Synthesis of 2-Amino-3-hydroxy- and of 2,3-Diamino-3*H*-1,4-benzodiazepines

Franco Gatta, Maria Rosaria Del Giudice, Luciano Di Simone and Guido Settimj

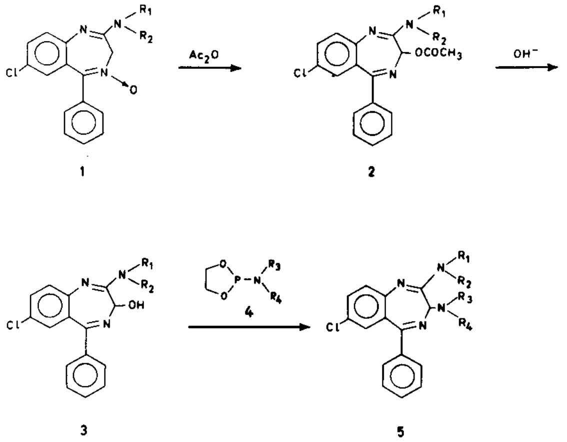
Istituto Superiore di Sanità, Laboratorio di Chimica del Farmaco,
Viale Regina Elena 299, 00161 Rome, Italy

December 17, 1979

A new synthesis of 7-chloro-2,3-diamino-5-phenyl-3*H*-1,4-benzodiazepines is described, which allows for the preparation of compounds bearing the same or different substituents at the 2 and 3 positions, starting from 2-amino-7-chloro-3-hydroxy-5-phenyl-3*H*-1,4-benzodiazepines.

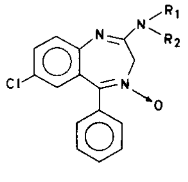
J. Heterocyclic Chem., **17**, 865 (1980).

For many years considerable importance has been attributed and intense chemical and pharmaceutical investigation have been devoted to the study of 1,4-benzodiazepine derivatives, in view of their depressant activity on the central nervous system. In this field, we have directed our interest to the study of new routes for the synthesis of certain amino derivatives (1) which have hitherto attracted only moderate attention. Both 2-amino-7-chloro-3-hydroxy-5-phenyl-3*H*-1,4-benzodiazepines **3** and 7-chloro-2,3-diamino-5-phenyl-3*H*-1,4-benzodiazepines **5** fall into this category. Concerning this first class of compounds, only the synthesis of 7-chloro-3-hydroxy-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine has been reported (2), while some 2,3-diamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxides have been obtained *via* the reaction of 2-dichloromethyl-4-phenylquinazoline 3-oxide with a number of primary and secondary amines, according to a Hoffmann-La Roche patent (3). However, no yields and melting points were given. By this method, only 2,3-diamino derivatives could be prepared in which the 2,3-substituents are the same. However, the synthetic pathway described in this paper allows for the synthesis of derivatives in which the substituted amino groups at positions 2 and 3 are different (see Scheme I).

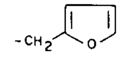


The starting 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-oxides **1**, prepared through various known methods depending on the *N*-substituents R_1 and R_2 (see

Table I

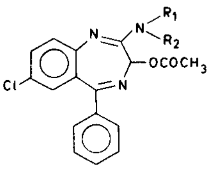


1

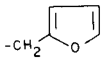
Compound No.	R_1	R_2	Yield %	M.p. °C	Recrystallized From	Molecular Formula	Analyses Found (Calcd.) C%	H%	N%
1d	$-C_2H_5$	$-C_2H_5$	76	133-135	Hexane	$C_{19}H_{20}ClN_3O$	66.54 (66.75)	6.00 (5.90)	12.21 (12.29)
1e	H	$-(CH_2)_2-N\begin{smallmatrix}C_2H_5\\C_2H_5\end{smallmatrix}$	60	154-156	Cyclohexane	$C_{21}H_{25}ClN_4O$	65.76 (65.53)	6.70 (6.55)	14.32 (14.56)
1f	H		86	225-227	Benzene	$C_{20}H_{16}ClN_3O_2$	65.56 (65.66)	4.40 (4.41)	11.25 (11.49)
1g	H	$-CH_2-CH_2-C_6H_5$	79	203-205	Ethanol	$C_{23}H_{20}ClN_3O$	70.94 (70.85)	5.12 (5.17)	10.84 (10.78)

0022-152X/80/050865-04$02.25

Table II

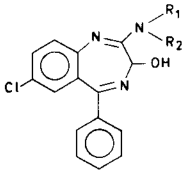


2

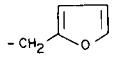
Compound No.	R_1	R_2	Yield %	M.p. °C	Recrystallized From	Molecular Formula	Analyses Found (Calcd.) C%	H%	N%
2a (a)	H	$-CH_3$							
2b	H	$-C_2H_5$	78	201-203	Cyclohexane	$C_{19}H_{18}ClN_3O_2$	64.19	5.18	11.55
							(64.13)	(5.10)	(11.81)
2c	$-CH_3$	$-CH_3$	82	132-134	Ethanol	$C_{19}H_{18}ClN_3O_2$	64.03	5.21	11.60
							(64.13)	(5.10)	(11.81)
2d	$-C_2H_5$	$-C_2H_5$	75	140-142	Benzene	$C_{21}H_{22}ClN_3O_2$	65.52	5.90	10.75
							(65.70)	(5.78)	(10.95)
2e (b)	H	$-(CH_2)_2-N\begin{smallmatrix}C_2H_5\\C_2H_5\end{smallmatrix}$	62						
2f	H		68	167-168	Benzene	$C_{22}H_{18}ClN_3O_3$	64.87	4.51	10.48
							(64.78)	(4.45)	(10.30)
2g	H	$-CH_2-CH_2-C_6H_5$	75	195-197	Benzene	$C_{25}H_{22}ClN_3O_2$	69.37	5.21	9.99
							(69.52)	(5.13)	(9.73)

(a) Lit. (2). (b) The crude product was directly submitted to hydrolysis.

Table III

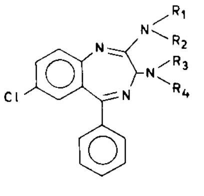


3

Compound No.	R_1	R_2	Yield %	M.p. °C	Recrystallized From	Molecular Formula	Analyses Found (Calcd.) C%	H%	N%
3a (a)	H	$-CH_3$							
3b	H	$-C_2H_5$	92	201-203	Ethanol	$C_{17}H_{16}ClN_3O$	65.20	5.18	13.45
							(65.07)	(5.14)	(13.39)
3c	$-CH_3$	$-CH_3$	85	142-144	Benzene	$C_{17}H_{16}ClN_3O$	64.90	5.28	13.50
							(65.07)	(5.14)	(13.39)
3d	$-C_2H_5$	$-C_2H_5$	85	150-152	Benzene	$C_{19}H_{20}ClN_3O$	66.49	5.81	12.28
							(66.75)	(5.90)	(12.29)
3e	H	$-(CH_2)_2-N\begin{smallmatrix}C_2H_5\\C_2H_5\end{smallmatrix}$	91	169-171	Cyclohexane	$C_{21}H_{25}ClN_4O$	65.26	6.64	14.43
							(65.53)	(6.55)	(14.56)
3f	H		87	153-155	Benzene	$C_{20}H_{16}ClN_3O_2$	65.40	4.50	11.37
							(65.66)	(4.41)	(11.49)
3g	H	$-CH_2-CH_2-C_6H_5$	89	200-202	Benzene	$C_{23}H_{20}ClN_3O$	70.71	5.19	10.68
							(70.85)	(5.17)	(10.78)

(a) Lit. 2.

Table IV



5

Compound No. (a)	Starting Material	R_3	R_4	Elution Solvent (b)	Yield %	M.p. °C	Molecular Formula	Analyses Found (Calcd.) C%	H%	N%
5a	**3a**	$-CH_3$	$-CH_3$	A	68	167-169	$C_{18}H_{19}ClN_4$	66.40	5.84	16.94
								(66.15)	(5.86)	(17.14)
5b	**3a**	$-C_2H_5$	$-C_2H_5$	B	62	170-172	$C_{20}H_{23}ClN_4$	67.42	6.52	16.05
								(67.69)	(6.53)	(15.79)
5c	**3a**	$-CH_3$	$-CH_2-C_6H_5$	B	77	169-171	$C_{24}H_{23}ClN_4$	71.56	5.77	13.93
								(71.54)	(5.75)	(13.91)
5d	**3a**	$-CH_3$	$-C_6H_5$	C	81	156-158	$C_{23}H_{21}ClN_4$	71.08	6.20	14.19
								(71.03)	(6.48)	(14.41)
5e	**3a**	$-(CH_2)_4-$		B	85	163-165	$C_{20}H_{21}ClN_4$	68.25	5.93	16.10
								(68.08)	(6.00)	(15.88)
5f	**3a**	$-(CH_2)_5-$		B	74	157-159	$C_{21}H_{23}ClN_4$	69.02	6.20	15.31
								(68.75)	(6.32)	(15.27)
5g	**3a**	$-(CH_2)_2-O-(CH_2)_2-$		B	80	212-214	$C_{20}H_{21}ClN_4O$	65.28	5.76	15.34
								(65.13)	(5.69)	(15.20)
5h	**3b**	$-CH_3$	$-CH_3$	F	77	106-108	$C_{19}H_{21}ClN_4$	67.06	6.25	16.67
								(66.95)	(6.21)	(16.44)
5i	**3b**	$-C_2H_5$	$-C_2H_5$	D	58	121-123	$C_{21}H_{25}ClN_4$	68.33	6.80	15.34
								(68.37)	(6.83)	(15.19)
5j	**3b**	$-CH_3$	$-CH_2-C_6H_5$	B	72	158-160	$C_{25}H_{25}ClN_4$	71.83	5.88	13.62
								(72.02)	(6.04)	(13.44)
5k	**3b**	$-CH_3$	$-C_6H_5$	D	85	133-135	$C_{24}H_{23}ClN_4$	71.31	5.76	14.00
								(71.54)	(5.75)	(13.91)
5l	**3b**	$-(CH_2)_4-$		F	71	138-140	$C_{21}H_{23}ClN_4$	68.52	6.49	15.45
								(68.75)	(6.32)	(15.27)
5m	**3b**	$-(CH_2)_5-$		D	57	190-192	$C_{22}H_{25}ClN_4$	69.17	6.61	14.94
								(69.36)	(6.61)	(14.71)
5n	**3b**	$-(CH_2)_2-O-(CH_2)_2-$		F	71	190-192	$C_{21}H_{23}ClN_4O$	65.61	6.09	14.68
								(65.87)	(6.05)	(14.63)
5o	**3c**	$-CH_3$	$-CH_3$	G	71	161-163	$C_{19}H_{21}ClN_4$	67.05	6.25	16.43
								(66.95)	(6.21)	(16.44)
5p	**3c**	$-C_2H_5$	$-C_2H_5$	D	65	120-122	$C_{21}H_{25}ClN_4$	68.46	6.87	15.39
								(68.37)	(6.83)	(15.19)
5q	**3c**	$-CH_3$	$-CH_2-C_6H_5$	G	59	144-146	$C_{25}H_{25}ClN_4$	72.29	6.06	13.48
								(72.02)	(6.04)	(13.44)
5r	**3c**	$-(CH_2)_4-$		F	75	173-175	$C_{21}H_{23}ClN_4$	68.52	6.35	15.16
								(68.75)	(6.32)	(15.27)
5s	**3c**	$-(CH_2)_5-$		F	78	167-169	$C_{22}H_{25}ClN_4$	69.43	6.48	14.42
								(69.37)	(6.62)	(14.71)
5t	**3c**	$-(CH_2)_2-O-(CH_2)_2-$		F	66	160-162	$C_{21}H_{23}ClN_4O$	66.00	6.02	14.74
								(65.87)	(6.05)	(14.63)
5u	**3e**	$-(CH_2)_2-O-(CH_2)_2-$		E (c)	68	129-131	$C_{25}H_{32}ClN_5O$	66.26	5.14	15.25
								(66.13)	(5.11)	(15.43)
5v	**3f**	$-(CH_2)_2-O-(CH_2)_2-$		C	80	174-176	$C_{24}H_{23}ClN_4O_2$	66.03	5.35	12.81
								(66.27)	(5.33)	(12.88)

(a) All compounds were crystallized from ethanol. Compound **5u** was crystallized from benzene. (b) Elution solvent: A ethyl acetate-hexane 1:1; B ethyl acetate-hexane 1:2; C ethyl acetate-hexane 1:3; D ethyl acetate-hexane 1:4; E ethyl acetate-hexane 1:5; F acetone-hexane 1:2; and G acetone-hexane 1:4. (c) Chromatographed on a neutral alumina (Merck, activity II-III).

Experimental), were acetylated with acetic anhydride (4) to give the corresponding 3-acetoxy derivatives **2**. These were hydrolyzed at room temperature with sodium hydroxide to give the 2-amino-7-chloro-3-hydroxy-5-phenyl-3*H*-1,4-benzodiazepines **3**. Reaction of the latter compounds with a number of 2-amino-4,5-dihydro-1,3,2-dioxaphospholes **4**, according to our published procedure (1), afforded 7-chloro-2,3-diamino-5-phenyl-3*H*-1,4-benzodiazepines **5** in good yields.

The structures of compounds **3** and **5** were supported by ir and ^{1}H-nmr spectral data. The ir spectra for all compounds show a very strong band at 1620-1600 cm^{-1} in accordance with Sternbach's findings for similar moieties (5). In the spectra of **3**, the OH stretching band at 3500-3300 cm^{-1} is also present.

The nmr spectra of **5** show a sharp singlet, not exchangeable with deuterium oxide, approximately in the region (3.4-3.9 ppm) of the methynic hydrogen atom of the corresponding 3-amino-1,4-benzodiazepin-2-ones. Such a singlet could only be attributed to a methynic proton in the 3 position, for the same previously reported reasons (1).

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. Ir spectra were obtained using a Perkin-Elmer model 21 double beam spectrophotometer (potassium bromide disc). Nmr spectra were recorded on a Varian T-60 spectrometer, using deuteriochloroform solutions and tetramethylsilane as a reference. Column chromatography was carried out using silica gel (Merck, 70-250 mesh ASTH) as the adsorbent. Thin layer chromatography was performed on silica gel plates (Merck GF_{254}). Anhydrous sodium sulfate was used as drying agent.

2-Amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepin-4-oxides (**1**).

The following compounds were prepared according to described procedures: **1a** (R_1 = H, R_2 = $-CH_3$) and **1b** (R_1 = H, R_2 = $-C_2H_5$) from 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (5); and **1c** (R_1 = R_2 = $-CH_3$) and **1d** (R_1 = R_2 = $-C_2H_5$) through reaction with methyl- and ethyl iodide of **1a** and **1b** respectively (6). Compounds **1e**, **1f** and **1g** resulted through substitution of the $-NH_2$ group of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (5) with the appropriate substituted amine according to what is reported for similar compounds (7). Thus, 3.2 g. of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide hydrochloride (0.01 mole) and the primary amine (0.03 mole; for **1e**: 2-diethylaminoethylamine; for **1f**: furfurylamine; and for **1g**: phenylethylamine) were refluxed for 6 hours in methanol (100 ml.). The resulting mixture was then concentrated, diluted with water and extracted with chloroform. The crude compounds **1f** and **1g** could be purified through simple crystallization. Crude **1e** was previously chromatographed on an alumina column (Merck, activity II-III), eluting with ethyl acetate.

In Table I only chemical and physical data for the new compounds are recorded.

3-Acetoxy-2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepines (**2**) (Table II).

All compounds except **2a** (R_1 = H, R_2 = $-CH_3$), which resulted from the reaction of **1a** with acetyl chloride (2), were obtained through heating compounds **1** (10 g.) at 100° for 20 minutes in acetic anhydride (100 ml.). The resulting solution was evaporated under reduced pressure and the residue, made alkaline with a saturated aqueous sodium bicarbonate solution, was extracted into chloroform. After evaporation of the solvent, the crude products which were obtained were crystallized.

2-Amino-7-chloro-3-hydroxy-5-phenyl-3*H*-1,4-benzodiazepines (**3**) (Table III).

Each compound **2** (0.01 mole) was dissolved in a 1:1 mixture of dioxane-ethanol (80 ml.), treated with 1*N* sodium hydroxide (10 ml.), and stirred for 3 hours at room temperature. After addition of water, the product was extracted with chloroform, the solvent was evaporated and the resulting solid residue was crystallized.

7-Chloro-2,3-diamino-5-phenyl-3*H*-1,4-benzodiazepines (**5**) (Table IV).

Each compound **3** (0.01 mole) and the appropriate 2-disubstituted-amino-4,5-dihydro-1,3,2-dioxaphosphole **4** (0.015 mole) were allowed to react for 4 hours in refluxing toluene (30 ml.) (1). After evaporation of toluene, the product was purified through column chromatography on silica gel (for elution solvents see Table IV) followed by crystallization.

Acknowledgement.

The authors are grateful to Dr. A. Mazzeo for elemental analyses and to Mr. P. Montani for technical assistance.

REFERENCES AND NOTES

(1) F. Gatta, M. R. Del Giudice and G. Settimj, *Synthesis*, 718 (1979).

(2) L. H. Sternbach, E. Reeder, A. Stempel and A. I. Rachlin, *J. Org. Chem.*, **29**, 332 (1964).

(3) *Netherlands Patent*, 6,603,736; *Chem. Abstr.*, **66**, 76044a (1967).

(4) S. C. Bell, C. Gochman and S. J. Childress, *J. Org. Chem.*, **28**, 3010 (1963).

(5) L. H. Sternbach and E. Reeder, *ibid.*, **26**, 1111 (1961).

(6) S. Farber, H. M. Wuest and R. I. Meltzer, *J. Med. Chem.*, **7**, 235 (1964).

(7) K. Megura, H. Natsugari, H. Tawada and Y. Kuwada, *Chem. Pharm. Bull.*, **21**, 2366 (1973).