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A Facile Synthesis of 1,3,4,6-Tetrahydro-1,6-benzodiazocine-2,5-diones*

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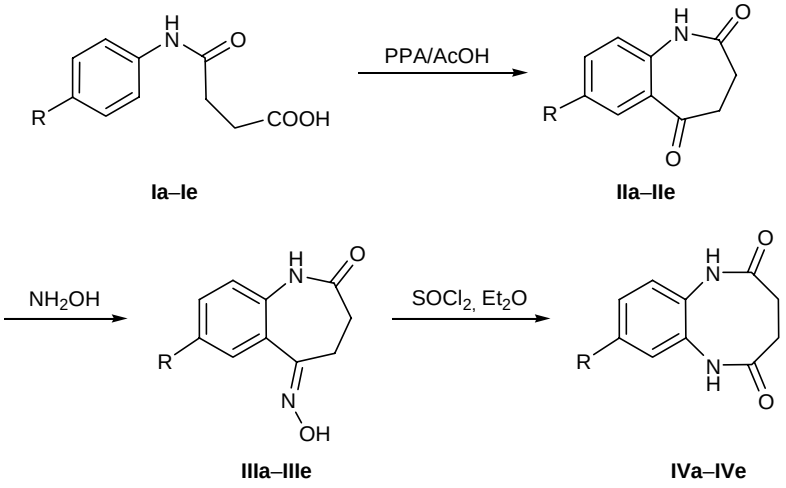
Abstract—1,3,4,6-Tetrahydro-1,6-benzodiazocine-2,5-diones were synthesized from 3,4-dihydro-1*H*-benzazepine-2,5-diones through the corresponding oximes using simple reagents and procedures.

Derivatives of 5,6-dihydro-6,11-dioxomorphanthridine 6-oxime are used as tranquilizers and antiepileptic agents [1]. 1,3,4-Trihydro-2,5-dioxomorphanthridine is the key intermediate product in the synthesis of a number of compounds for pharmacodynamic studies [2, 3]. Benzazepinediones **II** were synthesized previously by the Schmidt reaction with anthraquinone [4–6], followed by the Beckmann rearrangement of anthraquinone monooximes [7, 8]. Some diazocine derivatives exhibit amoebicidal activity [9], and several *N*-substituted aromatic acids have been proposed as nonsteroid antiinflammatory agents [10, 11]. We believe that the synthesis of dimeric anthranilic acid derivatives, specifically 7-substituted 1,3,4,6-tetrahydro-1,6-benzodiazocine-2,5-diones **IVa**–**IVe**, attracts considerable interest from the viewpoint of their pharmacological activity which could be comparable to that intrinsic to the monomeric acids. In addition, compounds **IV** could serve as prodrugs capable of releasing anthranilic acid via slow hydrolysis *in vivo*. As a result, the period of action should be longer at a smaller dose.

3,4-Dihydro-1*H*-1-benzazepine-2,5-diones **IIa**–**IIe** were synthesized in 65–81% yield by intramolecular

Scheme 1.



R = COOH (**a**), OH (**b**), NO_2 (**c**), OCH_3 (**d**), Cl (**e**).

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Yields, melting points, and elemental analyses of compounds **II**–**IV**

Comp. no.	R	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
IIa	COOH	79	268	60.25	4.12	6.35	$C_{11}H_9NO_4$	60.28	4.14	6.39
IIb	OH	75	192	62.78	4.70	7.30	$C_{10}H_9NO_3$	62.82	4.74	7.33
IIc	NO_2	81	171	54.52	3.61	12.70	$C_{10}H_8N_2O_4$	54.55	3.66	12.72
IId	OCH_3	77	221	64.36	5.42	6.75	$C_{11}H_{11}NO_3$	64.38	5.40	6.83
IIe	Cl	70	121	57.20	3.70	6.51	$C_{10}H_8ClNO_2$	57.30	3.85	6.68
IIIa	COOH	70	84	56.30	4.18	11.83	$C_{11}H_{10}N_2O_4$	56.41	4.30	11.96
IIIb	OH	78	162	58.16	4.75	13.47	$C_{10}H_{10}N_2O_3$	58.25	4.89	13.54
IIIc	NO_2	65	145	51.14	3.71	17.69	$C_{10}H_9N_3O_4$	51.07	3.86	17.87
IIId	OCH_3	72	253	59.79	5.38	12.67	$C_{11}H_{12}N_2O_3$	59.99	5.49	12.72
IIIe	Cl	67	191	53.36	3.89	12.32	$C_{10}H_9ClN_2O_2$	53.47	4.04	12.47
IVa	COOH	76	187	56.30	4.15	11.88	$C_{11}H_{10}N_2O_4$	56.41	4.30	11.96
IVb	OH	69	205	58.12	4.78	13.48	$C_{10}H_{10}N_2O_3$	58.25	4.89	13.54
IVc	NO_2	80	131	51.13	3.69	17.72	$C_{10}H_9N_3O_4$	51.07	3.86	17.87
IVd	OCH_3	78	167	59.89	5.35	12.63	$C_{11}H_{12}N_2O_3$	59.99	5.49	12.72
IVe	Cl	74	178	53.33	4.15	12.38	$C_{10}H_{10}ClN_2O_2$	53.47	4.04	12.47

condensation of succinic acid monoanilides **Ia**–**Ie** by the action of polyphosphoric acid in acetic acid. Initial amides **Ia**–**Ie** were obtained in quantitative yield by treatment of succinic anhydride with the corresponding substituted anilines [12]. Compounds **IIa**–**IIe** reacted with hydroxylamine hydrochloride to give oximes **IIIa**–**IIIe** in good yield. The latter were subjected to Beckmann rearrangement by the action of thionyl chloride in diethyl ether to afford the target benzodiazocines **IVa**–**IVe** (Scheme 1).

EXPERIMENTAL

The melting points were determined in open capillary on heating on a paraffin bath and were not corrected. The IR spectra were recorded in Nujol on a Perkin–Eimer 237 spectrophotometer. The ^{1}H NMR spectra were obtained from solutions in $CDCl_3$ using a Perkin–Elmer R-32 spectrometer; the chemical shifts were measured relative to TMS as internal reference.

7-Methoxy-3,4-dihydro-1*H*-1-benzazepine-2,5-dione (IId). A mixture of 2.23 g (0.01mol) of 3-(4-methoxyphenylcarbamoyl)propionic acid, polyphosphoric acid prepared from 10 g of P_2O_5 and 3 ml of H_3PO_4, and 20 ml of acetic acid was heated for 2 h at 95–100°C. The mixture was cooled, poured onto crushed ice, and left to stand for 2 h. The product was filtered off, washed with water, and recrystallized from acetic acid. Yield 1.57 g (77%), mp 221°C. IR spectrum, ν, cm^{-1}: 3280 br.s, 1710, 1690, 1665. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.5 t (2H, 3-H), 2.8 t (2H, 4-H), 4.2 s (3H, OCH_3), 7.27–8.0 m (4H, H_{arom}), 9.40 s (1H, CONH). Compounds **IIa**–**IIc** and **IIe** were synthesized in a similar way.

7-Methoxy-3,4-dihydro-1*H*-1-benzazepine-2,5-dione 5-oxime (IIId). A mixture of 2.05 g (0.01 mol) of compound **IId**, 0.7 g (0.01 mol) of hydroxylamine hydrochloride, 20 ml of ethanol, and 0.5 ml of pyridine was heated for 20 min under reflux on a water bath. The solvent was distilled off, the residue was treated with water (3×5 ml), and the mixture was stirred on cooling with ice until a solid precipitated. The product was filtered off, washed with water, and recrystallized from ethanol. Yield 1.58 g (72%), mp 253°C.

8-Methoxy-1,3,4,6-tetrahydro-1,6-benzodiazocine-2,5-dione (IVd). Oxime **IIId**, 2.2 g (0.01 mol), was dissolved in 20 ml of dry diethyl ether, 3 ml of thionyl chloride was added to the solution, and the mixture was stirred for 30 min. The solvent and excess thionyl chloride were distilled off, 25 ml of water was added to the residue, and the mixture was heated at the boiling point for several minutes. The product was filtered off, washed, and recrystallized from acetic acid. Yield 1.51 g (69%), mp 205°C. IR spectrum, ν, cm^{-1}: 3285, 1680, 1650. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.7 t (2H, 3-H), 3.0 t (2H, 4-H), 3.9 s (3H, OCH_3), 7.2–8.3 m (4H, H_{arom}), 9.2 s (1H, CONH).

Compounds **IVa**–**IVc** and **IVe** were synthesized in a similar way. The yields, melting points, and elemental analyses of compounds **II**–**IV** are given in table.

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