Synthesis of some 5-Aryl-4,5-dihydro[1]benzoxepin-3(2*H*)-ones and 5-Aryl-5,6,8,9-tetrahydro-7*H*-benzocyclohepten-7-ones from Benzoxepinoisoxazolone and Benzocycloheptaisoxazolone Derivatives

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Some 5-aryl-4,5-dihydro[1]benzoxepin-3(2*H*)-ones and 5-aryl-5,6,8,9-tetrahydro-7*H*-benzocyclohepten-7-ones were synthesized by hydrogenolytic cleavage of the isoxazole ring of 4-aryl-3-oxo-3,3a,4,10-tetrahydro[1]-benzoxepino[3,4-*c*]isoxazoles or 4-aryl-3-oxo-3a,4,9,10-tetrahydro-3*H*-benzo[4,5]cyclohepta[1,2-*c*]isoxazoles which in turn were prepared from ethyl 3-oxo-4-phenoxybutanoate or ethyl 3-oxo-5-phenylpentanoate by simple methods.

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The convenient methods available for the synthesis of 4,5-dihydro[1]benzoxepin-3(2*H*)-ones [1-4] and 5,6,8,9-tetrahydro-7*H*-benzocyclohepten-7-ones [5-12] are limited to the preparation of 5-unsubstituted [1-9] or 5,5-dimethyl [10-12] derivatives. We report here a new entry to these classes of bicyclic compounds through the intermediacy of benzoxepinoisoxazolones or benzocycloheptaisoxazolones which allow the synthesis of the hitherto unknown 5-aryl derivatives **10-11**.

4-Arylidene-3-phenoxymethyl or 3-(2-phenylethyl)isoxazol-5(4*H*)-ones **4** or **5** were easily obtained from the pot reaction between ethyl 3-oxo-4-phenoxybutanoate (**1**) or ethyl 3-oxo-5-phenylpentanoate (**2**), hydroxylamine and the appropriate aromatic aldehyde **3**. The reaction afforded a single (*Z*)-isomer in the case of compounds **4b** and **5a-c** or a respectively 9:1 mixture of (*Z*)- and (*E*)-isomers in the case of compounds **4a** and **4c**, as evidenced by the ^{1}H nmr spectra (Table 2). In the (*Z*)-isomer, the *ortho* protons of the arylidene group appeared in the 8-8.6 ppm region due to the magnetic anisotropy of the carbonyl group [13]. In

Scheme

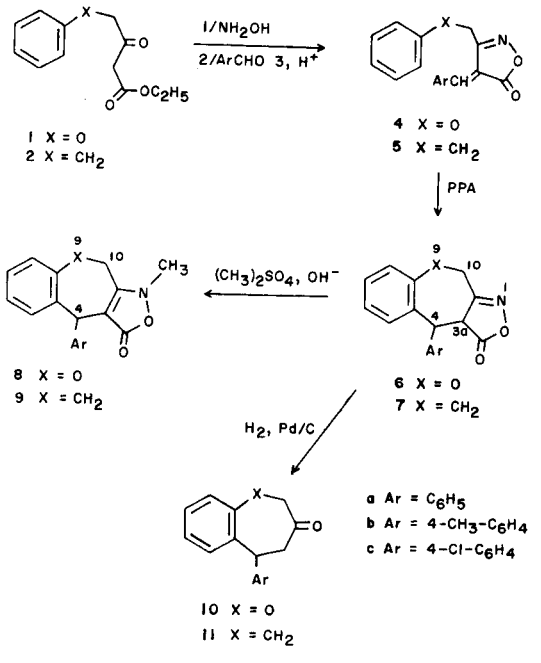

Table 1

Physical Data for Compounds **4**, **5**

Compound No.	Yield %	Mp (°C) Solvent	Molecular Formula	Analyses % Calcd./Found C	H	N	Cl	IR (cm^{-1}) (Potassium bromide)
4a	58	[a]	$C_{17}H_{13}NO_3$	73.11	4.69	5.02		1750, 1630
				73.26	4.64	5.03		
4b	60	154 [b] ethanol	$C_{18}H_{15}NO_3$	73.50	5.15	4.78		1755,1630
				73.65	5.15	4.88		
4c	57	[a]	$C_{17}H_{12}ClNO_3$	65.08	3.86	4.46	11.30	1740, 1620
				64.88	3.75	4.45	11.11	
5a	67	114 [b] ethanol	$C_{18}H_{15}NO_2$	77.96	5.45	5.05		1750, 1640
				78.02	5.75	4.76		
5b	66	90 [b] ethanol	$C_{19}H_{17}NO_2$	78.33	5.88	4.81		1750, 1625
				78.26	5.70	4.99		
5c	65	97 [b] ethanol	$C_{18}H_{14}ClNO_2$	69.34	4.53	4.49	11.37	1740, 1620
				69.29	4.61	4.33	11.39	

[a] 9:1 Mixture of (*Z*) and (*E*)-isomers. [b] (*Z*)-Isomer.

Table 2

Proton Magnetic Resonance Parameters of Compounds **4**, **5** in Deuteriochloroform

Compound No.	
4a	4.95 (s, 0.2H, (*E*)-isomer), 5.15 (s, 1.8H, (*Z*)-isomer), 6.93-7.70 (m, 8.2H), 7.93 (s, 0.9H, (*Z*)-isomer), 8.09 (s, 0.1H, (*E*)-isomer), 8.25-8.50 (m, 1.8H, (*Z*)-isomer)
4b	2.46 (s, 3H), 5.16 (s, 2H), 6.94-7.55 (m, 7H), 7.94 (s, 1H), 8.22-8.48 (m, 2H)
4c	4.94 (s, 0.2H, (*E*)-isomer), 5.19 (s, 1.8H, (*Z*)-isomer), 6.95-7.78 (m, 7.2H), 7.96 (s, 0.9H, (*Z*)-isomer), 8.15 (s, 0.1H, (*E*)-isomer), 8.31-8.57 (m, 1.8H, (*Z*)-isomer)
5a	2.75-3.26 (m, 4H), 7.16-7.78 (m, 9H), 8.16-8.40 (m, 2H)
5b	2.44 (s, 3H), 2.77-3.26 (m, 4H), 7.12-7.51 (m, 8H), 8.02-8.20 (m, 2H)
5c	2.77-3.27 (m, 4H), 7.10-7.58 (m, 8H), 8.10-8.34 (m, 2H)

Table 3

Physical Data for Compounds **6-9**

Compound No.	Yield %	Mp (°C) Solvent	Molecular Formula	Analyses % Calcd./Found C	H	N	Cl	IR (cm^{-1}) (Potassium bromide)
6a	52	180	$C_{17}H_{13}NO_3$	73.11	4.69	5.02		3300-2500,
		Acetonitrile		73.15	4.78	4.98		1700 sh, 1685
6b	62	208	$C_{18}H_{15}NO_3$	73.70	5.15	4.78		3200-2500,
		Acetonitrile		73.80	5.25	4.81		1700
6c	71	182	$C_{17}H_{12}ClNO_3$	65.08	3.86	4.46	11.30	3300-2550,
		Acetonitrile		64.92	3.71	4.50	11.20	1695, 1680 sh
7a	70	236	$C_{18}H_{15}NO_2$	77.96	5.45	5.05		3300-2400,
		Acetonitrile		77.68	5.42	5.09		1705 sh, 1690
7b	75	210	$C_{19}H_{17}NO_2$	78.33	5.88	4.81		3200-2200,
		Acetonitrile		78.29	5.88	4.82		1685, 1665
7c	65	204	$C_{18}H_{14}ClNO_2$	69.34	4.53	4.49	11.37	3300-2400,
		Acetonitrile		68.81	4.45	4.59	11.27	1695, 1675
8a	90	230	$C_{18}H_{15}NO_3$	73.70	5.15	4.78		1730
		Acetonitrile		73.63	5.19	4.87		
8b	55	147	$C_{19}H_{17}NO_3$	74.25	5.58	4.56		1735
		Acetonitrile		73.94	5.58	4.50		
8c	71	174	$C_{18}H_{14}ClNO_3$	65.96	4.30	4.27	10.82	1735
		Acetonitrile		65.96	4.32	4.24	10.64	
9a	60	168	$C_{19}H_{17}NO_2$	78.33	5.88	4.81		1735
		Acetonitrile		78.35	5.90	4.82		
9b	55	184	$C_{20}H_{19}NO_2$	78.66	6.27	4.59		1720
		Acetonitrile		78.41	6.29	4.62		
9c	60	157	$C_{19}H_{16}ClNO_2$	70.04	4.95	4.30	10.89	1730
		Acetonitrile		69.87	5.03	4.17	10.55	

Table 4

Pertinent ^{1}H-NMR Spectra Data of Compounds **6-9**

Compound No.	Solvent	H-4 (s)	H-9	H-10
6a	DMSO-d_6	4.94		4.79, 5.26 [a]
6b	DMSO-d_6	4.90		4.77, 5.23 [a]
6c	DMSO-d_6	4.96		4.79, 5.26 [a]
7a	DMSO-d_6	5.01	2.36 - 3.06 (m)	
7b	DMSO-d_6	4.94	2.32 - 3.06 (m)	
7c	DMSO-d_6	4.99	2.35 - 3.04 (m)	
8a	Deuteriochloroform	5.00		4.68, 5.10 [a]
8b	Deuteriochloroform	4.98		4.67, 5.08 [a]
8c	Deuteriochloroform	4.96		4.68, 5.09 [a]
9a	Deuteriochloroform	5.14	2.42 - 3.10 (m)	
9b	Deuteriochloroform	5.10	2.42 - 3.10 (m)	
9c	Deuteriochloroform	5.09	2.43 - 3.04 (m)	

[a] 2d, 2H, AB System, J_{AB} = 17 Hz.

Table 5

Physical Data for Compounds **10**, **11**

Compound No.	Yield %	Mp (°C) Solvent	Molecular Formula	Analyses Calcd./Found C	H	Cl	IR (cm^{-1}) (chloroform)
10a	60	104 hexane	$C_6H_{14}O_2$	80.64 80.78	5.92 6.10		1725
10b	60	91 hexane	$C_{17}H_{16}O_2$	80.92 80.84	6.39 6.44		1725
10c	63	70 hexane	$C_{16}H_{13}ClO_2$	70.46 70.66	4.80 4.88	13.00 12.72	1735
11a	55	80 hexane	$C_{17}H_{16}O$	86.40 86.32	6.83 7.03		1700
11b	80	63 hexane	$C_{18}H_{18}O$	86.36 86.14	7.25 7.42		1705
11c	70	73 hexane	$C_{17}H_{15}ClO$	75.40 75.57	5.58 5.88	13.09 14.21 [a]	1705

[a] No correct analysis could be obtained.

Table 6

Proton Magnetic Resonance Parameters of Compounds **10**, **11** in Deuteriochloroform

Compound No.	
10a	3.04-3.78 (m, 2H, AB part of an ABX system, J_{AB} = 13 Hz), 4.24-4.70 (m, 3H, X part of an ABX system, and AB system, J_{AB} = 17 Hz), 6.80-7.45 (m, 9H)
10b	2.31 (s, 3H), 3.03-3.55 (m, 2H, AB part of an ABX system, J_{AB} = 13 Hz), 4.23-4.68 (m, 3H, X part of an ABX system, and AB system, J_{AB} = 17 Hz), 6.85-7.43 (m, 8H)
10c	3.00-3.65 (m, 2H, AB part of an ABX system, J_{AB} = 13 Hz), 4.20-4.68 (m, 3H, X part of an ABX system, and AB system, J_{AB} = 17 Hz), 6.79-7.45 (m, 8H)
11a	2.45-3.45 (m, 6H), 4.40-4.54 (m, 1H, X part of an ABX system), 6.68-7.65 (m, 9H)
11b	2.33 (s, 3H), 2.50-3.60 (m, 6H), 4.35-4.53 (m, 1H, X part of an ABX system), 6.85-7.73 (m, 8H)
11c	2.48-3.75 (m, 6H), 4.35-4.53 (m, 1H, X part of an ABX system), 6.68-7.80 (m, 8H)

the case of a mixture of (*Z*)- and (*E*)-isomers, the (*E*)-isomers were diagnosed by comparison of their vinylic and methylene protons chemical shifts with those of the (*Z*)-isomers, according to the literature data [13].

The isoxazolones **4** or **5** were converted to the tricyclic system **6** or **7** by acid-catalyzed cyclization, using polyphos phoric acid. Unfortunately, when Ar = 4-CH_3O-C_6H_4, under a variety of conditions, we obtained a complicated mixture which was not further investigated. Treatment of compounds **6** or **7** with dimethyl sulfate, in basic conditions, furnished the *N*-methyl derivatives **8** or **9**. The structures of the tricyclic compounds **6**, **7**, **8** and **9** were proved by the microanalytical and spectral data (Tables 3 and 4). Compounds **6** and **7** exist as enol tautomers in DMSO-d_6 solution, as evidenced by the absence of signal for a proton in the C-3a position; however, the presence of a broad signal (3.4 ppm) for one proton (OH or NH) exchangeable with deuterium oxide, was observed only in the spectra of compounds **6a** and **6b**.

The reductive ring opening of the isoxazoles **6** or **7** followed by hydrolysis and decarboxylation of the resulting β-enaminocarboxylic acids afforded the bicyclic ketones **10** or **11**. The structures of these compounds were in agreement with the microanalytical and spectral data (Tables 5 and 6).

EXPERIMENTAL

All melting points were determined on a Kofler block apparatus and are uncorrected. The infrared spectra were recorded on a Beckmann Acculab 2 spectrometer. The proton nmr spectra were recorded using a Brücker WP 80 spectrometer. The chemical shifts reported are in parts per million from internal TMS. Elemental analysis were performed by Microanalytical Laboratory, Centre National de la Recherche Scientifique, 69390 Vernaison, France.

The starting compounds **1** [14] and **2** [15] were prepared as previously described.

4-Arylidene-3-phenoxymethylisoxazole-5(4*H*)-ones **4** and 4-Arylidene-3-(2-phenylethyl)isoxazol-5(4*H*)-ones **5**. General Procedure.

To a solution of hydroxylamine hydrochloride (0.7 g, 10 mmoles), in water (4 ml) was added aniline (0.93 g, 10 mmoles), the β-keto ester **1** or **2** (10 mmoles) and methanol (20 ml). The solution was allowed to stand at room temperature for 4 hours. The solution was then poured into ice water (150 ml) and extracted with methylene chloride (3 x 50 ml). The organic solution was washed with water, dried and evaporated. To the residue, the aromatic aldehyde **3** (15 mmoles) and ethanolic hydrogen chloride (prepared from 10 ml of absolute ethanol and 0.3 ml of acetyl chloride) were added. After standing for a night, the mixture was cooled

at 0°. The precipitated solid was collected, washed with ether and recrystallized from ethanol (Tables 1 and 2).

4-Aryl-3-oxo-3,3a,4,10-tetrahydro[1]benzoxepino[3,4-*c*]isoxazoles **6** and 4-Aryl-3-oxo-3a,4,9,10-tetrahydro-3*H*-benzo[4,5]cyclohepta[1,2-*c*]isoxazoles **7**. General Procedure.

A mixture of 4-arylideneisoxazolone **4** or **5** (10 mmoles) and polyphosphoric acid (orthophosphoric acid/phosphorus pentoxide = 1:1, 100 g) was stirred at 95° for 45 minutes. The resultant mixture was poured into crushed ice and extracted with ethyl acetate (4 x 50 ml). The ethyl acetate extract was washed with water and dried. After evaporation of the solvent, the crude product (yields, 85-90%) was sufficiently pure to be used for methylation reaction (see below). Recrystallization from acetonitrile gave pure compounds **6** or **7** Tables 3 and 4).

4-Aryl-1-methyl-3-oxo-1,3,4,10-tetrahydro[1]benzoxepino[3,4-*c*]isoxazoles **8** and 4-Aryl-1-methyl-3-oxo-1,4,9,10-tetrahydro-3*H*-benzo[4,5]cyclohepta-[1,2-*c*]isoxazoles **9**. General Procedure.

To a stirred solution of the crude compounds **6** or **7** (10 mmoles) in 2*N* potassium hydroxide (50 ml) cooled at 0°, was added dropwise, dimethyl sulfate (3 ml, 32 mmoles). The mixture was allowed to stand at room temperature for 2 hours, then basified and stirred again for 30 minutes. The reaction mixture was diluted with water (50 ml) and extracted with ethyl acetate. The combined extracts were dried, evaporated and the residue was recrystallized from acetonitrile to afford the pure compounds **8** or **9** (Tables 3 and 4).

5-Aryl-4,5-dihydro[1]benzoxepin-3(2*H*)-ones (**10**) and 5-Aryl-5,6,8,9-tetrahydro-7*H*-benzocyclohepten-7-ones (**11**). General Procedure.

The ethyl acetate extract of compounds **6** or **7**, saturated with water (see above) and 10% palladium on charcoal (1 g) were stirred in a hydrogen atmosphere at room temperature. After uptake of the calculated amount of hydrogen (~ 15 minutes), the reaction mixture was stirred for an additional hour to achieve the hydrolysis of the β-enaminoacid and the subsequent decarboxylation. The catalyst was filtered off and washed with warm ethyl acetate. Evaporation of the solvent left a solid which was column chromatographed on silica gel (30 g), eluting with methylene chloride (**10a,b**; **11a,b**) or hexane/ethyl acetate 1:9 (**10c**, **11c**). Analytically pure samples were obtained by recrystallization from hexane (Tables 5 and 6).

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