Annulated 1,2,3-Triazoles. 3 [1]. Synthesis of 1,2,3-Triazolo[4,5-*b*][1,5]benzoxazepin-10(9*H*)-ones and 10-(4-Substituted-1-piperazinyl)-1,2,3-triazolo[4,5-*b*][1,5]benzoxazepines

Flemming E. Nielsen [2] and Erik B. Pedersen [3]

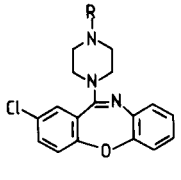
Department of Chemistry, Odense University,
DK-5230 Odense M, Denmark

Received April 18, 1985

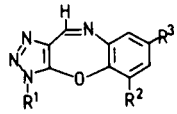
10-(4-Substituted-1-piperazinyl)-1,2,3-triazolo[4,5-*b*][1,5]benzoxazepines **11** were prepared in a three-step synthesis starting from easily available 5-chloro-1,2,3-triazole-4-carbonyl chlorides **7** by titanium tetrachloride catalyzed condensation of *N*-(substituted)piperazines with 1,2,3-triazolo[4,5-*b*][1,5]benzoxazepin-10(9*H*)-ones **10** formed by ring closure of the intermediate amides **9**. Although lactams **10** were obtained as the sole product of the cyclisation at 80°, the unexpected by-products **13** and **14** were formed in addition to **10c** at 150° from **9c**. The 4-methoxybenzyl group in **11j** was easily removed by solvolyses in TFA. Compounds **11d-f** and **11i** were tested for psychotropic activity.

J. Heterocyclic Chem., **22**, 1693 (1985).

Previous reports have highlighted the importance of dibenzoxazepines as pharmacologically active compounds [4-7]. For example, the neuroleptic drug loxapine (**1**) [8] is effective in treatment of schizophrenia while its desmethyl derivative amoxapine (**2**) [9] is an antidepressant agent. New heterocyclic compounds derived from dibenzoxazepine by replacement of one of the benzene rings with a heterocyclic system have been prepared in a search for new CNS agents with improved therapeutic profiles [10].



1, R=CH$_3$
2, R=H

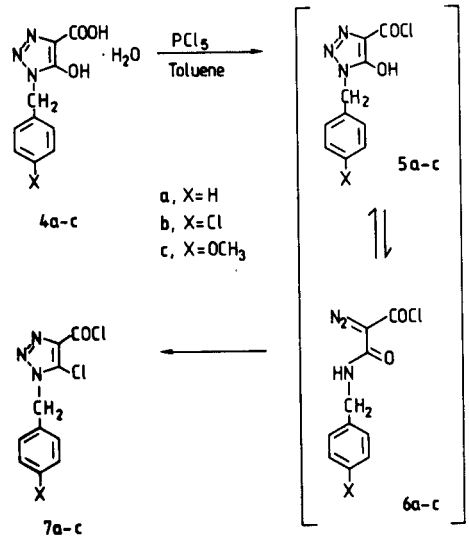


3

In a previous paper [1] we reported the successful synthesis of 1,2,3-triazolo[4,5-*b*][1,5]benzoxazepines **3** as a novel class of dibenzoxazepine analogues. Encouraged by these results, we undertook further studies to prepare the corresponding 10-(4-substituted-1-piperazinyl)-1,2,3-triazolo[4,5-*b*][1,5]benzoxazepine analogues **11** of loxapine. In a recent patent [11] 10-(4-alkyl-1-piperazinyl)-2,4-dihydro-1,2,3-triazolo[4,5-*b*][1,5]benzodiazepines, representing a novel heterocyclic ring system, are claimed to possess useful CNS activity with a high therapeutic index. This too, prompted us to investigate the above synthesis of **11**.

The starting compounds **4a-c**, readily prepared by our previous method [12], were refluxed with phosphorus pentachloride in toluene to give the 5-chloro-1,2,3-triazole-4-carbonyl chlorides **7a-c** in 52-95% yield. Lower temperatures only resulted in the formation of a mixture of the expected products **7** and the acid chloride of diazomalonic amides **6** according to ms and ^{1}H-nmr spectra. Intermediates **6** might be formed by ring opening of the isomeric *o*-hydroxy acid chlorides **5** (Scheme 1) in agreement with similar ring opening reactions of other hydroxytriazoles [12,13].

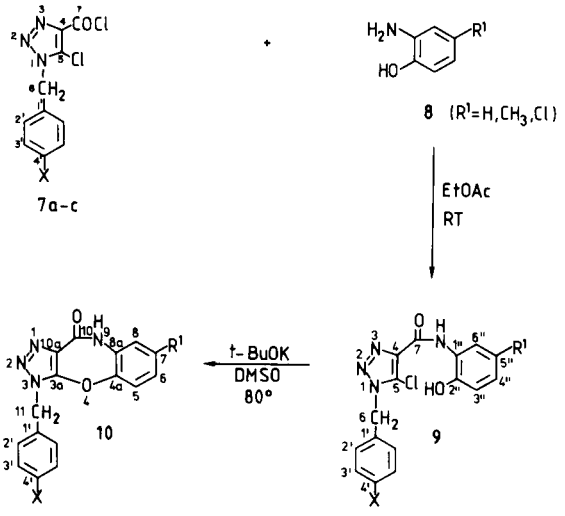
Scheme 1



The *o*-chloro acid chlorides **7** were subsequently condensed in a slightly exothermic reaction with the appropriate *o*-aminophenol **8** in ethyl acetate at room temperature according to General Procedure A to afford the amides **9** (Scheme 2) in excellent yields (Table 1). Related condensations are known for preparation of intermediate amides of other heterocyclic oxazepinones [14-18].

An attempt to cyclise the intermediate amide **9c**, using anhydrous potassium carbonate in *N,N*-dimethylformamide at 80° as in our preparation of **3** [1], completely failed as only starting material was recovered. Also treatment of **9c** with sodium hydride in *N,N*-dimethylformamide gave

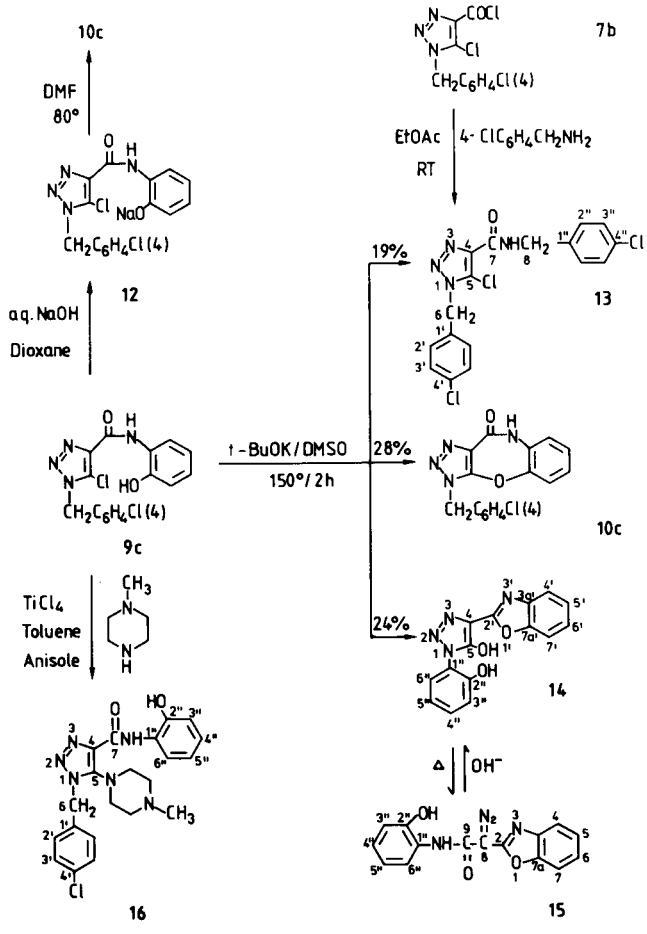
Scheme 2



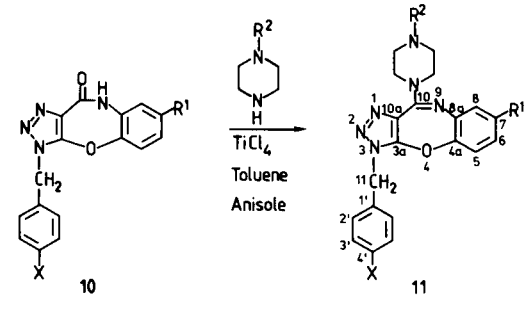
poor results. However, **9c** was ring closed to the lactam **10c** (Scheme 3) in modest yield by heating the intermediate sodium salt **12** in *N,N*-dimethylformamide at 80° for two days. We found, however, that treatment of amides **9** with potassium *t*-butoxide in dry dimethyl sulfoxide at 80° for 50 hours under nitrogen was the most convenient method to obtain the lactams **10** (Scheme 2). The yields were only moderate (Table 2). This might be due to side reactions as demonstrated by our reaction of **9c** according to General Procedure B at 150° for 2 hours (Scheme 3). In addition to the expected product **10c** we isolated the amide **13** and a product, identical with the benzoxazole **14** according to tlc, but attempted recrystallization from ethyl acetate resulted in the isomeric yellow diazoacetamide **15**. When treated with cold 2*N* sodium hydroxide, **15** was easily isomerized to the ring closed white product **14**. Further evidence for the proposed structure of the second by-product was obtained when a sample of **14** was reversed to **15** in boiling ethyl acetate. The structure of amide **13** was confirmed by an alternative synthesis from the acid chloride **7b** and *p*-chlorobenzylamine (Scheme 3). The isolated by-products **13** and **14** are probably the result of an initial intermolecular nucleophilic attack of one molecule of the phenoxide anion of **9c** on the chlorine atom of another molecule followed by rearrangement and cleavage of the dimer. This means that dilute solutions of **9** should be preferred in order to increase the yields of the desired products **10**.

Conversion of lactams **10** to the biologically interesting title compounds **11** was accomplished as outlined in Scheme 4 by a slight modification of the Schneider procedure [19-21] which is derived from the Fryer method [22]. In this method (General Procedure C) titanium tetrachloride is used to catalyze the direct condensation of *N*-(substituted)piperazines with the tricyclic lactams **10** affording the 10-(4-substituted-1-piperazinyl)-1,2,3-triazolo[4,5-*b*]-[1,5]benzoxazepines **11a-j** in 73-83% yield (Table 3).

Scheme 3



Scheme 4

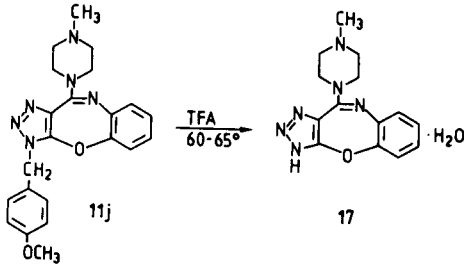


In a hopeful attempt to prepare the latter compounds directly from the amides **9** in one step, **9c** was subjected to the conditions of General Procedure C in a reaction with *N*-methylpiperazine. However, the only isolated product was the aminated triazole carboxamide **16** (Scheme 3).

In order to investigate the removal of the benzylic pro-

tecting group in the prepared tricyclic compounds, we subjected 3-benzyl-10-(4-methyl-1-piperazinyl)-3*H*-1,2,3-triazolo[4,5-*b*][1,5]benzoxazepine (**11a**) to debenzylation with (1) sodium in liquid ammonia [23,24] and (2) by catalytic hydrogenation [25] with 10% palladium on charcoal catalyst at 950 p.s.i. and 130° for 2 hours. Unfortunately, in both procedures the *N*-benzyl protected compound was recovered unchanged demonstrating the high stability of the *N*-benzyl bond in these tricyclic derivatives. However, the 4-methoxybenzyl group in **11j** was readily removed by solvolysis in trifluoroacetic acid [26] at 60-65° for 23 hours to give 51% of the deprotected triazolo[4,5-*b*][1,5]benzoxazepine as the monohydrate **17** (Scheme 5).

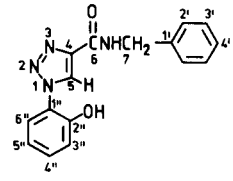
Scheme 5



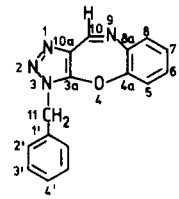
11j 17

Confirmatory evidence for the assigned structures **7a-c**, **9a-e**, **10a-e**, **11a-j** and **13-17** was obtained by ir and ^{1}H-nmr spectroscopy, mass spectrometry and elemental analysis. Spectral data for compounds **9-11** are given in Tables 4-6. Furthermore, structural assignment of compounds **7b**, **9c**, **10c**, **11e-f**, **13-16** and **17** was supported by ^{13}C-nmr spectroscopy. The assignments were based on literature values, on mutual comparisons and comparisons with the reference compounds **18** [27] and **19** [1] of the decoupled as well as the NOE proton-coupled spectra. The ^{13}C-nmr chemical shift values are given in Tables 7 and 8.

Scheme 6



18

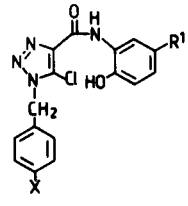


19

Compounds **11d-f** and **11i** were tested as psychotropic agents [28], but no activity was found in the exploratory motility test or the apomorphine-induced hypermotility test in rats (tests for minor tranquillizors and neuroleptics). Compounds **11d** and **11i**, however, exhibited a dubious effect in the nialamide-hypermotility potentiation test in mice, a test for 5-hydroxytryptamine potentiators, with ED_{50} ~30 mg/kg and bell-shaped dose-response curve.

Table 1

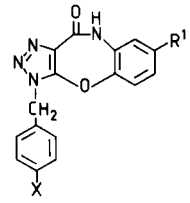
5-Chloro-*N*-(5-substituted-2-hydroxyphenyl)-1*H*-1,2,3-triazole-4-carboxamides **9a-e**



Compound No.	X	R'	Yield %	Mp °C	Recrystallization solvent	Molecular formula	Analyses % Calcd./Found C	H	N
9a	H	H	62	181-182	ethyl acetate	$C_{16}H_{13}ClN_4O_2$	58.46	3.99	17.04
							58.4	4.1	17.1
9b	H	CH_3	88	191-192	ethyl acetate	$C_{17}H_{15}ClN_4O_2$	59.57	4.41	16.34
							59.8	4.4	16.5
9c	Cl	H	83	213-215	toluene	$C_{16}H_{12}Cl_2N_4O_2$	52.91	3.33	15.43
							53.18	3.30	15.37
9d	Cl	Cl	85	240-241	acetonitrile	$C_{16}H_{11}Cl_3N_4O_2$	48.33	2.79	14.09
							48.38	2.71	14.14
9e	OCH_3	H	91	171-172	ethyl acetate	$C_{17}H_{15}ClN_4O_3$	56.91	4.21	15.62
							56.5	4.3	15.4

Table 2

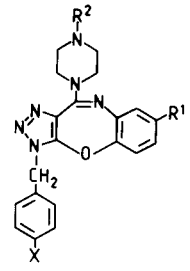
1,2,3-Triazolo[4,5-*b*][1,5]benzoxazepin-10(9*H*)-ones **10a-e**, Prepared by General Procedure B



Compound No.	X	R¹	Yield %	Mp °C	Recrystallization solvent	Molecular formula	Analyses % Calcd./Found C	H	N
10a	H	H	50	246-247	2-methoxyethanol	$C_{16}H_{12}N_4O_2$	65.75	4.14	19.17
							65.6	4.2	19.3
10b	H	CH_3	52	243-244	2-methoxyethanol	$C_{17}H_{14}N_4O_2$	66.66	4.61	18.29
							66.4	4.7	18.2
10c	Cl	H	43	269-270	2-methoxyethanol	$C_{16}H_{11}ClN_4O_2$	58.82	3.39	17.15
							58.71	3.45	17.04
10d	Cl	Cl	16	267-268	butanone	$C_{16}H_{10}Cl_2N_4O_2$	53.21	2.79	15.51
							53.68	2.71	15.75
10e	OCH_3	H	49	211-212	2-methoxyethanol	$C_{17}H_{14}N_4O_3$	63.35	4.38	17.38
							63.0	4.5	17.3

Table 3

10-(4-Substituted-1-piperazinyl)-3*H*-triazolo[4,5-*b*][1,5]benzoxazepines **11a-j**



Compound No.	X	R¹	R²	Yield %	Mp °C	Recrystallization solvent	Molecular formula	Analyses % Calcd./Found C	H	N
11a	H	H	CH_3	83	149-150	ligroin (80-100°)	$C_{21}H_{22}N_6O$	67.36	5.92	22.44
								67.3	5.9	22.5
11b	H	H	$CH_2C_6H_5$	78	131	ligroin (80-100°)	$C_{27}H_{26}N_6O$	71.98	5.82	18.65
								72.0	5.9	18.7
11c	H	H	4-FC_6H_4	77	153-154	ligroin (80-100°)	$C_{26}H_{23}FN_6O$	68.71	5.10	18.49
								68.7	5.2	18.6
11d	H	CH_3	CH_3	83	140-141	ligroin (80-100°)	$C_{22}H_{24}N_6O$	68.02	6.23	21.63
								68.2	6.3	21.6
11e	Cl	H	CH_3	78	153-154	ligroin (80-100°)	$C_{21}H_{21}ClN_6O$	61.69	5.18	20.55
								61.77	5.22	20.37
11f	Cl	H	$CH_2C_6H_5$	74	149-150	ligroin (80-100°)	$C_{27}H_{25}ClN_6O$	66.87	5.20	17.33
								66.87	5.19	17.24
11g	Cl	H	C_6H_5	74	170-171	ligroin (100-140°)	$C_{26}H_{23}ClN_6O$	66.31	4.92	17.84
								66.37	4.87	17.94
11h	Cl	H	4-FC_6H_4	77	178-179	ethyl acetate	$C_{26}H_{22}ClFN_6O$	63.87	4.53	17.19
								63.97	4.55	17.14
11i	Cl	Cl	CH_3	73	168-169	ethyl acetate-ligroin (80-100°)	$C_{21}H_{20}Cl_2N_6O$	56.89	4.55	18.97
								57.10	4.53	19.03
11j	OCH_3	H	CH_3	82	117-118	ligroin (80-100°)	$C_{22}H_{24}N_6O_2$	65.33	5.98	20.78
								65.5	6.0	20.5

Table 4

Spectra of Amides **9a-e**

Compound No.	IR (potassium bromide) ν (cm^{-1})	Mass Spectrum m/e (%)	^1H NMR (DMSO-d_6/TMS) δ (ppm)
9a	3380, 1670 (C=O), 1615, 1600	328 (M^+, 13), 91 (100)	5.72 (s, 2H, CH_2), 6.6-7.1 (m, 3H, aromatic), 7.36 (s, 5H, aromatic), 8.0-8.3 (m, 1H, aromatic), 9.53 and 10.25 (2s, 1H each, NH and OH, exchangeable)
9b	3380, 1665 (C=O), 1620, 1605	342 (M^+, 13), 91 (100)	2.27 (s, 3H, CH_3), 5.73 (s, 2H, CH_2), 6.83 (m, 2H, aromatic) , 7.40 (s, 5H, aromatic), 8.07 (m, 1H, aromatic), 9.53 and 10.03 (2s, 1H each, NH and OH, exchangeable)
9c	3360, 1665 (C=O), 1605, 1590	362 (M^+, 13), 127 (32), 125 (100)	5.73 (s, 2H, CH_2), 6.7-7.1 (m, 3H, aromatic), 7.2-7.6 (m, 4H, aromatic), 8.1-8.3 (m, 1H, aromatic), 9.53 and 10.23 (2s, 1H each, NH and OH, exchangeable)
9d	3380, 1670 (C=O), 1605, 1595	398 (M^++2, 7), 396 (M^+, 7), 127 (33), 125 (100)	5.80 (s, 2H, CH_2), 7.07 (m, 2H, aromatic), 7.3-7.7 (m, 4H, aromatic), 8.33 (m, 1H, aromatic), 9.60 and 10.73 (2s, 1H each, NH and OH, exchangeable)
9e	3380, 1670 (C=O), 1615	358 (M^+, 3), 121 (100)	3.77 (s, 3H, OCH_3), 5.63 (s, 2H, CH_2), 6.7-7.1 (m, 3H, aromatic), 7.13 (AB quartet, J = 9 Hz, $\Delta\nu$ = 21 Hz, 4H, aromatic), 8.1-8.3 (m, 1H, aronmatic), 9.55 and 10.30 (2s, 1H each, NH and OH, exchangeable)

Table 5

Spectra of Lactams **10a-e**

Compound No.	IR (potassium bromide) ν (cm^{-1})	Mass Spectrum m/e (%)	^1H NMR (DMSO-d_6/TMS) δ (ppm)
10a	1685 (C=O), 1620	292 (M^+, 21), 91 (100)	5.68 (s, 2H, CH_2), 7.1-7.4 (m, 4H, aromatic), 7.47 (s, 5H, aromatic), 10.25 (broad s, 1H, NH, exchangeable)
10b	1675 (C=O), 1620	306 (M^+, 27), 91 (100)	2.27 (s, 3H, CH_3), 5.70 (s, 2H, CH_2), 6.8-7.2 (s, 3H, aromatic), 7.49 (s, 5H, aromatic), 10.18 (broad s, 1H, NH, exchangeable)
10c	1680 (C=O), 1605	326 (M^+, 11), 127 (33), 125 (100)	5.68 (s, 2H, CH_2), 7.0-7.4 (m, 4H, aromatic), 7.50 (s, 4H, aromatic), 10.20 (broad s, 1H, NH, exchangeable)
10d	1690 (C=O), 1615	360 (M^+, 4), 127 (33), 125 (100)	5.70 (s, 2H, CH_2), 7.0-7.7 (m, 7H, aromatic), 10.27 (broad s, 1H, NH, exchangeable
10e	1680 (C=O), 1610	322 (M^+, 5), 121 (100)	3.80 (s, 3H, OCH_3), 5.57 (s, 2H, CH_2), 6.9-7.6 (m, 8H, aromatic), 10.20 (broad s, 1H, NH, exchangeable)

EXPERIMENTAL

The ir spectra were recorded on a Perkin-Elmer 580 IR spectrophotometer. The ^1H-nmr spectra were recorded on a JEOL JNM-PMX 60 spectrometer, while ^{13}C-nmr spectra were obtained on a JEOL JNM-FX 60Q Fourier Transform NMR spectrometer. Mass spectra were determined with a Varian MAT 311A and a Varian MAT CH 7A. The microanalyses were carried out by Novo Microanalytical Laboratory A/S, Novo Allé, DK-2880 Bagsvaerd, supervised by Dr. R. E. Amsler and by Ciba-Geigy AG, Basel.

1-Substituted-5-hydroxy-1*H*-1,2,3-triazole-4-carboxylic acids **4a-c** were prepared as previously described [12].

5-Chloro-1-(phenylmethyl)-1*H*-1,2,3-triazole-4-carbonyl Chloride (**7a**).

To a stirred suspension of phosphorus pentachloride (187.4 g, 0.90 mole) in 700 ml of dry toluene was added 5-hydroxy-1-(phenylmethyl)-1*H*-1,2,3-triazole-4-carboxylic acid monohydrate (**4a**, 71.2 g, 0.30 mole) with cooling in a water bath. Evolution of hydrogen chloride was observed immediately after the addition. After about 10 minutes the mixture was stirred in an oil bath at 40° for 4 hours, and the clear solution was concentrated to dryness *in vacuo*. However, ^1H-nmr and ms indicated that the residue consisted of a mixture of the expected product **7a** and the ring opened intermediate **6a**. Therefore the oily residue was dissolved in 250 ml of toluene and an additional amount of phosphorus pentachloride (41.7 g, 0.20 mole) was added. The mixture was refluxed with stirring on an oil bath for 4 hours and then evaporated to dryness. The crude product was dissolved in 150 ml of methylene chloride and the solution was washed with 50 ml of saturated aqueous sodium hydrogen carbonate and water (2 × 50 ml), dried with sodium sulfate and evaporated to dryness. The crystals, which slowly formed in the residue, were washed with 200 ml of petroleum ether (65-70°) and recrystallized from ethyl acetate/petroleum ether (65-70°) to give 60.6 g (79%) of pure **7a**, mp 80-82°; ir (potassium bromide): 1760 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 5.60 (s, 2H, CH_2), 7.38 (s, 5H, aromatic); ms: m/e (relative intensity) 255 (M^+, 1), 200 (15), 198 (23), 92 (15), 91 (100), 89 (10), 65 (42), 63 (13), 51 (15), 39 (26).

Anal. Calcd. for $C_{10}H_7Cl_2N_3O$ (256.09): C, 46.90; H, 2.76; N, 16.41. Found: C, 47.14; H, 2.76; N, 16.75.

Table 6

Spectra of Piperazinyl Compounds **11a-j**

Compound No.	IR (potassium bromide) ν (cm^{-1})	Mass Spectrum m/e (%)	^1H NMR (deuteriochloroform/TMS) δ (ppm)
11a	1605, 1580	347 (M^+, 7), 305 (12), 304 (55), 292 (38), 91 (89), 83 (100), 70 (38), 56 (13), 43 (18), 42 (18)	2.35 (s, 3H, CH_3), 2.4-2.7 (m, 4H, $2CH_2N$), 3.8-4.1 (m, 4H, $2CH_2N$), 5.47 (s, 2H, CH_2), 6.6-7.3 (m, 4H, aromatic), 7.37 (s, 5H, aromatic)
11b	1605, 1580	450 (M^+, 8), 304 (19), 292 (22), 159 (72), 146 (19), 91 (100)	2.5-2.8 (m, 4H, $2CH_2N$), 3.57 (s, 2H, CH_2), 3.8-4.1 (m, 4H, $2CH_2N$), 5.43 (s, 2H, CH_2), 6.5-7.3 (m, 4H, aromatic), 7.33 (s, 10H, aromatic)
11c	1605, 1580	454 (M^+, 16), 318 (12), 317 (51), 305 (21), 304 (100), 163 (12), 150 (18) 122 (13), 91 (82)	3.1-3.4 (m, 4H, $2CH_2N$), 4.0-4.3 (m, 4H, $2CH_2N$), 5.50 (s, 2H, CH_2), 6.6-7.4 (m, 8H, aromatic), 7.45 (s, 5H, aromatic)
11d	1605, 1580	388 (M^+, 11), 331 (11), 319 (16), 318 (81), 307 (12), 306 (61), 91 (88), 83 (100), 70 (36), 56 (16), 43 (21), 42 (19)	2.23 (s, 3H, CH_3), 2.33 (s, 3H, NCH_3), 2.4-2.7 (m, 4H, $2CH_2N$), 3.8-4.1 (m, 4 H , $2CH_2N$), 5.42 (s, 2H, CH_2), 6.4-7.0 (m, 3H, aromatic), 7.33 (s, 5H, aromatic)
11e	1605, 1575	408 (M^+, 3), 338 (25), 326 (11), 127 (18), 125 (55), 83 (100), 70 (55), 56 (13), 43 (18), 42 (21)	2.37 (s, 3H, NCH_3), 2.4-2.7 (m, 4H, $2CH_2N$), 3.8-4.1 (m, 4H, $2CH_2N$), 5.42 (s, 2H, CH_2), 6.6-7.3 (m, 4H, aromatic), 7.33 (s, 4H, aromatic)
11f	1605, 1575	484 (M^+, 5), 338 (11), 326 (13), 160 (13), 159 (100), 146 (40), 127 (15), 125 (47), 91 (83), 42 (11)	2.5-2.8 (m, 4H, $2CH_2N$), 3.60 (s, 2H, CH_2), 3.8-4.1 (m, 4H, $2CH_2N$), 5.42 (s, 2H, CH_2), 6.6-7.5 (m, 13H, aromatic)
11g	1600, 1580	470 (M^+, 17), 353 (24), 352 (18), 351 (68), 340 (29), 339 (17), 338 (84), 226 (26), 145 (25), 133 (21), 132 (100), 127 (25), 125 (82), 105 (17), 104 (23), 91 (13), 77 (15), 56 (12)	3.2-3.5 (m, 4H, $2CH_2N$), 4.0-4.3 (m, 4H, $2CH_2N$), 5.42 (s, 2H, CH_2), 6.6-7.5 (m, 13H, aromatic)
11h	1605, 1580	488 (M^+, 13), 353 (18), 352 (13), 351 (53), 340 (34), 339 (20), 338 (100), 226 (20), 163 (18), 150 (41), 127 (26), 125 (79), 123 (13), 122 (22)	3.1-3.4 (m, 4H, $2CH_2N$), 3.9-4.2 (m, 4H, $2CH_2N$), 5.43 (s, 2H, CH_2), 6.6-7.4 (m, 12H, aromatic)
11i	1610, 1575	442 (M^+, 3), 372 (11), 127 (11), 125 (31), 83 (100), 70 (58)	2.36 (s, 3H, NCH_3), 2.4-2.7 (m, 4H, $2CH_2N$), 3.8-4.1 (m, 4H, $2CH_2N$), 5.43 (s, 2H, CH_2), 6.4-7.5 (m, 7H, aromatic)
11j	1605, 1580	404 (M^+, 6), 334 (21), 322 (31), 226 (10), 121 (100), 83 (60), 70 (18), 43 (10)	2.36 (s, 3H, NCH_3), 2.4-2.7 (m, 4H, $2CH_2N$), 3.80 (s, 3H, OCH_3), 3.8-4.1 (m, 4H, $2CH_2N$), 5.40 (s, 2H, CH_2), 6.7-7.5 (m, 8H, aromatic)

Table 7

^{13}C-NMR Spectral Data of Triazoles **7b, 9c, 13, 14, 16** and **18**, and Diazo Compound **15** [a]

Product No	C-4	C-5	C-6	C-7	C-1′	C-2′	C-3′	C-4′	C-1″	C-2″	C-3″	C-4″	C-5″	C-6″	Other
7b	135.0	129.0	50.7	160.4	133.1	129.6	128.9	131.1							
9c	136.4	127.7	50.6	155.9	133.0	129.5	128.8	133.0	125.6	146.6	114.8	124.4	(119.1,	119.9)	
13	136.5	127.2	50.4	158.4	133.1	(129.5,	128.8)	133.1	138.3	(129,1,	128.1)	133.0			[b]
14	115.7	153.6				157.4		118.1	122.5	152.1	117.3	130.7	119.2	127.3	[c]
15	117.8	(124.5,	124.0)	110.4					126.7	146.5	114.6	124.9	(119.0,	119.7)	[d]
16	134.3	146.7	49.2	157.3	134.6	129.4	128.6	132.6	126.1	146.2	114.6	123.8	(119.1,	119.3)	[e]
18	142.4	127.7	159.5	41.9	139.4	127.2	128.1	126.6	124.0	149.8	116.9	130.5	119.4	125.3	

[a] Determined in DMSO-d_6 (ppm, rel. TMS). For numbering the carbon atoms, see Schemes 2, 3 and 6. Chemical shifts given in brackets may be interchanged. [b] 41.2 (C-8). [c] 139.4 (C-3a′); 124.6, 124.8 (C-5′ and C-6′); 110.7 (C-7′), 148.8 (C-7a′). [d] 155.2 (C-2); 141.1 (C-3a); 148.8 (C-7a); 65.8 (C-8); 157.3 (C-9). [e] 45.8 (CH_3); 49.2 ($NCH_2CH_2NCH_3$); 54.6 ($NCH_2CH_2NCH_3$).

Table 8

^{13}C-NMR Spectral Data of 3*H*-1,2,3-Triazolo[4,5-*b*][1,5]benxozazepines **10c**, **11e-f** and **19** [a]

Product No	C-3a	C-4a	C-5	C-6	C-7	C-8	C-8a	C-10	C-10a	C-11	C-1′	C-2′	C-3′	C-4′	Other
10c	150.7	146.1	120.8	(123.0,	125.1,	127.0)	128.2	159.0	133.0	49.0	133.0	(128.8,	129.9)	133.0	
11e	151.2	149.6	119.1	(124.0,	126.4,	130.0)	132.3	150.0	125.6	49.8	138.5	(129.1,	129.3)	134.7	[b]
11f	151.2	149.6	119.1	(123.9,	126.4,	130.0)	132.3	149.9	125.6	49.7	138.6	(129.1,	129.3)	134.6	[c]
19	152.6	149.5	120.3	(126.9,	129.8,	133.7)	138.1	152.6	128.1	50.5	-[d]	(128.0,	128.8,	129.1)	

[a] Spectra of **11e-f** and **19** were obtained in deuteriochloroform, while **10c** was run in DMSO-d_6 (ppm, rel. TMS). For numbering the carbon atoms, see Schemes 2, 4 and 6. Chemical shifts given in brackets could not be exactly assigned. [b] 46.0 ($NCH_2CH_2NCH_3$); 55.0 ($NCH_2CH_2NCH_3$). [c] 46.0 ($NCH_2CH_2NCH_2$); 53.0 ($NCH_2CH_2NCH_2$); 62.9 ($NCH_2CH_2NCH_2$); 127.0, 128.1, 129.1 and 137.7 (phenyl). [d] Not measurable due to overlap.

5-Chloro-1-[(4-chlorophenyl)methyl]-1*H*-1,2,3-triazole-4-carbonyl Chloride (**7b**).

To a stirred suspension of phosphorus pentachloride (125.0 g, 0.60 mole) in 600 ml of dry toluene was added 1-[(4-chlorophenyl)methyl]-5-hydroxy-1*H*-1,2,3-triazole-4-carboxylic acid monohydrate (**4b**, 54.3 g, 0.2 mole) with cooling in a water bath. After about 10 minutes the slurry was stirred on an oil bath at 40° for 2 hours, then at 80° for 2 hours and finally at reflux for 2 hours. The cooled solution was evaporated to dryness *in vacuo*, and the solid residue was washed with 100 ml of ice-cold petroleum ether (65-70°) giving 55.0 g (95%) almost pure **7b**. An analytical sample was prepared by recrystallization from ethyl acetate/petroleum ether (65-70°), mp 109-110°; ir (potassium bromide): 1760 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 5.53 (s, 2H, CH_2), 7.1-7.5 (m, 4H, aromatic); ms: m/e (relative intensity) 289 (M^+, 4), 232 (10), 127 (33), 125 (100), 89 (13).

Anal. Calcd. for $C_{10}H_6Cl_3N_3O$ (290.54): C, 41.34; H, 2.08; N, 14.46. Found: C, 41.49; H, 2.12; N, 14.47.

5-Chloro-1-[(4-methoxyphenyl)methyl]-1*H*-1,2,3-triazole-4-carbonyl Chloride (**7c**).

5-Hydroxy-1-[(4-methoxyphenyl)methyl]-1*H*-1,2,3-triazole-4-carboxylic acid monohydrate (**4c**, 5.3 g, 0.02 mole) was added to stirred slurry of phosphorus pentachloride (12.5 g, 0.06 mole) in 60 ml of dry toluene. The mixture was stirred on an oil bath at 40° for 7 hours, and then the clear solution was evaporated to dryness. The oily residue was a mixture of the expected product **7c** and the ring opened isomer **6c** according to ^{1}H-nmr and ms. Therefore it was dissolved in 50 ml of dry toluene and refluxed for 4 hours with phosphorus pentachloride (4.2 g, 0.02 mole). The mixture was cooled and evaporated to dryness *in vacuo*. The residue was triturated with 25 ml of petroleum ether (65-70°) on an ice bath for 2-3 hours and the crude product was isolated by filtration and recrystallized from ligroin (80-100°) giving 3.0 g (52%) of pure **7c**, mp 112-114°; ir (potassium bromide): 1760 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 3.87 (s, 3H, CH_3), 5.55 (s, 2H, CH_2), 7.15 (AB quartet, J = 9 Hz, Δν = 26 Hz, 4H, aromatic); ms: m/e (relative intensity) 285 (M^+, 5), 121 (100).

Anal. Calcd. for $C_{11}H_9Cl_2N_3O_2$ (286.12): C, 46.18; H, 3.17; N, 14.69. Found: C, 46.60; H, 3.19; N, 14.62.

5-Chloro-*N*-(5-substituted-2-hydroxyphenyl)-1*H*-1,2,3-triazole-4-carboxamides. **9a-e**. General Procedure A.

Nitrogen was bubbled through a stirred solution of the acid chloride **7** (0.2 mole) in 600 ml of ethyl acetate for about 10 minutes. Then 0.4 mole of the appropriate *o*-aminophenol **8** was added in one portion and the mixture was stirred at room temperature for 3 hours. The slightly exothermic reaction was carried out under a flow of nitrogen. The suspension was chilled on an ice bath and the precipitate was filtered off and washed successively with 100 ml of cold ethyl acetate, ice-water (3 × 100 ml) and 100 ml of ether. Recrystallization from suitable solvents afforded the pure amides **9a-e**.

1,2,3-Triazolo[4,5-*b*][1,5]benzoxazepin-10(9*H*)-ones **10a-e**. General Procedure B.

3-(Phenylmethyl)-3*H*-1,2,3-triazolo[4,5-*b*][1,5]benzoxazepin-10(9*H*)-one (**10a**).

A solution of potassium *t*-butoxide (14.8 g, 0.132 mole) in 200 ml of dry dimethyl sulfoxide was added dropwise during 15 minutes to a stirred solution of **9a** (39.5 g, 0.12 mole) in 200 ml of dry dimethyl sulfoxide, while a stream of nitrogen was bubbled through the mixture. The reaction mixture was heated with stirring on an oil bath at 80° for 50 hours under a flow of nitrogen and was then poured into 2.0 ℓ of ice water. The suspension was adjusted to *p*H > 10 with 100 ml of 1*N* sodium hydroxide. The precipitate was filtered off and washed with water, dried and recrystallized to yield the tricyclic compound **10a**.

7-Methyl-3-(phenylmethyl)-3*H*-1,2,3-triazolo[4,5-*b*][1,5]benzoxazepin-10(9*H*)-one (**10b**).

This compound was prepared by the method described in General Procedure B from 8.6 g, (0.025 mole) of the carboxamide **9b** at 80° for 42 hours.

3-[(4-Chlorophenyl)methyl]-3*H*-1,2,3-triazolo[4,5-*b*][1,5]benzoxazepin-10(9*H*)-one (**10c**).

a:

Compound **10c** was prepared by the method described in General Procedure B from 18.2 g (0.05 mole) of the amide **9c** at 80° for 28 hours.

b:

Compound **10c** was also prepared by a modified literature method [29]. The reaction was carried out under a flow of nitrogen. A suspension of **9c** (3.6 g, 0.01 mole) in 11.0 ml (0.011 mole) of 1*N* sodium hydroxide and 11 ml of dioxane was heated at 50° for 20 minutes. The resulting solution was evaporated to dryness and the residue was further dried by azeotropic distillation with benzene. The sodium salt **12** was now heated in 50 ml of dry dimethylformamide at 80° for 48 hours. Work-up as in General Procedure B afforded 1.0 g (31%) of lactam **10c**.

7-Chloro-3-[(4-chlorophenyl)methyl]-3*H*-1,2,3-triazolo[4,5-*b*][1,5]benzoxazepin-10(9*H*)-one (**10d**).

This compound was prepared by the method described in General Procedure B from 39.8 g (0.1 mole) of **9d** by heating at 80° for 2 hours followed by 150° for 90 minutes.

3-[(4-Methoxyphenyl)methyl]-3*H*-1,2,3-triazolo[4,5-*b*][1,5]benzoxazepin-10(9*H*)-one (**10e**).

Compound **10e** was prepared by the method described in General Procedure B from 5.4 g (0.015 mole) of **9e** at 80° for 42 hours.

10-(4-Substituted-1-piperazinyl)-3-(4-substituted-benzyl)-3*H*-1,2,3-triazolo[4,5-*b*][1,5]benzoxazepins **11a-j**. General Procedure C.

The procedure is a slight modification of the Schneider [19] method. The reactions were carried out under a flow of nitrogen. To a stirred mixture of titanium tetrachloride (1.90 g, 0.01 mole) in 20 ml of dry toluene and 2.1 ml of anisole was added a solution of 0.04 mole of the appropriate *N*-substituted piperazine in 2.3 ml of dry toluene with cooling in a water-bath. To this complex was added 0.01 mole [30] of the 3*H*-1,2,3-triazolo[4,5-*b*][1,5]benzoxazepin-10(9*H*)-one **10** and 0.02 mole of the appropriate piperazine, and the reaction mixture was refluxed for 3 hours with stirring. The mixture was cooled to 60° and 3.0 ml of 2-propanol was added, followed by 0.2 g of diatomaceous earth and 3.0 ml of concentrated ammonium hydroxide. The mixture was filtered and the solid cake was washed with methylene chloride (3 × 25 ml). The combined filtrates were washed with water (3 × 25 ml), dried with sodium sulfate and evaporated to dryness. The crude product was triturated with 100 ml of ice-water, and finally recrystallized to yield pure **11**.

Reaction of Amide **9c** with Potassium *t*-Butoxide in Dimethyl Sulfoxide at Elevated Temperature.

The carboxamide **9c** (36.3 g, 0.1 mole) was treated as described in General Procedure B, except that the oil bath temperature was 150° for 2 hours. The reaction mixture was poured into 2.0 ℓ of ice-water and acidified with 30 ml of 4*N* hydrochloric acid. The precipitate was isolated by filtration and the acidic filtrate was discarded. The crude solid was then washed with 1*N* sodium hydroxide (2 × 200 ml) and several times with water. Recrystallization from 2-methoxyethanol yielded 9.3 g (28%) of the expected lactam **10c**.

The mother liquor was concentrated to a small volume and the resulting precipitate was filtered off and recrystallized from absolute ethanol to give 3.7 g (19%) of 5-chloro-*N*,1-bis-[(4-chlorophenyl)methyl]-1*H*-1,2,3-triazole-4-carboxamide (**13**). An additional recrystallization from toluene yielded an analytically pure sample, mp 169-170°. Mixed mp 168-170° with an authentic sample prepared according to General Procedure A from **7b** (0.9 g, 3 mmoles) and 4-chlorobenzylamine in a yield of 1.0 g (84%); ir (potassium bromide): 3350, 1670 cm^{-1} (C=O); ^{1}H-nmr (DMSO-d_6): δ 4.47 (d, J = 6 Hz, 2H, NHCH_2, collapses to a singlet when treated with deuterium oxide), 5.72 (s, 2H, CH_2), 7.2-7.6 (m, 8H, aromatic), 9.28 (broad t, J = 6 Hz, NH, exchangeable); ms: m/e (relative intensity) 396 (M^++2, 7), 394 (M^+, 7), 269 (15), 142 (15), 140 (46), 127 (33), 125 (100), 89 (13).

Anal. Calcd. for $C_{17}H_{13}Cl_3N_4O$ (395.7): C, 51.60; H, 3.31; N, 14.16. Found: C, 51.80; H, 3.34; N, 14.19.

The combined alcaline filtrate and washing water from above was acidified to *p*H = 2 with 4*N* hydrochloric acid. The cream-coloured precipitate was isolated by filtration and washed with water and ether (2 × 100 ml) giving 3.6 g (24%) of 4-(2-benzoxazolyl)-1-(2-hydroxyphenyl)-1*H*-1,2,3-triazol-5-ol (**14**) as the only product according to tlc (see text). However, recrystallization from ethyl acetate caused a ring-opening of the triazole ring to yield 2.0 g (14%) of *N*-(2-hydroxyphenyl)-α-(2-benzoxazolyl)diazoacetamide (**15**) as a yellow solid, mp 208° dec; ir (potassium bromide): 3250, 2120 (=N_2), 1650 (C=O), 1620 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 6.7-8.4 (m, 8H, aromatic), 10.2 (broad s, 1H, NH or OH, exchangeable), 10.6 (s, 1H, OH or NH, exchangeable); ms: m/e (relative intensity) 295 (15), 294 (M^+, 82), 237 (14), 210 (18), 160 (17), 159 (100), 130 (13), 120 (38), 119 (35), 108 (30), 103 (23), 92 (11), 80 (29), 76 (14), 65 (14), 64 (12), 63 (11), 52 (14).

Anal. Calcd. for $C_{15}H_{10}N_4O_3$ (294.3): C, 61.23; H, 3.43; N, 19.04. Found: C, 61.13; H, 3.33; N, 18.81.

Diazoamide **15** (0.3 g, 1 mmole) was easily converted to its ring-closed isomer **14**, when stirred in 25 ml of 2*N* sodium hydroxide at 0° for 1 hour. The yellow suspension was transformed to a colourless solution, from which a white precipitate could be obtained by the addition of 15 ml of ice-cold 4*N* hydrochloric acid. The product was filtered, washed with water and dried *in vacuo* over phosphorus pentoxide to yield 0.3 g (96%) of pure monohydrate of **14**, mp 203° dec; ir (potassium bromide): 3200-2500, 1650, 1630 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 5.48 (s, 4H, 2 × OH + H_2O, exchangeable), 6.8-7.9 (m, 8H, aromatic); ms: m/e (relative intensity) 295 (15), 294 (M^+, 91), 237 (13), 210 (18), 160 (16), 159 (100), 130 (12), 120 (35), 119 (35), 108 (27), 103 (20), 92 (10), 80 (27), 76 (11), 65 (12), 64 (11), 63 (10), 52 (12).

Anal. Calcd. for $C_{15}H_{10}N_4O_3 \cdot H_2O$ (312.3): C, 57.68; H, 3.87; N, 17.94. Found: C, 58.04; H, 3.81; N, 18.02.

When a sample of **14** was boiled in ethyl acetate, a yellow product identical with the diazoamide **15** was obtained according to tlc and ir.

1-[(4-Chlorophenyl)methyl]-*N*-(2-hydroxyphenyl)-5-(4-methyl-1-piperazinyl)-1*H*-1,2,3-triazole-4-carboxamide (**16**).

The compound was prepared from 1.8 g (5 mmoles) of the amide **9c** and *N*-methylpiperazine by General Procedure C. The mixture was cooled to 60° and 1.5 ml of 2-propanol was added, followed by 0.1 g of diatomaceous earth and 2.0 ml of concentrated ammonium hydroxide. The suspension was filtered and the dark solid cake was washed with toluene (3 × 20 ml). The combined filtrates were acidified with 25 ml of 2*N* hydrochloric acid and the precipitate was filtered off and suspended in excess concentrated ammonium hydroxide with stirring and cooling on an ice-bath. The product was filtered, washed with water and dried. Recrystallization from ethyl acetate/ligroin (80-100°) afforded 0.4 g (19%) of pure **16**, mp 218-220°; ir (potassium bromide): 3380, 1675 (C=O), 1610, 1600 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.23 (s, 3H, NCH_3), 2.2-2.6 (m, 4H, 2 CH_2N), 2.8-3.2 (m, 4H, 2 CH_2N), 5.53 (s, 2H, CH_2), 6.6-7.1 (m, 3H, aromatic), 7.38 (AB quartet, J = 8 Hz, Δν = 11 Hz, 4H, aromatic), 8.1-8.4 (m, 1H, aromatic), 9.63 (s, 1H, NH or OH, only one exchangeable proton is seen in the spectrum); ms: m/e (relative intensity) 426 (M^+, 16), 343 (10), 127 (29), 125 (90), 84 (13), 83 (43), 71 (17), 70 (100), 58 (13), 56 (16), 44 (11), 43 (26), 42 (27).

Anal. Calcd. for $C_{21}H_{26}ClN_5O_2$ (426.9): C, 59.08; H, 5.43; N, 19.69. Found: C, 59.27; H, 5.41; N, 19.74.

10-(4-Methyl-1-piperazinyl)-1*H*-1,2,3-triazolo[4,5-*b*][1,5]benzoxazepine Monohydrate (**17**).

This compound was prepared by modification of the deprotection procedure reported by Buckle and Rockell [26].

A solution of the 4-methoxybenzyl compound **11j** (0.8 g, 2 mmoles) in 50 ml of trifluoroacetic acid was stirred at 60-65° for 23 hours. The trifluoroacetic acid was removed *in vacuo* and the residue was triturated with 50 ml of water. Saturated aqueous sodium hydrogen carbonate was added to *p*H = 7 and some water-insoluble material was removed by filtration. The aqueous layer was extracted continuously with methylene chloride for 3 days. The dried extract afforded a crystalline solid on evaporation which crystallized from ethyl acetate/ligroin (80-100°) to give the deprotected title compound **17** (0.31 g, 51%); mp 170-172° dec; ir (potassium bromide): 1630, 1605, 1585 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.33 (s, 3H, NCH_3), 2.4-2.7 (m, 4H, 2 CH_2N), 3.8-4.1 (m, 4H, 2 CH_2N), 5.37 (s, 3H, H_2O + NH, exchangeable), 7.20 (s, 4H, aromatic); ms: m/e (relative intensity), 284 (M^+, 13), 214 (29), 83 (78), 71 (12), 70 (100), 56 (10), 43 (19), 42 (17).

Anal. Calcd. for $C_{14}H_{16}N_6O \cdot H_2O$ (302.3): C, 55.62; H, 6.00; N, 27.80. Found: C, 55.6; H, 6.0; N, 27.6.

1-(2-Hydroxyphenyl)-*N*-(phenylmethyl)-1*H*-1,2,3-triazole-4-carboxamide (**18**).

This compound was prepared from 2.2 g (0.01 mole) of 5-chloro-1-(phenylmethyl)-1*H*-1,2,3-triazole-4-carboxaldehyde [12] and 1.1 g (0.01 mole) of 2-aminophenol by thermal isomerization of the intermediately formed 4-[[(2-hydroxyphenyl)imino]methyl]-1-(phenylmethyl)-1*H*-1,2,3-triazol-5-ol by our previously reported method [12]. Recrystallization from 2-butanone gave 0.7 g (24%) of pure **18**, mp 250-251°; ir (potassium bromide): 3300, 1640 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 4.53 (d, J = 6 Hz, CH_2, collapses to a singlet when treated with deuterium oxide), 6.8-7.8 (m, 9H, aromatic), 8.84 (s, 1H, triazole-H), 9.15 (broad t, J = 6 Hz, 1H, NH, exchangeable, 10.6 (broad s, 1H, OH, exchangeable); ms: m/e (relative intensity) 295 (15), 294 (M^+, 86), 175 (43), 160 (18), 159 (31), 133 (26), 120 (20), 106 (22), 104 (10), 92 (10), 91 (100), 77 (11), 65 (20).

Anal. Calcd. for $C_{16}H_{14}N_4O_2$ (294.3): C, 65.29; H, 4.79; N, 19.04. Found: C, 65.36; H, 4.81; N, 19.06.

REFERENCES AND NOTES

[1] Part 2. F. E. Nielsen and E. B. Pedersen, *Chem. Scripta,* (submitted).

[2] Present address: A/S Ferrosan, Research Division, Sydmarken 5, DK-2860 Soeborg, Copenhagen, Denmark.

[3] To whom correspondence should be addressed.

[4] J. Schmutz, *Arzneim.-Forsch.*, **25**, 712 (1975) and references cited therein.

[5] C. O. Okafor, *Heterocycles*, **7**, 391 (1977) and references cited therein.

[6] K. Nagarajan, *Stud. Org. Chem. (Amsterdam)*, **3**, 317 (1979) and references cited therein.

[7] G. Marchand, B. Decroix and J. Morel, *J. Heterocyclic Chem.*, **21**, 877 (1984) and references cited therein.

[8] D. M. Paton, *Med. Actual./Drugs of Today*, **14**, 245 (1978).

[9] *Med. Actual./Drugs of Today*, **16**, 73 (1980).

[10] See references cited in ref [1].

[11] J. K. Chakrabarti, T. M. Hotten and D. J. Steggles, European Patent Application 54,416 (June 23, 1982); *Chem. Abstr.*, **97**, 182468c (1982).

[12] P. H. Olesen, F. E. Nielsen, E. B. Pedersen and J. Becher, *J. Heterocyclic Chem.*, **21**, 1603 (1984).

[13] O. Dimroth, *Ann. Chem.*, **399**, 91 (1913).

[14] C. Hoffman and A. Faure, British Patent 1,156,782 (July 2, 1969); *Chem. Abstr.*, **71**, 91550j (1969).

[15] C. Hoffman and A. Faure, French Patent 5,315 (September 25, 1967); *Chem. Abstr.*, **71**, 101899w (1969).

[16] J. B. Press and S. R. Safir, U. S. Patent, 4,157,444 (June 5, 1979); *Chem. Abstr.*, **91**, 157777k (1979).

[17] J. B. Press, N. H. Eudy and S. R. Safir, *J. Org. Chem.*, **45**, 497 (1980).

[18] J. B. Press and S. R. Safir, U. S. Patent 4,144,235 (March 13, 1979); *Chem. Abstr.*, **91**, 5255a (1979).

[19] J. Schneider, German Patent 2,316,438 (October 11, 1973); *Chem. Abstr.*, **80**, 14969m (1974).

[20] J. B. Press, C. M. Hofmann, N. H. Eudy, W. J. Fanshawe, J. P. Day, E. N. Greenblatt and S. R. Safir, *J. Med. Chem.*, **22**, 725 (1979).

[21] J. B. Press, C. M. Hofmann, N. H. Eudy, J. P. Day, E. N. Greenblatt and S. R. Safir, *J. Med. Chem.*, **24**, 154 (1981).

[22] R. I. Fryer, J. V. Earley, G. F. Field, W. Zally and L. H. Sternbach, *J. Org. Chem.*, **34**, 1143 (1969).

[23] R. H. Wiley, K. F. Hussung and J. Moffat, *J. Org. Chem.*, **21**, 190 (1956).

[24] A. Albert and H. Taguchi, *J. Chem. Soc., Perkin Trans. I*, 1629 (1973).

[25] D. R. Buckle and C. J. M. Rockell, *J. Heterocyclic Chem.*, **19**, 1147 (1982).

[26] D. R. Buckle and C. J. M. Rockell, *J. Chem. Soc., Perkin Trans. I*, 627 (1982).

[27] Prepared by our previous method described in ref [12].

[28] Report from A/S Ferrosan, Research Division, Copenhagen, 1984.

[29] K. Nagarajan, A. Venkateswarlu, C. L. Kulkarni and R. K. Shah, *Indian J. Chem.*, **12**, 227 (1974).

[30] Compounds **11a**, **11e** and **11j** were prepared in a 25, 3 and 5 mmole scale, respectively.