Synthesis of α-Oxo and α-Hydroxy-1-benzyl-1,4-dihydro-3(2*H*)-isoquinolinones

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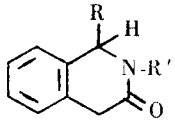
Received May 9, 1983

The reaction of some primary amines with the methyl 2-[(α-oxobenzyl)-(α-bromo)methyl]phenylacetate (**5**) afforded the isoquinolinones **7a-d**, which in turn were hydrogenated to **10a-d**. The synthesis of these compounds was designed on the basis of a potential depressant and antiinflammatory activity found in other structurally related compounds.

J. Heterocyclic Chem., **21**, 297 (1984).

Analgetic-antipyretic and antiinflammatory activity has been reported in the literature for some isoquinolines [1] and tetrahydroisoquinolines [2]. In this regard we have previously described [3] the synthesis of various 1,2-disubstituted-1,4-dihydro-3(2*H*)-isoquinolinones **1** structurally related to those which might have analogous activity.



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In order to achieve significant structure-activity correlations we have now prepared compounds **7a-d** and their hydroxy analogous **10a-d**.

The synthetic approach to the required compounds **7a-d** was made from the unknown intermediate **5** purposely prepared, as depicted in Scheme I, starting from dimethyl *o*-phenylenediacetate (**2**) [4]. The isoquinolinones **7a-c** were straightaway obtained, according to the Scheme II, in good yields by reaction of **5** with primary amines in benzene at room temperature whereas under the same conditions **5** with aniline afforded 92% of **6**. Alternatively the same reaction carried out in refluxing benzene for 24 hours yielded only 16% of **7d** besides 73% of **6**. The latter was then converted to **7d** in refluxing acetic acid. The two steps cyclization of **7d** (*via* **6**) is most likely due to the reduced basicity of the anilino group which requests dehydrating acidic conditions for the formation of the cyclic amide.

The hydrogenation of **7a-d** over palladised charcoal gave almost quantitatively yields of **10a-d**. An alternative route to **10d** involves the cyclization of the carbinol **8** obtained from the reduction of **6**. During the course of this hydrogenation we were able to isolate **9** (40%) whose structure was unambiguously confirmed by the reduction of **4** with palladised charcoal. This accounts for an unusual hydrogenolysis of the anilino group which seems subsequent to a previous reduction of the carbonyl group.

The structures of all described compounds were supported by analytical and spectroscopic data and are listed in the Tables 1 and 2. In particular the nmr spectra of the compounds **7a-d** exhibited an AB system for the -CH_2-CO- (J_{AB} = 19 Hz) group in agreement with analogous compounds [5], while those of the carbinols **10a-d** show a second AB pattern (J_{AB} = 4 Hz) in the range δ 4.65-5.10 attributable to CH-CH group, which confirms the reduction occurred.

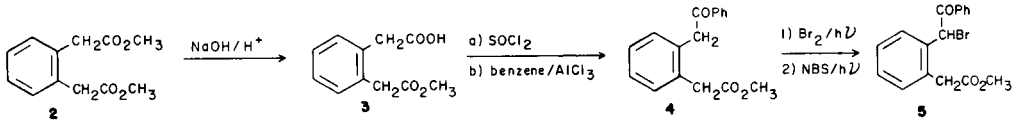
EXPERIMENTAL

Melting points were determined with a Kofler apparatus and are uncorrected. The ir spectra were obtained with a Perkin-Elmer 157/G spectrophotometer and the nmr spectra were recorded on a Hitachi Perkin-Elmer R/24 spectrometer with tetramethylsilane as the internal standard. Elemental analyses were performed by Microanalytical Laboratories of the Istituto di Chimica Farmaceutica dell'Università di Padova, and the Istituto di Scienze Farmaceutiche dell'Università di Genova.

Methyl 2-(Carboxymethyl)phenylacetate (**3**).

To a solution of 111 g (0.5 mole) of dimethyl *o*-phenylenediacetate (**2**) [4] in 120 ml of methanol a solution of 28.05 g (0.5 mole) of potassium hydroxide in water (35 ml) was added dropwise. After stirring at room temperature for 7 hours, the methanol was removed under reduced pressure and the resulting suspension was filtered to give potassium *o*-phenylenediacetate (10.9 g). The filtrate was then diluted with water (300 ml) and extracted with ether affording 32 g (29%) of unreacted **2**. Finally the

Scheme I



2 **3** **4** **5**

Scheme II

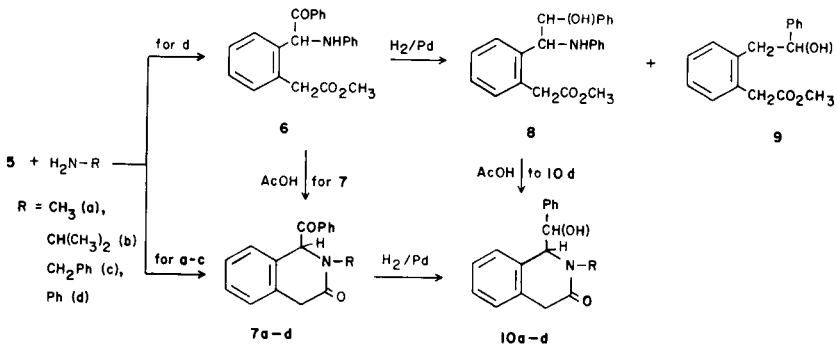


Table 1

Analytical and Physical Data for **7a-d**

Compound	R	Yield %	Mp °C	Molecular Formula	Analysis % Calcd./Found C	H	N	IR, cm^{-1} (potassium bromide) CO-N COPh	^1H NMR, δ (Deuteriochloroform)
7a	CH_3	80	146-147	$C_{17}H_{15}NO_2$	76.96 76.75	5.70 5.69	5.28 5.10	1690 1650	3.02 (s, CH_3, 3H), 3.51 and 3.92 (dd, CH_2CO, 2H, J = 19 Hz), 6.05 (s, CH, 1H), 6.90-8.10 (m, aromatic, 9H)
7b	$CH(CH_3)_2$	54	188-189	$C_{19}H_{19}NO_2$	77.79 77.80	6.33 6.59	4.77 4.66	1680 1640	1.05 and 1.22 (dd, 2 CH_3, 6H, J = 6.7 Hz), 3.62 and 4.05 (dd, CH_2CO, 2H, J = 19 Hz), 5.00 (m, $CH(CH_3)_2$, 1H), 6.05 (s, CH, 1H), 7.10-8.20 (m, aromatic, 9H)
7c	CH_2Ph	71	133-135	$C_{23}H_{19}NO_2$	80.91 80.74	5.61 5.66	4.10 4.28	1685 1650	3.71 and 4.08 (dd, CH_2CO, 2H, J = 19 Hz), 4.17 and 5.29 (dd, CH_2Ph, 2H, J = 15 Hz), 5.95 (s, CH, 1H), 6.90-7.80 (m, aromatic, 14H)
7d	Ph	16	184-185	$C_{22}H_{17}NO_2$	80.71 80.60	5.23 5.09	4.28 4.23	1680 1655	3.73 and 4.21 (dd, CH_2CO, 2H, J = 19 Hz), 6.40 (s, CH, 1H), 7.10-8.00 (m, aromatic, 14H)

aqueous solution was adjusted to *p*H 4-5 with 6*N* hydrochloric acid and further extracted with ether. The organic layer was dried and then evaporated *in vacuo* to give crude **3**, which was crystallized from benzene (56 g, 53%), mp 90-92°; ir (nujol): 1730 ($COOCH_3$), 1710 (COOH) cm^{-1}; nmr (deuteriochloroform): δ 3.65 (s, CH_3, 3H), 3.75 (s, 2 CH_2, 4H), 7.30 (s, aromatic, 4H), 11.20 (broad s, OH, 1H).

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.01; H, 5.47.

Methyl 2-[(α-Oxobenzyl)methyl]phenylacetate (**4**).

A mixture of 26 ml of thionyl chloride and 50 g (0.24 mole) of **3** in 150 ml of benzene was stirred at 60° for 4 hours. After removing the solvent and the excess of reagent under reduced pressure, the crude acyl chloride was dissolved in anhydrous benzene (240 ml) and slowly added to a cooled suspension of 64 g of anhydrous aluminum chloride in benzene (500 ml), while keeping the temperature at 10-15°. The reaction mixture was then vigorously stirred at room temperature for 10 hours, poured into 500 ml of ice-water and acidified with 6*N* hydrochloric acid. After separation of the benzene layer, the aqueous layer was further extracted with benzene. The combined extracts were dried, evaporated under reduced pressure and the oily residue was distilled *in vacuo* (bp 165-170°/0.05 mm). The liquid by trituration with methanol gave 44.6 g (70%) of **4** as a white solid, mp 62-64°; ir (nujol): 1735 ($COOCH_3$), 1675 (COPh) cm^{-1}; nmr (carbon tetrachloride): δ 3.55 (s, CH_2-$COOCH_3$, 2H), 3.60 (s, CH_3, 3H), 4.30 (s, CH_2COPh, 2H), 7.00-8.05 (m, aromatic, 9H).

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.98; H, 6.03.

Methyl 2-[(α-Oxobenzyl)-(α-bromo)methyl]phenylacetate (**5**).

Method A.

To a stirred solution of 5 g (0.018 mole) of **4** in benzene (50 ml), 3.2 g (0.02 mole) of bromine was added and the mixture was refluxed for 30 minutes under irradiation with a 300 watt lamp. The organic layer was evaporated under reduced pressure and the residue was triturated with methanol to give 4.6 g (74%) of **5**, mp 95-96°; ir (nujol): 1735 ($COOCH_3$), 1690 (COPh) cm^{-1}; nmr (deuteriochloroform): δ 3.65 (s, CH_3, 3H), 3.72 and 4.12 (dd, CH_2CO, 2H, J = 15 Hz), 6.80 (s, CH, 1H), 7.20 (m, aromatic, 9H).

Anal. Calcd. for $C_{17}H_{15}BrO_3$: C, 58.84; H, 4.35; Br, 23.03. Found: C, 58.86; H, 4.40; Br, 23.06.

Method B.

A stirred suspension of 5 g (0.018 mole) of **4**, 3.75 g (0.02 mole) of *N*-bromosuccinimide and 0.1 g of benzoyl peroxide in 80 ml of carbon tetrachloride was irradiated for 5 hours with a 300 watt lamp. After stirring for an additional 12 hours without irradiation, the succinimide was filtered off and the filtrate was evaporated under reduced pressure. The resulting oily residue (6.7 g) was purified by chromatography on silica gel

Table 2

Analytical and Physical Data for **10a-d**

Compound	R	Yield %	Mp °C	Molecular Formula	Analysis % Calcd./Found C	H	N	IR, cm^{-1} (potassium bromide) CO-N COPh	^1H NMR, δ (Deuteriochloroform)
10a	CH_3	84	236-239	$C_{17}H_{17}NO_2$	76.38 76.12	6.41 6.50	5.24 5.37	3360 1640	3.15 (s, CH_3, 3H), 2.55 and 3.10 (dd, CH_2CO, 2H, J = 19 Hz), 4.60 and 4.95 (dd, CH-CH, 2H, J = 4 Hz), 5.25 (s, OH, 1H), 6.80-7.40 (m, aromatic, 9H) [a]
10b	$CH(CH_3)_2$	85	186-188	$C_{19}H_{21}NO_2$	77.26 77.02	7.17 7.17	4.74 4.67	3280 1630	1.30 and 1.55 (dd, 2 CH_3, 6H, J = 6.7 Hz), 2.09 and 3.01 (dd, CH_2CO, 2H, J = 19 Hz), 3.10 (s, OH, 1H), 4.60 (m, CH, 1H), 4.67 and 4.98 (dd, CH-CH, 2H, J = 5.3), 6.70-7.30 (m, aromatic, 9H)
10c	CH_2Ph	90	133-135	$C_{23}H_{21}NO_2$	80.43 80.33	6.16 6.39	4.07 4.27	3350 1625	3.05 and 5.55 (dd, CH_2CO, 2H, J = 16 Hz), 3.50 (s, OH, 1H), 4.02 and 4.26 (dd, CH_2Ph, 2H, J = 4.6 Hz), 4.63 and 5.05 (dd, CH-CH, 2H, J = 5.3 Hz), 6.80-7.40 (m, aromatic, 14H)
10d	Ph	73	207-209	$C_{22}H_{19}NO_2$	80.22 80.17	5.81 5.71	4.25 4.28	3360 1630	2.18 and 3.05 (dd, CH_2CO, 2H, J = 19 Hz), 3.15 (s, OH, 1H), 4.80 and 5.12 (dd, CH-CH, 2H, J = 4 Hz), 6.80-7.60 (m, aromatic, 14H)

[a] Deuteriochloroform-dimethylsulphoxide-d_6.

column (35:1), with benzene as eluent, to yield in succession 4.5 g (78%) of **5**, identical in all respects to the sample described above, and 0.5 g (10%) of unreacted **4**.

General Procedure for 1-(α-Oxobenzyl)-1,4-dihydro-3(2*H*)-isoquinolinones (**7a-c**, Table 1).

To a cooled solution of primary amine (0.01 mole) in 10 ml of benzene, a solution of **5** (0.005 mole) in 25 ml of benzene was added dropwise. The reaction mixture was then allowed to react for 24 hours at room temperature with stirring. After filtration of the amine hydrobromide, the solution was washed with water, dried on sodium sulfate and concentrated to dryness *in vacuo*. The required compounds **7a-c** were recovered from the crude residue either by trituration with methanol (**7a**) or by chromatography on silica gel column and successive crystallization from methanol (**7b** and **7c**).

Methyl 2-[(α-Phenylamino)-(α-oxobenzyl)methyl]phenylacetate (**6**) and 1-(α-Oxobenzyl)-2-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone (**7d**).

A solution of 8 g (0.023 mole) of **5** and 4.41 g (0.05 mole) of aniline in 100 ml of benzene was stirred for 48 hours at room temperature. The aniline hydrobromide was filtered off, the organic layer was washed with water, dried and concentrated to dryness. The solid residue was crystallized from methanol to give 7.6 g (92%) of **6**, mp 131-132°; ir (nujol): 3355 (NH), 1725 ($COOCH_3$), 1680 (COPh) cm^{-1}; nmr (deuteriochloroform): δ 3.65 (s, CH_3, 3H), 3.75 and 4.05 (dd, CH_2CO, 2H, J = 16 Hz), 4.55 (s, NH, 1H), 6.35 (s, CH, 1H), 6.50-8.10 (m, aromatic, 14H).

Anal. Calcd. for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 77.11; H, 5.80; N, 4.06.

Alternatively the above condensation was carried out by refluxing for 24 hours to yield **6** (73%) and successively, by chromatography on silica gel column (35:1) eluting with chloroform, **7d** (16%) (Table 1).

Cyclization of **6** to **7d**.

A suspension of 0.5 g (0.0014 mole) of **6** in 5 ml of acetic acid was refluxed for 5 hours. After cooling, evaporation of the solvent left a solid residue which was triturated with methanol to give 0.25 g (55%) of **7d**.

General Procedure for 1-(α-Hydroxybenzyl)-1,4-dihydro-3(2*H*)-isoquinolinones (**10a-d**, Table 2).

A suspension of **7a-d** (0.005 mole) and 10% palladised charcoal (0.13-0.17 g) in anhydrous ethanol was hydrogenated in a Parr apparatus at 50° under 3 atmospheres of pressure. After 7 hours the uptake of hydrogen ceased, the catalyst was filtered off and washed with ethanol. The filtrate was concentrated to dryness under reduced pressure affording crude **10a-d**, which were purified by crystallization from methanol.

Reduction of **6** Affording Methyl 2-[(α-Phenylamino)-(α-hydroxybenzyl)-methyl]phenylacetate (**8**) and Methyl 2-[(α-Hydroxybenzyl)methyl]phenylacetate (**9**).

Following the above procedure a solution of 4 g (0.01 mole) of **6** in 50 ml of tetrahydrofuran-ethanol (1:1) was hydrogenated in the presence of 0.4 g of palladised charcoal. The catalyst was filtered off, the filtrate was evaporated to dryness *in vacuo* and the residue was triturated with 5 ml of ethanol yielding 0.6 g (15%) of unreacted **6**. The filtrate was then treated with a saturated solution of anhydrous hydrogen chloride in ether to give 1.3 g (31%) of **8** as the hydrochloride, mp 150-153° (anhydrous ethanol-ether); ir (nujol): 3280 (NH), 1740 ($COOCH_3$) cm^{-1}; nmr (deuteriodimethylsulfoxide): δ 3.20 (s, CH_2CO, 2H), 3.55 (s, CH_3, 3H), 4.90 and 5.25 (dd, CH-CH, 2H, J = 4 Hz), 6.50-7.50 (m, aromatic, 14H), 7.95 (broad s, NH + OH, 2H).

Anal. Calcd. for $C_{23}H_{23}NO_3$·HCl: C, 69.43; H, 6.08; N, 3.52; Cl, 8.92. Found: C, 69.27; H, 6.07; N, 3.49; Cl, 9.12.

The ethereal solution, after removal of **8**, was washed with 5% sodium hydrogencarbonate solution dried and concentrated to dryness. The resulting residue was then chromatographed on silica gel column (50:1), with benzene as eluent, to give 1.1 g (40%) of **9**, bp 194-196°/0.05 mm; ir (film): 3450 (OH), 1730 ($COOCH_3$) cm^{-1}; nmr (deuteriochloroform): δ 2.20

(s, OH, 1H), 3.05 (d, CH_2-CHPh, 2H, J = 6 Hz), 3.65 (s, CH_2CO, 2H), 3.70 (s, CH_3, 3H), 4.90 (t, CH, 1H), 7.15 and 7.25 (ds, aromatic, 9H).

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.39; H, 6.69.

Alternatively the above reduction was carried out at room temperature and atmospheric pressure affording the same products.

Cyclization of **8** to **10d**.

A solution of **8** (0.0017 mole), as free base, in 5 ml of acetic acid, was refluxed for 5 hours. After removing the solvent, the oily residue was triturated with ether to give 0.41 g (70%) of **10d**.

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