

On the Behavior of α -Brominated Dimethyl *o*-Benzenediacetate Toward Nitrogen Nucleophiles. Part II. Reaction of Dimethyl α -Bromo-*o*-benzenediacetate with Hydrazines

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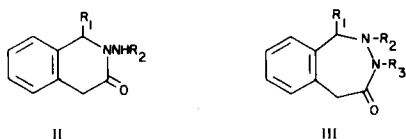
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Dimethyl α -bromo-*o*-benzenediacetate (**1**) condensed with hydrazine and acetylhydrazine to give respectively 1-carbomethoxy-2-amino-1,4-dihydro-3-(2*H*)isoquinolinone (**2**) and its *N*-acetyl derivative (**9**). Replacement of the bromine atom of **1** with the *N*-1-methylhydrazino (**3**) and the *N*-1-phenylhydrazino (**5**) groups occurred by allowing **1** to react respectively with methylhydrazine and phenylhydrazine. In the latter case alkylation by **1** at the *N*-2 also occurred which led to the formation of the 2-phenylaminoisoquinolinone (**8**). Derivatives **3** and **5** smoothly cyclized to the 1-carbomethoxy-5(*H*)-1,2,3,4-tetrahydro-2,3-benzodiazepin-4-ones **4** and **6**. A series of derivatives of **2** were also pharmacologically tested as antiinflammatory and CNS depressant agents.

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In a preceding paper (1) we described the condensation of dimethyl α,α -dibromo-*o*-benzenediacetate with hydrazines which led to isoindole, isoindoline and tetrahydrophthalazine derivatives depending upon the hydrazine employed and the configuration of the starting dibromo-diester.

As an extension of this research we have now submitted dimethyl α -bromo-*o*-benzenediacetate (**2**) (**1**), to the action of hydrazines expecting to obtain 1,4-dihydro-3-(2*H*)isoquinolinones (II) and/or 1,2,3,4-tetrahydro(5*H*)-2,3-benzodiazepin-4-ones (III).



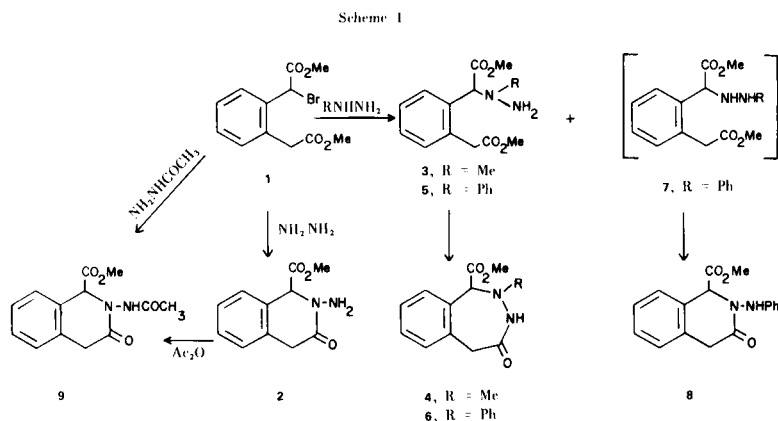
Beyond the chemical interest, we were stimulated by structural analogies of II ($R_1 = \text{CO}_2\text{Me}$) with a series of 2-substituted 1,4-dihydro-3-(2*H*)isoquinolinones (II, $R_1 = \text{H}$, $R_2 = \text{COR}$), recently found active as CNS depressant and antiinflammatory agents (3). With regard to III, this class seems not to have been reported in the literature, in spite of attempts at synthesis (4). Conversely, the related 3,5-dihydro(4*H*)-2,3-benzodiazepin-4-ones are widely reported (5a-c), some are claimed as CNS depressant (5c).

The reaction of **1** with hydrazine hydrate in refluxing

methanol gave in good yield 1-carbomethoxy-2-amino-1,4-dihydro-3-(2*H*)isoquinolinone (**2**) which was isolated as the hydrochloride, m.p. 183-185°. The structure of **2** was supported by the formation with benzaldehyde of a benzyldienimino derivative from which the starting **2** was obtained with phenylhydrazine (**6**), and by the identity of the *N*-acetylamino derivative (**9**) obtained by heating **2** with acetic anhydride, with the reaction product of **1** and acetylhydrazine.

Methylhydrazine condensed with **1** in benzene and at room temperature to give 70% of dimethyl α -(*N*-1-methylhydrazino)-*o*-benzenediacetate (**3**) isolated as the hydrochloride, m.p. 123-125°, besides minor amounts of 1-carbomethoxy-2-methyl-(5*H*)-1,2,3,4-tetrahydro-2,3-benzodiazepin-4-ones (**4**) m.p. 121-122°. The latter compound originated from **3** by cyclization, as demonstrated by the gradual increase of the **4/3** ratio by allowing **3** to stand at room temperature, as well as by its rapid conversion into **4** in refluxing acetic acid. Compound **4** exhibits its absorptions at 3180, 3080 (NH) and at 1685 (lactamic CO) cm^{-1} , while the nmr is characterized by an AB pattern (dd at 3.42 and 4.60 δ) and by a deuterium oxide-exchangeable peak at 7.60 δ , respectively attributed to a non equivalent methylene group and to a lactamic NH.

The formation of **3** and **4** is consistent with the known selective alkylation of methylhydrazine at the more nucleophilic *N*-1. Conversely, the reaction of **1** with phenylhydrazine in benzene and at room temperature



appeared to involve alkylation at both N-1 and N-2 atoms in about a 3:1 ratio, as suggested by the isolation of 45% of the N-1 phenylhydrazino derivative (5), m.p. 140-142° and 15% of the isoquinolinone 8, m.p. 139-140°, the latter being formed by cyclization of the unstable 7, isomer of 5 (see Scheme 1). Structure 5 was assigned to the isomer m.p. 140-142° on the basis of the characteristic ir pattern in the region 3500-3100 cm⁻¹ attributable to the N-NH₂ group (7a,b) and by its rapid conversion in refluxing acetic acid into the benzodiazepinone 6, m.p. 149-151°.

Finally, for the pharmacological evaluation *N*-aroyl derivatives of 2, 10-12 were synthesized from the appropriate acid chlorides. For the same purpose compounds 8-11 were transformed into the 1-carbamoyl derivatives 13-16 with methanolic ammonia (see Table I).

The isoquinolinones 2, 8-16 were found inactive or slightly active as antiinflammatory and CNS depressant agents, using, respectively, the anticarragenin (rat paw edema) screen and the Irwin test on mice. The benzodiazepinones 4 and 6 were also found devoid of CNS activity.

EXPERIMENTAL

Ir spectra were determined with a Perkin-Elmer model 157/G spectrophotometer; nmr spectra were obtained in the solvent indicated with a Hitachi Perkin-Elmer spectrometer with TMS as the internal standard.

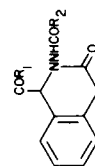
Reaction of 1 with Hydrazines.

Hydrazine Hydrate Affording 1-Carbomethoxy-2-amino-1,4-dihydro-3-(2*H*)isoquinolinone (2).

A solution of 30.01 g. of 1 (2), 10 g. (0.2 mole) of hydrazine hydrate and 60 ml. of methanol was refluxed for 6 hours. After cooling, the hydrazine hydrobromide was filtered off and the solution was evaporated *in vacuo*. The residue was partitioned between water and chloroform. The solvent was dried over sodium sulphate and was evaporated to leave oily 2 which was transformed into the hydrochloride with a solution of hydrogen chloride in ether. Crystallization from methanol-ether (1:2)

Table I

1-Substituted-2-acylamino-1,4-dihydro-3-(2*H*)isoquinolinones



Compound	R ₁	R ₂	M.p. °C	Yield %	Empirical Formula	Calcd.		Found			
						C	H	N	C	H	N
9	OCH ₃	CH ₃	178-180 (a)	52	C ₁₃ H ₁₄ N ₂ O ₄	59.53	5.38	10.68	59.80	5.51	10.39
10	OCH ₃	C ₆ H ₅	173-175 (a)	62	C ₁₈ H ₁₆ N ₂ O ₄	66.66	4.97	8.64	66.79	5.14	8.67
11	OCH ₃	3,4,5-(OCH ₃) ₃ C ₆ H ₂	247-248 (b)	58	C ₂₁ H ₂₂ N ₂ O ₇	60.86	5.35	6.76	60.61	5.61	6.66
12	OCH ₃	p.F. C ₆ H ₄ CH ₂	157-159 (c)	41	C ₁₉ H ₁₇ N ₂ O ₄	63.83	4.83	7.90	63.90	4.85	7.78
13	NH ₂	CH ₃	270-271 (d)	71	C ₁₂ H ₁₃ N ₃ O ₃	58.29	5.30	17.00	58.04	5.43	17.20
14	NH ₂	C ₆ H ₅	248-250 (c)	60	C ₁₇ H ₁₅ N ₃ O ₃	66.01	4.89	13.58	65.79	5.01	13.33
15	NH ₂	3,4,5-(OCH ₃) ₃ C ₆ H ₂	281-282 (b)	75	C ₂₀ H ₂₁ N ₃ O ₆	60.14	5.30	10.52	60.13	5.32	10.44

Crystallization solvent: (a) benzene; (b) acetic acid; (c) ethanol; (d) water.

gave 19.3 g. (75%) of the hydrochloride of **2**, m.p. 183-185° dec.; ir (Nujol): 2250 (N-NH₃⁺) 1730 (ester) and 1700 (lactamic CO) cm⁻¹; nmr (DMSO-d₆): δ 3.70 (s, COOCH₃), 3.82 (s, CH₂), 5.85 (s, CH), 7.20-7.50 (m, 4 aromatic H), 7.95 (broad singlet which disappeared after deuteration, NH₃⁺).

Anal. Calcd. for C₁₁H₁₃ClN₂O₃: C, 51.47; H, 5.10; N, 10.9; Cl, 13.81. Found: C, 51.68; H, 5.25; N, 11.10; Cl, 13.66.

The benzylideneimino derivative **17**, m.p. 143-144° (methanol) was obtained in 90% yield by reaction of the hydrochloride of **2** with equimolar benzaldehyde in water at room temperature for 2 hours.

Anal. Calcd. for C₁₈H₁₆N₂O₃: C, 70.11; H, 5.23; N, 9.09. Found: C, 69.90; H, 5.16; N, 9.22.

By heating **17** for 1 hour (0.43 g.) with phenylhydrazine (0.147 g.) in 5 ml. of methanol containing two drops of concentrated hydrochloric acid, then concentrating and cooling the mixture, 0.21 g. (88%) of benzylidene phenylhydrazine, m.p. 158-160° was separated. By adding to the filtrate a solution of hydrogen chloride in ether, 0.24 g. (68%) of the hydrochloride of **2** was recovered.

Methylhydrazine Affording Dimethyl α -(*N*₁-Methylhydrazino)-*o*-benzenediacetate (**3**) and 1-Carbomethoxy-2-methyl-(5*H*)-1,2,3,4-tetrahydro-2,3-benzodiazepin-4-one (**4**).

A solution of 15.7 g. (0.052 mole) of **1**, 4.9 g. (0.104 mole) of methylhydrazine and 60 ml. of benzene was stirred under nitrogen for 12 hours at room temperature. The methylhydrazine hydrobromide (5.6 g., 85%) was filtered and the filtrate was evaporated to leave 15 g. of a yellowish oil which was dissolved in a small amount of ethanol and was treated with a solution of hydrogen chloride in ether. The solid which precipitated (13 g.) was filtered and crystallized from methanol-ether to give 11.3 g. (71%) of **3** as the hydrochloride, m.p. 123-125°; ir (nujol): 3500, 3100 (NH₂), 2600-2500 (NH⁺CH₃), 1715-1730 (ester) cm⁻¹; nmr (DMSO-d₆): δ 2.52 (s, NCH₃), 3.60 and 3.65 (2s, 2COOCH₃), 3.92 (s, CH₂), 7.30-7.40 (m, 4 aromatic H), 9.80 (broad singlet which disappeared after deuteration, NH₂).

Anal. Calcd. for C₁₃H₁₉ClN₂O₄: C, 51.56; H, 6.47; N, 9.25; Cl, 11.71. Found: C, 51.30; H, 6.50; N, 9.12; Cl, 11.84.

The filtrate from the precipitation of the hydrochloride was evaporated and the residue partitioned between 5% sodium carbonate and chloroform. The solvent was dried and evaporated to leave 2.0 g. of an oil which was chromatographed on silica gel eluting with chloroform and collecting 1.52 g. (6.5%) of **4**, m.p. 121-122° (water); ir (nujol): 3100 and 3040 (lactamic NH), 1720 (ester), 1690 (lactamic CO) cm⁻¹; nmr (deuteriochloroform): δ 2.90 (s, N-CH₃), 3.42 and 4.60 (dd, J = 11 Hz, CH₂), 3.72 (s, COOCH₃), 4.80 (s, CH), 7.20-7.34 (m, 4 aromatic H), 7.60 (broad singlet which disappeared after deuteration, NH).

Anal. Calcd. for C₁₂H₁₄N₂O₃: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.62; H, 5.93; N, 12.08.

Cyclization of **3** to **4**

Five g. of oily **3** freshly liberated from the hydrochloride was allowed to stand at room temperature. Periodical checking by tlc (silica gel, chloroform as the mobil phase) of a sample of the oil in comparison with **3** and **4** indicated a gradual increase of the **4/3** ratio. After two weeks the oil was chromatographed on a silica gel column eluting with chloroform to give 3.2 g. (73%) of **4**, m.p. 121-122°.

For preparative purposes **4** was obtained in 82% yield by refluxing for 1 hour a solution of **3** in acetic acid, evaporating the solvent and crystallizing the residue from water.

Phenylhydrazine Affording Dimethyl α -(*N*₁-Phenylhydrazino)-*o*-benzenediacetate (**5**) and 1-Carbomethoxy-2-phenylamino-1,4-dihydro-3-(2*H*)isoquinolinone (**8**).

A solution of 33.85 g. (0.112 mole) of **1**, 24.2 g. (0.224 mole) of phenylhydrazine and 300 ml. of benzene was stirred at room temperature under nitrogen for 24 hours. The precipitate (22.5 g.) was filtered and treated with water to dissolve the phenylhydrazine and to leave 5.6 g. of a solid, m.p. 138-142°. The benzene filtrate was evaporated *in vacuo* at 50-60° and the semisolid residue was partitioned between water and ether. The insoluble (11.5 g.), m.p. 135-140°, was filtered, joined to the solid m.p. 138-142° and the whole was crystallized from methanol to give 16 g. (45%) of **5**, m.p. 140-142°.

The organic layer was dried and evaporated to leave an oily residue which was dissolved in methanol. After standing in a refrigerator for 3 days, 4.97 g. (15%) of **8**, m.p. 139-140° was separated.

The analytical data of **5** is: ir (nujol): 3350 (NH₂), 1730 (COOCH₃) cm⁻¹; ir (carbon tetrachloride): 3460, 3375, 3270 and 3150 (N-NH₂), 1740 (COOCH₃) cm⁻¹; nmr (deuteriochloroform): δ 3.50 and 3.78 (2s, 2 COOCH₃), 3.60 (broad singlet with disappeared after deuteration, N-NH₂) 3.66 (d, CH₂), 5.96 (s, CH), 6.80-7.50 (m, 9 aromatic H).

Anal. Calcd. for C₁₈H₂₀N₂O₄: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.33; H, 6.06; N, 8.59.

The analytical data of **8** is: ir (nujol): 3318 (NH), 1748 (ester), 1690 (lactamic CO) cm⁻¹; nmr (deuteriochloroform): δ 3.72 (s, COOCH₃), 3.90 (d, CH₂), 5.35 (s, CH), 6.68-7.50 (m, 9 aromatic H + NH).

Anal. Calcd. for C₁₇H₁₆N₂O₃: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.44; H, 5.42; N, 9.67.

Cyclization of **5** to 1-Carbomethoxy-2-phenyl-5(*H*)-1,2,3,4-tetrahydro-2,3-benzodiazepin-4-one (**6**).

A solution of 10 g. of **5** and 15 ml. of acetic acid was refluxed for 1 hour. Evaporation of the solvent left a viscous oil which was dissolved in 80 ml. of hot ethanol. On cooling 7.4 g. (80%) of **6**, m.p. 149-151° was separated; ir (nujol) 3140-3040 (NH), 1730 (ester), 1685 (lactamic CO) cm⁻¹; nmr (deuteriochloroform): δ 3.34 and 4.24 (dd, J = 16; CH₂), 3.70 (s, COOCH₃), 5.90 (s, CH), 6.75-7.60 (m, 9 aromatic H), 8.40 (broad singlet which disappeared after deuteration, NH).

Acetylhydrazine Affording 1-Carbomethoxy-2-acetylamino-1,4-dihydro-3-(2*H*)isoquinolinone (**9**).

A solution of 2 g. (0.0066 mole) of **1**, 0.98 g. (0.0132 mole) of acetylhydrazine and 10 ml. of methanol was refluxed for 6 hours. Evaporation of the solvent left a residue which was partitioned between water and chloroform. The organic layer was dried and evaporated. The solid residue crystallized from benzene to give 0.9 g. (52%) of **9**, m.p. 178-180°; ir (nujol): 3250 (NH), 1740 (ester) 1700-1710 (lactamic CO), 1665 (amide CO) cm⁻¹; nmr (deuteriochloroform): δ 2.02 (s, COCH₃), 3.70 (s, COOCH₃), 3.80 (d, CH₂), 5.40 (s, CH), 7.10-7.40 (m, 4 aromatic H), 8.58 (broad singlet which disappeared after deuteration).

Anal. Calcd. for C₁₃H₁₄N₂O₄: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.80; H, 5.51; N, 10.37.

Compound **9** was also obtained in 45% yield by allowing **2** to react (1.68 g.) with acetic anhydride (3 ml.) for 0.5 hours at 50°. 1-Carbomethoxy-2-benzoylamino-1,4-dihydro-3-(2*H*)isoquinolinone (**10**) (see Table I).

The hydrochloride of **2** (2.56 g., 0.01 mole) was suspended in 5% sodium bicarbonate solution and the resulting oil was extracted with chloroform. After drying, the solvent was evaporated to leave free **2** which was refluxed for 1 hour with 1.4 g. (0.01 mole) of benzoyl chloride and 1.0 g. (0.01 mole) of triethylamine in 20 ml. of benzene. After cooling, the precipitate was filtered and triturated with water. The insoluble material was added to the solid residue from the evaporation of the benzene filtrate and the entire amount was crystallized from benzene to give 1.94 g. (60%) of **10**, m.p. 173-175°. Similarly prepared from **2** and the appropriate chloride were **11** and **12** (reaction time: 6 hours).

1-Carbamyl-2-phenylamino-1,4-dihydro-3-(2H)isoquinolinone (**16**).

Into a suspension of 2.5 g. of **8** in 20 ml. of methanol at 0°, ammonia was bubbled until saturation was complete. A solution was obtained at first, followed by a gradual separation of a solid product. The flask was tightly stoppered and was kept at room temperature overnight.

The precipitate (1.8 g.) was collected, added to an additional crop (0.5 g.) from the concentration of the methanolic solution, and the entire product was crystallized from ethanol to give 1.78 g. (75%) of **16**, m.p. 180-182°.

Anal. Calcd. for C₁₆H₁₅N₃O₂: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.38; H, 5.51; N, 14.74.

Similarly prepared from the appropriate 1-carbomethoxy derivative were **13,15** (see Table 1).

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