Synthesis of Some Heterocyclic Derivatives of 3,5-Dinitro-*o*-toluic Acid

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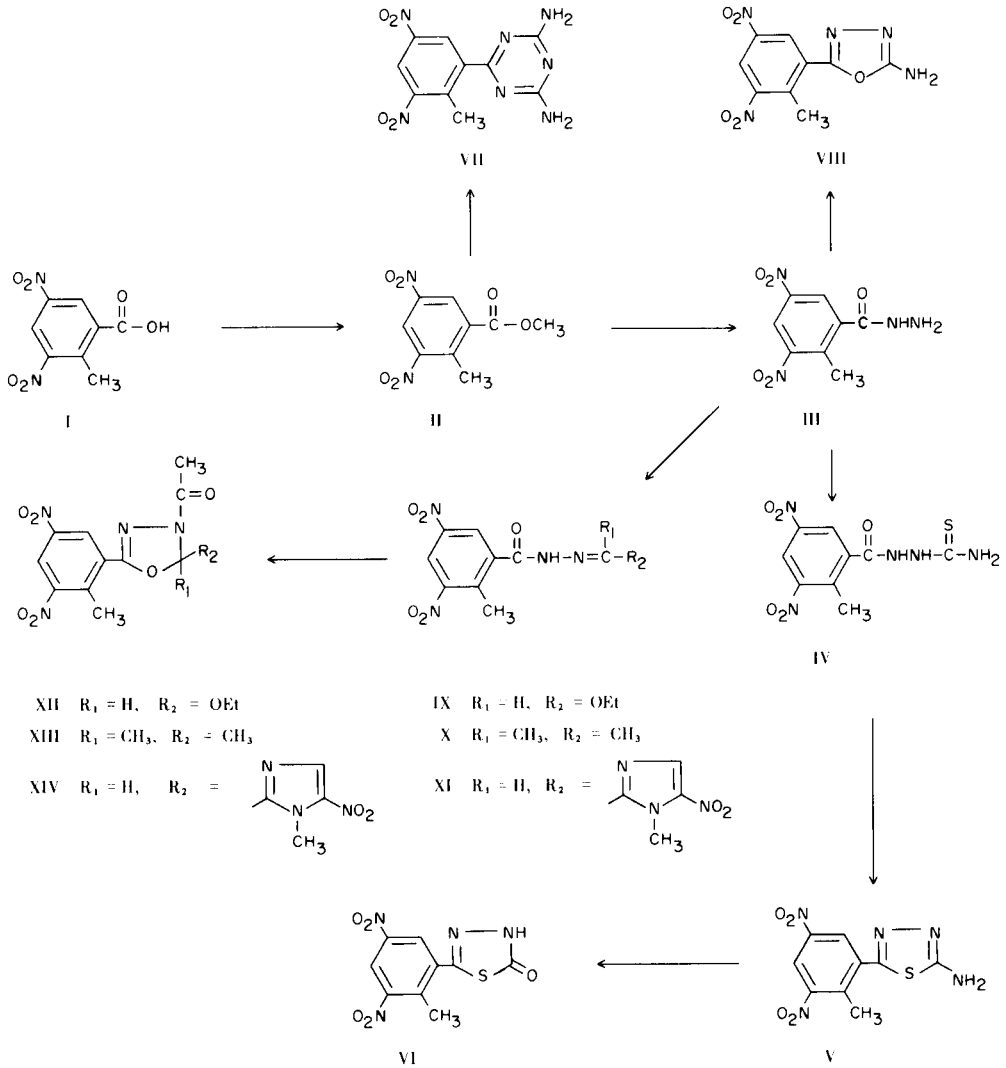
The synthesis of a series of heterocyclic derivatives of 3,5-dinitro-*o*-toluic acid is described.

In connection with a general study of the chemistry of heterocyclic compounds, we became interested in the replacement of an aromatic carboxyl group by a heterocyclic group. This paper describes the synthesis of some heterocyclic derivatives of 3,5-dinitro-*o*-toluic acid (I) (1).

Methyl 3,5-dinitro-*o*-toluate (II) (2), prepared by the esterification of I, was treated with hydrazine hydrate to give 3,5-dinitro-*o*-toluic acid hydrazide (III) (3).

Treatment of III with ammonium thiocyanate in acidic solution gave 3,5-dinitro-*o*-toluoyl thiosemicarbazide (IV)



which could be cyclized to 5-amino-2-(2-methyl-3,5-dinitrophenyl)-1,3,4-thiadiazole (V) by concentrated sulfuric acid (4).

When V is treated with nitrous acid followed by hydrolysis, 2-(2-methyl-3,5-dinitrophenyl)-1,3,4-thiadiazole-5-one (VI) is obtained in good yield. The infrared spectrum of the thiadiazolone has a strong absorption at 6.02 μ (Nujol mull) supporting the keto structure VI, at least in the solid state.

The condensation of esters of heterocyclic acids, with biguanide, provides a convenient route to diaminotriazines (5). Compound II reacts in this way to produce 2,4-diamino-6-(2-methyl-3,5-dinitrophenyl)-1,3,5-triazine (VII).

2-Amino-5-(2-methyl-3,5-dinitrophenyl)-1,3,4-oxadiazole (VIII) was prepared by refluxing a mixture of III and cyanogen bromide (6) in methanol, although in low yield.

When III is allowed to react with triethyl orthoformate, acetone, and 1-methyl-5-nitroimidazole-2-carboxaldehyde (7), the hydrazones are formed (IX-XI).

The reaction of the hydrazones with acetic anhydride (8) yielded 4-acetyl-5-ethoxy-2-(2-methyl-3,5-dinitrophenyl)-Δ^2-1,3,4-oxadiazoline (XII), 4-acetyl-5,5-dimethyl-2-(2-methyl-3,5-dinitrophenyl)-Δ^2-1,3,4-oxadiazoline (XIII), and 4-acetyl-5-(1-methyl-5-nitroimidazolo)-2-(2-methyl-3,5-dinitrophenyl)-Δ^2-1,3,4-oxadiazoline (XIV), respectively.

EXPERIMENTAL

All melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were obtained as nujol mulls using a Perkin-Elmer Infracord spectrophotometer. The nuclear magnetic resonance spectra were obtained with a Varian A-60A spectrometer.

Methyl 3,5-Dinitro-*o*-toluate (II).

3,5-Dinitro-*o*-toluic acid (I) (45.2 g., 0.2 mole) was heated under reflux with dry methanol (200 ml.) and concentrated sulphuric acid (10 ml.) for 24 hours. The colorless needles which separated on cooling were recrystallized from methanol to yield 42 g. (88%) of methyl 3,5-dinitro-*o*-toluate (II), m.p. 71-72° (lit. (2), m.p. 73-74°).

Anal. Calcd. for $C_9H_8N_2O_6$: C, 45.01; H, 3.36; N, 11.66. Found: C, 44.78; H, 3.45; N, 11.38.

3,5-Dinitro-*o*-toluic Acid Hydrazide (III).

Compound II (24 g., 0.1 mole) and 6.5 ml. of hydrazine hydrate (85%) were dissolved in 100 ml. of ethanol and heated on a steam bath for 4 hours. The colorless prisms which separated on cooling were recrystallized from methanol to yield 11 g. (45.8%) of 3,5-dinitro-*o*-toluic acid hydrazide (III), m.p. 175-176° (lit. (3), 177.6-178.2°).

Anal. Calcd. for $C_8H_8N_4O_5$: C, 40.01; H, 3.36; N, 23.33. Found: C, 39.90; H, 3.31; N, 23.20.

3,5-Dinitro-*o*-toluoylthiosemicarbazide (IV).

A mixture of III (2.4 g., 0.01 mole), ammonium thiocyanate (2.3 g., 0.03 mole), concentrated hydrochloric acid (4 ml.) and 200 ml. of ethanol was heated under reflux for 22 hours. The solvent was distilled and water added. The solid residue was crystallized from aqueous ethanol to obtain 1.7 g. (57%) of 3,5-dinitro-*o*-toluoyl thiosemicarbazide, m.p. 218-219°; ir λ max (Nujol) 2.90, 3.00, 3.10, 3.20, 6.00, 6.55, and 7.45 μ.

Anal. Calcd. for $C_9H_9N_5SO_5$: C, 36.13; H, 3.03; N, 23.41; S, 10.70. Found: C, 35.90; H, 3.18; N, 23.31; S, 10.63.

5-Amino-2-(2-methyl-3,5-dinitrophenyl)-1,3,4-thiadiazole (V).

A mixture of 600 mg. (0.002 mole) of IV and 6 ml. of concentrated sulphuric acid was heated 1 hour on a steam bath. The solution was poured onto cracked ice and precipitated product was then crystallized from ethanol giving 310 mg. of white material, m.p. 225-227°; ir λ max (Nujol) 2.96, 3.05, 3.16, 3.22, 6.55, and 7.45 μ. An additional 130 mg. was obtained by neutralizing the sulphuric acid solution. The total yield was 78%.

Anal. Calcd. for $C_9H_7N_5SO_4$: C, 38.44; H, 2.51; N, 24.91; S, 11.38. Found: C, 38.66; H, 2.62; N, 25.39; S, 11.59.

2-(2-Methyl-3,5-dinitrophenyl)-1,3,4-thiadiazole-5-one (VI).

Compound V (1.8 g., 0.0064 mole) in concentrated sulphuric acid (30 ml.) was treated with sodium nitrite (2 g.) in water (6 ml.) over 15 minutes at 10 ~ 15°. After ½ hour, 20 ml. of 50% glacial acetic acid was added and the mixture stirred at room temperature for 24 hours. The mixture was poured onto cracked ice and the solid which separated was collected, washed with water and recrystallized from aqueous methanol to obtain 1.35 g. (75%) of VI, m.p. 180-182°; ir λ max (Nujol) 3.15, 3.22, 6.02, 6.56 and 7.45 μ.

Anal. Calcd. for $C_9H_6N_4SO_5$: C, 38.31; H, 2.14; N, 19.86; S, 11.34. Found: C, 37.96; H, 2.32; N, 20.18; S, 11.35.

2,4-Diamino-6-(2-methyl-3,5-dinitrophenyl)-1,3,5-triazine (VII).

To a stirred solution of II (2.4 g., 0.01 mole) in 120 ml. of absolute methanol is added a solution of biguanide (1.01 g., 0.01 mole) in 20 ml. of absolute methanol. Reaction started immediately, producing a dark brown solution. After stirring for 2 days at room temperature, any undissolved material was filtered and the filtrate was evaporated under reduced pressure and the water added. The tan-colored solid is collected, washed with water, finally triturated with acetone and dried. The yield is 460 mg. (16% of theory), melting with decomposition at 297-299°; ir λ max (Nujol) 2.85, 2.90, 3.00, 3.15, 6.00, 6.12, 6.47, and 7.40 μ.

Anal. Calcd. for $C_{10}H_9N_7O_4$: C, 41.21; H, 3.09; N, 33.70. Found: C, 41.35; H, 3.13; N, 33.58.

2-Amino-5-(2-methyl-3,5-dinitrophenyl)-1,3,4-oxadiazole (VIII).

Compound III (2.4 g., 0.01 mole) and cyanogen bromide (1.56 g., 0.015 mole) were heated together under reflux in 100 ml. of methanol for 18 hours. The reaction mixture was concentrated and the product precipitated by the addition of water. Crystallization from acetonitrile gave a bright yellow solid, m.p. 210 ~ 213°, weighing 350 mg. (13%); ir λ max (Nujol) 2.85, 2.98, 3.05, 3.20, 6.00, 6.52, and 7.42 μ.

Anal. Calcd. for $C_9H_7N_5O_5$: C, 40.76; H, 2.66; N, 26.41. Found: C, 40.95; H, 2.73; N, 26.69.

3,5-Dinitro-*o*-toluic Acid Ethoxymethylenehydrazide (IX).

Compound III (2.4 g., 0.01 mole) and 20 ml. of triethyl orthoformate were heated under reflux for 18 hours. The products which separated on cooling were recrystallized from ethyl acetate-*n*-hexane to give 1.7 g. (58%) of IX, m.p. 168-170°; ir λ max (Nujol) 3.08, 3.18, 6.01, 6.57, and 7.45 μ; nmr spectrum

in deuteriochloroform, τ 3.61 (*s*, N=CH-), 5.78 (*q*, $-OCH_2$), 7.40 (*s*, aromatic CH_3), 8.59 (*t*, $-CH_3$).

Anal. Calcd. for $C_{11}H_{12}N_4O_6$: C, 44.60; H, 4.08; N, 18.91. Found: C, 44.70; H, 4.14; N, 19.05.

3,5-Dinitro-*o*-toluic Acid Isopropylidenehydrazide (X).

This was prepared in the same way as IX above using acetone (50 ml.). In this way, a quantitative yield of X was obtained. Crystallization from acetone gave a light tan solid, m.p. 217-219°.

Anal. Calcd. for $C_{11}H_{12}N_4O_5$: C, 47.15; H, 4.32; N, 19.99. Found: C, 46.96; H, 4.41; N, 19.83.

3,5-Dinitro-*o*-toluic Acid-[2-(1-methyl-5-nitroimidazolo)methyl]-hydrazide (XI).

This was prepared as above for IX using 1-methyl-5-nitroimidazole-2-carboxaldehyde (1.55 g., 0.01 mole) (7) and 50 ml. of ethanol. The mixture was heated for 18 hours under reflux. Cooling gave 3.2 g. (85%) of XI, m.p. 220°.

Anal. Calcd. for $C_{13}H_{11}N_7O_7$: C, 41.36; H, 2.94; N, 26.00. Found: C, 41.96; H, 3.22; N, 25.81.

4-Acetyl-5-ethoxy-2-(2-methyl-3,5-dinitrophenyl)-Δ^2-1,3,4-oxadiazoline (XII).

A mixture of IX (1.3 g., 0.0044 mole) and 20 ml. of acetic anhydride was refluxed for 1.5 hours. The excess acetic anhydride was removed *in vacuo* and the residue poured onto cracked ice. The solid was recrystallized from aqueous ethanol to give 0.45 g. (30%) of XII, m.p. 148-150°; ir λ max (Nujol) 5.95, 6.50, and 7.38 μ; nmr spectrum in deuteriochloroform, τ 2.92 (*s*, 1H), 6.10 (*q*, $-OCH_2$), 7.18 (*s*, aromatic CH_3), 7.62 (*s*, $>NCOCH_3$), 8.68 (*t*, CH_3).

Anal. Calcd. for $C_{13}H_{14}N_4O_7$: C, 46.16; H, 4.17; N, 16.56. Found: C, 46.35; H, 4.13; N, 16.93.

4-Acetyl-5,5-dimethyl-2-(2-methyl-3,5-dinitrophenyl)-Δ^2-1,3,4-oxadiazoline (XIII).

This compound was prepared in a manner similar to the synthesis of XII. From 2.52 g. (0.009 mole) of X and 30 ml. of acetic anhydride, 1.90 g. (65.6%) of XIII, m.p. 154-156° was obtained; ir λ max (Nujol) 6.04, 6.52, and 7.45 μ; nmr spectrum in deuteriochloroform, τ 7.18 (*s*, aromatic CH_3), 7.67 (*s*, $NCOCH_3$), 8.07 (*s*, $2CH_3$).

Anal. Calcd. for $C_{13}H_{14}N_4O_6$: C, 48.45; H, 4.38; N, 17.38. Found: C, 48.25; H, 4.40; N, 17.39.

4-Acetyl-5-(1-methyl-5-nitroimidazolo)-2-(2-methyl-3,5-dinitrophenyl)-Δ^2-1,3,4-oxadiazoline (XIV).

Following the procedure for the synthesis of XII, 1.89 g. (0.005 mole) of XI and acetic anhydride (25 ml.) gave 1.85 g. (88%) of XIV, m.p. 171-174°; ir λ max (Nujol) 6.00, 6.50, and 7.24 μ; nmr spectrum in deuteriochloroform, τ 2.02 (*s*-, vinyl H), 2.81 (*s*, 1H), 5.75 (*s*, $-NCH_3$), 7.13 (*s*, aromatic CH_3), 7.62 (*s*, $NCOCH_3$).

Anal. Calcd. for $C_{15}H_{13}N_7O_8$: C, 42.90; H, 3.12; N, 23.38. Found: C, 42.88;. H, 3.23; N, 23.36.

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