Synthesis of Some 4*H*,10*H*[1]Benzoxepino[3,4-*c*]pyrazol-4-one Derivatives

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1*H*(or 2*H*),4*H*10*H*[1]Benzoxepino[3,4-*c*]pyrazol-4-ones were prepared from phenoxymethylpyrazolecarboxylic acids which in turn were synthesized from simple starting materials. Different pathways to allow the predominant formation of the N-1 or N-2 substituted derivatives are described. The isomeric 1 or 2-substituted structures were supported by ^{13}C-nmr.

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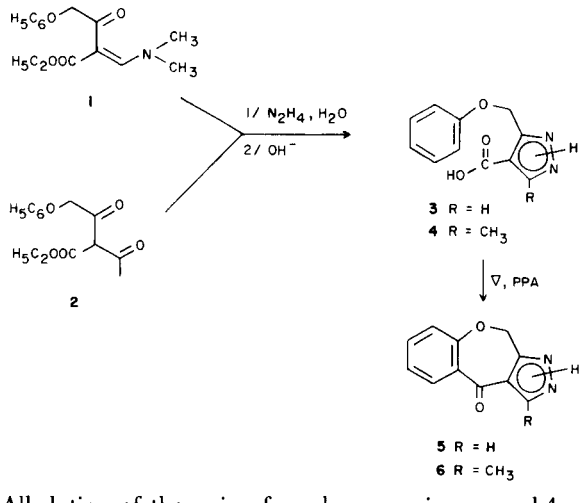
Heterobenzoxepin analogs of 6,11-dihydro-11-oxodibenz[*b*,*e*]oxepin are compounds of practical interest because of their biological activities [1-7]. Examples of a pyrazole ring as the heterocycle moiety are limited to 1*H*(or 2*H*),4*H*,10*H*[1]benzoxepino[3,4-*c*]pyrazol-4-ones which were synthesized by reaction of hydrazine hydrate with 5-hydroxy-3-oxo-2,3-dihydro-1-benzoxepin-4-carboxaldehyde [4]. We have explored an alternative route to 1*H*(or 2*H*),4*H*,10*H*[1]benzoxepino[3,4-*c*]pyrazol-4-ones starting from ethyl 3-oxo-4-phenoxybutanoate derivatives. Different pathways to allow the predominant or exclusive formation of the 1 or 2-substituted benzoxepinopyrazol-4-ones have been investigated.

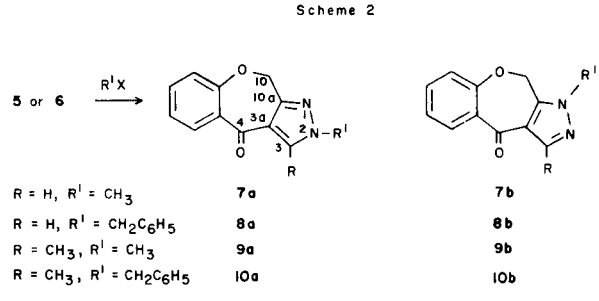
Reaction of hydrazine hydrate with ethyl 2-dimethylaminomethylene-3-oxo-4-phenoxybutanoate (**1**) or ethyl 2-acetyl-3-oxo-4-phenoxybutanoate (**2**), followed by basic hydrolysis afforded 3(or 5)-phenoxymethylpyrazol-4-carboxylic acid (**3**) or (**4**). Cyclization of the acid **3** or **4** by means of polyphosphoric acid gave rise to 1*H*(or 2*H*),-4*H*,10*H*[1]benzoxepino[3,4-*c*]pyrazole (**5**) or (**6**).

Scheme 1



Alkylation of the anion from benzoxepinopyrazol-4-one **5** or **6** by methyl iodide or benzyl chloride produced a mixture of isomeric compounds. The main product of the reaction was the 2-alkyl derivative (series **a**), 75% and the minor compound the 1-alkyl derivative (series **b**), 25%, as shown by the ^{1}H and ^{13}C-nmr studies. Pure compounds 2*H*,4*H*,10*H*[1]benzoxepino[3,4-*c*]pyrazol-4-ones **7a-10a** were easily obtained by column chromatography in reasonable yields (55-70%).

Scheme 2



Valuable access to 1*H*,4*H*,10*H*[1]benzoxepino[3,4-*c*]pyrazol-4-ones **7b-10b** and **20** and **21** (R^{1} = Ph), was achieved by cyclization of 1-substituted-5-phenoxymethylpyrazol-4-carboxylic acids **11b, 12, 13, 17-19**, using polyphosphoric acid. These precursors were obtained by two different routes according to the nature of the substituent R. When R = H, reaction of compound **1** with an appropriate hydrazine (R^{1}-NH-NH$_2$) followed by basic hydrolysis af-

Scheme 3

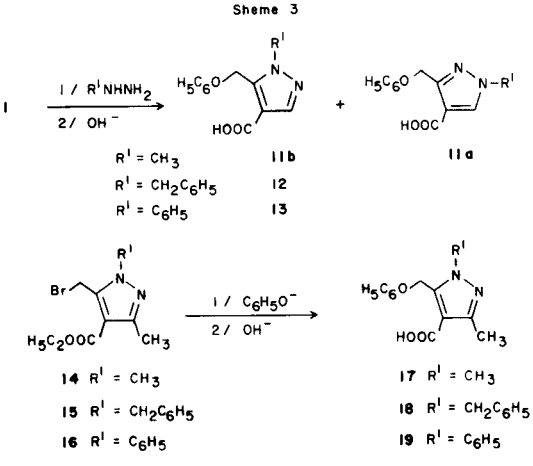


Table 1

Pertinent ^{13}C-NMR Spectral Data of Benzoxepinopyrazol-4-ones **5, 6, 7, 9** (Hexadeuterioacetone) (δ ppm, J Hz [a])

Product No.	R	R^1	C-3	C-3a	C-4	C-10	C-10a
5	H	—	135.8 [b]	122.6	181.9	67.8	150.9 [f]
7a	H	CH_3	136.1 [c]	122.9	181.5	69.0	152.1 [f]
7b	H	CH_3	140.5 [b]	123.3	181.2	66.4	144.9 [g]
6	CH_3	—	147.9 [d]	118.5	182.6	69.3	152.1 [h]
9a	CH_3	CH_3	146.5 [e]	119.2	182.4	69.3	151.2 [h]
9b	CH_3	CH_3	151.6 [d]	120.0	182.1	66.5	145.4 [i]

[a] Determined by examination of the coupled spectra. [b] d, ^1J = 190. [c] d q, ^1J = 190, ^3J = 2.5. [d] q, ^2J = 7. [e] This signal is significantly broadened by the ^2J and ^3J long range proton-carbon coupling with the methyl protons and with the *N*-methyl protons. [f] This signal is broadened by the ^2J and ^3J long range proton-carbon coupling with the methylene protons and with the proton at C-3. [g] This signal is significantly broadened by the ^2J and ^3J long range proton-carbon coupling with the methylene protons and with the *N*-methyl protons and the proton at C-3. [h] t, ^2J = 4. [i] This signal is significantly broadened by the ^2J and ^3J long range proton-carbon coupling with the methylene protons and with the *N*-methyl protons.

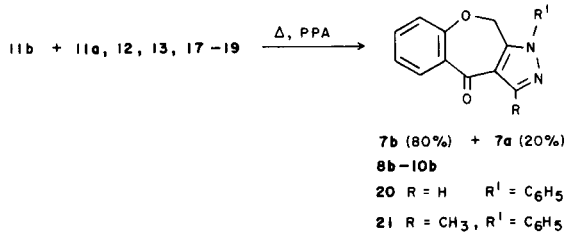
Table 2

Physical Data for Compounds **3, 4, 11a + 11b, 12, 13, 17-19**

Compound No.	Yield %	Mp (°C) Solvent	Molecular Formula	Analyses % Calcd./Found C	H	N
3	50	275 ethanol	$C_{11}H_{10}N_2O_3$	60.54 60.26	4.62 4.69	12.84 12.75
4	50	>280 ethanol	$C_{12}H_{12}N_2O_3$	62.06 61.60	5.21 5.27	12.06 12.10
11a + 11b	80	[a] acetonitrile	$C_{12}H_{12}N_2O_3$	62.06 61.95	5.21 5.34	12.06 12.09
12	75	190 acetonitrile	$C_{18}H_{16}N_2O_3$	70.11 70.18	5.23 5.16	9.09 9.11
13	85	140 acetonitrile	$C_{17}H_{14}N_2O_3$	69.37 69.45	4.80 4.96	9.52 9.51
17	70	178 acetonitrile	$C_{13}H_{14}N_2O_3$	63.40 63.34	5.73 5.80	11.38 11.53
18	75	161 acetonitrile	$C_{19}H_{18}N_2O_3$	70.79 69.43 [b]	5.63 5.62	8.69 8.68
19	65	182 acetonitrile	$C_{18}H_{16}N_2O_3$	70.11 70.10	5.23 5.33	9.09 8.91

[a] Mixture **11a + 11b** in a ratio 1:4. [b] No correct analysis could be obtained.

forded a single isomer **12** (R^1 = CH_2-Ph) or **13** (R^1 = Ph) or an isomeric mixture **11a + 11b** (R^1 = CH_3) respectively in a ratio 1:4. When R = CH_3, nucleophilic substitution of 1-substituted-5-bromomethyl-4-ethoxycarbonyl-3-methylpyrazoles **14-16** [8,9] by sodium phenoxide and subsequent basic hydrolysis gave rise to the phenoxymethylpyrazole acids **17-19** (Scheme 3).



Proof of the structures **a** or **b** was clearly established by ^{13}C-nmr comparison of the C-3, C-3a and C-10a signals of the isomeric pairs. It is known that a carbon adjacent to a substituted nitrogen (pyrrole-like) resonates upfield of the signal of the same carbon in the other isomer (pyridine-like) in isomeric pyrazoles [10-14]. The carbon shifts are listed in Table 1, they were assigned on the basis of chemical shift data in the pyrazole literature, off-resonance decoupling and observation of the coupled spectra [10-14]. The ^{13}C-nmr chemical shifts of the *N*-unsubstituted compounds **5** and **6** in tautomeric equilibrium, are closer in magnitude to the corresponding chemical shifts in the 2-methyl derivatives than to those in the 1-methyl compounds. These results would strongly suggest that the unalkylated derivatives exist predominantly, at least in hexadeuterioacetone, in the tautomeric form N(2H).

Table 3

Proton Magnetic Resonance Parameters of Compounds **3**, **4**, **11a + 11b**, **12**, **13**, **17-19** in DMSO-d_6

Compound	
3	5.28 (s, 2H), 6.93-7.47 (m, 5H), 8.13 (s, 1H), 12.9 (br, 2H exchangeable with deuterium oxide)
4	2.42 (s, 3H), 5.30 (s, 2H), 6.75-7.45 (m, 5H), 9.5 (br, 2H, exchangeable)
11a + 11b	3.68 (s, 3H), 5.14 (s, 0.4H), 5.45 (s, 1.6H), 6.78-7.41 (m, 5H), 7.76 (s, 0.8H), 8.14 (s, 0.2H), 12.5 (br, 1H, exchangeable)
12	5.46 (s, 4H), 6.82-7.42 (m, 10H), 7.93 (s, 1H), 12.6 (br, 1H, exchangeable)
13	5.35 (s, 2H), 6.87-7.72 (m, 10H), 8.17 (s, 1H), 12.9 (br, 1H, exchangeable)
17	2.50 (s, 3H), 3.95 (s, 3H), 5.51 (s, 2H), 6.95-7.51 (m, 5H), 11.0 (br, 1H exchangeable)
18	2.35 (s, 3H), 5.36 (s, 2H), 5.44 (s, 2H), 6.81-7.42 (m, 10H), 12.5 (br, 1H exchangeable)
19	2.58 (s, 3H), 5.25 (s, 2H), 6.80-7.68 (m, 10H), 12.6 (br, 1H exchangeable)

EXPERIMENTAL

All melting points were determined on a Kofler block apparatus. The infrared spectra were recorded on a Beckman Acculab 2 spectrometer in chloroform. The ultraviolet spectra were obtained on a Beckman DB spectrometer in ethanol. The proton nmr spectra were recorded using a Brucker WP 80 spectrometer; ^{13}C-nmr spectra were obtained with a Varian XL-100-12FT. 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.

Ethyl 3-oxo-4-phenoxybutanoate [14], and compounds **14** [9], **15** and **16** [8] were prepared as previously described.

Ethyl 2-Dimethylaminomethylene-3-oxo-4-phenoxybutanoate (**1**).

A solution of dimethylformamide dimethyl acetal (1.90 g, 0.016 mole), ethyl 3-oxo-4-phenoxybutanoate (2.22 g, 0.010 mole) in benzene (30 ml) was refluxed for two hours. Evaporation of the solvent under reduced pressure afforded crude compound **1** which was used for the next step without further purification.

Ethyl 2-Acetyl-3-oxo-4-phenoxybutanoate (**2**).

To a stirred suspension of magnesium ethoxide (12.5 g, 0.11 mole) in dry toluene (150 ml) was added under reflux, ethyl 3-oxobutanoate (13 g, 0.10 mole). The mixture was refluxed with stirring for two hours. After cooling to room temperature, a solution of phenoxyacetyl chloride (17.2 g, 0.10 mole) in acetonitrile (100 ml) was added with stirring. The mixture was allowed to stand at room temperature for two hours, then poured on to 10% sulfuric acid. After extraction with ethyl ether, the organic layer was dried and the solvent evaporated. The residue was distilled to give compound **2**, Eb 1 mm Hg = 155°, yield = 79%, which was directly used in the subsequent reaction without further purification.

3(or 5)-Phenoxymethylpyrazole-4-carboxylic Acids **3** and **4**. General Procedure.

A solution of compound **1** or **2** (0.010 mole) and hydrazine hydrate (0.5 g, 0.010 mole) in acetic acid (20 ml) was allowed to stand overnight at room temperature. Acetic acid was evaporated *in vacuo* and chloroform added to the residue. The solution was washed with 5% sodium hydrogenocarbonate, water and then dried. Chloroform was evaporated. To the residue was added 0.7 *N* ethanolic potassium hydroxide (50 ml) and the

Table 4

Physical Data for Compounds **5**, **6**, **7a-10a**, **7b-10b**, **20**, **21**

Compound No.	Yield %	Mp (°C) Solvent	Molecular Formula	Analyses % Calcd./Found C	H	N	UV λ max nm [a]	IR (cm^{-1})
5	80	155 [a] acetonitrile	$C_{11}H_8N_2O_2$	65.99 65.70	4.03 4.03	13.99 13.89	268 (13400)	3450, 3220, 1635, 1600
6	65	190 acetonitrile	$C_{12}H_{10}N_2O_2$	67.28 67.20	4.71 4.92	13.08 12.70	270 (11900)	3450, 3250 1635, 1600
7a [b]	60	130 [c]	$C_{12}H_{10}N_2O_2$, H_2O	62.06 62.25	5.21 5.08	12.06 12.08	272 (12800)	1635 1600
7b	70	152 [c]	$C_{12}H_{10}N_2O_2$	67.28 67.28	4.71 4.73	13.08 13.38	272 (10500)	1640 1600
8a	58	178 [c]	$C_{18}H_{14}N_2O_2$	74.47 74.61	4.86 4.86	9.65 9.73	273 (15500)	1635 1600
8b	80	127 cyclohexane	$C_{18}H_{14}N_2O_2$	74.47 74.51	4.86 4.98	9.65 9.47	273 (12500)	1640 1600
9a	70	102 [c]	$C_{13}H_{12}N_2O_2$	68.41 68.20	5.30 5.28	12.27 12.03	274 (12800)	1635 1600
9b	79	118 acetonitrile	$C_{13}H_{12}N_2O_2$	68.41 68.21	5.30 5.27	12.27 12.07	276 (7700)	1635 1600
10a	56	129 [c]	$C_{19}H_{16}N_2O_2$	74.98 74.78	5.30 5.32	9.21 9.09	276 (15200)	1635 1600
10b	80	80 [c]	$C_{19}H_{16}N_2O_2$	74.98 75.16	5.30 5.37	9.21 8.98	276 (12900)	1635 1600
20	75	126 ethanol	$C_{17}H_{12}N_2O_2$	73.90 73.97	4.38 4.37	10.14 10.08	280 (15700)	1640 1600
21	78	131 hexane/ethyl acetate 1:1	$C_{18}H_{14}N_2O_2$	74.47 74.40	4.86 4.62	9.65 9.52	282 (15100)	1640 1600

[a] Lit mp 146-148° [4]. [b] This compound recrystallized from ethanol with one molecule of water. [c] Purified by column chromatography.

Table 5

Proton Magnetic Resonance Parameters of Compounds **5**, **6**, **7a-10a**, **7b-10b**, **20**, **21** in DMSO-d_6

Compound	
5	5.26 (s, 2H), 7.15-7.73 (m, 3H), 8.05 (2d, 1H, J_{ortho} = 8 Hz, J_{meta} = 2 Hz), 8.42 (s, 1H), 13.5 (br, 1H exchangeable with deuterium oxide)
6	2.65 (s, 3H), 5.20 (s, 2H), 7.10-7.65 (m, 3H), 8.20 (2d, 1H, J_{ortho} = 8 Hz, J_{meta} = 2 Hz), 9.8 (br, 1H exchangeable)
7a	3.90 (s, 3H), 5.17 (s, 2H), 7.10-7.70 (m, 3H), 7.93-8.10 (m, 1H), 8.45 (s, 1H)
7b	3.68 (s, 3H), 5.40 (s, 2H), 7.18-7.75 (m, 3H), 7.95-8.15 (m, 2H with a singlet at 8.04)
8a	5.18 (s, 2H), 5.40 (s, 2H), 7.10-7.65 (m, 8H), 7.91-8.15 (m, 1H), 8.68 (s, 1H)
8b	5.40 (s, 2H), 5.46 (s, 2H), 7.10-7.68 (m, 8H), 7.95 (2d, 1H, J_{ortho} = 8 Hz, J_{meta} = 2 Hz), 8.10 (s, 1H)
9a	2.65 (s, 3H), 3.85 (s, 3H), 5.20 (s, 2H), 7.20-7.82 (m, 3H), 8.20 (2d, 1H, J_{ortho} = 8 Hz, J_{meta} = 2 Hz)
9b	2.45 (s, 3H), 3.85 (s, 3H), 5.42 (s, 2H), 7.22-7.83 (m, 3H), 8.10 (2d, 1H, J_{ortho} = 8 Hz, J_{meta} = 2 Hz)
10a	2.64 (s, 3H), 5.18 (s, 2H), 5.43 (s, 2H), 7.10-7.70 (m, 8H), 8.08 (2d, 1H, J_{ortho} = 8 Hz, J_{meta} = 2 Hz)
10b	2.45 (s, 3H), 5.36 (s, 2H), 5.42 (s, 2H), 7.10-7.66 (m, 8H), 8.04 (2d, 1H, J_{ortho} = 8 Hz, J_{meta} = 2 Hz)
20	5.43 (s, 2H), 7.18-7.83 (m, 8H), 8.04 (2d, 1H, J_{ortho} = 8 Hz, J_{meta} = 2 Hz), 8.35 (s, 1H)
21	2.55 (s, 3H), 5.35 (s, 2H), 7.12-7.73 (m, 8H), 8.03 (2d, 1H, J_{ortho} = 8 Hz, J_{meta} = 2 Hz)

solution was refluxed for four hours. After evaporation of ethanol, water was added. The aqueous layer was extracted with ethyl ether and then acidified with acetic acid. The crude pyrazole acid **3** or **4** was collected by filtration and recrystallized (Table 2 and 3).

1-Substituted-5-phenoxymethylpyrazole-4-carboxylic Acids **11a + 11b**, **12** and **13**. General Procedure.

A solution of compound **1** and the appropriate hydrazine (0.010 mole) in ethanol (50 ml) was allowed to stand overnight at room temperature (methylhydrazine or benzylhydrazine) or was refluxed for six hours (phenylhydrazine). After evaporation of the solvent *in vacuo*, the residue was submitted to basic hydrolysis as described above except that the aqueous layer was acidified with concentrated hydrochloric acid. The crude pyrazole acids **11a + 11b**, **12** and **13** were recrystallized (Tables 2 and 3).

1-Substituted-3-methyl-5-phenoxymethylpyrazole-4-carboxylic Acids (**17-19**). General Procedure.

To a solution of sodium ethoxide (0.030 mole), prepared from sodium (0.69 g) in absolute ethanol (100 ml) was added a solution of phenol (3.1 g, 0.033 mole) in absolute ethanol (50 ml) and then bromomethylpyrazole **14**, **15** or **16** (0.30 mole). The mixture was refluxed for four hours. Ethanol was evaporated *in vacuo* and ethyl ether was added to the residue. The organic layer was washed with water and dried. Ether was removed and the residue was submitted to basic hydrolysis as described above. The crude pyrazole acids obtained by acidification with concentrated hydrochloric acid were recrystallized (Tables 2 and 3).

1*H*(or 2*H*),4*H*,10*H*[1]Benzoxepino[3,4-*c*]pyrazol-4-ones **5** and **6** and 1*H*,4*H*,10*H*[1]Benzoxepino[3,4-*c*]pyrazol-4-ones **7b-10b**, **20** and **21**. General Procedure.

A mixture of pyrazole acid **3**, **4**, **11a + 11b**, **12**, **13**, **17**, **18** or **19** (0.010 mole) and polyphosphoric acid (phosphoric acid/phosphorus pentoxide, 1/1, 60 g) was stirred at 130° for 40 minutes. The resultant mixture was poured into crushed ice and extracted with ethyl acetate. The extracts were dried and the solvent evaporated under reduced pressure.

Work-up Procedure for Products **5**, **6**, **8b**, **9b**, **20** and **21**.

The residual product was recrystallized from a suitable solvent (Tables 4 and 5).

Work-up Procedure for Products **7b** and **10b**.

The residual product was column chromatographed on silica gel (150 g) eluting with ethyl ether (**7a + 7b**) or methylene chloride (**10b**). The compound **7a**, 0.3 g (14%) was first eluted and then the compound **7b**, 1.5 g (70%). Analytical samples were obtained by recrystallization from ethanol (**7b**) or hexane/cyclohexane 3:7 (**10b**) (Tables 4 and 5).

2*H*,4*H*,10*H*[1]Benzoxepino[3,4-*c*]pyrazol-4-ones (**7a-10a**). General Procedure.

A mixture of benzoxepinopyrazol-4-one **5** or **6** (0.010 mole), potassium carbonate (1.5 g, 0.011 mole), methyl iodide (7.1 g, 0.050 mole) or benzyl chloride (1.4 g, 0.011 mole) in dimethylsulfoxide (10 ml) was stirred overnight at room temperature. Water was added and the resulting mixture was extracted with ethyl acetate. The extracts were washed with 5% aqueous sodium hydroxide (10 ml) and water, then dried and evaporated to leave a mixture of isomeric benzoxepinopyrazol-4-ones **7-10a** and **b** respectively in a ratio of 3:1. The crude mixture was column chromatographed on silica gel (150 g) eluting with ethyl ether (**7** and **9**) or methylene chloride (**8** and **10**). The compounds of series **a** were first eluted: **7a**, 1.3 g (60%); **8a**, 1.7 g (58%); **9a**, 1.6 g (70%); **10a**, 1.7 g (56%); then a mixture **a + b: 8a + 8b**, 0.5 g (17%); **10a + 10b**, 0.5 g (14%) and finally the compounds of series **b: 7b**, 0.5 g (23%); **8b**, 0.4 g (14%); **9b**, 0.5 g (22%); **10b**, 0.5 g (14%). Analytical samples were obtained by recrystallization from ethanol (**7a**), ethyl acetate (**8a**), cyclohexane (**9a**) or hexane/cyclohexane 1:1 (**10a**) (Tables 4 and 5).

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