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SYNTHESIS AND REACTIONS OF 1-METHYL-3-FORMYLINDAZOLE

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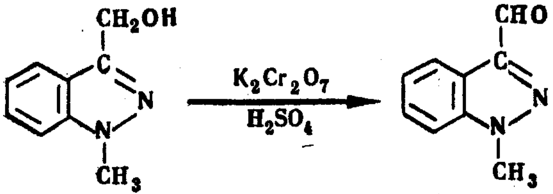
It is shown that oxidation of 1-methyl-3-hydroxymethylenediazole with a solution of potassium dichromate in dilute sulfuric acid gives a 30% yield of 1-methyl-3-formylindazole. Condensation products of the latter with malonic acid, nitromethane acetophenone, hippuric acid, hydantoin, thiohydantoin, and rhodanine are obtained. An oxime and a semicarbazone are prepared.

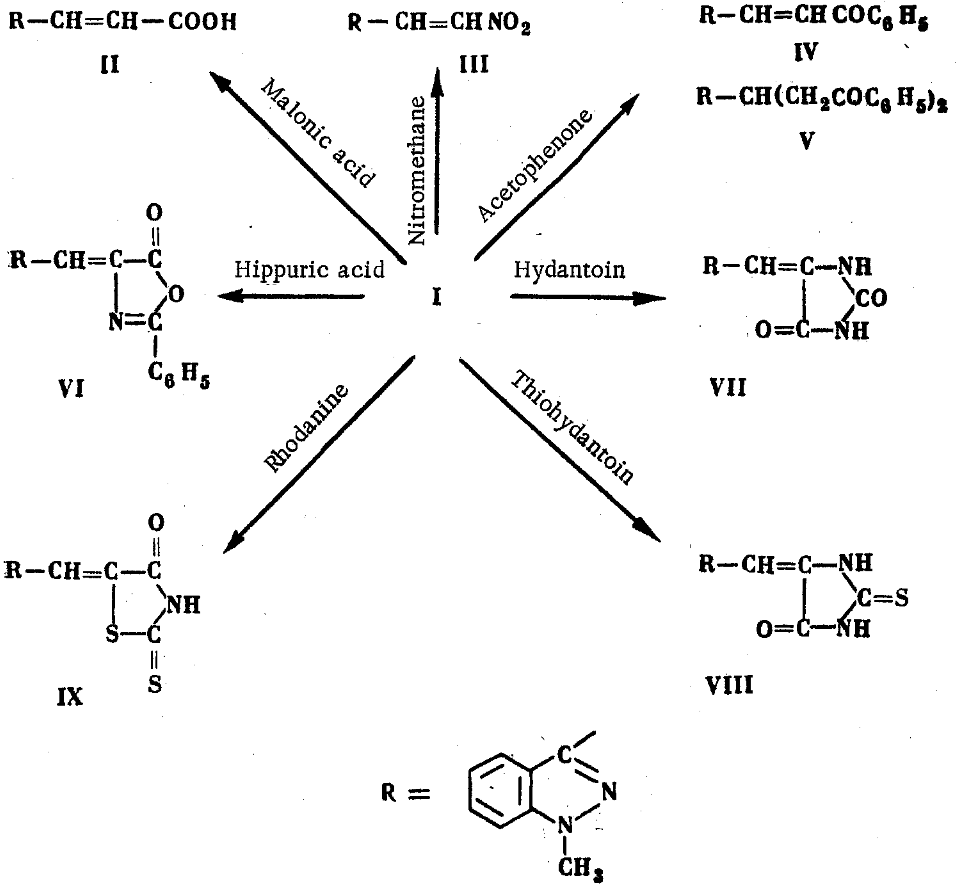
Up to the present, indazole aldehydes have not been described in the literature, meanwhile they are of interest for synthesizing a number of indazole derivatives.

An attempt has been made to synthesize 1-methyl-3-formylindazole (I) analogously to 1-phenyl-4-formylpyrazole [1], by the Sommelet reaction, but a positive result was not obtained. I was obtained in small amount by decomposing, using the method of [2, 3], 1-methylindazole-3-carboxylic acid hydrazide toluene sulphonylate. The best yield of the aldehyde I is obtained by rapid oxidation of a hot saturated aqueous solution of 1-methyl-3-hydroxymethylindazole with dilute chromic acid mixture.



I

After purification via the bisulfite compound, and recrystallizing from aqueous alcohol, I forms colorless crystals mp 47-48°. It gives an oxime, semicarbazone, and other condensation products characteristic of aldehydes.



1-Methyl-3-hydroxymethylindazole, the starting compound for synthesis of the aldehyde I, was prepared by reducing methyl 1-methylindazole-3-carboxylate with lithium aluminum hydride [4, 5].

Experimental

1-Methyl-3-formylindazole (I). 2 g (12 mmole) 1-methyl-3-hydroxymethylindazole was dissolved, with heating, in 50-60 ml water, 1 ml concentrated sulfuric acid added, followed by 1. 2 g (4. 1 mmole) potassium dichromate in 20 ml water. The mixture was rapidly cooled, and extracted three times with 25 ml ether. The ether was distilled off, the residue dissolved in 10 ml alcohol, a saturated solution of sodium bisulfite added, and the bisulfite compound of 1-methyl-3-formylindazole precipitated with ether. Decomposition of the bisulfite compound with potash solution gave 0. 6 g (30%) of a colorless substance mp 43-44°. Recrystallized from aqueous alcohol, it gave I, mp 47-48°. Found: N 17. 32, 17. 19%. Calculated for $C_9H_8N_2O$: N 17. 49%.

Oxime. Colorless needles mp 194-195° (from aqueous alcohol). Found: C 61. 97, 61. 78; H 5. 39, 5. 30%. Calculated for $C_9H_9N_3O$: C 61. 90; H 5. 15%.

Semicarbazone. Colorless plates, mp 204-205° (from alcohol). Found: N 32. 14, 32. 25%. Calculated for $C_{10}H_{11}N_5O$: N 32. 22%.

β-(1-Methylindazole-3)acrylic acid (II).

a) 0. 2 g (1. 3 mmole) 1-methyl-3-formylindazole and 0. 25 g (2. 4 mmole) malonic acid in 1 ml dry pyridine containing 1-2 drops of piperdine, were heated for 1 hr at 85°. Then the mixture was refluxed for 2 hr, cooled, and acidified with dilute hydrochloric acid until acid to congo red. The precipitate was filtered off, washed with water, and dried. Colorless crystals, mp 219-220° (from dilute acetic acid). Yield 0. 2 g (80%). Found: N 13. 91, 13. 95%. Calculated for $C_{11}H_{10}N_2O_2$: N 13. 88%.

b) 0. 2 g (1. 3 mmole) I, 0. 2 g (2 mmole) fused potassium acetate, and 0. 5 ml acetic anhydride were heated for 1 hr at 160°, then for 2 hr at 170°. Yield 0. 075 g (30%).

1-Methyl-3-(β-nitrovinyl)indazole (III). 0. 16 g (2. 6 mmole) nitromethane was added to a solution of 0. 2 g (5 mmole) sodium hydroxide in 3 ml water containing 1 ml methanol at 0°. Then 0. 32 g (2 mmole) 1-methyl-3-formylindazole in 4 ml methanol was added with good stirring, and the cold solution poured into cold dilute (1: 4) sulfuric acid. After 0. 5 hr the yellow precipitate was filtered off, washed with water, and dried. Yield 0. 25 g (64%). Yellow needles mp 102-103° (from methanol), soluble in chloroform, sparingly soluble in benzene and ether. Found: N 20. 82, 20. 75%. Calculated for $C_{10}H_9N_3O_2$: N 20. 68%.

1-Methyl-3-(β-nitro-α-phenylaminoethyl)indazole. A solution of 0. 25 g (1. 2 mmole) III, 0. 2 g (2. 2 mmole) aniline in 20 ml dry benzene was refluxed for 1 hr, after which the benzene was distilled off, and the solid residue washed with 5-6 ml dry ether. Yield 0. 28 g (77%). Colorless crystals mp 113-114° (from methanol). Found: C 64. 55, 64. 71; H 5. 22, 5. 26%. Calculated for $C_{16}H_{16}N_4O_2$: C 64. 85; H 5. 44%.

1-Methyl-3-(β-nitro-α-morpholinoethyl)indazole. A mixture of 0. 2 g (1 mmole) III, 0. 1 g (1. 2 mmole), morpholine and 2 ml dry benzene was refluxed for 0. 5 hr. The benzene was distilled off, the residue treated with 2-3 ml water to remove excess morpholine, and the solid residue filtered off. Yield 0. 25 g (86%), colorless crystals mp 94-95° (from alcohol), soluble in benzene and ether. Found: C 57. 73, 57. 86; H 6. 08, 6. 15%. Calculated for $C_{14}H_{18}N_4O_3$: C 57. 91; H 6. 24%.

1-Methyl-3-(β-benzoylvinyl)indazole (IV). 0. 5 ml 2% sodium hydroxide solution was added, with stirring, to a solution of 0. 32 g (2 mmole) 1-methyl-3-formylindazole and 0. 24 g (2 mmole) acetophenone in 1. 5 ml methanol. After 0. 5 hr the precipitate was filtered off, and washed with a few drops of methanol and ether. Yield 0. 45 g (80%), yellow needles mp 84-85° (from methanol), soluble in benzene, chloroform, and acetone, sparingly soluble in water. A concentrated sulfuric acid solution of the substance was orange. Found: N 10. 63, 10. 53%. Calculated for $C_{17}H_{14}N_2O$: N 10. 68%.

1-Methyl-3-[(bisphenacyl)methyl]indazole (V). 1 ml 20% potassium hydroxide solution was added to a solution of 0. 16 g (1 mmole) I and 0. 2 g (1. 7 mmole) acetophenone in 1. 5 ml alcohol, and the whole refluxed for 4-5 min. After standing for one hour, the precipitate was filtered off, washed with alcohol, and ether. Yield 0. 27 g (70%), colorless crystals mp 107-108° (from methanol), soluble in benzene, chloroform, sparingly soluble in water. Found: C 78. 50, 78. 52; H 5. 90, 5. 85%. Calculated for $C_{25}H_{22}N_2O_2$: C 78. 51; H 4. 79%.

2-Phenyl-4(1'-methyl-3'-indazolylmethylene)oxazolone-5 (VI). A mixture of 0. 2 g (1. 3 mmole) I, 0. 25 g (1. 6 mmole) hippuric acid, 0. 22 g (2. 7 mmole) fused sodium acetate, and 1 ml acetic anhydride was boiled for 1 min, after which the homogeneous products were heated for 30 min more, 10-15 ml water added, and the whole left overnight. The precipitate was filtered off, washed with water, and dried, yield 0. 3 g (79%). Yellow crystals mp 151-152° (from benzene-petroleum ether), sparingly soluble in alcohol, ether, insoluble in water. Found: C 70. 96, 70. 88; H 4. 79, 4. 77%. Calculated for $C_{18}H_{13}N_3O_2$: C 71. 00; H 4. 64%.

5-(1'-Methyl-3'-indazolylmethylene)hydantoin VII.

a) A mixture of 0. 16 g (1 mmole) I, 0. 15 g (1. 5 mmole) hydantoin, 5 ml alcohol, 0. 1 ml dry pyridine, and 1-2 drops of piperidine were refluxed for 5-6 hr. Then the products were evaporated to half volume, the precipitate formed filtered off, and washed with water, alcohol, and ether. The yield of VII was quantitative. Pale yellow needles, mp 284-285° (decomp., from methanol), slightly soluble in alcohol, chloroform, benzene, and ether, insoluble in water. Found: C 59. 60, 59. 55; H 3. 96, 3. 97%. Calculated for $C_{12}H_{10}N_4O_2$: C 59. 49; H 4. 16%.

b) A mixture of 0. 16 g (1 mmole) I, 0. 1 g (1 mmole) hydantoin, 0. 1 g (1. 2 mmole) anhydrous sodium acetate, and 1-2 ml glacial acetic acid was refluxed for 4-5 hr; yield 80%.

5-(1'-Methyl-3'-indazolylmethylene)thiohydantoin (VIII). 0. 18 g (1. 6 mmole) thiohydantoin was dissolved, with heating, in 1. 5 ml glacial acetic acid, the solution kept at 90-95°, and 0. 25 g I added, after which the mixture was refluxed for 20 min. On cooling the orange-red solution deposited fine red crystals, which were filtered off, washed with acetic acid, water, alcohol, and ether. Yield 0. 25 g (84%), orange needles mp 282-283° (from glacial acetic acid), slightly soluble in alcohol and chloroform, insoluble in benzene, ether, and water. Found: C 55. 69, 55. 73; H 4. 10, 4. 00%. Calculated for $C_{12}H_{10}N_4OS$: C 55. 79; H 3. 90%.

5-(1'-Methyl-3'-indazolylmethylene)rhodanine (IX). 0. 15 g rhodanine was heated on a water bath with 1. 5 ml glacial acetic acid, to effect solution, and 0. 2 g (1. 3 mmole) I added. After cooling, the precipitate was filtered off, and repeatedly washed with ether. Yield 0. 26 g (70%), yellow crystals mp 293-295° (decomp., from aqueous dioxane), slightly soluble in ether, benzene, chloroform, and insoluble in water. Found: C 52. 48, 52. 37; H 3. 54, 3. 39%. Calculated for $C_{12}H_9N_3OS_2$: C 52. 37; H 3. 29%.

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