Enolethers. XX [1]. Synthesis of Azepino[4,5-*b*]quinoxalines and Pyridopyrazino[2,3-*d*]azepines

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Dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday.

1,6-Diethoxy-1,5-hexadiene-3,4-dione (**1**) reacts with primary amines **3** and ammonia respectively in a molar ratio of 1:1 to give mainly aminoalkyl- and small amounts of bis(aminoalkyl)-1,5-hexadiene-3,4-diones **4** and **2**, respectively. On heating in dichlorobenzene above 150° the mixtures of **2** and **4** cyclize to yield 1-alkyl-1*H*-azepine-4,5-diones **5** by elimination of ethanol or amine. 3*H*-3-Alkylazepino[4,5-*b*]-quinoxalines **7**, **8**, **10** and **12** are easily accessible by condensation of the diketones **5a** and **b** with various substituted *o*-phenylenediamines **6**, **9** and 3,3',4,4'-tetraaminobiphenyl (**11**) in *p*-xylene or *n*-butanol. 8-Isopropylpyridopyrazino[2,3-*d*]azepines **14** were obtained by condensation of **5b** with pyridinediamines **13** in *p*-xylene. The azepine-4,5-diones **5a-c** can be hydrogenated selectively by sodium borohydride in ethanol at room temperature to give the azepin-4-ol-5-ones **15a-c**.

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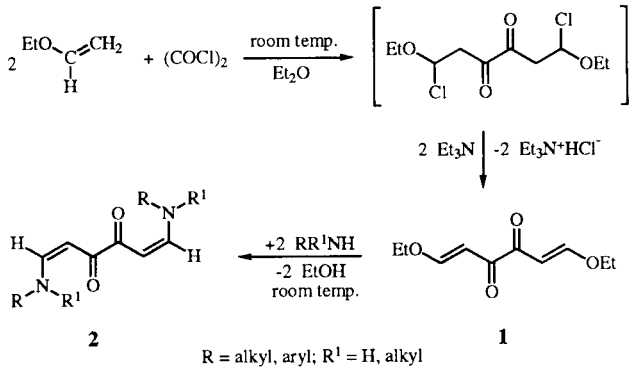
Introduction.

Seven-membered rings containing nitrogen are of great interest with respect to their versatile pharmacological activities and, on the other hand, in their maximal unsaturated form as cyclic conjugated π systems. Hexahydroazepinones, for example, show significant CNS activity [3a] and markedly stronger analgetic properties than morphine with no demonstrable addiction liability [3b]. The pharmacological activity of benzazepines is much lower than that of benzodiazepines, but their spectrum of biological activity is also of interest for applications [4]. Azepine-2-, 3- or 4-ones and some diones as well as their benzo and dibenzo derivatives have been investigated as azatropones or azatropolones particularly with regard to their aromatic character [5a,b].

Surprisingly, only a few fused heterocycles with azepine as a part of a condensed system have yet been described in the literature. The tetrahydro derivatives of azepino-[4,5-*b*]quinoxaline [6], for example, are useful as appetite depressants and as bactericides. Tetrahydro- and hexahydroazepine-4,5-diones are often used as starting materials for the synthesis of condensed azepine systems [7a-c].

In our investigations of the acylation of enolethers [8a-c] we have obtained di- and tetracarbonyl compounds which we have successfully applied in some cases for the synthesis of heterocycles [9a-c]. 1,6-Diethoxy-1,5-hexadiene-3,4-dione (**1**), for example, could be prepared from vinyl ethyl ether and oxalyl chloride in good yield [9a] (Scheme 1). Compound **1** is a 1, 3, 4, 6-tetracarbonyl compound with two potential aldehyde functions in the 1,6 and two keto groups in the 3,4 positions. The two adjacent carbonyl groups in the 3,4 position should be most suitable for the synthesis of fused ring systems [7a-c].

Scheme 1



In the present paper we report on the preparation of azepine-4,5-diones and their synthetic potential for the synthesis of condensed heteroaromatic systems with an azepine ring.

Synthesis of 1-Alkyl-1*H*-azepine-4,5-diones **5**.

1,6-Diethoxy-1,5-hexadiene-3,4-dione (**1**) has already been applied successfully as twofold 1,3-dicarbonyl compound for the synthesis of heterocycles [9a]. For example, with amidines 4,4'-bipyrimidines are formed [9a]. Bipyrazoles derived from **1** and hydrazines can be coupled in the 3,3'-, 3,5'- or 5,5' positions [9a,10a,b,11]. With primary and secondary amines **1** reacts in a molar ratio of 2:1 at room temperature to give the bisamino compounds **2** by substitution of both ethoxy groups in **1** [9a] (Scheme 1).

The reaction of **1** with primary amines or ammonia in a molar ratio of 1:1 could afford azepine-4,5-diones if an intramolecular reaction of the initially formed monoamino product can be reached. We have therefore treated **1** with the primary amines **3a-e** and ammonia (**3f**) in a 1:1

ratio at room temperature in diethyl ether and could obtain predominantly the monosubstitution products **4** besides small amounts of the disubstituted derivatives **2** (Scheme 2, Table 1). The crude product mixtures **2/4** were obtained - after evaporating the diethyl ether - as yellow to red oils consisting of **2** as minor and **4** as major products. The mixture of the two products could not be separated by crystallization or by chromatography. The ratio of **2** and **4** could be determined easily and reliably by their ^{1}H nmr spectra. The spectra show that compounds **4** exist as *Z,E* isomers. Coupling constants $^3J_{HH}$ of 7.2-7.4 Hz (*cis* coupling) and of 13.0 Hz (*trans* coupling) were obtained for the olefinic protons. On the contrary, compounds **2** exclusively exist as *Z,Z* isomers with a coupling constant $^3J_{HH}$ of 6.4-7.0 Hz for the olefinic protons. The mixtures of **2** and **4** were used without further purification and separation for the intramolecular cyclization. It turned out that the bisamino derivatives **2** also cyclize to azepinediones **5**.

Scheme 2

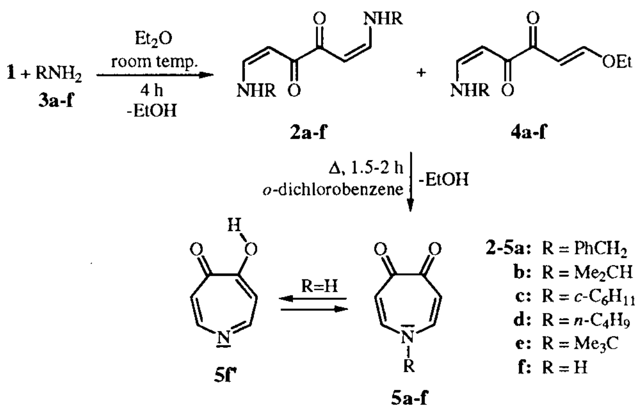


Table 1). With the exception of the *n*-butyl derivative **5d**, which was isolated as an oil and chromatographed on silica gel, the crystalline azepine-4,5-diones **5a-c,e** and **f** were purified by recrystallization.

1-Alkyl-1*H*-azepine-4,5-diones **5**, easily accessible by this route, have not yet been described in the literature. They are of particular interest for the preparation of condensed azepine systems as well as for their pharmacological activity. Treibs *et al.* [5b] have hardly tried to synthesize **5f**, which, in his tautomeric form **5f'**, would be of great interest as azatropolone with respect to his aromatic character. We have no spectroscopic evidence for the existence of the tautomer **5f'** in the isolated product **5f** (Scheme 2).

Synthesis of 3*H*-3-Alkylazepino[4,5-*b*]quinoxalines **7**.

The classical synthesis of quinoxalines from 1,2-diketones and aromatic *ortho*-diamines was developed by Körner and Hinsberg [12a-c]. Quinoxalines were even applied for the characterization of *o*-diamines and 1,2-diketones respectively due to their ease of formation and their ability for excellent crystallization [13]. Azepine-4,5-diones, however, are not "normal" 1,2-diketones but "vinylogous" acid amides [14a-d] with a clearly reduced carbonyl activity in comparison with "normal" diketones [14]. We have investigated and optimized the conditions for the condensation reaction of the benzyl derivative **5a** with various *o*-phenylenediamines **6a-d** yielding the 3*H*-3-benzylazepino[4,5-*b*]quinoxalines **7a-d** (Scheme 3, Table 2).

In boiling ethanol (method A) even after reaction times of 15 hours to 3 days compounds **7** were obtained only in unsatisfactory yields (Table 2). In boiling *p*-xylene using a water separator (method B) the yields of the condensation products **7** were markedly increased at shorter reaction times (Table 2). Scheme 4 represents the synthesis of the *N*-isopropylazepino[4,5-*b*]quinoxalines **8a,b**, **10** and **12** starting from 1-isopropyl-1*H*-azepine-4,5-dione (**5b**) and the aromatic *o*-diamines **6a,e**, **9** and **11**.

Table 1

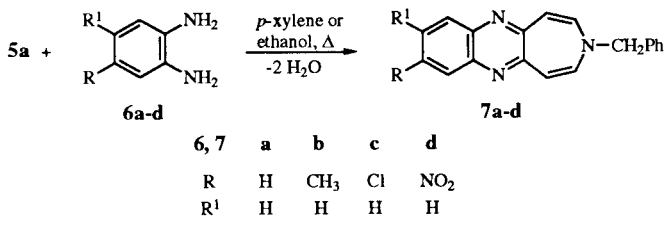
Reaction of **1** with Amines **3a-f** in a Molar Ratio of 1:1 in Diethyl Ether at Room Temperature to Compounds **2** and **4** and Their Subsequent Condensation in *o*-Dichlorobenzene at Temperatures >150° to Azepinediones **5**

Starting Amine **3**	R=	Substitution Products **4** and **2**	Yield [%] [a]		Yield [%] [a]	Azepinediones **5**	Yield [%] [b]
3a	$C_6H_4CH_2$	**4a**	68	**2a**	11	**5a**	54
3b	$(CH_3)_2CH$	**4b**	78	**2b**	15	**5b**	66
3c	c-C_6H_{11}	**4c**	78	**2c**	12	**5c**	51
3d	n-C_4H_9	**4d**	73	**2d**	19	**5d**	54
3e	$(CH_3)_3C$	**4e**	63	**2e**	19	**5e**	18
3f	H	**4f**	63	**2f**	5	**5f**	63

[a] Determined by ^{1}H nmr spectroscopy. [b] Related to the starting compound **1**.

On heating the mixtures **2f/4f** to 150° and **2a-e/4a-e** to 175-180°, respectively, in *o*-dichlorobenzene, the 1-alkyl-1*H*-azepine-4,5-diones **5a-f** are formed by elimination of ethanol or the respective amine (Scheme 2,

Scheme 3



6a-d **7a-d**

6, 7	a	b	c	d
R	H	CH_3	Cl	NO_2
R^1	H	H	H	H

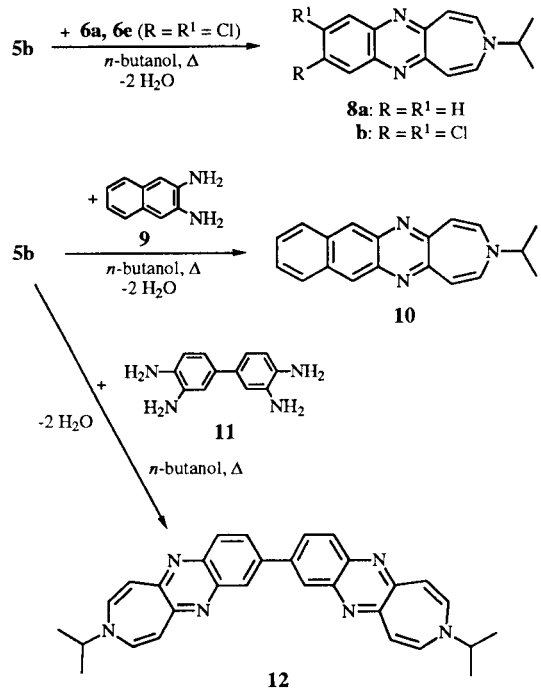
Table 2

Reaction of 1-Benzyl-1*H*-azepine-4,5-dione (**5a**) with Substituted *o*-Phenylenediamines **6** to 3*H*-3-Benzylazepino[4,5-*b*]quinoxalines **7**

Amine **6**	Reaction Conditions			Quinoxaline **7**	
	Solvent	Reaction time [h]	Method		Yield[%]
6a	ethanol	24	A [a]	**7a**	11
6a	*p*-xylene	4	B [b]	**7a**	48
6b	ethanol	24	A	**7b**	9
6b	*p*-xylene	4	B	**7b**	29
6c	ethanol	48	A	**7c**	11
6c	*p*-xylene	5	B	**7c**	32
6d	ethanol	96	A	**7d**	8
6d	*p*-xylene	8	B	**7d**	13

[a] Method A: reaction temperature 78°. [b] Method B: reaction temperature 160-165°, with water separator.

Scheme 4



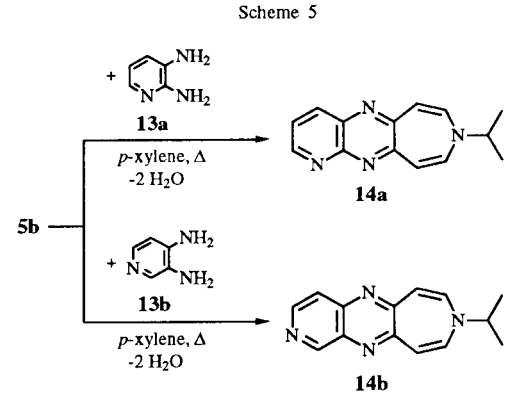
These condensation reactions were carried out in boiling *n*-butanol because of the better solubility of these components in butanol. The bis(azepinoquinoxaline) **12** was isolated after chromatography as a brick-red powder which could not be recrystallized.

Synthesis of 8-Isopropylpyrido[3',2':5,6] or [4',3':5,6]-pyrazino[2,3-*d*]azepines **14**.

Pyridopyrazines show manifold biological activities [15]. They are of interest as anti-metabolites and folic acid antagonists due to their structural relationship to pteridines [16a-c]. Amino substituted derivatives exhibit antibacterial, antiviral, diuretic and anti-inflammatory properties [17a-c]. Pyridopyrazinoazepines, which possibly possess pharmacological activities, have not yet been described in the literature.

We were now able to prepare 8-isopropylpyrido-[3',2':5,6]pyrazino[2,3-*d*]azepine (**14a**) and 8-isopropylpyrido[4',3':5,6]pyrazino[2,3-*d*]azepine (**14b**) in satisfactory yields by simple condensation of **5b** with 2,3- and 3,4-diaminopyridine (**13a**) and (**13b**), respectively, in boiling *p*-xylene.

Scheme 5

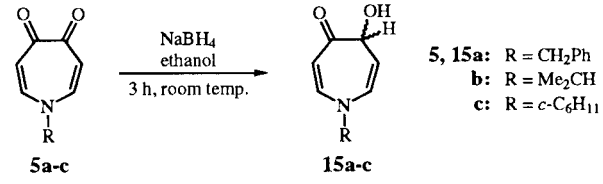


Synthesis and Reactions of 1-Alkyl-1*H*-azepin-4-ol-5-ones **15**.

α-Hydroxyketones are important starting compounds for the synthesis of five-membered heterocycles like imidazoles, oxazoles or thiazoles [18]. We therefore have investigated the partial hydrogenation of the α-diketones **5** to get α-hydroxyketones **15** which could be of interest for the preparation of imidazolo- and oxazoloazepines.

Dibenzoazepin-10-one, which can be considered as a "vinylogous" acid amide also, was successfully hydro-

Scheme 6



5a-c **15a-c**

genated by sodium borohydride in ethanol at room temperature [19]. Under similar conditions the azepinediones **5a-c** were selectively hydrogenated to give the 1-alkyl-1*H*-azepin-4-ol-5-ones **15a-c** (Scheme 6).

The crude α-hydroxyketones **15** were purified by chromatography. Compounds **15** were obtained as yellow oils in 58-77% yield; **15c** crystallized on cooling.

All efforts to prepare fused imidazolo- or oxazoloazepines by reacting **15a** with formamide and acetamidine, respectively, under conditions described in the literature [20], failed completely. Only dark and tarry decomposition products could be obtained in these reactions.

EXPERIMENTAL

All melting points are determined on a Büchi SMP 20 and are uncorrected. The ^{1}H nmr spectra are recorded on a Bruker ACF 250 at 250 MHz with tetramethylsilane (TMS) as internal standard. The ^{13}C nmr spectra are recorded on a Bruker ACF 250 at 62.9 MHz. For column chromatography glass columns with different volumes are used; silica gel S, size 0.032-0.063 mm from Riedel-de Haen, basic aluminum oxide Alumina Woelm B Super 1 from Woelm Pharma. All solvents and aliphatic amines used are purified and dried as described in the literature.

1,6-Bis(alkylamino)-1,5-hexadiene-3,4-diones **2a-e** and 1-Alkylamino-6-ethoxy-1,5-hexadiene-3,4-diones **4a-e**.

To a stirred solution of **1** [9a, 11] (3.96 g, 20 mmoles) in dry diethyl ether (100 ml), a solution of the respective amine **3** (20 mmoles) in dry diethyl ether (30 ml) was added dropwise within 3 hours at room temperature, and the reaction mixture was stirred for an additional 1 hour. The solvent was removed and the residue was dried *in vacuo* for 1.5-2 hours to give mixtures of **2** and **4**. The yields were determined by integration of the olefinic protons from ^{1}H nmr spectra (Table 3). The crude product mixtures **2/4** were used for the ring closure without further purification.

1,6-Diamino-1,5-hexadiene-3,4-dione (**2f**) and 1-Amino-6-ethoxy-1,5-hexadiene-3,4-dione (**4f**).

Ammonia **3f** (0.68 g, 40 mmoles) was liquefied at -78° and passed into a stirred solution of **1** (3.96 g, 20 mmoles) in dry diethyl ether (100 ml) within 1 hour by slowly increasing the temperature. The reaction mixture then was stirred for 3 hours. The solvent was removed and the residue dried *in vacuo* for 2 hours to yield 6.38 g crude mixture of **2f** and **4f**; ^{1}H nmr data see Table 3.

General Procedure for the Ring Closure of **2** and **4** to 1-Alkyl-1*H*-azepine-4,5-diones **5**.

The crude product mixtures of **2/4** were dissolved in *o*-dichlorobenzene (300 ml) and heated at 150° for **2/4f** or 175-180° for **2/4a-e** for 1.5 hours in the case of **2/4a-d,f** or for 2 hours for **2/4e**. The solvent was removed *in vacuo*, and the residue was taken up in a solvent (Table 4), refluxed with charcoal for 20 minutes and filtered. On cooling (16 hours at -15°) the products **5** crystallized as brown needles, **5a-c** or white pellets, **5e**. Compound **5f** was obtained as a brown powder.

General Procedures for the Preparation of 3*H*-3-Benzylazepino-[4,5-*b*]quinoxalines **7**.

Method A.

A solution of **5a** (639.0 mg, 3 mmoles) and the respective amine **6** (3 mmoles) in ethanol (50 ml) was heated with stirring at 78° so that some ethanol is distilled over. After the reaction is complete

Table 3

^{1}H NMR Data of Compounds **2** and **4**

Compound	^{1}H NMR (in $CDCl_3$) ppm
2a	4.38 (d, 4H, CH_2, $J_{CH_2,NH}$ = 6.0 Hz), 5.90 (d, 2H, 2-, 5-H, J = 7.3 Hz) 7.03 (dd, 2H, 1-, 6-H), 7.16-7.28 (m, 10H, Ph), 10.50 (broad s, 2H, NH)
2b	1.24 [d, 12H, $(CH_3)_2CH$], 3.47 [sept, 2H, $(CH_3)_2CH$], 5.90 (d, 2H, 2-, 5-H, J = 7.2 Hz), 7.11 (dd, 2H, 1-, 6-H), 10.35 (broad s, 2H, NH)
2c	1.20-1.97 (m, 20H, cyclohexyl-H), 3.17 (m, 2H, cyclohexyl-H), 5.90 (d, 2H, 2-, 5-H, J = 7.2 Hz), 7.11 (dd, 2H, 1-, 6-H), 10.45 (broad s, 2H, NH)
2d	0.92 (t, 6H, CH_3), 1.34-1.43 (m, 4H, CH_3CH_2), 1.52-1.65 (m, 4H, $CH_3CH_2CH_2$), 3.20-3.34 (m, 4H, CH_2), 5.87 (d, 2H, 2-, 5-H, J = 7.2 Hz), 7.04 (dd, 2H, 1-, 6-H), 10.35 (broad s, 2H, NH)
2e	1.33 (s, 18H, CH_3), 5.94 (d, 2H, 2-, 5-H, J = 7.3 Hz), 7.14 (dd, 2H, 1-, 6-H), 10.70 (broad s, 2H, NH)
2f	5.97 (d, 2H, 2-, 5-H, J = 7.5 Hz), 7.14 (ddd, 2H, 1-, 6-H, J_1 = 7.5, J_2 = 6.0 Hz), 9.55 (broad s, 4H, NH_2)
4a	1.30 (t, 3H, OCH_2CH_3), 3.95 (q, 2H, OCH_2CH_3), 4.42 (d, 2H, CH_2, $J_{CH_2,NH}$ = 6.0 Hz), 5.81 (d, 1H, 2-H, $J_{2,1}$ = 7.2 Hz), 6.35 (d, 1H, 5-H, $J_{5,6}$ = 12.8 Hz), 7.11 (dd, 1H, 1-H), 7.19-7.35 (m, 5H, Ph), 7.78 (d, 1H, 6-H), 10.55 (broad s, 1H, NH)
4b	1.21 [d, 6H, $(CH_3)_2CH$], 1.28 (t, 3H, OCH_2CH_3), 3.45 [sept, 1H, $(CH_3)_2CH$], 3.94 (q, 2H, OCH_2CH_3), 5.77 (d, 1H, 2-H, $J_{2,1}$ = 7.2 Hz), 6.32 (d, 1H, 5-H, $J_{5,6}$ = 12.7 Hz), 7.15 (dd, 1H, 1-H), 7.73 (d, 1H, 6-H), 10.30 (broad s, 1H, NH)
4c	1.20-1.97 (m, 10H, cyclohexyl-H), 1.35 (t, 3H, OCH_2CH_3), 3.17 (m, 1H, cyclohexyl-H), 4.01 (q, 2H, OCH_2CH_3), 5.78 (d, 1H, 2-H, $J_{2,1}$ = 7.2 Hz), 6.41 (d, 1H, 5-H, $J_{5,6}$ = 12.8 Hz), 7.16 (dd, 1H, 1-H), 7.80 (d, 1H, 6-H), 10.45 (broad s, 1H, NH)
4d	0.94 (t, 3H, CH_3), 1.34-1.43 (m, 2H, CH_3CH_2), 1.36 (t, 3H, OCH_2CH_3), 1.52-1.65 (m, 2H, $CH_3CH_2CH_2$), 3.20-3.34 (m, 2H, CH_2), 3.99 (q, 2H, OCH_2CH_3), 5.75 (d, 1H, 2-H, $J_{2,1}$ = 7.1 Hz), 6.37 (d, 1H, 5-H, $J_{5,6}$ = 12.8 Hz), 7.08 (dd, 1H, 1-H), 7.79 (d, 1H, 6-H), 10.35 (broad s, 1H, NH)
4e	1.28 (s, 9H, CH_3), 1.29 (t, 3H, OCH_2CH_3), 3.95 (q, 2H, OCH_2CH_3), 5.75 (d, 1H, 2-H, $J_{2,1}$ = 7.2 Hz), 6.35 (d, 1H, 5-H, $J_{5,6}$ = 12.7 Hz), 7.19 (dd, 1H, 1-H), 7.75 (d, 1H, 6-H), 10.70 (broad s, 1H, NH)
4f	1.36 (t, 3H, OCH_2CH_3), 4.02 (q, 2H, OCH_2CH_3), 5.83 (d, 1H, 2-H, $J_{2,1}$ = 7.5 Hz), 6.33 (d, 1H, 5-H, $J_{5,6}$ = 12.7 Hz), 7.17 (ddd, 1H, 1-H), 7.81 (d, 1H, 6-H), 9.50 (broad s, 2H, NH_2)

Table 4

Ring Closure of **2/4** to **5**, ^1H and ^{13}C NMR Data as well as Elemental Analyses

Crude **2/4** (g)		Solvent	Product	Yield (g)	mp [°C]
a	5.0	benzene/dioxane	**5a**	2.30	145-147
b	4.21	dioxane	**5b**	2.16	219-220.5
c	5.19	benzene	**5c**	2.07	191-193
d	4.50	[a]	**5d**	1.93	-
e	3.98	chloroform	**5e**	0.64	225-226.5
f	6.38	[b]	**5f**	3.08	>280

^1H NMR (in $CDCl_3$) ppm

5a 4.97 (*s*, 2H, CH_2), 6.08 (d, 2H, 3-, 6-H, $J_{3,2} = J_{6,7} = 10.5$ Hz), 7.05 (d, 2H, 2-, 7-H), 7.15-7.30 (m, 5H, Ph)

5b 1.38 [d, 6H, $(CH_3)_2CH$], 4.09 (sept, 1H, CH), 6.08 (d, 2H, 3-, 6-H, $J_{3,2} = J_{6,7} = 10.7$ Hz), 6.99 (d, 2H, 2-, 7-H)

5c 1.10-2.16 (m, 10H, cyclohexyl-H), 3.65 (tt, 1H, cyclohexyl-H), 6.21 (d, 2H, 3-, 6-H, $J_{3,2} = J_{6,7} = 10.7$ Hz), 7.01 (d, 2H, 2-, 7-H)

5d 0.82 (t, 3H, CH_3), 1.24 (sext, 2H, CH_3CH_2), 1.65 (quint, 2H, $CH_3CH_2CH_2$), 3.75 (t, 2H, CH_2), 6.05 (d, 2H, 3-, 6-H, $J_{3,2} = J_{6,7} = 10.6$ Hz), 7.01 (d, 2H, 2-, 7-H)

5e 1.58 (*s*, 9H, CH_3), 6.17 (d, 2H, 3-, 6-H, $J_{3,2} = J_{6,7} = 11.0$ Hz), 7.25 (d, 2H, 2-, 7-H)

5f [c] 6.04 (d, 2H, 3-, 6-H, $J_{3,2} = J_{6,7} = 10.2$ Hz), 7.30 (d, 2H, 2-, 7-H), 11.5 (broad *s*, 1H, NH)

^{13}C NMR (in $CDCl_3$) ppm

5a 64.5 (CH_2), 112.6 (C-3, 6), 127.6 (Ph), 129.2 (Ph), 129.6 (Ph), 134.9 (Ph), 140.3 (C-2, 7), 183.1 (C-4, 5)

5b 22.6 (CH_3), 62.8 (CH), 112.6 (C-3, 6), 137.7 (C-2, 7), 182.8 (C-4, 5)

5c 24.8 (cyclohex), 25.6 (cyclohex), 33.2 (cyclohex), 70.9 (cyclohex), 112.6 (C-3, 6), 137.7 (C-2, 7), 182.8 (C-4, 5)

5d 13.5 (CH_3), 19.3, 32.9, 61.5 (CH_2), 112.3 (C-3, 6), 140.0 (C-2, 7), 182.9 (C-4, 5)

5e 30.2 (CH_3), 64.7 (t-butyl-C), 112.5 (C-3, 6), 135.7 (C-2, 7), 182.8 (C-4, 5)

5f [c] 110.9 (C-3, 6), 137.4 (C-2, 7), 182.7 (C-4, 5)

	Molecular Formula	Elemental Analysis (%) Calcd./Found C	H	N
5a	$C_{13}H_{11}NO_2$	73.23	5.20	6.57
	(213.2)	73.04	5.13	6.41
5b	$C_9H_{11}NO_2$	65.44	6.71	8.48
	(165.2)	65.41	6.79	8.30
5c	$C_{12}H_{15}NO_2$	70.22	7.37	6.82
	(205.3)	70.43	7.39	6.71
5e	$C_{10}H_{13}NO_2$	67.02	7.31	7.82
	(179.2)	67.00	7.25	7.81
5f	$C_6H_5NO_2$	58.54	4.09	11.38
	(123.1)	58.34	4.22	11.26

[a] Oil, no crystallization. [b] The residue was mixed with diethyl ether (50 ml) and filtered. [c] In DMSO-d_6.

the solvent was removed, and the residue chromatographed on aluminum oxide with diethyl ether/ethyl acetate (3:1).

Method B.

A solution of **5a** (639.0 mg, 3 mmoles) and the respective amine **6** (3 mmoles) in *p*-xylene (50 ml) was heated with stirring at 160-165° (bath temperature) with a water separator (tlc control). The solvent was removed *in vacuo*, and the residue taken

Table 5

Reaction of **5a** with Amines **6a-d** to Azepino[4,5-*b*]quinoxalines **7a-d**, ^1H and ^{13}C NMR Data and Elemental Analyses

6	mg (mmoles)	Method	Product	Yield (mg)	mp [°C]
a	324.0 (3.0)	A	**7a**	93.0	148.5-149.5
a	324.0 (3.0)	B	**7a**	410.0	
b	366.0 (3.0)	A	**7b**	80.0	142-143
b	366.0 (3.0)	B	**7b**	260.0	
c	426.0 (3.0)	A	**7c**	107.0	168-169
c	426.0 (3.0)	B	**7c**	307.0	
d	459.0 (3.0)	A	**7d**	75.2	187.5-188.5
d	459.0 (3.0)	B	**7d**	129.0	

^1H NMR (in $CDCl_3$) ppm

7a 4.02 (*s*, 2H, CH_2), 4.62 (d, 2H, 1-, 5-H, $J_{1,2}$,$J_{5,4} = 10.5$ Hz), 5.31 (d, 2H, 2-, 4-H), 7.13-7.24 (m, 4H, 7-, 8-, 9-, 10-H), 7.35-7.44 (*s*, 5H, Ph)

7b 2.29 (*s*, 3H, 8-CH_3), 3.97 (*s*, 2H, CH_2), 4.58 (d, 2H, 1-, 5-H, $J_{1,2}$,$J_{5,4} = 10.7$ Hz), 5.26 (dd, 1H, 2- or 4-H, $^4J = 4.5$ Hz), 5.27 (dd, 1H, 2- or 4-H), 6.97 (dd, 1H, 9-H, $J_{9,10} = 8.2$, $J_{9,7} = 2.0$ Hz), 7.03 (d, 1H, 7-H), 7.12 (d, 1H, 10-H), 7.36-7.43 (m, 5H, Ph)

7c 3.98 (*s*, 2H, CH_2), 4.56 (d, 2H, 1-, 5-H, $J_{1,2}$,$J_{5,4} = 10.8$ Hz), 5.27 (dd, 1H, 2- or 4-H, $^4J = 4.3$ Hz), 5.31 (dd, 1H, 2- or 4-H), 7.07 (dd, 1H, 9-H, $J_{9,10} = 8.6$, $J_{9,7} = 2.1$ Hz), 7.12 (d, 1H, 10-H), 7.19 (d, 1H, 7-H), 7.33-7.46 (m, 5H, Ph)

7d 4.07 (*s*, 2H, CH_2), 4.62 (d, 1H, 1- or 5-H, J = 10.6 Hz), 4.65 (d, 1H, 1- or 5-H), 5.38 (dd, 1H, 2- or 4-H, $^4J = 2.0$ Hz), 5.42 (dd, 1H, 2- or 4-H), 7.20 (d, 1H, 10-H, $J_{10,9} = 8.8$ Hz), 7.34-7.48 (m, 5H, Ph), 7.90 (dd, 1H, 9-H, $J_{9,7} = 2.5$ Hz), 8.01 (d, 1H, 7-H)

^{13}C NMR (in $CDCl_3$) ppm

7a 60.7 (CH_2), 109.8 (C-1, 5), 127.0 (Ph), 127.3 (C-8, 9 or C-7, 10), 128.3 (Ph), 128.5 (C-8, 9 or C-7, 10), 129.1 (Ph), 135.8 (Ph), 140.4 (C-2, 4), 141.4 (C-6a, 10a), 157.0 (C-5a, 11a)

7b 21.4 (CH_3), 60.7 (CH_2), 109.7 (C-1 or C-5), 109.9 (C-1 or C-5), 127.0 (Ph, C-7, 10), 128.3 (Ph), 129.2 (Ph), 130.2 (C-9), 135.9 (Ph), 138.7 (C8), 139.5 (C-6a or C-10a), 140.1 (C-2 or C-4), 140.5 (C-2 or C-4), 141.2 (C-6a or C-10a), 156.1 (C-5a or C-11a), 157.0 (C-5a or C-11a)

7c 60.9 (CH_2), 109.7 (C-1 or C-5), 110.0 (C-1 or C-5), 126.6 (C-7), 127.1 (Ph), 128.4 (C-10), 128.4 (Ph), 128.8 (C-9), 129.2 (Ph), 133.6 (C-8), 135.6 (Ph), 140.1 (C-6a or C-10a), 140.6 (C-2 or C-4), 141.1 (C-2 or C-4), 142.1 (C-6a or C-10a), 157.3 (C-5a or C-11a), 158.1 (C-5a or C-11a)

7d 61.2 (CH_2), 109.9 (C-1 or C-5), 110.6 (C-1 or C-5), 122.6 (C-9), 123.0 (C-7), 127.1 (Ph), 127.9 (C-10), 128.6 (Ph), 129.3 (Ph), 135.1 (Ph), 141.1 (C-8), 141.3 (C-2 or C-4), 142.4 (C-2 or C-4), 145.7 (C-6a or C-10a), 146.9 (C-6a or C-10a), 159.1 (C-5a or C-11a), 160.3 (C-5a or C-10a)

	Molecular Formula	Elemental Analysis (%) Calcd./Found C	H	N	Cl
7a	$C_{19}H_{15}N_3$	79.98	5.30	14.73	
	(285.3)	79.74	5.14	14.65	
7b	$C_{20}H_{17}N_3$	80.24	5.72	14.04	
	(299.4)	80.16	5.68	13.76	
7c	$C_{19}H_{14}ClN_3$	71.36	4.41	13.14	11.09
	(319.8)	71.42	4.45	13.15	11.02
7d	$C_{19}H_{14}N_4O_2$	69.08	4.27	16.96	
	(330.4)	68.92	4.25	16.74	

up in diethyl ether/ethyl acetate (3:1), refluxed with charcoal for 15-20 minutes and filtered through a silica gel column. The filtrate was concentrated and the residue recrystallized from acetonitrile to yield compounds **7** as red needles, **7a-c** or a black pellet, **7d**.

3*H*-3-Isopropylazepino[4,5-*b*]quinoxaline (**8a**).

A solution of **5b** (330.2 mg, 2 mmoles) and *o*-phenylenediamine (**6a**) (216.3 mg, 2 mmoles) in *n*-butanol (6 ml) was heated with stirring at 160-165° (bath temperature) for 4 hours with a water separator. The solvent was removed *in vacuo*, and the residue was taken up in diethyl ether (50 ml), refluxed with charcoal for 15-20 minutes and filtered through a silica gel column then washed with diethyl ether (150 ml). The filtrate was concentrated, and the residue recrystallized from diethyl ether to give **8a** as red needles, 194.7 mg (41%), mp 119-121°; ^{1}H nmr (deuteriochloroform): δ 1.17 [d, 6H, $(CH_3)_2CH$], 3.06 [sept, 1H, $(CH_3)_2CH$], 4.57 (d, 2H, 1-, 5-H, $J_{1,2}$, $J_{5,4}$ = 10.6 Hz), 5.28 (d, 2H, 2-, 4-H), 7.08-7.22 (m, 4H, 7-, 8-, 9-, 10-H); ^{13}C nmr (deuteriochloroform): δ 21.2 (CH_3), 57.9 (CH), 109.7 (C-1, 5), 127.3 (C-7, 10), 128.3 (C-8, 9), 138.2 (C-2, 4), 141.5 (C-6a, 10a), 157.4 (C-5a, 11a).

Anal. Calcd. for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71. Found: C, 76.04; H, 6.37; N, 17.71.

8,9-Dichloro-3*H*-3-isopropylazepino[4,5-*b*]quinoxaline (**8b**) and 3*H*-3-Isopropylazepino[4,5-*b*]benzo[*g*]quinoxaline (**10**).

A solution of **5b** (495.3 mg, 3 mmoles or 330.2 mg, 2 mmoles) and the respective amine **6e** or **9** (molar ratio 1:1, Table 6) in *n*-butanol was heated with stirring at 150-165° with a water separator. The solvent was removed *in vacuo*, and the residue taken up in 80 ml of solvent (Table 6), refluxed with charcoal for 15-20 minutes and filtered through a silica gel column (2 x 3 cm), then washed with warmed solvent (100-120 ml). The filtrate was concentrated and the residue recrystallized from the given solvent to yield **8b** and **10** as red needles.

8,8'-Bis(3*H*-3-isopropylazepino[4,5-*b*]quinoxaline) (**12**).

A solution of **5b** (330.2 mg, 2 mmoles) and 3,3'-diamino-*p*-benzidine (**11**) (214.3 mg, 1 mmole) in *n*-butanol (6 ml) was heated with stirring at 155-160° for 5 hours. The solvent was removed and the residue chromatographed on silica gel with tetrahydrofuran (THF). Since the product could not be recrystallized, it was washed with diethyl ether and filtered off to yield **12** as a red powder, 224.1 mg (47%), mp 268° dec; ^{1}H nmr (deuteriochloroform): δ 1.18 [d, 12H, $(CH_3)_2CH$], 3.07 [sept, 2H, $(CH_3)_2CH$], 4.59 (d, 4H, 1-, 1'-, 5-, 5'-H, J = 10.6 Hz), 5.29 (d, 4H, 2-, 2'-, 4-, 4'-H), 7.20 (d, 2H, 10-, 10'-H, J = 8.3 Hz), 7.36 (dd, 2H, 9-, 9'-H, $^3J_1$ = 8.4, $^4J_2$ = 2.0 Hz), 7.39 (d, 2H, 7-, 7'-H); ^{13}C nmr (deuteriochloroform): δ 21.1 (CH_3), 58.0 (CH), 109.8 (C-1, 1' and C-5, 5'), 124.9 (C-7, 7'), 127.1 (C-9, 9'), 127.5 (C-10, 10'), 138.3 (C-2, 2' and C-4, 4'), 139.7 (C-6a, 6a' or C-8, 8' or C-10a, 10a'), 141.1 (C-6a, 6a' or C-8, 8' or C-10a, 10a'), 141.7 (C-6a, 6a' or C-8, 8' or C-10a, 10a'), 157.3 (C-5a, 5a' or C-11a, 11a'), 157.8 (C-5a, 5a' or C-11a, 11a').

General Procedure for the Reaction of **5b** with Amines **13**.

A stirred solution of **5b** (495.3 mg, 3 mmoles) and the respective amine **13a** or **b** (327.3 mg, 3 mmoles) in *p*-xylene (30 ml) was heated at 185° for 1.5-2 hours with a water separator. The solvent was removed *in vacuo*, the residue was taken up in THF (30 ml) and heated for 15 minutes. Unreacted **5b** was filtered off, the filtrate was concentrated and the residue was chromatographed on silica gel with THF to yield **14a** or **14b** in 49 and 45% yield, respectively.

8-Isopropylpyrido[3',2':5,6]pyrazino[2,3-*d*]azepine (**14a**).

This compound was obtained as wine-red needles (petroleum ether/THF), mp 134-135°; ^{1}H nmr (deuteriochloroform): δ 1.19 [d, 6H, $(CH_3)_2CH$], 3.10 [sept, 1H, $(CH_3)_2CH$], 4.60 (d, 1H, 6- or 10-H, J = 11.0 Hz), 4.70 (d, 1H, 6- or 10-H), 5.31 (dd, 1H, 7- or 9-H, $^3J_1$ = 9.0, $^4J_2$ = 2.0 Hz), 5.35 (dd, 1H, 7- or 9-H), 7.00 (dd, 1H, 3-H, $J_{3,4}$ = $J_{3,2}$ = 8.0 Hz), 7.43 (dd, 1H, 4-H, $J_{4,2}$ = 2.0

Table 6

Condensation of **5b** with Diamines **6e** and **9** to Azepino[4,5-*b*]quinoxalines **8b** and **10**, ^{1}H and ^{13}C NMR Data as well as Elemental Analyses

	Amine mg (mmoles)	Reaction time [h]	BuOH (ml)	Solvent (Purification)	Product **8b, 10**	Yield mg (%)	mp [°C]
6e	531.0 (3.0)	12	60	Et_2O	**8b**	296.0 (32)	186-187
6e	354.0 (2.0)	4	6	Et_2O	**8b**	375.2 (61)	
9	474.6 (3.0)	15	50	Et_2O/EA (5:1)	**10**	168.0 (20)	211-213
9	316.4 (2.0)	4	6	Et_2O/EA (5:1)	**10**	187.2 (33)	

^{1}H NMR (in $CDCl_3$) ppm

8b 1.18 (d, 6H, CH_3), 3.09 (sept, 1H, CH), 4.53 (d, 2H, 1-, 5-H, $J_{1,2}$,$J_{5,4}$ = 10.6 Hz), 5.31 (d, 2H, 2-, 4-H), 7.23 (s, 2H, 7-, 10-H)

10 1.23 (d, 6H, CH_3), 3.23 (sept, 1H, CH), 4.93 (d, 2H, 1-, 5-H, $J_{1,2}$,$J_{5,4}$ = 10.6 Hz), 5.56 (d, 2H, 2-, 4-H), 7.26-7.31 (m, 2H, 9-, 10-H), 7.65-7.71 (m, 4H, 7-, 8-, 11-, 12-H)

^{13}C NMR (in $CDCl_3$) ppm

8b 21.2 (CH_3), 58.3 (CH), 109.7 (C-1, 5), 128.0 (C-7, 10), 131.6 (C-8, 9), 138.8 (C-2, 4), 140.9 (C-6a, 10a), 158.5 (C-5a, 11a)

10 21.4 (CH_3), 58.7 (CH), 110.2 (C-1, 5), 124.8 (C-7, 12), 126.0 (C-9, 10), 128.0 (C-8, 11), 133.8 (C-7a, 11a), 137.1 (C-2, 4), 138.9 (C-6a, 12a), 156.7 (C-5a, 13a)

Anal. Calcd. for $C_{15}H_{13}Cl_2N_3$ **8b**: C, 58.84; H, 4.28; N, 13.72; Cl, 23.16. Found: C, 58.83; H, 4.33; N, 13.58; Cl, 23.11.

Anal. Calcd. for $C_{19}H_{17}N_3$ **10**: C, 79.41; H, 5.96; N, 14.62. Found: C, 79.42; H, 6.08; N, 14.50.

Et_2O = diethyl ether, EA = ethyl acetate.

Table 7

Hydrogenation of **5a-c** to Azepin-4-ol-5-ones **15a-c**, ^1H and ^{13}C NMR Data and Elemental Analyses

Azepinone	g (mmoles)	$NaBH_4$ g (mmoles)	EtOH (ml)	Product **15**	Solvent (Chromatogr)	Yield g (%)
5a	4.26 (20)	0.38 (10)	50	**15a**	acetonitrile	3.31 (77)
5b	0.66 (4)	0.08 (2)	15	**15b**	dioxane	0.39 (58)
5c	0.82 (4)	0.08 (2)	15	**15c**	dioxane	0.58 (70)

^1H NMR (in $CDCl_3$) ppm

15a 4.35 (broad s, 1H, 4-H), 4.49 (broad s, 1H, OH), 4.69 (d, 2H, CH_2), 4.90 (dd, 1H, 3-H, $J_{3,2}$ = 8.3, $J_{3,4}$ = 3.4 Hz), 5.56 (d, 1H, 6-H, $J_{6,7}$ = 9.2 Hz), 6.12 (ddd, 1H, 2-H, $J_{2,4}$ = 2.4, $J_{2,7}$ = 0.8 Hz), 6.93 (d, 1H, 7-H), 7.18-7.44 (m, 5H, Ph)

15b 1.35 and 1.38 (d, 6H, CH_3), 3.82 (sept, 1H, CH), 4.22 (broad s, 1H, 4-H), 4.56 (broad s, 1H, OH), 4.91 (dd, 1H, 3-H, $J_{3,2}$ = 8.4, $J_{3,4}$ = 3.6 Hz), 5.50 (d, 1H, 6-H, $J_{6,7}$ = 9.2 Hz), 6.21 (ddd, 1H, 2-H, $J_{2,4}$ = 2.2, $J_{2,7}$ = 0.7 Hz), 6.96 (d, 1H, 7-H)

15c 1.11-1.99 (m, 10H, cyclohex), 3.32 (ttt, 1H, cyclohex), 4.22 (broad s, 1H, 4-H), 4.53 (broad s, 1H, OH), 4.91 (dd, 1H, 3-H, $J_{3,2}$ = 8.3, $J_{3,4}$ = 3.6 Hz), 5.51 (d, 1H, 6-H, $J_{6,7}$ = 9.4 Hz), 6.18 (ddd, 1H, 2-H, $J_{2,4}$ = 2.3, $J_{2,7}$ = 0.6 Hz), 6.93 (d, 1H, 7-H)

^{13}C NMR (in $CDCl_3$) ppm

15a 61.1 (CH_2), 72.0 (C-4), 101.0 (C-6), 112.3 (C-3), 126.3 (Ph), 127.0 (C-2), 127.8 (Ph), 128.5 (Ph), 135.3 (Ph), 144.8 (C-7), 182.3 (C-5)

15b 22.1 (CH_3), 58.5 (CH), 72.4 (C-4), 100.7 (C-6), 112.8 (C-3), 124.7 (C-2), 143.2 (C-7), 182.8 (C-5)

15c 25.0 (cyclohex), 25.6 (cyclohex), 32.6 (cyclohex), 66.5 (cyclohex), 72.5 (C-4), 100.6 (C-6), 112.8 (C-3), 125.4 (C-2), 143.4 (C-7), 182.8 (C-5)

	Molecular Formula	Elemental Analysis (%) Calcd./Found C	H	N
15a	$C_{13}H_{13}NO_2$	72.54	6.09	6.51
	(215.3)	72.39	6.18	6.57
15b	$C_9H_{13}NO_2$	64.65	7.84	8.38
	(167.2)	64.49	7.93	8.16
15c	$C_{12}H_{17}NO_2$	69.54	8.27	6.76
	(207.3)	69.48	8.25	6.64

Hz), 8.32 (dd, 1H, 2-H); ^{13}C nmr (deuteriochloroform): δ 21.2 (CH_3), 58.3 (CH), 109.7 (C-6 or C-10), 110.2 (C-6 or C-10), 123.5 (C-3), 135.0 (C-4), 136.9 (C-4a or C-11a), 138.9 (C-7 or C-9), 139.5 (C-7 or C-9), 150.3 (C-2), 152.7 (C-4a or C-11a), 158.6 (C-5a or C-10a), 161.2 (C-5a or C-10a).

Anal. Calcd. for $C_{14}H_{14}N_4$: C, 70.57; H, 5.92; N, 23.51. Found: C, 70.41; H, 6.02; N, 23.79.

8-Isopropylpyrido[4',3':5,6]pyrazino[2,3-*d*]azepine (**14b**).

This compound was obtained as wine-red powder (THF), mp 150-151°; ^1H nmr (deuteriochloroform): δ 1.19 [d, 6H, $(CH_3)_2CH$], 3.12 [sept, 1H, $(CH_3)_2CH$], 4.57 (d, 1H, 6- or 10-H, $J_{6,7}$, $J_{10,9}$ = 11.0 Hz), 4.63 (d, 1H, 6- or 10-H), 5.30 (dd, 1H, 7- or 9-H, $J_{7,9}$ = 2.0 Hz), 5.34 (dd, 1H, 7- or 9-H), 6.96 (dd, 1H, 4-H, $J_{4,3}$ = 5.5, $J_{4,1}$ = 0.5 Hz), 8.17 (d, 1H, 3-H), 8.43 (d, 1H, 1-H); ^{13}C nmr (deuteriochloroform): δ 21.2 (CH_3), 58.5 (CH), 109.4 (C-6 or C-10), 110.8 (C-6 or C-10), 120.0 (C-4), 137.6 (C-4a or C-11a), 138.3 (C-7 or C-9), 140.3 (C-7 or C-9), 145.7 (C-4a or C-11a), 147.7 (C-3), 150.6 (C-1), 159.2 (C-5a or C-10a), 162.1 (C-5a or C-10a).

Anal. Calcd. for $C_{14}H_{14}N_4$: C, 70.57; H, 5.92; N, 23.51. Found: C, 70.55; H, 5.95; N, 23.54.

General Procedure for the Reduction of **5a-c** with Sodium Borohydride to 1-Alkyl-1*H*-azepin-4-ol-5-ones **15a-c**.

A solution of the diketone **5** and sodium borohydride in ethanol was stirred at room temperature for 3 hours. Ethanol was removed, and the yellow residue was taken up in water/dichloromethane 1:1 (20 ml), stirred for additional 1 hour and extracted three times with dichloromethane (each 50 ml). The combined extracts were dried (magnesium sulfate), concentrated and chromatographed on silica gel to give **15a-c** as yellow oils. Compound **15c** crystallized on cooling (12 hours at -15°), mp 64-65° (diethyl ether).

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