Synthesis of some Isomeric 4,11-Dihydro-5*H*-[1]benzoxocino[4,3-*d*] or [3,4-*c*]isoxazol-5-ones and Isomeric 4,5,10,11-Tetrahydrobenzo[5,6]-cycloocta[2,1-*d*] or [1,2-*c*]isoxazol-5-ones

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The title compounds were prepared by acid-catalyzed cyclization of aryloxymethyl- or (2-arylethyl)-4-carboxymethylisoxazoles which in turn were synthesized from aryloxymethyl- or (2-arylethyl)isoxazole-4-carboxylic acids by Arndt-Eistert homologation.

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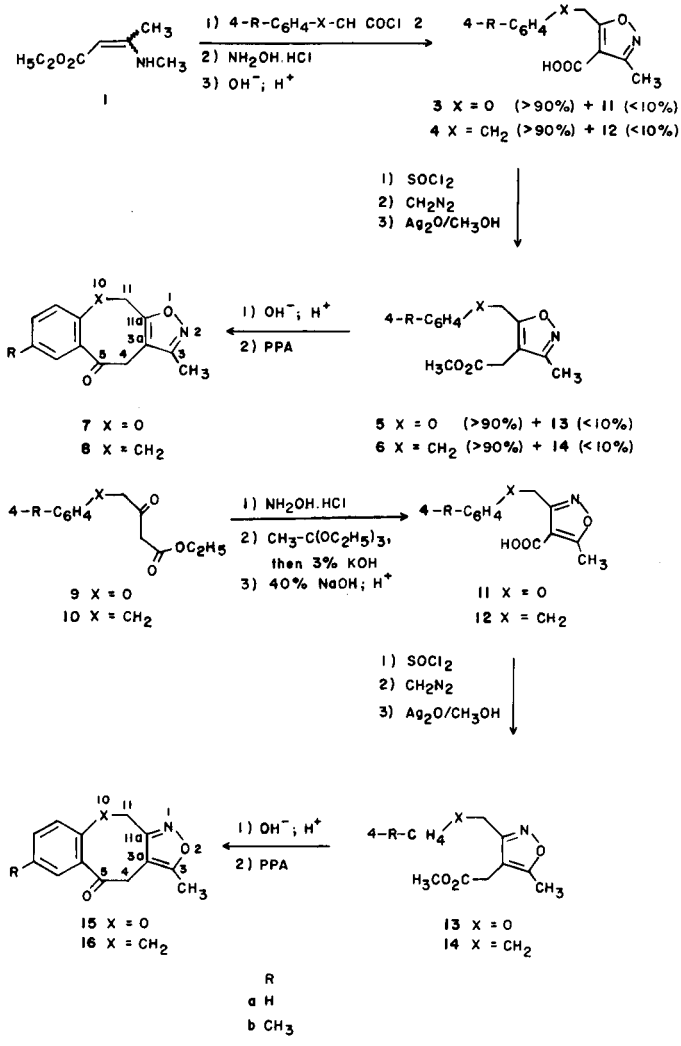
We previously described the utilization of isoxazole-4-carboxylic acids **3a,b**, **4a** and **11a** in the synthesis of 4*H*,10*H*-[1]benzoxepino[4,3-*d*] or [3,4-*c*]isoxazol-4-ones and 9,10-dihydro-4*H*-benzo[4,5]cyclohepta[2,1-*d*]isoxazol-4-one [1,2]. In this report, the isomeric isoxazole-4-carboxylic acids **3** and **11** or **4** and **12** are converted to 4-carboxymethylisoxazoles by Arndt-Eistert homologation; subsequent cyclization allows the synthesis of isomeric 4,11-dihydro-5*H*-[1]benzoxocino[4,3-*d*] or [3,4-*c*]isoxazol-5-ones **7** and **15** or the isomeric 4,5,10,11-tetrahydrobenzo-[5,6]cycloocta[2,1-*d*] or [1,2-*c*]isoxazol-5-ones **8** and **16**. No example of these classes of tricyclic compounds, containing either an isoxazole or an heterocyclic moiety was found in the literature.

The synthesis of 3-methyl-5-substituted isoxazole-4-carboxylic acids **3** or **4** [2] from ethyl 3-methylamino-2-butenoate (**1**) and of 5-methyl-3-substituted isoxazole-4-carboxylic acids **11** or **12** [1] from the β-keto esters **9** or **10** was achieved following the synthetic schemes previously described. The acids **3** or **4** were obtained as mixtures containing a minor amount (< 10%) of their isomers **11** or **12**. These mixtures were used in the next step. Arndt-Eistert homologation [3] of compounds **3**, **4**, **11** and **12** furnished the 4-methoxycarbonylmethylisoxazoles **5**, **6**, **13** and **14**. No attempt was made to separate compounds **5** or **6** from the small amount of their isomers **13** or **14** and the mixtures were submitted to the following step. The structures of compounds **5**, **6**, **13** and **14** were constitent with the microanalytical and spectral data (Tables 1 and 2).

Alkaline hydrolysis of the methyl esters **5**, **6**, **13** and **14** and subsequent acid-catalyzed cyclization led to isomeric tricyclic compounds **7** and **15** or **8** and **16**. These compounds were all purified by column chromatography on silica gel, eluting with methylene chloride. In particular, compounds **7** or **8** were easily separated from the minor amount of their isomers **15** or **16** which are eluted first. The structures of compounds **7**, **8**, **15** and **16** were in agreement with the microanalytical and spectral data (Tables 3 and 4). The junction of the isoxazole ring in



isomeric pairs **7** and **15** or **8** and **16** is unambiguously established by the synthetic scheme. In the ^{13}C-nmr spectra of isomeric pairs of the benzoxocinoisoxazolones **7a** and **15a** or benzocyclooctaisoxazolones **8a** and **16a**, the carbon adjacent to the nitrogen resonates upfield as compared with the carbon adjacent to the isoxazole oxygen (Table 5). These results are similar to the reported data for

Table 1

Physical Data for Compounds **5**, **6**, **13**, **14**

Compound No.	Yield	Bp (°C)/torr	Molecular Formula	Analyses % Calcd./Found C	H	N	IR (cm^{-1}) ($CHCl_3$)
5a	80 [a]	165-170/0.7	$C_{14}H_{15}NO_4$	64.36	5.79	5.36	1745
				64.30	5.76	5.25	
5b	80 [a]	190-195/1	$C_{15}H_{17}NO_4$	65.44	6.22	5.09	1745
				65.24	6.01	5.05	
6a	75 [b]	170/0.5	$C_{15}H_{17}NO_3$	69.48	6.61	5.40	1745
				69.20	6.63	5.21	
6b	55 [b]	185-190/1	$C_{16}H_{19}NO_3$	70.31	7.01	5.13	1745
				70.39	7.12	4.88	
13a	85	188/2	$C_{14}H_{15}NO_4$	64.36	5.79	5.36	1745
				64.35	5.72	5.31	
13b	85	180/0.5	$C_{15}H_{17}NO_4$	65.44	6.22	5.09	1740
				65.15	6.16	4.86	
14a	85	180/1	$C_{15}H_{17}NO_3$	69.48	6.61	5.40	1745
				69.22	6.60	5.33	
14b	85	170-175/0.5	$C_{16}H_{19}NO_3$	70.31	7.01	5.13	1745
				70.12	6.92	5.08	

[a] Mixture of compounds **5** (> 90%) + **13** (< 10%). [b] Mixture of compounds **6** (> 90%) + **14** (< 10%).

Table 2

Proton Magnetic Resonance Parameters of Compounds **5**, **6**, **13**, **14** in Deuteriochloroform

Compound No.	
5a	2.26 (s, 3H), 3.49 (s, 2H), 3.68 (s, 3H), 5.15 (s, 2H), 6.85-7.08 (m, 3H), 7.20-7.42 (m, 2H)
5b	2.25 (s, 3H), 2.28 (s, 3H), 3.45 (s, 2H), 3.65 (s, 3H), 5.12 (s, 2H), 6.72-7.21 (m, 4H)
6a	2.22 (s, 3H), 2.98 (s, 4H), 3.11 (s, 2H), 3.65 (s, 3H), 7.05-7.33 (m, 5H)
6b	2.20 (s, 3H), 2.30 (s, 3H), 2.93 (s, 4H), 3.13 (s, 2H), 3.64 (s, 3H), 7.03 (s, 4H)
13a	2.37 (s, 3H), 3.48 (s, 2H), 3.65 (s, 3H), 5.18 (s, 2H), 6.85-7.07 (m, 3H), 7.17-7.40 (m, 2H)
13b	2.28 (s, 3H), 2.35 (s, 3H), 3.48 (s, 2H), 3.63 (s, 3H), 5.13 (s, 2H), 6.75-7.18 (m, 4H)
14a	2.35 (s, 3H), 2.84-3.09 (m, 4H), 3.21 (s, 2H), 3.69 (s, 3H), 7.13-7.34 (m, 5H)
14b	2.32 (s, 3H), 2.34 (s, 3H), 2.85-3.00 (m, 4H), 3.23 (s, 2H), 3.68 (s, 3H), 7.10 (s, 4H)

isomeric isoxazoles [1,4-8].

Attempts were made to prepare the benzothiocino analog of compound **7** (X = S) following the same procedure, but unfortunately, under a variety of conditions, we failed in the final cyclization step.

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 obtained using a Brücker WP 80 spectrometer. The ^{13}C-nmr spectra were recorded on a Brücker AC 200 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.

Ethyl 3-methylamino-2-butenoate **1** was prepared as previously described [9]. The acyl chlorides **2** were obtained from the corresponding acids (commercially available or prepared as previously described [10,11]) by reaction with thionyl chloride (yields, 80-95%).

Ethyl 4-Aryloxy-3-oxobutanoates **9** and Ethyl 5-Aryl-3-oxopentanoates **10**. General Procedure.

To a refluxing suspension of magnesium ethoxide (77.7 g, 0.68 mole) in anhydrous toluene (300 ml) was added dropwise, with stirring, ethyl hydrogen malonate (45 g, 0.34 mole). The mixture was refluxed for 3 hours and the solvent was evaporated. To the residue was added tetrahydrofuran (400 ml) and then the acyl chloride **2** (0.34 mole) at room temperature. The resultant mixture was refluxed for 1 hour and then poured into 5% hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with ether. The combined extracts were washed with saturated sodium hydrogen carbonate solution, water, dried and evaporated. The residue was distilled *in vacuo* to afford the β-ketoester **9** or **10** (yields; **9a** [12], 75%; **9b**, 80%; **10a** [13,14], 75%; **10b**, 65%).

Compound **9b**.

This compound had bp 145-150°/0.5 torr.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.39; H, 6.67.

Compound **10b**.

This compound had bp 153-158°/1 torr.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.97; H, 7.92.

3-Methyl-5-substituted Isoxazole-4-carboxylic Acids **3**,**4** and 5-Methyl-3-substituted Isoxazole-4-carboxylic Acids **11**,**12**. General Procedure.

The isoxazole-4-carboxylic acids **3**, **4** [2] and **11**, **12** [1] were prepared following the procedures previously described. The crude acids were

Table 3

Physical Data for compounds **7**, **8**, **15**, **16**

Compound No.	Yield	Mp (°C) Solvent	Molecular Formula	Analyses % Calcd./Found C	H	N	IR (cm^{-1}) ($CHCl_3$)
7a	55	105 cyclohexane	$C_{13}H_{11}NO_3$	68.11 68.02	4.84 4.88	6.11 5.84	1690
7b	60	100 cyclohexane	$C_{14}H_{13}NO_3$	69.12 69.09	5.39 5.47	5.76 5.70	1680
8a	60	144 acetonitrile	$C_{14}H_{13}NO_2$	73.99 73.76	5.77 5.72	6.16 6.07	1675
8b	65	138 hexane/ethyl acetate 4:1	$C_{15}H_{15}NO_2$	74.66 74.83	6.27 6.27	5.81 5.69	1675
15a	65	112 cyclohexane	$C_{13}H_{11}NO_3$	68.11 68.20	4.84 4.68	6.11 5.99	1680
15b	70	113 hexane/ethyl acetate 4:1	$C_{14}H_{13}NO_3$	69.12 68.77	5.39 5.45	5.76 5.57	1680
16a	55	111 hexane/ethyl acetate 7:3	$C_{14}H_{13}NO_2$	73.99 73.82	5.77 5.90	6.16 6.01	1680
16b	60	138 hexane/ethyl acetate 3:2	$C_{15}H_{15}NO_2$	74.66 74.67	6.27 6.37	5.81 5.62	1675

Table 4

Proton Magnetic Resonance Parameter of Compounds **7**, **8**, **15**, **16** in Deuteriochloroform

Compound No.	
7a	2.25 (s, 3H), 3.98 (s, 2H), 5.33 (s, 2H), 7.03-7.35 (m, 2H), 7.43-7.70 (m, 1H), 7.79-8.00 (m, 1H)
7b	2.25 (s, 3H), 2.34 (s, 3H), 3.97 (s, 2H), 5.32 (s, 2H), 7.13 (d, 1H, J_{ortho} = 8 Hz), 7.41 (dd, 1H, J_{ortho} = 8 Hz, J_{meta} = 2 Hz), 7.73 (d, 1H, J_{meta} = 2 Hz)
8a	2.17 (s, 3H), 3.08-3.40 (m, 4H), 3.90 (s, 2H), 7.00-7.50 (m, 3H), 7.57-7.73 (m, 1H)
8b	2.18 (s, 3H), 2.28 (s, 3H), 3.04-3.45 (m, 4H), 3.88 (s, 2H), 7.11 (d, 1H, J_{ortho} = 8 Hz), 7.28 (dd, 1H, J_{ortho} = 8 Hz, J_{meta} = 2 Hz), 7.48 (d, 1H, J_{meta} = 2 Hz)
15a	2.36 (s, 3H), 4.01 (s, 2H), 5.42 (s, 2H), 7.09-7.33 (m, 2H), 7.45-7.71 (m, 1H), 7.75-7.90 (m, 1H)
15b	2.30 (s, 3H), 2.34 (s, 3H), 3.97 (s, 2H), 5.35 (s, 2H), 7.09 (d, 1H, J_{ortho} = 8 Hz), 7.30 (dd, 1H, J_{ortho} = 8 Hz, J_{meta} = 2 Hz), 7.55 (d, 1H, J_{meta} = 2 Hz)
16a	2.26 (s, 3H), 3.28 (s, 4H), 3.89 (s, 2H), 7.05-7.63 (m, 4H)
16b	2.28 (s, 3H), 2.30 (s, 3H), 3.24 (s, 4H), 3.86 (s, 2H), 6.98-7.40 (m, 3H)

recrystallized from acetonitrile (yields, 50-60%). Compounds **3** or **4** were obtained as mixtures with a minor amount of their isomers **11** or **12** (< 10%).

4-Methoxycarbonylmethyl-3-methyl-5-substituted Isoxazoles **5**,**6** and 4-Methoxycarbonylmethyl-5-methyl-3-substituted Isoxazoles **13**,**14**. General Procedure.

To the mixtures of isoxazole-4-carboxylic acids **4** + **11**, **5** + **12** or to the isoxazole-4-carboxylic acids **11**, **12** (0.03 mole) was added thionyl chloride (16.6 g, 0.14 mole). The resulting mixture was refluxed for 3 hours. The excess thionyl chloride was evaporated. The crude residue was dissolved in anhydrous ether and added dropwise, at 0°, to an anhydrous ethereal solution (150 ml) (dried over potassium hydroxide) of diazomethane prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (21.5 g, 0.10 mole). The mixture was kept overnight at room temperature and the ether was then evaporated. The crude diazoketone ir (chloroform): ν N-N bond = 2090-2100 cm^{-1}, ν C=O = 1620-1630 cm^{-1}) was dissolved in methanol (100 ml) and the solution was refluxed. To this solution was added one-sixth of a slurry of sliver oxide (prepared from 10 ml of 10% aqueous silver nitrate) in methanol (30 ml). Further additions were made every five minutes, so that after six additions all of it had been added. The mixture was then refluxed for 2 hours. The solvent was evaporated and the residue was distilled to afford mixtures of compounds **5** (> 90%) + **13** (< 10%), **6** (> 90%) + **14** (< 10%) or pure compounds **13** and **14** (Tables 1 and 2).

4,11-Dihydro-5*H*-[1]benzoxocino[4,3-*d*] or [3,4-*c*]isoxazol-5-ones **7** and **15** and 4,5,10,11-Tetrahydrobenzo[5,6]cycloocta[2,1*d*] or [1,2-*c*]isoxazol-5-ones **8** and **16**. General Procedure.

The mixtures of compounds **5** + **13**, **6** + **14** or the compounds **13**, **14** (0.005 mole) were dissolved in a solution of potassium hydroxide (1 g) in ethanol (30 ml) and refluxed for 3 hours. After evaporation of the solvent, water was added. The aqueous layer was extracted with ether and then acidified with concentrated hydrochloric acid. Extractive work-up with ethyl acetate left a crude acid. A mixture of this crude acid and polyphosphoric acid (Phosphoric acid/phosphorus pentoxide: 1/1, 150 g) was stirred at the temperature T for a time t, according to the following conditions:

Tricyclic compound obtained No.	**7a**	**7b**	**8a**	**8b**	**15a**	**15b**	**16a**	**16b**
T (°C)	160	180	220	170	165	160	200	160
t (minutes)	40	15	30	60	30	30	30	90

The resultant mixture was poured into crushed ice and extracted with methylene chloride. The extracts were dried and the solvent evaporated under reduced pressure. The residue was column chromatographed on silica gel (60 g) eluting with methylene chloride to afford pure compounds **7**, **8**, **15** and **16**. In the case of mixtures of compounds **7** + **15** or **8** + **16**, the isomer **15** or **16** is eluted first. Analytical samples were obtained by recrystallization from a suitable solvent (Tables 3 and 4).

Table 5

Pertinent ^{13}C-NMR Spectral Data of Compounds **7a**, **15a** and **8a**, **16a** (Hexadeuterioacetone) (δ ppm [a])

Compound No.	C-3	C-3a	C-4	C-5	C-10	C-11	C-11a
7a	160.1 [b]	109.8	38.4	196.4	–	71.1	165.0 [c]
15a	168.0 [b]	108.3	39.2	197.2	–	69.9	160.8 [c]
8a	160.3 [b]	108.4	38.7	201.8	30.2 [d]	29.2 [d]	168.3 [e]
16a	167.2 [b]	108.4	39.5	202.5	30.0 [d]	27.0 [d]	161.6 [e]

[a] Determined by examination of the coupled spectra. [b] The resonance of C-3 appears as a sextuplet (outermost peaks interval ~ 29-31.5 Hz) due to ^{2}J and ^{3}J long range proton-carbon coupling with the methyl protons and the methylene protons at C-4. [c] The resonance of C-11a appears as a pentuplet (outermost peaks interval ~ 18-21 Hz) due to ^{2}J and ^{3}J long range proton-carbon coupling with the methylene protons at C-11 and at C-4. [d] The resonance assignments for C-10 and C-11 may be interconverted. [e] The resonance of C-11a appears as a featureless broad absorption due to ^{2}J and ^{3}J long range proton-carbon coupling with the methylene protons at C-11, C-4 and C-10.

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