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Synthesis of the Imidazo[4,5-d]Azepine Ring System

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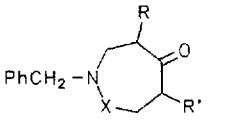
Although a substantial number of bicyclic ring systems are known in which azepines participate [1], until quite recently imidazoazepines had not been reported [2], excepting those having bridgehead nitrogen [3]. 1-Benzyl-5-bromo-4-azepanone **1a** was prepared as a starting material.

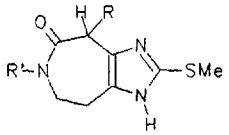
Attempted condensation of **1a** with S-methylisothiourea in a variety of different conditions gave decomposition products. This may be attributed to the instability of this type of bromoketone **1a** under the applied reaction conditions.

Whereas the amidic analogue **1b** was condensed successfully in DMF yielding the imidazo-azepine derivative **2a;** which exhibited two magnetically non-equivalents at δ = 2.75 and δ = 3.15 ppm for C-3 in its ^{1}H-NMR spectrum.



1a-d

	X	R	R'
a	CH_2	H	Br
b	CO	H	Br
c	CO	CN	H
d	CO	H	H



2a-c

	R	R'
a	H	$PhCH_2$
b	Cl	Ph
c	Cl	$PhCH_2$

Compound **1b** was prepared starting from 3-(N-benzyl amino) propionitrile **3** [4], which was treated with succinic anhydride to give **4a.** The ester **4b** was subjected to Dieckmann reaction with K^{t}OBu to afford **1c** which largely exist as the enol form i.e. exhibited stretching frequency at 3450 cm^{-1} (broad) in its IR data. In addition it has an exchangeable proton at δ = 12.1 ppm (enolic OH group). Compound **1c** easily hydrolysed and decarboxylated when refluxed with HCl (20 %) and acetic acid to give N-benzyl-azepan-2,5-dione (**1d**). This material seemed less enolic than **1c** thus it exhibited IR carbonyl absorptions at 1710 and 1600 cm^{-1}. Bromination of **1d** with Br_2 in acetic acid gave the highly stable bromoketone **1b** .

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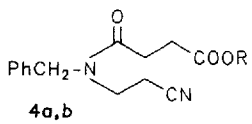
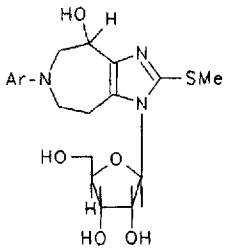


4a,b

a: R = H b: R = Et

The chloroderivative (**2b,c**) is of interest in converting it to functionalized new nucleosides **5** and their derivatives. For their synthesis, 1-aryl-5-bromo-3-chloro azepan-2,4-dione (**6c,d**) was chosen as a starting material. Firstly, reaction of amine (Ar=Ph, $PhCH_2$) with ethyl 4-bromobutyrat gave the ethyl 4-(phenylamino)butyrate and 4-benzylaminobutyrate. Acetylation of which with chloroacetyl chlorid in the presence of triethylamine yielded the ethyl 4-(N-aryl, N-chloroacetylamino) butyrate **7a,b**.



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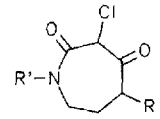
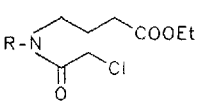


6a-d

	R	R'
a	H	Ph
b	H	$PhCH_2$
c	Br	Ph
d	Br	$PhCH_2$

Attempted cyclization of **7a,b** with NaH or K^{t}OBu failed. In the presence of Crown ether, **7a,b** cyclized to give the required 1-aryl 3-chloro-azepan-2,4-dione (**6a,b**). In this case the ions were separated, thus simplifying the intramolecular nucleophilic substitution on the ester group. Compounds **6a,b** did not dissolve in aqueous carbonate solution, but were soluble in aqueous sodium hydroxide to form enolate, and seemed less enolic, thus they exhibited the IR carbonyl absorption for the ketonic carbonyl group. Where the C-3 proton was partially changed by long treatment in D_2O.



7a,b

a: R = Ph b: R = $PhCH_2$

Bromination of **6a,b** gave preferable the α-bromoketone **6c,d** which easily condensed with S-methylisothiourea in ethanol and sodium acetate anhydrous giving the imidazoazepine derivatives **2b,c**.

Experimental

^{1}H-NMR spectra were recorded at 90 MH_2 in $CDCl_3$ as a solvent. Al_2O_3 was used for chromatography unless otherwise stated. Melting points were uncorrected and were taken in open pyrex capillaries. IR spectra were taken with 828 Perkin Elmer Spectrophotometer in KBr and as film in liquids.

*4-[N-Benzyl-N-(2-cyanoethyl)amino]-4-oxo-butane carboxylic acid (**4a**)*

The aminonitrile **3** (16.0 g, 0.1 mol), succinic anhydride (12.0 g, 0.12 mol) and anhydrous Na_2CO_3 (31.8 g, 0.3 mol) in acetonitrile (50 ml) were refluxed with stirring for 4h. After cooling, the reaction mixture was poured in water and acidified with HCl (2M), the separated product **4a** (22 g, 84.6 %) was crystallized (ethanol) to give a white product m.p. 90 °C. [Found, C, 64.5; H, 6.4 and N, 10.9 %, $C_{14}H_{16}N_2O$ req.: C, 64.6; H, 6.2 and N, 10.75 %]. ν_{max}3500 (OH, carboxylic) 2260 (CN), 1740 (CO, carboxylic and 1640 (CO, amidic) cm^{-1}. δ (60 MH_2) 2.2 (4H, two triplets, C-2 and C-3), 3.3 and 3.5 (4H, two triplets, N-CH_2-CH_2CN), 5.0 (2H, s, PhCH_2), 7.1 (5H, s, aromatic) and 9.4 (1H, S, exch. COOH) ppm.

*Ethyl-4-[N-benzyl-N-(2-cyanoethyl)amino] 4-oxo-butane carboxylic acid ester (**4b**)*

A solution of **4a** (13 g, 0.05 mol) in thionyl chloride (25 ml) was stirred at room temp. for 3 h, then the reaction mixture was cooled to 0 °C and ethyl alcohol absolute (30 ml) was added dropwise during 15 min. The reaction mixture left to raise to room temp. during 10 h. Excess solvent was removed in vacuo, the residue was dissolved in aqueous $NaHCO_3$ (2M), extracted with $CHCl_3$ and washed with water (3x). The extract was dried and evaporated to give the crude ester (9.0 g, 62.5 %) which was distilled (120 °C/0.01 mbar) to afford a pure product **4b** [Found: C, 66.7; H, 7.1 and N, 9.9 % $C_{16}H_{20}NO_2$ req.: C, 66.65; H, 7.0 and N, 9.7 %]. ν_{max} 2270 (CN), 1735 (CO ester) and 1650 (CO amidic) cm^{-1}, δ (60 MH_2) 1.2 (3H, t, CH_3, ester), 2.0 (2H, t, C-3), 2.7 (2H, t, C-2), 3.5 (4H, m, N-CH_2-CH_2CN), 4.0 (2H, q, CH_2 ester), 4.7 (2H, d, PhCH_2), 7.2 (5H, s, aromatic) ppm.

Ethyl-4-(phenylamino)butanoate

Ethyl-4-bromobutyrate (19.5 g, 0.1 mol) was added to a solution of distilled aniline (22.3 g, 0.24 mol) in n-heptane (200 ml) at 50 °C with vigorous stirring for 5 days. After evaporation of n-heptane in vacuo, the residue was treated with aqueous $NaHCO_3$ solution (excess). The product was obtained by extraction with diethyl ether and distillation (120 C/0.05 mbar), m.p. 40 °C (17 g, 81.1 %). [Found: C, 69.5; H, 8.5; N, 6.7 %, $C_{12}H_{17}NO_2$ req.: C, 69.55; H, 8.25; N, 6.75 %]. ν_{max} 3330 (NH) and 1720 (CO, ester) cm^{-1}. δ 1.1 (2H, t, $CO_2CH_2CH_3$), 1.8 (2H, q, C-3), 3.1 (2H, t, N-CH_2), 3.55 (1H, s, N-H, exch), 4.0 (2H, q, $CO_2CH_2CH_3$), 6.5 and 7.05 (5H, 2m, aromatic) ppm.

Ethyl-4-(benzylamino) butanoate

Benzylamine (64 g, 0.6 mol), ethyl 4-bromobutyrate (58 g, 0.6 mol) and dry ether (200 ml) were stirred at room temperature for 5 days, then cooled to 0 °C. The filtrate was evaporated under reduced pressure and purified by chromatography (Al_2O_3) using ethyl ether as eluent to give the amino ester **14b** (50 g, 76.3 %) which was used directly in the next step.

*Ethyl-4-(N-phenyl-N-chloroacetyl amino) butanoate (**7a**)*

Chloroacetyl chloride (11.86 g, 0.105 mol, 8.36 ml) in dry THF (50 ml) was added dropwise over 30 min to ethyl-4-(phenylamino)butanoate (28.5 g, 0.105 mol) and triethylamine (11 g, 0.105 mol, 15 ml) in dry THF (100 ml) at −10 °C under nitrogen. After the addition was completed, the temperature was raised to room temp. and left for 4 h. After addition of $CHCl_3$ and HCl (2M), the organic layer was separated, dried and evaporated to give compound **7a** (25 g, 83.9 %), b.p. 160 °C/0.05 mbar. [Found: C, 59.3; H, 6.4 and N, 4.8 %, $C_{14}H_{18}ClNO_3$ req.: C, 59.25; H, 6.4 and N, 4.9 %]. ν_{max} 1740 (CO, ester) and 1670 (CO amidic) cm^{-1} δ 1.2 (3H, t, CH_3, ester), 1.8 (2H, q, C-3), 2.4 (2H, t, C-2), 3.8 (2H, t, C-4), 4.0 (2H, s, CH_2Cl) and 7.0 (5H, s, aromatic) ppm.

*Ethyl-4-(N-benzyl-N-chloroacetylamino) butanoate (**7b**)*

The same procedure as for **7a.** The separated yellow oil **7b** was collected at 145 °C/0.05 mbar with yield 82 %. [Found; C, 60.5; H, 6.7 and N, 4.8 %, $C_{15}H_{20}ClNO_3$ req.: C, 60.0; H, 6.76 and N, 4.7 %]. ν_{max} 1730 (CO, ester) and 1650 (CO, amidic) cm^{-1}. δ 1.2 (3H, t, CH_3, ester), 1.8 (2H, q, C-3), 2.3 (2H, t, C-2), 3.9 (2H, t, C-4), 4.95 (2H, s, CH_2Cl), 4.4 (2H, d, PhCH_2) and 7.0 (5H, s aromatic) ppm.

General procedure for the cyclization

A solution of starting compound (0.02 mol) in dry toluene (30 ml) was added under nitrogen to potassium tert. butoxide (from potassium, 1.6 g, 0.04 mol in dry toluene 30 ml) dropwise at 80 °C during 30 min with stirring. After the addition was completed, the temperature was raised to 125 °C for 4 h, the mixture cooled and poured on cold water-ice mixture. The aqueous layer was separated and acidified with dil. HCl (2M), the precipitated product was filtered off and purified as described later.

a) 1-Benzyl-6-cyano-5-hydroxy-3(H)-4(H)-7(H)-2-oxo-azepine **(1c)**

The separated material (4 g, 82.6 %) was purified by chromatography (dichloromethane: ethanol: ammonia 300:8:1) to give a white powder: m. p. 99 °C (diethylether). [Found; C, 69.3, H, 5.8 and N, 11.7 %, $C_{14}H_{14}N_2O_2$ req.: C, 69.4; H, 5.8 and N, 11.55 %]. ν_{max} 3500 (OH, enolic), 2188 (CN) and 1680 (CO, amidic) cm^{-1}. δ 2.0 (2H, t, C-3), 2.4 (2H, t, C-4), 3.9 (2H, s, C-7), 4.2 (2H, s, PhCH_2), 7.1 (5H, s, aromatic) and 12.1 (1H, s, exch. OH) ppm.

*b) 3-Chloro-1-phenyl-azepan-2,4-dione (**6a**)*

The same procedure as for azepine **(1c)** but additional 18-Crown-6 (2 drops) was added during the addition of starting material **7b.** Yield 84 %, b.p. 130 °C 0.05 mbar. [Found: C, 60.8; H, 5.4; Cl; 14.8 and N, 6.0 %, $C_{12}H_{12}ClNO_2$ req.: C, 60.65; H, 5.1; Cl, 14.9 and N, 5.9 %]. ν_{max} 1715 (CO, ketone) and 1662 (CO, amidic) cm^{-1}. δ 1.7 (2H, q, C-6), 2.6 (2H, t, C-5), 3.6 (2H, t, C-7), 4.0 (1H, s, C-3) and 7.5 (5H, m, aromatic) ppm.

*c) 1-Benzyl 3-chloro-azepan-2,4-dione (**6b**)*

The same prodecure as for azepandione **6a.** Yield 78 %, b.p. 120 °C/0.05 mbar. [Founds: C, 62.1; H, 5.5, Cl, 14.5 and

N, 5.5 %, $C_{13}H_{14}ClNO_2$, req.: C, 62.05; H, 5.6; Cl, 14.1 and N, 5.55 %]. ν_{max} 1725 (CO, ketone) and 1670 (CO, amidic) cm^{-1}. δ 1.9 (2H, q, C-6), 2.5 (2H, t, C-5), 3.7 (2H, t, C-7), 4.1 (1H, s, C-3), 4.0 (2H, s, $PhCH_2$) and 7.4 (5H, s, aromatic) ppm.

*1-Benzyl-azepan-2,5-dione (***1d**)

The cyano compound (2.42 g, 0.01 mol), ethanol (20 ml), glacial acetic acid (60 ml), concentrated HCl (10 ml) and water (40 ml) were refluxed for 30 h and the mixture allowed to cool. After dilution with water (100 ml), the precipitated product (**1d,** 1.6 g, 73.7 %) was filtered off and crystallized (ethyl acetate: petroleum ether 80:100 °C) to give pure crystalls m.p. 57 °C. [Found: C, 71.7; H, 7.0 and N, 6.6 % Calcd. for $C_{13}H_{15}NO_2$; C, 71.85; H, 6.95 and N, 6.45 %]. ν_{max} 1710 (CO, ketone) and 1690 (CO, amidic) cm^{-1}. δ 2.2 (2H, t, C-3), 2.5 (4H, m, C-4 and C-6), 3.8 (2H, t, C-7), 4.4 (2H, s, $PhCH_2$) and 7.4 (5H, s, aromatic) ppm.

General procedure for Bromination

A solution of bromine (3.2 g, 0.02 mol) in glacial acetic acid (30 ml) was added dropwise, over an 1.5 h period, to a solution of the ketone (0.02 mol) in glacial acetic acid (125 ml), kept protected from moisture at 27 °C. The solution was stirred until the starting material disappeared, poured in cold water extracted with $CHCl_3$, washed with water (3x), $NaHCO_3$ solution 10 %, and dried over Na_2SO_4. Removal of the solvent in vacuo left a crude material which was purified as mentioned below.

*a) 1-Benzyl-4-bromo-azepan-2,5-dione (***1b**)

The residue (62.0 % Yield) was triturated with dry diethyl ether and the precipitated material was filtered off to give α-bromoketone **1b,** m.p. 70 °C (petroleum ether 60:80 °C). [Found: C, 52.5; H, 4.8 and N, 4.5 %, $C_{13}H_{14}BrNO_2$ req.: C, 52.7; H, 4.5 and N, 4.7 %]. ν_{max} 1720 (CO, ketone) and 1695 (CO, amidic) cm^{-1}. δ 2.3 (2H, d, C-3), 2.5 (2H, t, C-6), 3.8 (1H, t, C-4), 4.0 (2H, t, C-7), 4.4 (2H, s, $PhCH_2$) and 7.4 (5H, s, aromatic) ppm.

*b) 5-Bromo-3-chloro-1-phenyl-azepan-2,4-dione (***6c**)

The same procedure as for bromoketone **1b**. Yield (82 %), m.p. 50 °C (diethyl ether). [Found: C, 45.6; H, 3.5 and N, 4.5 % $C_{12}H_{11}BrClNO_2$ req.: C, 45.5; H, 3.5 and N, 4.4 %]. ν_{max} 1720 (CO, ketone) and 1665 (CO, amidic) cm^{-1}. δ 2.0 (2H, m, C-6), 3.8 (3H, m, C-5 and C-7), 5.0 (1H, s, C-3, exch.) and 7.2 (5H, s, aromatic) ppm.

*c) 1-Benzyl-5-bromo-3-chloro-azepan-2,4-dione (***6d**)

The same procedure as for **6c** yield (73 %), b.p. 140 °C/ 0.05 mbar. [Found: C, 47.4; H, 4.0 and N, 4.5 %, $C_{13}H_{13}BrClNO_2$ req.: C, 47.2; H, 3.95 and N, 4.25 %]. ν_{max} 1730 (CO, ketone) and 1665 (CO, amidic) cm^{-1}. δ 2.1 (2H, m, C-6), 3.7 (1H, t, C-5), 3.9 (2H, t, C-7), 4.5 (2H, s, $PhCH_2$) 4.8 (1H, s, C-3), exch.) and 7.0 (5H, s, aromatic) ppm.

General procedure for condensation

The bromoketone (0.01 mol), S-methylisothiouronium sulphate (0.012 mol) and sodium acetate (fused, 0.03 mol) in DMF (dry, 50 ml) were refluxed until the starting material disappeared (TlC). The reaction mixture was stirred at room temperature overnight, poured in cold water, and the precipitated material was filtered off and purified by chromatography (dichloromethane: ethanol: ammonia: 200:8:1).

*a) 1-Benzyl-6-methylthioimidazo[4-5-d]-2-oxo-azepine (***2a**)

The product (**2a,** 48 %) was crystallized (petroleum ether 80:100 °C ethyl acetate) and melted at 140 °C. [Found: C, 62.6; H, 5.9, N, 14.6 and S, 11.2 %, $C_{15}H_{17}N_3SO$ req.: C, 62.7; H, 5.95; N, 14.6 and S, 11.5 %]. ν_{max}3450 (NH, br.) and 1700 (CO, amidic) cm^{-1}. δ 1.4 (3H, S, SCH_3), 2.2 (2H, t, C-7), 2.75 and 3.15, (2H, 2s, C-3), 3.2 (2H, t, C,8), 4.4 (2H, s, $PhCH_2$), 7.0 (5H, s, aromatic) and 8.4 (1H, br. N-H, exch.) ppm.

*b) 3-Chloro-1-phenyl-6-methylthio-imidazo[4,5-d]-2-oxo-azepine (***2b**)

The same procedure as for **2a** with using ethanol as a solvent instead of DMF. The product **2b** (62 % yield) was crystallized (ethylacetate, petroleum ether 80:100 °C) and melted at 92 °C. [Found: C, 54.5; H, 4.6; N, 13.7 and S, 10.5 %, $C_{14}H_{14}ClN_3SO$ req.: C, 54.6; H, 4.6; N, 13.65 and S, 10.4 %]. ν_{max} 3320 (NH, br.) and 1670 (CO, amidic) cm^{-1}. δ 2.2 (2H, t, C-7), 2.4 (3H, s, SCH_3), 3.5 (1H, s, C-3), 3.8 (2H, t, C-8), 7.0 (5H, s, aromatic) and 8.0 (1H, s, NH, exch.) ppm.

*c) 1-Benzyl-3-chloro-6-methylthio-imidazo[4,5-d]-2-oxo-azepine (***2c**)

The experimental was as for **2a.** The product (**2c,** 58 %) was crystallized (ethyl acetate+pet.ether 80:100 °C) and melted at 85 °C. [Found: C, 55.7; H, 5.0; N, 13.3 and S, 9.8 %, $C_{15}H_{16}ClN_3SO$ req.: C, 55.95; H, 5.0; N, 13.05 and S, 9.95 %]. ν_{max} 3400 (NH, br) and 1655 (CO, amidic) cm^{-1}. δ 2.00 (2H, t, C-7), 2.8 (3H, s, SCH_3), 3.5 (1H, d, C-3), 4.0 (2H, t, C-8), 4.4 (2H, d, $PhCH_2$), 7.1 (5H, s, aromatic) and 7.9 (1H, s, NH, exch.) ppm.

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