2,5-dichloro-1,4-naphthoquinone in 4 ml. of ethanol, boiled for 1 min. and cooled. The product separated on cooling, and recrystallized from ethanol in pale orange needles, m.p. 175–176°, not depressed by admixture with material (*b*) obtained above. Yield 58%.

*2,5-Dichloro-3-p-tolylthio-1,4-naphthoquinone.* Solutions of 250 mg. of 2,5-dichloro-1,4-naphthoquinone in 4 ml. of ethanol, and 70 mg. of toluene-*p*-thiol in 1 ml. of ethanol, were mixed in the cold. After 4 hr. the red precipitate was collected and crystallized from light petroleum in lustrous, dark red needles, m.p. 148–149°. Yield 62%.

*Anal.* Calcd. for $C_{17}H_{10}Cl_2O_2S$: C, 58.45; H, 2.9. Found: C, 58.6; H, 3.1.

*Acknowledgment.* J.W.M. is indebted to Ross & Cromarty Education Committee for a Maintenance Allowance.

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[CONTRIBUTION FROM THE PIONEERING RESEARCH LABORATORY, TEXTILE FIBERS DEPARTMENT, E. I. DU PONT DE NEMOURS & CO., INC.]

# Synthesis of Two Atom-Bridged Tetracyclic Ketones

H. K. HALL, JR.

*August 31, 1959*

Addition of acrylonitrile to bicycloheptadiene gave 6-cyano-tetracyclo[3:2:1:$1^{3,8}$:$0^{2,4}$]nonane, I, which was converted by standard reactions to tetracyclo[3:2:1:$1^{3,8}$:$0^{2,4}$]nonan-6-one, IV, and tetracyclo[3:3:1:$1^{3,9}$:$0^{2,4}$]decan-6-one, VII.

In connection with the synthesis of various atom-bridged lactams,[1] polycyclic ketones were required as intermediates. Dr. D. C. England of the Central Research Department[2] had found that acrylonitrile adds to bicycloheptadiene in a homoconjugate manner to give nitrile I (for analogous reactions see ref. 3 and 4). In the present work, this nitrile was converted to the interesting tetracyclo[3:2:1:$1^{3,8}$:$0^{2,4}$]nonan-6-one, IV, and tetracyclo[3:3:1:$1^{3,8}$:$0^{2,4}$]decane-6-one, VII, as shown in the reaction sequences diagram. Yields were mediocre, however, and no conversions to lactams were carried out.

(1) H. K. Hall, Jr., *J. Am. Chem. Soc.*, in press.
(2) Unpublished work.
(3) E. F. Ullman, *Chem. and Ind.*, 1173 (1958).
(4) A. T. Blomquist and Y. C. Meinwald, *J. Am. Chem. Soc.*, **81**, 667 (1959).

## EXPERIMENTAL

*6-Cyano-tetracyclo[3:2:1:$1^{3,8}$:$0^{2,4}$]nonane* (I). A mixture of 500 g. (5.44 mol.) of bicycloheptadiene, 300 g. (5.66 mol.) of acrylonitrile, and 3 g. of cupric acetate was heated at 200° for 12 hr. The product was poured into 4 l. of hexane

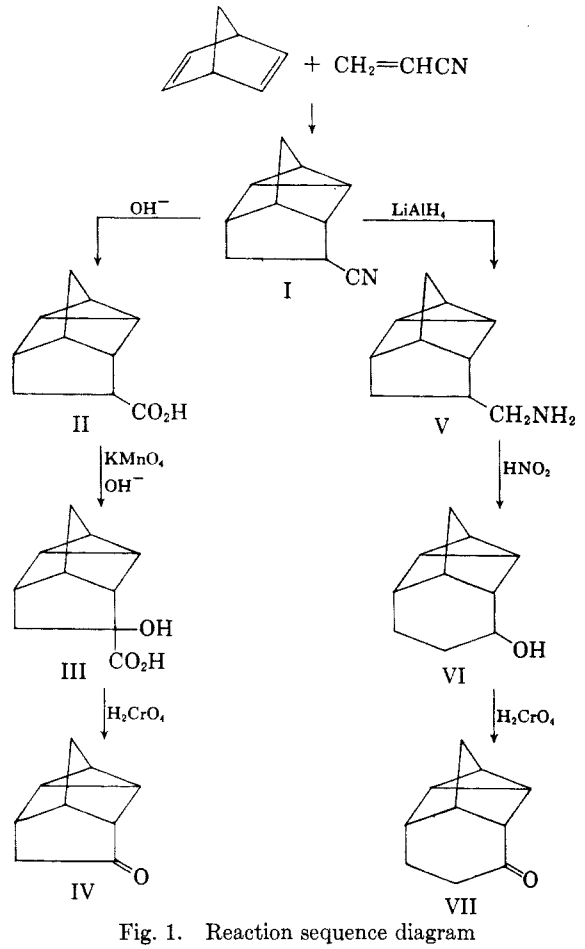


Fig. 1. Reaction sequence diagram

and filtered through Celite. The hexane was evaporated to leave 160 g. of crude product. This was dissolved in 300 ml. of acetone and to it was added, with stirring, a solution of 100 g. of potassium permanganate and 100 g. of anhydrous magnesium sulfate in 3.2 l. of water. A permanent purple color was reached, and the mixture was decolorized with sulfur dioxide. The salts were filtered and rinsed with hexane. The filtrate was extracted with hexane and the combined hexane extracts were dried and distilled to give 98.0 g. (12.4%) of I, b.p. 124–127° (17 mm.), $n_D^{25}$ 1.5053.

*Anal.* Calcd. for $C_{10}H_{11}N$: N, 9.66. Found: N, 9.55.

*Tetracyclo[3:2:1$^{3,8}$:0$^{2,4}$]nonane-6-carboxylic acid* (II).[5] A solution of 95.0 g. (0.65 mol.) of nitrile II, 90.0 g. of sodium hydroxide, 100 ml. of ethanol, and 260 ml. of water was boiled for 50 hr. under reflux. The ethanol was distilled and the residue was cooled and extracted with two 100 ml. portions of ether, which were discarded. The aqueous layer was acidified with sulfuric acid and was again extracted twice with 100 ml. portions of ether. The ether extracts were dried and distilled to give 47 g. (43.6%) of II, b.p. 106–107° (0.25 mm.), $n_D^{25}$ 1.4972.

*Anal.* Calcd. for $C_{10}H_{12}O_2$: C, 73.1; H, 7.4. Found: C, 72.6, 72.8; H, 7.33, 7.33.

The acid solidified on standing, m.p. 55–58°. Recrystallization from hexane raised the melting point to 61–62°.

*6-Hydroxy-tetracyclo[3:2:1:1$^{3,8}$:0$^{2,4}$]nonane-6-carboxylic acid* (III). Hydroxylation of acid II was carried out according to Kenyon and Symons.[6] To a solution of 41.0 g. (0.25 mol.) of II and 500 g. of potassium hydroxide in 625 ml. of water was added with stirring a solution of 78.7 g. of potassium permanganate and 250 g. of potassium hydroxide in 1.5 l. of water over 20 min. The temperature was not allowed to exceed 43°. Stirring was continued for an additional 45 min. The deep green solution was decolorized with excess sulfur dioxide. The mixture was filtered through Celite and the filtrate was extracted with 1 l. of ether. Drying and evaporation of this gave in two crops 11.11 g. of recovered acid II, m.p. 64–66°, undepressed when mixed with starting material.

Acidification of the aqueous layer with 1 l. of 6*M* sulfuric acid and extraction with three 70 ml. portions of ether led to an oil which crystallized on keeping for several hours. Recrystallization from hexane-benzene gave a first crop of 4.34 g. white crystals of III, m.p. 110–115° and a second crop of 1.23 g. (combined yield 16.9%), m.p. 102–110°.

*Anal.* Calcd. for $C_{10}H_{12}O_3$: O, 26.6. Found: O, 26.32.

*Tetracyclo[3:2:1:1$^{3,8}$:0$^{2,4}$]nonanone-6* (IV). The two crops of hydroxyacid were added to a solution of 9.4 g. of potassium dichromate and 4.3 ml. of 96% sulfuric acid in 50 ml. of water.[7] The mixture was warmed on the steam bath for 30 min., at which time no more carbon dioxide was evolved. The mixture was cooled and extracted with 100 ml. of hexane. The hexane layer was washed with 5% sodium hydroxide, water, 5% hydrochloric acid, water, and was then dried and distilled in a small Claisen flask. There was obtained 1.37 g. (33.0%) of ketone IV, b.p. 104° (19 mm.), $n_D^{25}$ 1.5225.

*Anal.* Calcd. for $C_9H_{10}O$: O, 11.9. Found: O, 11.97.

*6-Aminomethyl-tetracyclo[3:2:1:1$^{3,8}$:0$^{2,4}$]nonane* (V). To a stirred mixture of 15.5 g. of lithium aluminum hydride and 150 ml. of ether was added, over 30 min. with stirring and refluxing, a solution of 97.0 g. (0.670 mol.) of nitrile I in 150 ml. of ether. The mixture was stirred for 5 hr. and was then decomposed with 150 ml. of ice and water. A solution of 80 g. of sodium hydroxide in 250 ml. of water was added and the mixture was steam-distilled until 2 l. of distillate had been collected. The latter was extracted three times with 400 ml. portions of ether, which were dried over magnesium sulfate, evaporated and distilled through a spinning band column. This gave 27.5 g. (30.7%) of amine V, b.p. 109–112° (17 mm.), $n_D^{25}$ 1.5110, an intermediate fraction weighing 5.5 g., and 9.9 g. of recovered nitrile, b.p. 124–127° (17 mm.).

*Anal.* Calcd. for $C_{10}H_{15}N$: N, 9.39. Found: N, 9.43.

Fraction 1, 26.4 g. when mixed with a solution of *p*-toluenesulfonic acid monohydrate in 230 ml. of ethyl acetate, gave a crystalline precipitate weighing 31.2 g., m.p. 155–156°. Addition of hexane to the filtrate precipitated an additional 18.6 g., m.p. 138.0–138.5°. Similarly, from fraction 2 was obtained 2.5 g. of salt, m.p. 155–157°.

*Anal.* Calcd. for $C_{17}H_{23}NO_3S$: O, 14.93. Found: O, 14.91.

*Tetracyclo[3:3:1:1$^{3,9}$:0$^{2,4}$]decane-6-ol* (VI). The three crops of hydrotosylate were combined (0.163 mol.) and submitted to the Demjanov rearrangement according to Alder and Windemuth.[8] The product was distilled in a small spinning band column to give, after 4.2 g. of forerun, 7.5 g. (30.7%) of alcohol VI, b.p. 128° (22 mm.), $n_D^{25}$ 1.5240.

*Anal.* Calcd. for $C_{10}H_{14}O$: O, 10.65. Found: O, 11.04.

A vapor phase chromatogram showed the presence of three components. Peak 1 (3.4%) is an impurity, while peaks 2 (5.4%) and 3 (91.2%) appear from the oxidation results (see below) to be the isomeric alcohols.

*Tetracyclo[3:3:1:1$^{3,9}$:0$^{2,4}$]decane-6-one* (VII). Oxidation of alcohol VI gave ketone VII in 49.1% yield, b.p. 126–129° (20 mm.), $n_D^{25}$ 1.5138.

*Anal.* Calcd. for $C_{10}H_{12}O$: O, 10.8. Found: O, 11.42.

A vapor phase chromatogram showed the presence of two components in amounts of 5.8% and 94.2%.

(5) This compound was first prepared by Dr. H. E. Knipmeyer of the Central Research Department.

(6) J. Kenyon and M. C. R. Symons, *J. Chem. Soc.*, 2129 (1953).

(7) I am indebted to Prof. Harold Kwart for suggesting this procedure.

(8) K. Alder and E. Windemuth, *Ber.*, **71B**, 1939, 2404 (1938).

The major constituent of the ketone was established as the 6- rather than the 7-keto derivative by formation of a monobenzal derivative, no dibenzal derivative being isolated.

The ketone, 470 mg. (3.17 mmol.) was dissolved in 5 ml. of 5% potassium hydroxide in methanol[9] and 1.1 ml. of benzaldehyde was added. After 20 hr. the mixture was diluted with 11 ml. of water and extracted with 10 ml. of hexane. The hexane layer was dried over magnesium sulfate and concentrated. Excess benzaldehyde was removed by maintaining the residue at 60° (0.25 mm.) for several hours. The cooled semicrystalline residue was recrystallized twice from 3 ml. portions of hexane to give 0.151 g. (0.639 mmol., 20.1%) of pale yellow monobenzal derivative, m.p. 74.0–77.0°.

*Anal.* Calcd. for $C_{17}H_{16}O$: O, 6.77. Found: O, 6.63.

The infrared spectra of all compounds encountered in this investigation were measured routinely and supported the proposed structures. In particular, these nortricyclene derivatives absorbed at 12.3–12.4 microns, as first noted by Roberts and co-workers.[10]

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(10) J. D. Roberts, E. R. Trumbull, Jr., W. Bennett, and R. Armstrong, *J. Am. Chem. Soc.*, **72**, 3116 (1950).

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[CONTRIBUTION FROM THE "ASSIA" CHEMICAL LABORATORIES LTD.]

# α-Hydrazino- Acids. I. α-Hydrazinoaliphatic Acids and α-(1-Methylhydrazino)aliphatic Acids

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An improved method for the preparation of α-hydrazino-aliphatic acids is presented. The reaction is extended to the preparation of α-(1-methylhydrazino)-aliphatic acids, the structures of which are proved. The ultraviolet spectra are described.

Thiele[1] prepared α-hydrazinoisobutyric acid by the action of acetone semicarbazone on hydrocyanic acid. He also synthetized[2] α-hydrazinopropionic acid starting from acetaldehyde. Traube *et al.*[3] described the preparation of a series of α-hydrazino-aliphatic acids by the reduction of the isonitramino acids. Darapski *et al.*,[4] Bailey,[5] and Berger[6] obtained these compounds by the action of α-bromo acids on excess hydrazine in alcohol or in water.

Our interest in these compounds and their derivatives stems from their possible use as antimetabolites, especially in cancer chemotherapy.

We found the Darapski method convenient for the preparation of some of the higher members, as these hydrazino acids crystallize directly from the aqueous reaction mixture in fair yield. However, the preparation of the α-hydrazino acetic, propionic, and isobutyric acids is extremely cumbersome, requiring a Fischer esterification and a subsequent tedious saponification with barium hydroxide.

We found that by the use of ion exchange resins the isolation of these compounds is considerably simplified and the yields increased. When a weak anion exchanger is used, the addition of acetone is necessary to bind the hydrazine in the form of the ketazine, thus making the acid available for absorption on a weak anion exchanger (Method A).

The hydrazino acids are also absorbed on strong cation exchange resins, from which they can be eluted with ammonia and recovered by evaporation of the effluent (Method B). The yields by both methods are almost identical.

However, hydrazineacetic acid is not obtained directly in the highest purity by these methods. The preparation of the ester hydrochloride is still required, but saponification is conveniently carried out by a strong cation exchanger.

Berger[6] made a thorough study of the reaction between α-bromo-α-ethylbutyric acid and hydrazine and obtained α-hydroxy-α-ethylbutyric acid as the only product. He also failed to prepare the hydrazino diethylacetic acid by other methods and attributed the "non-formation" of this hydrazino acid to the influence of the tertiary carbon

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(2) J. Thiele and J. Bailey, *Ann.*, **303**, 85 (1898).

(3) W. Traube and G. G. Longinescu, *Ber.*, **29**, 673 (1896); W. Traube and E. Hoffa, *Ber.*, **29**, 2729 (1896); W. Traube and E. Hoffa, *Ber.*, **31**, 146 (1898).

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