Synthesis and Reactions of 3-Carboxytropolone. Conversion to Heterocycle-fused Troponoid Compounds

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Received December 5, 1990

The haloform reaction of 3-acetyltropolone (**1**) afforded 3-carboxytropolone (**2**) which was treated with diazomethane to give 2-methoxy-3-methoxycarbonyltropone (**3a**) and 2-methoxy-7-methoxycarbonyltropone (**3b**). The tropolone **2** reacted with hydrazine to afford 2-hydrazino-3-hydrazinocarbonyltropone (**10**) or 2-hydrazinotropone (**11**), depending on the reaction time. The reaction of **2** with phenylhydrazine produced 3-hydroxy-1-phenyl-1,8-dihydrocycloheptapyrazol-8-one (**14**). The treatment of 2-methoxy-3-methoxycarbonyltropone (**3a**) with hydrazine or phenylhydrazine gave cyclization products **12** and **15**, respectively. The reaction of 2-methoxy-7-methoxycarbonyltropone (**3b**) with hydrazine, phenylhydrazine, or methylhydrazine gave 2-hydrazino- (**13**), 2-(2-phenylhydrazino)- (**16**), and 2-(2-methylhydrazino)-7-methoxycarbonyltropone (**17**), respectively.

J. Heterocyclic Chem., **28**, 717 (1991).

In the past ten years, our research work has been focused on the synthesis of heterocycle-fused tropoid compounds from 3-acetyltropolone [1-3]. This tropolone is very useful starting material because it has a reactive acetyl group at the 3-position and exists partly in tautomeric β-diketo form.

Now, 3-carboxytropolone was derived from 3-acetyltropolone by application of haloform reaction. It is thought that this compound is a new synthon to heterocycle-fused troponoid compounds. This paper deals with the synthesis and several reactions of 3-carboxytropolone.

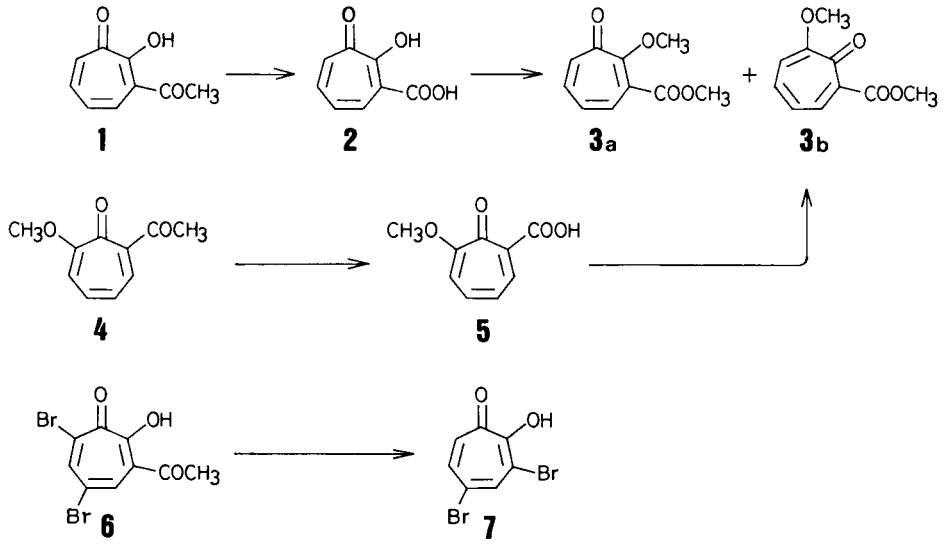
Results and Discussion.

Synthesis.

Although 3-carboxytropolone (**2**) had been obtained by alkaline [4] or acidic hydrolysis [5] of 3-cyanotropolone and by iodine-catalyzed dehydrogenation of diethyl cycloheptane-2,3-dione-1,4-dicarboxylate [6], its reaction has been relatively unknown.

Now, application of the haloforom reaction to 3-acetyltropolone (**1**) gave readily 3-carboxytropolone (**2**) in a good yield (83%). When the tropolone **2** was treated with diazomethane, both the hydroxyl and carboxyl groups were methylated to afford two isomeric compounds, 2-methoxy-3-methoxycarbonyltropone (**3a**) and 2-methoxy-7-methoxycarbonyltropone (**3b**). The haloform reaction of 7-acetyl-2-methoxytropone (**4**) also afforded 7-carboxy-2-methoxytropone (**5**) which gave the methyl ether **3b** with

Scheme 1

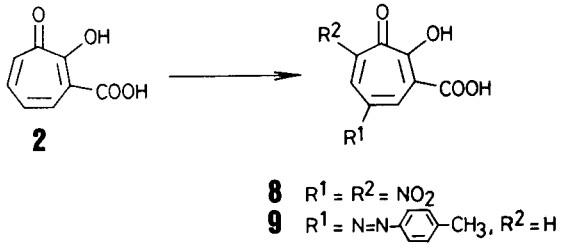


diazomethane. On the other hand, the treatment of 3-acetyl-5,7-dibromotropolone (**6**) with hypochlorite solution gave 3,5-dibromotropolone (**7**). It is though that this reaction proceeded by haloform reaction of the acetyl group followed by elimination of the resulted carboxyl group.

Electrophilic Substitution Reactions.

Although there is little known of the reaction of 3-carboxytropolone (**2**), it is known that the reaction with bromine gave 3,5,7-tribromotropolone [7]. Then, as typical electrophilic reactions, nitration and azo-coupling reactions were carried out to give respectively 3-carboxy-5,7-dinitrotropolone (**8**) and 3-carboxy-5-(4-methylphenylazo)-tropolone (**9**). This chemical behavior is similar to that of other tropolones.

Scheme 2



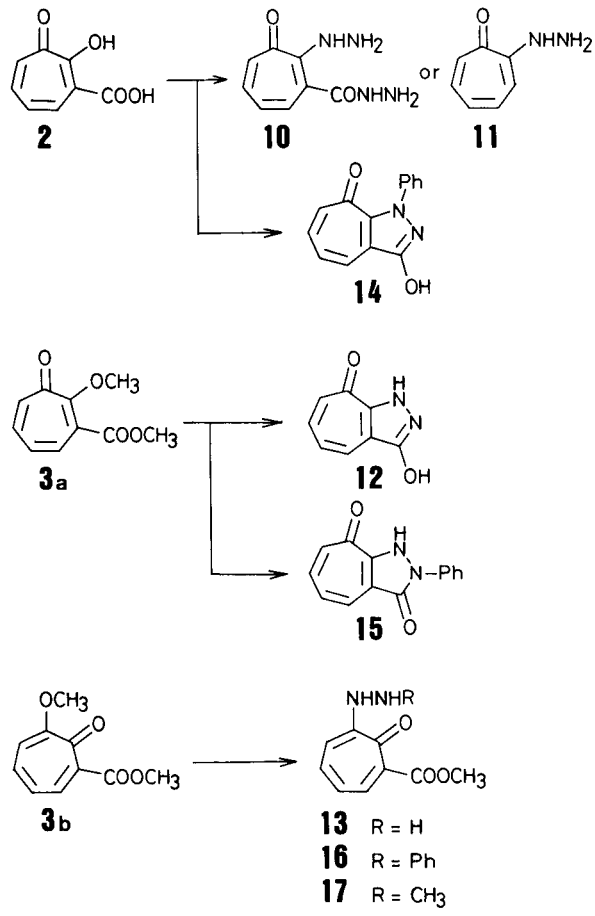
Reactions with Hydrazines.

When as ethanolic solution of 3-carboxytropolone (**2**) and hydrazine hydrate was heated for a few minutes, the solution deposited 2-hydrazino-3-hydrazinocarbonyltropone (**10**). The prolonged reaction (2 hours) caused elimination of the hydrazinocarbonyl group and gave 2-hydrazinotropone (**11**). The reaction of 2-methoxy-3-methoxycarbonyltropone (**3a**) with hydrazine gave 3-hydroxy-1,8-dihydrocycloheptapyrazol-8-one (**12**) as a cyclization product, while the reaction of 2-methoxy-7-methoxycarbonyltropone (**3b**) gave no cyclization product and afforded 2-hydrazino-7-methoxycarbonyltropone (**13**).

On the other hand, a solution of 3-carboxytropolone (**2**) and phenylhydrazine was refluxed to afford a cyclization product, 3-hydroxy-1-phenyl-1,8-dihydrocycloheptapyrazol-8-one (**14**). The reaction of 2-methoxy-3-methoxycarbonyltropolone (**3a**) with phenylhydrazine gave 2-phenyl-1,2,3,8-tetrahydrocycloheptapyrazole-3,8-dione (**15**). The treatment of 2-methoxy-7-methoxycarbonyltropone (**3b**) with phenylhydrazine gave 7-methoxycarbonyl-2-(2-phenylhydrazino)tropone (**16**).

The structures of the isomeric products **14** and **15** were established by their elemental analyses ($C_{14}H_{10}N_2O_2$) and spectral data. The ir and ^1H nmr spectral data (ν max 3425, 1598 cm^{-1} and δ 6.75-7.55) of the product **14** are different from those (ν max 1690, 1627 cm^{-1} and δ 6.95-8.15) of the product **15** and more similar to those (ν max 3284, 1612 cm^{-1} and δ 6.6-7.9) of 3-hydroxy-1,8-dihydrocycloheptapyrazol-8-one (**12**). These structures are also supported by the following: As the tropolone nucleus of **2** is less reactive, phenylhydrazine attacked the carbonyl group. On the other hand, the tropone nucleus of **3a** is more reactive than the methoxycarbonyl group, phenylhydrazine reacted at the 2-position bearing the methoxyl group to afford **15**. This difference in the reactivities of the tropone ring and the methoxycarbonyl side-chain was observed in the reactions of 2-methoxy-7-methoxycarbonyltropone (**3b**) with hydrazines.

Scheme 3



Finally, 3-carboxytropolone (**2**) and 2-methoxy-3-methoxycarbonyltropone (**3a**) were treated with methylhydrazine to give complex mixture, hence characterization was not performed. The reaction of 2-methoxy-7-methoxycarbonyltropone (**3b**) with methylhydrazine afforded a single product, 7-methoxycarbonyl-2-(2-methylhydrazino)tropone (**17**) in 68% yield.

EXPERIMENTAL

Measurements.

The melting points were uncorrected. The ir spectra were taken on a Perkin Elmer 1730 spectrophotometer. The ^{1}H nmr spectra were measured with a JEOL JNM-PMX 60 spectrometer.

Haloform Reaction of 3-Acetyltropolone (**1**).

To a stirred mixture of 40% sodium hydroxide solution (1 ml) and sodium hypochlorite solution, prepared from chlorine gas and sodium hydroxide (1.84 g) in ice-water (15 ml), was added a solution of 3-acetyltropolone (**1**) (820 mg, 5 mmoles) in 6% sodium hydroxide solution (3 ml) with cooling in an ice-water bath. The reaction mixture was stirred for 1 hour at 15°. The mixture was added to a solution of sodium hydrogensulfite (500 mg) in water (2 ml) to remove an excess of sodium hypochlorite. The mixture was carefully made slightly acidic with concentrated hydrochloric acid. The precipitate was collected and dissolved in hot water, the solution was made acidic with concentrated hydrochloric acid to give crystals which were recrystallized from methanol to give 3-carboxytropolone (**2**) as yellow needles in a yield of 690 mg (83%), mp 217-218° (lit [5] 217-218°); ir (potassium bromide): ν max 3212 (OH), 1718 (COOH), 1585 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 7.05-7.8 (3H, m), 8.15 (1H, d, J = 10 Hz, H-4), 10.3 (2H, br, OH).

Reaction of 3-Carboxytropolone (**2**) with Diazomethane.

An ethereal solution of diazomethane was slowly added to a suspended solution of 3-carboxytropolone (**2**) (5 g, 30 mmoles) in chloroform. The mixture was allowed to stand until the resulting mixture gave no coloration with iron(III) chloride solution. After removal of the solvent under reduced pressure, the residue was chromatographed on a silica gel column by using ethyl acetate as an eluant.

The former fractions gave 2-methoxy-3-methoxycarbonyltropone (**3a**) as an oil in a yield of 2.3 g (40%); ir (neat): ν max 1736 (COOR), 1608 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 3.71 (6H, s, OCH_3 x 2), 6.5-7.8 (4H, m).

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.70; H, 5.20.

The latter fractions were combined and recrystallized from chloroform-petroleum ether to give 2-methoxy-7-methoxycarbonyltropone (**3b**) as colorless needles in a yield of 2.9 g (50%), mp 70°; ir (potassium bromide): ν max 1729 (COOR), 1619 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 3.87 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 7.75-7.15 (3H, m), 7.53 (1H, d, J = 8 Hz, H-6).

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.75; H, 5.00.

Haloform Reaction of 7-Acetyl-2-methoxytropone (**4**).

To a stirred basic solution of sodium hypochlorite, prepared as described above, was added dropwise a solution of 7-acetyl-2-methoxytropone (**4**) (890 mg, 5 mmoles) in chloroform (1 ml) with cooling in an ice-water bath. To the mixture, dioxane (5 ml) was slowly added. After stirring for 1 hour, to the mixture was added a solution of sodium hydrogensulfite (500 mg) in water (2 ml) to remove an excess of sodium hypochlorite. The mixture was made slightly acidic with 6*M* hydrochloric acid and extracted with chloroform. The extract was washed twice with water, dried over sodium sulfate, and evaporated. The residue was recrystallized from chloroform to give 7-carboxy-2-methoxytropone (**5**) in a yield of 300 mg (33%), mp 210°; ir (potassium bromide): ν max 1733 (COOH), 1602 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 3.93 (3H, s, OCH_3), 7.0-7.25 (2H, m), 7.48 (1H, d, J = 8 Hz, H-5), 8.12 (1H, d, J = 8 Hz, H-6).

Anal. Calcd. for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 60.15; H, 4.20.

Reaction of 7-Carboxy-2-methoxytropone (**5**) with diazomethane.

To a solution of 7-carboxy-2-methoxytropone (**5**) (90 mg, 0.5 mmole) in chloroform (20 ml) added a ethereal diazomethane solution. After standing overnight, the evaporation residue was recrystallized from methanol to afford 2-methoxy-7-methoxycarbonyltropone (**3b**) in a yield of 85 mg (88%).

Haloform Reaction of 3-Acetyl-5,7-dibromotropolone (**6**).

A mixture of 3-acetyl-5,7-dibromotropolone (**6**) (1.61 g, 5 mmoles) and 6% sodium hydroxide solution (3 ml) in dioxane (10 ml) was added to a stirred solution of basic sodium hypochlorite solution, prepared as mentioned above. After stirring for 2 hours, the mixture was worked up, as mentioned above. The collected crystals were recrystallized from benzene-petroleum ether to give 3,5-dibromotropolone (**7**) in a yield of 420 mg (30%), mp 153° (lit [8] 152.5-153°); ir (potassium bromide): ν max 1614 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 8.05 (1H, d, J = 2 Hz, H-4), 8.3-8.65 (3H, m).

Nitration of 3-Carboxytropolone (**2**).

A mixture of concentrated nitric acid (1 ml) and acetic acid (1 ml) was added dropwise into an ice-water cooled solution of 3-carboxytropolone (2) (160 mg, 1 mmole) in acetic acid (1 ml). After stirring for 2 hours, the mixture was diluted with water (10 ml) and extracted with ethyl acetate. The evaporation residue from the extract was recrystallized form chloroform-methanol to give 3-carboxy-5,7-dinitrotropolone (**8**) in a yield of 20 mg (8.4%), mp 238°; ir (potassium bromide): ν max 3167 (OH), 1709 (COOH), 1619 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 8.87 (1H, d, J = 2 Hz, H-4), 9.27 (1H, d, J = 2 Hz, H-6).

Anal. Calcd. for $C_8H_3N_2O_8$: C, 37.51; H, 1.57; N, 10.95. Found: C, 37.30; H, 1.50; N, 11.00.

Azo-coupling Reaction of 3-Carboxytropolone (**2**).

To a stirred ice-cooled solution of 3-carboxytropolone (**2**) (160 mg, 1 mmole) in pyridine (5 ml) was added dropwise *p*-methoxybenzenediazonium chloride solution, prepared from *p*-toluidine (150 mg). After stirring for 2 hours, the mixture was diluted with water to deposit a precipitate which was collected and recrystallized from 95% ethanol to give 3-carboxy-5-(4-methylphenylazo)-tropolone (**9**) as red prisms in a yield of 145 mg (50%), mp 201-202°; ir (potassium bromide): ν max 1687 (COOH), 1620 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 2.37 (3H, s, CH_3), 7.27 (2H, d, J = 8 Hz, H-3',5'), 7.63 (2H, d, J = 8 Hz, H-2', 6'), 7.85-8.0 (1H, m, H-4), 8.32 (1H, d, J = 8 Hz, H-7), 8.70 (1H, d, J = 8 Hz, H-6), 9.3 (2H, br, OH x 2).

Anal. Calcd. for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.26; N, 9.86. Found: C, 63.60; H, 4.52; N, 10.10.

Reaction of 3-Carboxytropolone (**2**) with Hydrazine.

a) A mixture of 3-carboxytropolone (**2**) (250 mg, 1.5 mmoles) and hydrazine hydrate (0.1 ml) in absolute ethanol (10 ml) was refluxed for a few minutes. A precipitate was collected and

recrystallized from ethanol to give 2-hydrazino-3-hydrazinocarbonyltropone (**10**) in a yield of 150 mg (55%), mp 140°; ir (potassium bromide): ν max 3262 (NH), 1651 (CONH), 1616 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 5.1 (6H, br, NH x 2 + NH_2 x 2), 6.2-7.2 (3H, m), 8.2 (1H, d, J = 10 Hz, H-4).

Anal. Calcd. for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.68; H, 5.23; N, 28.88.

b) A mixture of 3-carboxytropolone (**2**) (165 mg, 1 mmole) and hydrazine hydrate (0.1 ml) in absolute ethanol (10 ml) was refluxed for 2 hours. The reaction mixture was diluted with water and extracted with chloroform. The evaporation residue was recrystallized from benzene to afford 2-hydrazinotropone (**11**) in a yield of 70 mg (43%), mp 92-93° (lit [9] 95-96°).

Reaction of 2-Methoxy-3-methoxycarbonyltropone (**3a**) with Hydrazine.

To a stirred solution of 2-methoxy-3-methoxycarbonyltropone (**3a**) (380 mg, 2 mmoles) in ethanol (10 ml) was added hydrazine hydrate (0.1 ml). After stirring for 30 minutes, a precipitate was collected and recrystallized form ethanol-benzene to afford 3-hydroxy-1,8-dihydrocycloheptapyrazol-8-one (**12**) in a yield of 200 mg (50%), mp 280°; ir (potassium bromide): ν 3284 (OH), 1612 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 6.6-7.9 (m).

Anal. Calcd. for $C_8H_6N_2O_2.2H_2O$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.19; H, 5.30; N, 14.34.

Reaction of 2-Methoxy-7-methoxycarbonyltropone (**3b**) with Hydrazine.

To a stirred solution of 2-methoxy-7-methoxycarbonyltropone (**3b**) (380 mg, 2 mmoles) in ethanol (10 ml) was added hydrazine hydrate (0.1 ml). After a few minutes, a precipitate was collected and recrystallized from ethanol to afford 2-hydrazino-7-methoxycarbonyltropone (**13**) in a yield of 350 mg (90%), mp 174°; ir (potassium bromide): ν max 3328 (NH), 1698 (COOR), 1646 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 3.8 (3H, br, NH x 3), 3.85 (3H, s, OCH_3), 6.6 (1H, dd, J = 8, 2 Hz, H-6), 7.2-7.8 (3H, m).

Anal. Calcd. for $C_9H_{10}N_2O_3$: C, 55.55; H, 5.19; N, 14.43. Found: C, 55.35; H, 5.30; N, 14.80.

Reaction of 3-Carboxytropolone (**2**) with Phenylhydrazine.

A solution of 3-carboxytropolone (**2**) (250 mg, 1.5 mmoles) and phenylhydrazine (320 mg, 3 mmoles) in methanol (10 ml) was heated for 2 hours at 75°. The mixture was diluted with water, acidified with hydrochloric acid, and extracted with chloroform. After removal of the solvent, the residue was chromatographed on a GF 254 plate (20 x 20 cm) with chloroform to give yellow crystals which were recrystallized form benzene-petroleum ether to afford 3-hydroxy-1-phenyl-1,8-dihydrocycloheptapyrazol-8-one (**14**) in a yield of 160 mg (45%), mp 147-148°; ir (potassium bromide): ν max 3245 (OH), 1598 cm^{-1} (C=O); uv (methanol): λ max 335, 397 nm; ^1H nmr (deuteriochloroform): δ 6.75-7.55 (m).

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.34; H, 4.51; N, 11.86.

Reaction of 2-Methoxy-3-methoxycarbonyltropone (**3a**) with Phenylhydrazine.

A solution of 2-methoxy-3-methoxycarbonyltropone (**3a**) (380 mg, 2 mmoles) and phenylhydrazine (220 mg, 2 mmoles) in methanol (10 ml) was refluxed for 2 hours. After removal of the solvent, the residue was recrystallized from benzene-methanol to afford 2-phenyl-1,2,3,8-tetrahydrocycloheptapyrazole-3,8-dione (**15**) in a yield of 140 mg (30%), mp 230-231°; ir (potassium bromide): ν 1690 (C=O), 1617 cm^{-1} (C=O); uv (methanol): λ max 339 nm; ^1H nmr (deuteriochloroform): δ 6.95-8.15 (m).

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.95; H, 4.16; N, 11.60.

Reaction of 2-Methoxy-7-methoxycarbonyltropone (**3b**) with Phenylhydrazine.

A solution of 2-methoxy-7-methoxycarbonyltropone (**3b**) (385 mg, 2 mmoles) and phenylhydrazine (432 mg, 4 mmoles) in methanol (10 ml) was refluxed for 2 hours. After removal of the solvent, the residue was recrystallized from ethanol to afford 7-methoxycarbonyl-2-(2-phenylhydrazino)tropone (**16**) in a yield of 407 mg (75%), mp 147-149°; ir (chloroform): ν 3332 (NH), 1728 (COOR), 1603 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 3.91 (3H, s, OCH_3), 6.32 (1H, s, NH), 6.15-7.4 (9H, m), 7.59 (1H, d, J = 9 Hz, H-3), 8.73 (1H, br, NH).

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.81; H, 4.99; N, 10.33.

Reaction of 2-Methoxy-7-methoxycarbonyltropone (**3b**) with Methylhydrazine.

A solution of 2-methoxy-7-methoxycarbonyltropone (**3b**) (390 mg, 2 mmoles) and methylhydrazine (185 mg, 4 mmoles) in methanol (10 ml) was refluxed for 2 hours. After removal of the solvent, the residue was chromatographed on two Wakogel B-10 plates (30 x 30 cm) with ethyl acetate to give 7-methoxycarbonyl-2-(2-methylhydrazino)tropone (**18**) as orange prisms in a yield of 285 mg (68%), mp 89-91° (from ethanol); ir (chloroform): ν max 3332 (NH), 1727 (COOR), 1602 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 2.71 (3H, s, NCH_3), 3.92 (3H, s, OCH_3), 6.5-6.8 (1H, m), 7.25-7.45 (2H, m), 7.58 (1H, d, J = 10 Hz, H-3), 8.9 (2H, br, NH x 2).

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.76; N, 13.46. Found: C, 57.43; H, 5.77; N, 13.51.

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