Study of the Reactions of 3-Acetoacetyl-7-methyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione with Aromatic Amines

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Dedicated in the memory of Professor Raymond N. Castle for his important contribution to heterocyclic chemistry and his devotion in serving the heterocyclic community.

The reactions of 3-acetoacetyl-7-methyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione with aromatic amines afforded 3-(arylaminomethylene)-6-methylpyran-2,4-dione. Our results allowed the correction of the structures reported in the literature for the products of these reactions.

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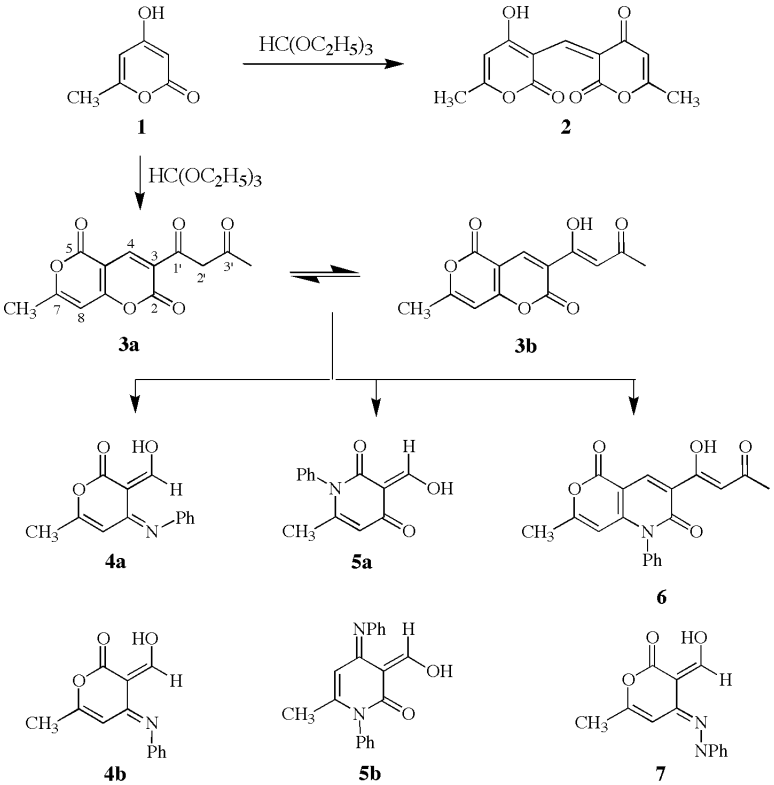
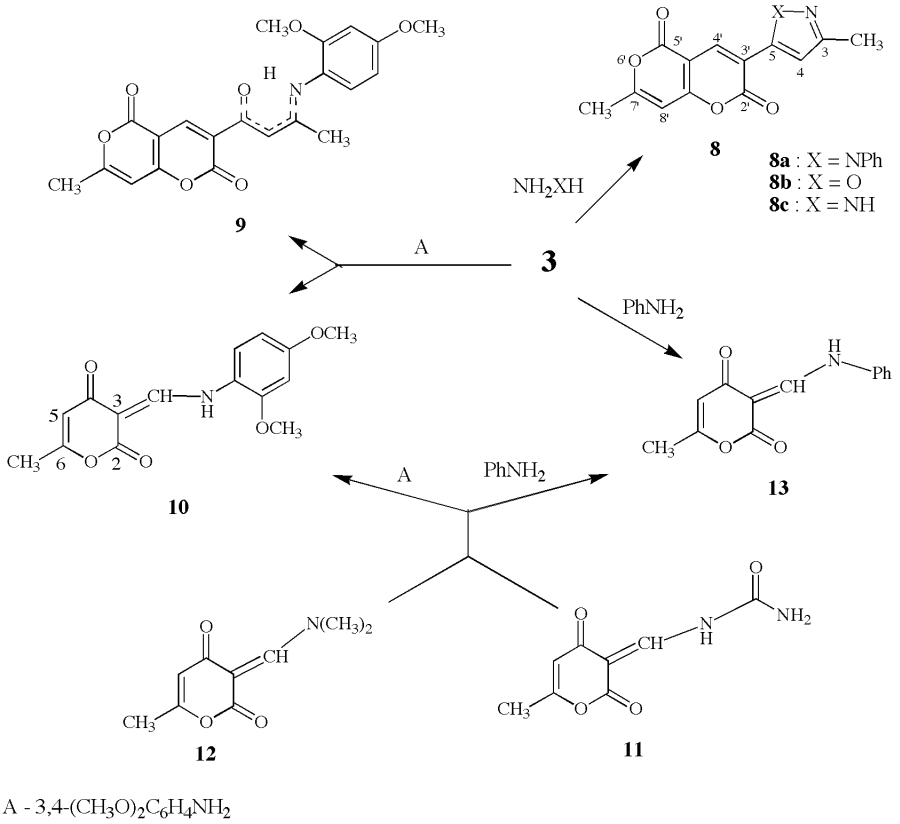
Introduction.

At the beginning of this decade we started a program of research aiming to revisit the reaction of ethyl orthoformate with triacetic acid lactone **1** (TAL) and the structure of the product of this reaction. Structure **2** has been proposed by Hirsch and Hoefgen [1] for the product they have isolated. However, this structure was not compatible with our X-ray result [2], which agrees with the structure of the dione **3a** [3,4] (Scheme 1). Zaman *et al.* [5] have also studied this reaction and proposed the structure **3b** for the product. This structure **3b** is the enolic form of the dione **3a**; in solution there is an equilibrium between these two species (*vide experimental*) (Scheme 1).

Scheme 1



Scheme 2



Zaman *et al.* [5] have also studied the reactivity of **3** towards aniline and phenylhydrazine. From the reaction of **3** with aniline they established the structure of the products as a mixture of *syn*- and *anti*-4-benzimino-3-hydroxy-methine-6-methylpyran-2-one, **4a** and **4b**, the pyridine derivatives **5a** and **5b** and also the pyridinolactone derivative **6**. In the reaction of **3** with phenylhydrazine they assigned phenylhydrazone **7** for the structure of the product (Scheme 1).

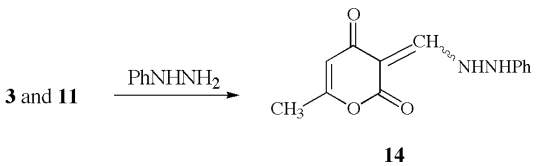
We have studied the reaction of compounds **3** [6] with aniline and phenylhydrazine and the results obtained [3,4] are completely different from those of Zaman *et al.* [5]. In order to confirm these results, we have revisited these reactions under the experimental conditions reported by Zaman *et al.* [5] and we present here our results. The reaction mechanisms are also discussed.

Results and Discussion.

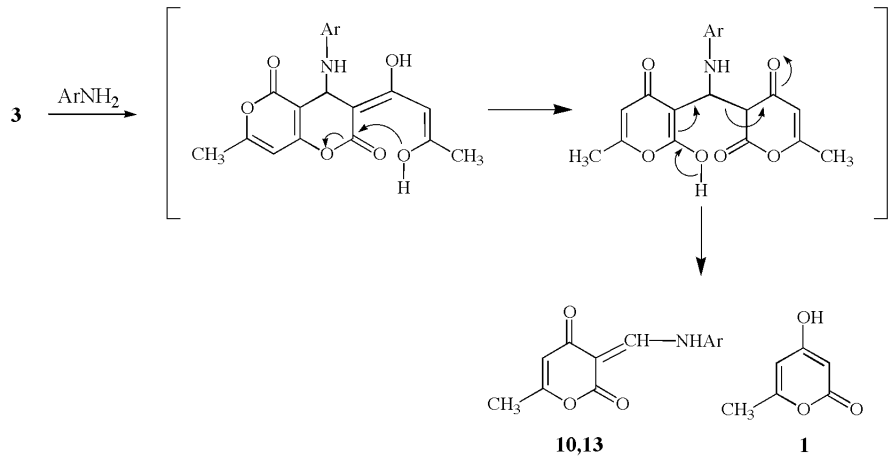
The reaction of compound **3** with phenylhydrazine, in acidic medium, gave only one pure product. The analytical data for this product indicate that a condensation reaction took place with the loss of two water molecules, and the structure still has the pyranopyran-2,5-dione skeleton **8a** (Scheme 2). The X-ray structure of this compound **8a** unequivocally proves the position of the phenyl moiety on the pyrazole ring [6] and at the same time establishes that the reaction of **3** with phenylhydrazine is regioselective. Structure **8a** was also described by Zaman *et al.* [5] but with a lower melting point. A condensation also took place between compounds **3** and hydroxylamine and hydrazine, giving, regioselectively, the corresponding isoxazole **8b** and pyrazole **8c** derivatives (Scheme 2).

The reaction of **3** with 2,4-dimethoxyaniline, in a 1:1 mixture of acetic acid and ethanol, gave two products, **9** and **10** (Scheme 2). The former is a Shiff base, formed by attack of the amine at C-3' of **3**, whereas the latter confirms that the amino group can attack other sites in the molecule. The mass spectrum of compound **10** presents a peak at m/z 289 and the elemental analysis indicate a molecular formula of $C_{15}H_{15}NO_5$. The ^1H nmr spectrum of this compound presents two signals at δ 11.75 and 13.73 ppm, in a proportion of 1:4, which disappear after shaking with deuterium oxide. Two other doublets are observed at δ

Scheme 3



Scheme 4



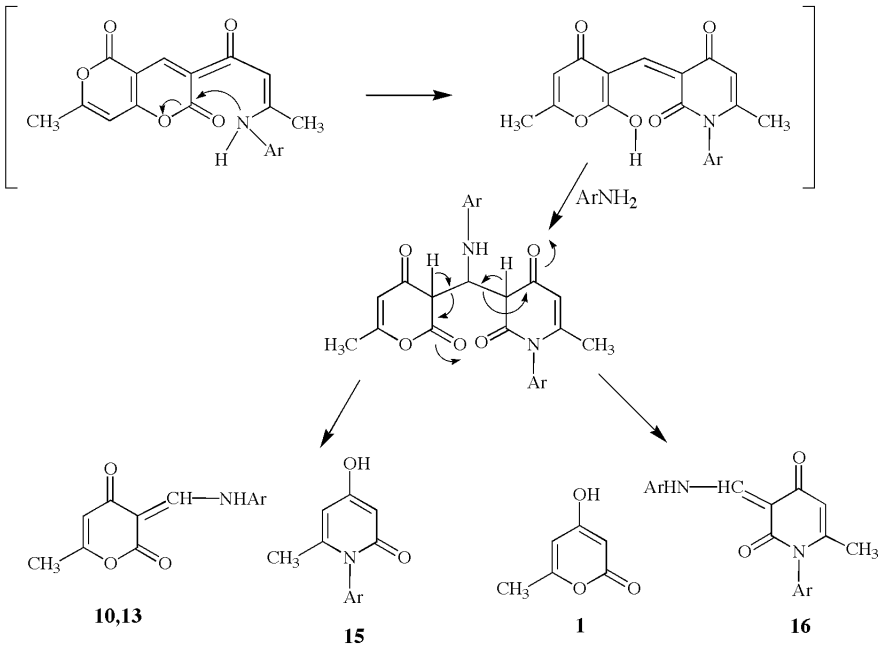
8.52 and 8.69 ppm, in the same ratio, which are assigned to the proton resonances of the imino group. These analytical data are only compatible with the structure of 3-(2,4-dimethoxyanilinomethylene)-6-methylpyran-2,4-dione **10**. This compound can exist in *E* and *Z* configurations, which explains the presence of two signals, in a 1:4 proportion, for the resonance of each proton.

The unexpected formation of **10** was very interesting, since we have recently reported the preparation of an analogue 3-(anilinomethylene)-6-methylpyran-2,4-dione **13** from the reaction of compounds **11** and **12** with aniline [7]. This analogue **13** was also obtained as a mixture of *E* and *Z* diastereomers, in a 1:4 proportion (Scheme 2). Compound **10** was also obtained from reaction of 2,4-dimethoxyaniline with **11** and **12**.

Aniline does not react with compound **3** in a cold ethanolic solution, but under reflux we can observe by tlc the formation of triacetic acid lactone **1** and a new product. The analytical data of this new product indicate the presence of compound **13**. This reaction was also carried out in ethanol with some drops of acetic acid, as described by Zaman *et al.* [5], but we have also obtained the products, **1** and **13** (Scheme 2), and not those (**4a,b**, **5a,b** and **6**) reported by the authors (Scheme 1).

The treatment of compound **3** with phenylhydrazine in ethanol gave 3-(phenylhydrazinomethylene)-6-methylpyran-2,4-dione **14** (Scheme 3). This compound

Scheme 5



was also obtained from the reaction of **11** with phenylhydrazine. The ^{1}H nmr spectrum of **14** indicates that only one diastereomer, *E* or *Z*, is present. The proton resonances reported by Zaman *et al.* [5] for phenylhydrazone **7** are very similar to those which we attributed to compound **14**. However, the melting points values of these two compounds are very different (222-225 ºC for **7** and 197-198 °C for **14**).

The formation of compounds **10** and **13** from the reaction of **3** with aromatic amines (Scheme 2) prompted us to suggest the mechanism depicted in Scheme 4 for these transformations. However, if we consider that a retrocondensation can also occur under the experimental conditions, an alternative mechanism can also be proposed (Scheme 5). Our results support the first mechanism, but the results of Castillo *et al.* [8] showing that compound **15** was obtained from the reaction of **1** with aniline, indicate that the second mechanism is also possible. As our results do not exclude the second mechanism, other transformations are being carried out in order get more information to prove or to eliminate this alternative mechanism (Scheme 5).

In summary, we have shown that the reaction of 3-acetoacetyl-7-methyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione **3** with aniline derivatives and with phenylhydrazine follows the same pathway, giving 3-(arylaminomethylene)-4–oxo-6-methyl-2-pyrone derivatives **10** and **13** and 3-(phenylhydrazinomethylene)-4-oxo-6-methyl-2-pyrone **14**, respectively. Although these transformations were carried out under the experimental conditions reported by Zaman *et al.* [5], our results are completely different. On the other hand the reaction mechanism they propose does not explain the formation of the products that we have obtained.

EXPERIMENTAL

Melting points were determined in an Electrothermal apparatus. ^{1}H nmr and ^{13}C spectra were recorded on a Bruker AC 200 and an ARX Bruker WM 300 instruments; the chemical shifts are expressed in δ (ppm) values relative to tetramethylsilane as an internal reference. Mass spectra were recorded on a Nermag R10-10C quadrupole mass spectrometer.

3-Acetoacetyl-7-methyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione **3a** and its Enolic Form **3b**.

A solution of 4-hydroxy-6-methylpyran-2-one **1** (triacetic lactone) (0.02 mole) and triethyl orthoformate (9 mL) in ethanol (30 mL) was refluxed for 4 hours. The precipitate was collected and recrystallized from ethanol or toluene to yield compounds **3** (1.8 g, 70%), mp 192-193 °C; ^{1}H nmr (deuteriochloroform): δ 2.23 (s, 3H, 7-C*H*$_3$), 2.40 (s, 3H, H-4'), 4.11 (s, 2H, H-2', dione), 6.23 (m, 1H, H-8), 6.61 (s, 1H, H-4), 8.76 (s, 1H, H-2', enol), 15.74 (s, 1H, OH, enol); ms (EI): m/z (relative intensity) 262 (M$^{+\cdot}$, 32), 247 (14), 219 (6), 205 (100), 150 (8), 95 (11), 84 (6), 69 (25), 67 (5), 57 (9).

Anal. Calcd. for $C_{13}H_{10}O_6$: C, 59.54; H, 3.82. Found: C, 59.55; H, 3.80.

3-Methyl-5-(7-methyl-2,5-dioxopyrano[4,3-*b*]pyran-3-yl)-1-phenylpyrazole **8a**.

A solution of **3** (0.01 mole) and phenylhydrazine (0.01 mole) in a mixture of ethanol-acetic acid (50 mL) was refluxed for 6 hours. After evaporation of the solvent, the residue was poured into cooled water to afford a yellow solid, which was collected and recrystallized from methanol yielding pyrazole **8a** (2.7 g, 80%), mp 186 ºC; ^{1}H nmr (deuteriochloroform): δ 2.23 (s, 3H, 7'-C*H*$_3$), 2.37 (s, 3H, 3-C*H*$_3$), 6.13 (s, 1H, H-8'), 6.51 (s, 1H, H-4'), 7.35 (s br, 5H, C_6H_5), 7.64 (s, 1H, H-4); ms (EI): m/z (relative intensity) 334 (M$^{+\cdot}$, 100), 306 (37), 305 (20), 291 (16), 276 (18), 222 (82), 85 (50), 83 (44), 77 (63), 69 (28), 63 (16), 51 (24), 43 (41).

Anal. Calcd. for $C_{19}H_{14}N_2O_4$: C, 68.26; H, 4.19; N, 8.38. Found: C, 67.96; H, 3.96; N, 8.31.

3-Methyl-5-(7-methyl-2,5-dioxopyrano[4,3-*b*]pyran-3-yl)-isoxazole **8b**.

A solution of **3** (0.01 mole) and hydroxylamine (0.01 mole) in a mixture of ethanol- acetic acid (50 mL) was refluxed for 4 hours. After cooling, the reaction mixture was filtered and the solvent evaporated to dryness. The obtained residue was recrystallized from toluene to give isoxazole **8b** (2.2 g, 83%), mp 272 ºC; ^{1}H nmr (deuteriochloroform): δ 2.35 (s, 3H, 7'-C*H*$_3$), 2.39 (s, 3H, 3-C*H*$_3$), 6.25 (s, 1H, H-8'), 6.87 (s, 1H, H-4'), 8.50 (s, 1H, H-4); ms (EI): m/z (relative intensity) 259 (M$^{+\cdot}$, 100), 205 (18), 134 (13), 120 (17), 106 (16), 85 (47), 83 (63), 82 (46), 78 (17), 69 (21), 63 (16), 53 (17), 50 (17), 47 (14), 43 (68).

Anal. Calcd. for $C_{13}H_9NO_5$: C, 60.23; H, 3.47; N, 5.40. Found: C, 60.43; H, 3.30; N, 5.20.

3-Methyl-5-(7-methyl-2,5-dioxopyrano[4,3-*b*]pyran-3-yl)-pyrazole **8c**.

A solution of **3** (0.01 mole) and hydrazine (0.01 mole) in a mixture of ethanol and acetic acid (50 mL) was refluxed for 3 hours. After cooling, the solvents were evaporated to dryness and the residue was recrystallized from toluene to yield pyrazole **8c** (1.8 g, 70%), mp 230 °C; ^{1}H nmr was not registered due to the insolubility of **8c** in common solvents; ms (EI): m/z (relative intensity) 258 (M$^{+\cdot}$, 100), 230 (18), 109 (15), 106 (18), 105 (14), 89 (16), 85 (29), 83 (33), 77 (17), 69 (14), 63 (18), 55 (11), 43 (57), 39 (13).

Anal. Calcd. for $C_{13}H_{10}N_2O_4$: C, 60.46; H, 3.87; N, 10.85. Found: C, 60.26; H, 4.02; N, 11.02.

Synthesis of Compounds **9** and **10**.

A solution of **3** (0.01 mole) and 2,4-dimethoxyaniline (0.01 mole) in a mixture of ethanol and acetic acid (50 mL) was refluxed for 1 hour. After cooling, the mixture was filtered and the solvent was evaporated. The obtained residue was washed with hot ethanol giving a soluble fraction which corresponds to pyranopyran-2,5-dione **9** (1.6 g, 40%), whereas the rest was recrystallised in ethanol giving pyran-2,4-dione **10** (1.1 g, 38%).

3-[3-(2,4-Dimethoxyphenylimino)-1-oxobutan-1-yl]-7-methyl-2*H*,5*H*-pyrano[4,3-*b*] pyran-2,5-dione **9**, mp 270 ºC; ^{1}H nmr (deuteriochloroform): δ 2.06 (d, 3H, 7-C*H*$_3$), 2.21 (s, 3H, 3'-C*H*$_3$), 3.75 (s, 3H, OC*H*$_3$), 3.84 (s, 3H, OC*H*$_3$), 6.19 (s, 1H, H-8), 6.56 (m, 2H, C_6H_3), 6.85 (m, 1H, C_6H_3), 7.00 (s, 1H, H-4), 8.92 (s, 1H, 2'-H); ms (EI): m/z (relative intensity) 397 (M$^{+\cdot}$, 100), 396 (29), 340 (18), 285 (17), 282 (30), 84 (27), 59 (12), 55 (13), 43 (28).

Anal. Calcd. for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.78, N, 3.52. Found: C, 63.13; H, 4.80; N, 3.35.

3-(2,4-Dimethoxyanilinomethylene)-6-methylpyran-2,4-dione **10**, mp 229-230 ºC; ^{1}H nmr (deuteriochloroform): δ 2.15 (d, 3H, 6-C*H*$_3$), 3.80 (s, 3H, OC*H*$_3$), 3.91 (s, 3H, OC*H*$_3$), 5.72 (s, 1H, H-5), 6.46-6.57 (m, 2H, C_6H_3), 7.21-7.33 (m, 1H, C_6H_5), 8.52 and 8.69 (2d, 1H, =C*H*-N, *E* and *Z*), 11.75 and 13.73 (2d, 1H, N*H*, *E* and *Z*); ms (EI): m/z (relative intensity) 289 ($M^{\pm}$, 100), 274 (16), 246 (9), 209 (14), 190 (42), 177 (14), 176 (14), 174 (31), 164 (13), 163 (12), 162 (22), 151 (31), (150 (21), 139 (42), 138 (31), 137 (15), 135 (12), 134 (17), 124 (14), 119 (13), 95 (11), 85(23), 83 (15), 77 (9), 69 (12), 53 (17), 43 (29), 39 (13).

Anal. Calcd. for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.19; N, 4.84. Found: C, 62.35; H, 5.2; N, 4.76.

3-(Anilinomethylene)-6-methylpyran-2,4-dione **13**.

A solution of **3** (0.01 mole) and aniline (0.01 mole) in 2-propanol (50 mL) was refluxed for 4 hours. After solvent evaporation, the residue was washed with toluene to give two products. The compound insoluble in toluene corresponds to 4-hydroxy-6-methyl-2-pyrone **1**. The soluble fraction gave, after solvent evaporation and recrystallization from 2-propanol, pyran-2,4-dione **13** (1.6 g, 70%), mp 177 ºC; ^{1}H nmr (deuterio-chloroform): δ 2.23 (s, 3H, 6-C*H*$_3$), 5.75 (s, 1H, H-5), 7.25-7.43 (m, 5H, C_6H_5), 8.82 and 8.98 (2d, 1H, =C*H*-N, *E* and *Z*), 11.62 and 13.62 (2d, 1H, N*H*, *E* and *Z*); ms (EI): m/z (relative intensity) 229 ($M^{\pm}$, 100), 205 (16), 186 (10), 144 (22), 117 (40), 98 (33), 93 (34), 55 (11), 53 (14), 51 (24), 43 (71), 39 (20).

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.8; N, 6.11. Found: C, 68.66; H, 4.7; N, 5.80.

3-(Phenylhydrazinomethylene)-6-methylpyran-2,4-dione **14**.

A solution of **3** (0.01 mole) and phenylhydrazine (0.01 mole) in ethanol (20 mL) was refluxed for 15 minutes. The reaction mixture was cooled and filtered to give a precipitate which was recrystallized from ethanol to give pyran-2,4-dione **14** (1.7 g, 68%), mp 197-198 ºC; 1H nmr (dimethyl sulfoxide-d6): δ 2.19 (s, 3H, 6-C*H*$_3$), 6.14 (s, 1H, H-5), 6.91-6.94 (m, 3H, C_6H_5), 7.23-7.29 (m, 2H, C_6H_5), 8.11 (s, 1H, =C*H*-N, *E* or *Z*) 10.18 and 13.19 (2s, 2H, 2x N*H*, *E* or *Z*); ms (EI): m/z (relative intensity) 244 ($M^{\pm}$, 7), 229 (11), 187 (71), 186 (13), 160 (11), 153 (16), 105 (14), 93 (48), 92 (27), 91 (21), 85 (46), 78 (12), 77 (72), 69 (64), 68 (12), 65 (59), 57 (11), 54 (17), 53 (22), 51 (22), 43 (100), 42 (16), 41 (35), 40 (16), 39 (57), 38 (12).

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.91; N, 11.48. Found: C, 63.62; H, 4.75; N, 11.29.

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