Heterocyclic Groups [*b*]-Annulated to the 1,4-Benzodiazepine System

M.A. Berghot

Department of Chemistry, Faculty of Science, Mansoura University, Mansoura, A.R. Egypt

Received March 25, 1991

Pyrazoles, isoxazoles, pyrimidinones, thiazines, mercaptopyrimidines, pyridones, and triazepinthiones were fused with diazepam (**1**) by reaction of the arylidenes **2a-h** with hydrazines, hydroxylamine, urea or its derivatives, thiourea, ammonium thiocyanate, ethyl cyanoacetate, and thiosemicarbazide.

An der [*b*]-Seite heterocyclisch anellierte 1,4-Benzodiazepine

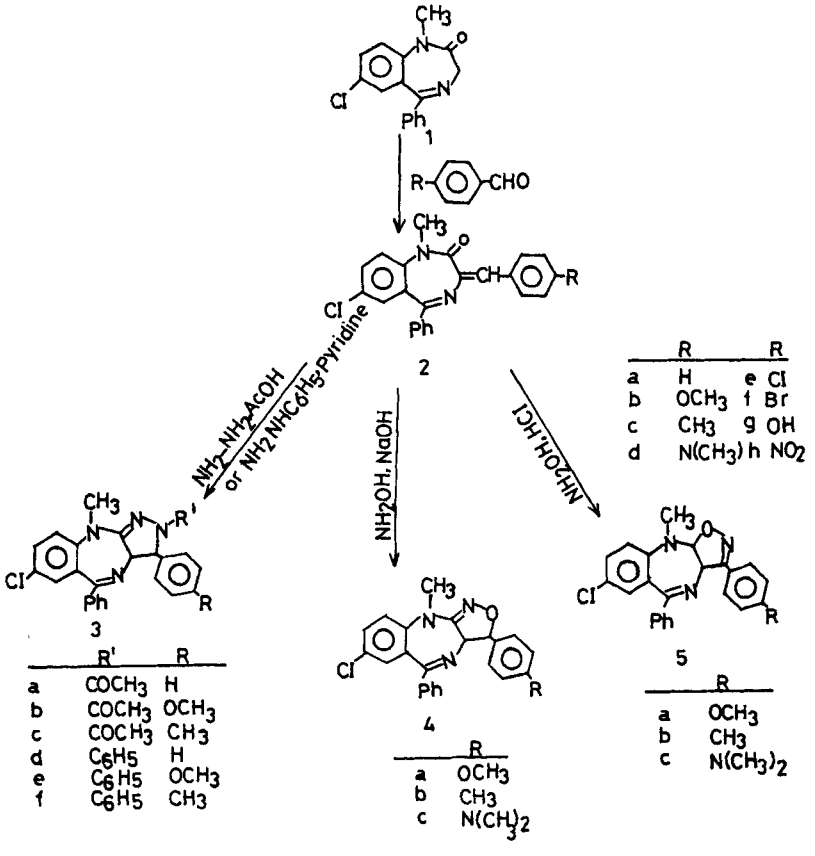
Durch Umsetzung der Arylidene **2a-h** mit Hydrazin, Hydroxylamin, Harnstoff und seinen Derivaten, Thioharnstoff, Ammoniumthiocyanat, Ethyl-cyanoacetat und Thiosemicarbazid entstehen Pyrazol-, Isoxazol-, Pyrimidinon-, Thiazin-, Mercaptopyrimidin-, Pyridon- und Triazepinthion-kondensierte Derivate des Diazepams (**1**).

1,4-Benzodiazepines are therapeutically used drugs acting on the central nervous system (CNS)[1]. More recently it was shown that several derivatives with heterocyclic rings annulated to the [*a*]-face of the molecule greatly enhance the CNS activity[2]. The nature and substitution of the additional heterocyclic nuclei are related to the physical[3], chemical[4], and biological[5] properties. Some derivatives with heterocycles fused to the [*d*]-face are also known[6]. Diazepam (7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one) (**1**), a tranquilizer with broad spectrum, is one of these important therapeutic drugs[7]. In continuation of our interest in better useful drugs acting on the CNS, we report here on an investigation of hitherto unknown derivatives related to compound **1** where the heterocyclic group is fused to the [*b*]-face which are not yet recorded in literature.

Compound **1** was subjected to condensation with various substituted aromatic aldehydes in ethanolic KOH to furnish the arylidene derivatives **2a-h** in good yield (Scheme 1). These derivatives reacted at their α,β-unsaturated enone system with some nucleophiles.

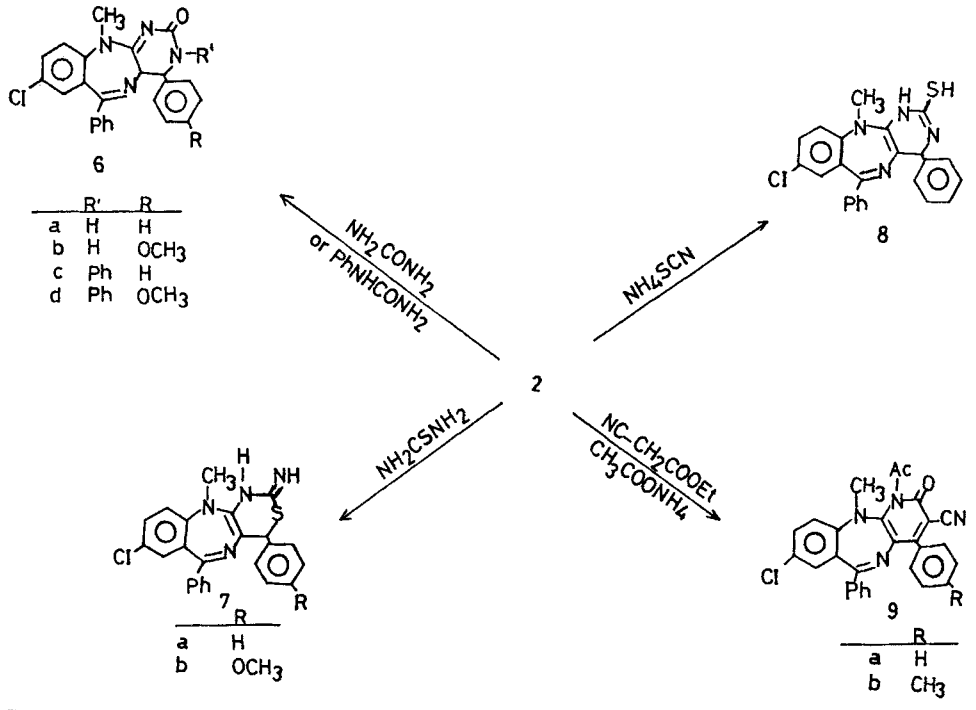
The IR spectra of **1a-h** reveals strong bands at 1685-1665 cm^{-1} due to α,β-unsaturated CO. ^{1}H-NMR spectra of **2a-d** and **2g** showed a singlet at δ = 5.82-6.62 ppm (vinylic H).

Treatment of **2a-c** with hydrazine hydrate in boiling acetic acid or with phenylhydrazine hydrochloride in boiling pyridine afforded the *N*-acetyl or *N*-phenyl pyrazolo deriva-



Scheme 1

 ©VCH Verlagsgesellschaft mbH, D-6940 Weinheim, 1992 0365-6233/92/0505-0285 $ 3.50 + .25/0

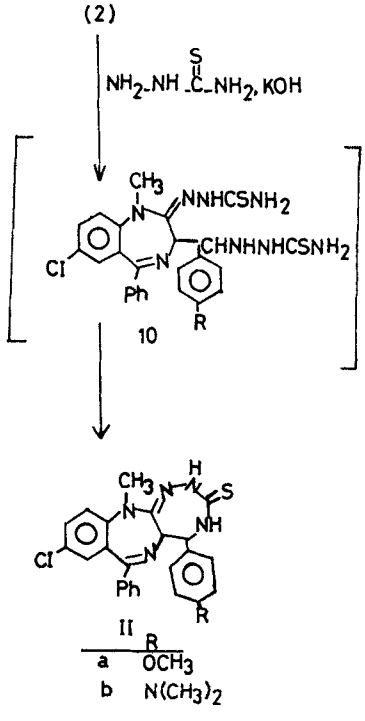


Scheme 2

tives **3a-f** (Scheme 1). Elemental analysis, IR and ^{1}H-NMR spectra were consistent with their structure. Analogously, treatment of **2b-d** with hydroxylamine/NaOH gave isoxazolines **4a-c**, while the isomeric products **5a-c** were obtained when the same reaction takes place in the presence of HCl (Scheme 1).

The IR spectra of **4a-c** show bands at 1640-1650 cm^{-1} due to C=N of isoxazolines, while **5a-c** show bands at 1620-1640 cm^{-1} probably due to overlapping with C=C of the aromatic nucleus[9]. ^{13}C-NMR spectra were recorded for **4a** and **5a** (Experim. Part). Formation of **4a-c** and its isomeric compounds **5a-c** takes place through 1,2- and 1,4-addition, respectively[8].

Pyrimidinones **6a-d** were prepared from the reaction of derivatives **2a,b** with urea or *N*-phenylurea in acidic ethanolic solution (Scheme 2). A CO group in **6a-d** was indicated by strong IR bands around 1600 cm^{-1}. The arylidenes **2a,b** were reacted with thiourea in an alkaline medium to afford the thiazines **7a,b** as the only isolable products (Scheme 2). Similar observation has been recorded[10]. ^{1}H-NMR spectra of **7a,b** show singlets at δ = 2.56 and 2.83 ppm (C=NH). IR spectra display a band for the C=N group at 1650 and 1660 cm^{-1} for **7a,b**, respectively. Heating **2a** in xylene and cyclohexanol with NH_4SCN and removing the water formed as an azeotropic mixture with xylene yielded the pyrimidine thiol **8** (Scheme 2). The formation of **8** is analogous to that reported[11]. Structures **7a** and **8** were confirmed by their ^{13}C-NMR spectra (Experim. Part). When **2a,c** reacted with ethyl cyanoacetate in the presence of $CH_3CO_2NH_4$ at 180-200°C, the pyridone acetate derivatives **9a,b** were obtained (Scheme 2). The same result has been obtained by *Sammour*[12]. The band of the C≡N group in **9a,b** appeared around 2220 cm^{-1}.



Scheme 3

The reaction of **2b,d** with thiosemicarbazide in alkaline medium gave the corresponding triazepine derivatives **11a,b** (Scheme 3). The formation of **11a,b** probably takes place through the labile thiosemicarbazino-thiosemicarbazone **10a,b**, which underwent cyclization. ^{1}H-NMR spectra of **11a,b** show singlets around 4.5 ppm due to NH groups, their IR spectra reveale bands at 1200 and 1250 cm^{-1} due to the C=S group.

Experimental Part

M.p.'s are uncorrected.- IR spectra (KBr, cm^{-1}): Pye Unicam SP-2000.- ^{1}H-NMR spectra (DMSO): EM-90 MHz and ^{13}C-NMR spectra (DMSO) at 20.1 MHz, TMS as int. standard; chemical shifts in δ values (ppm).- Microanalytical data: Microanalytical Data Unit at Mansoura and Cairo Universities.- Temp. in °C.

1-Methyl-3-arylidene-1,3-dihydro-5-phenyl-7-chloro-2H-1,4-benzodiazepin-2-ones (**2a-h**)

A mixture of **1** (0.01 mol) and the appropriate aromatic aldehyde (benzaldehyde, anisaldehyde, toulaldehyde, *p*-dimethylaminobenzaldehyde, *p*-chlorobenzaldehyde, *p*-bromobenzaldehyde, *p*-hydroxybenzaldehyde or *p*-nitrobenzaldehyde) (0.015 mol) was treated slowly with ethanolic KOH (4%; 20-25 ml). The reaction mixture was refluxed for 2-3 h, left overnight and the resultant solid was mixed with H_2O (50 ml); acidified with dil. HCl, filtered and crystallized from EtOH.

2a: Yellow powder; yield 80%; m.p. 241°.- IR: 1675 (α,β-unsat. CO); 1650 (C=N); 750 (monosubstituted benzene).- ^{1}H-NMR: δ = 2.31 (s, 3H, NCH_3); 5.82 (s, 1H, C=CH-arom.); 7.78-7.91 (m, 13H, aromat.).- $C_{23}H_{17}ClN_2O$ (372.8) Calc. C 74.1 H 4.59 N 7.5 Found C 74.3 H 4.62 N 7.4.

2b: Yellow crystals; yield 75%; m.p. 210°.- IR: 1670 (α,β-unsat. CO); 1640 (C=N); 1250 (arom. *o*-CH_3); 840 (*p*-disubst. benzene).- ^{1}H-NMR: δ = 2.32 (s, 3H, NCH_3); 3.81 (s, 3H, OCH_3); 5.83 (s, 1H, C=CH-arom.); 7.51-7.83 (m, 12H, aromat.).- $C_{24}H_{19}ClN_2O_2$ (402.9) Calc. C 71.5 H 4.75 N 6.9 Found C 71.6 H 4.77 N 6.8.

2c: Pale yellow crystals; yield 75%; m.p. 218°.- IR: 1680 (α,β-unsat. CO); 1640 (C=N); 1200 (Ar-CH_3); 850 (*p*-disubst. benzene).- ^{1}H-NMR: δ = 1.51 (s, 3H, arom.-CH_3); 2.41 (s, 3H, NCH_3); 6.62 (s, 1H, -C=CH-arom.); 7.82-7.93 (m, 12 H, aromat.).- $C_{24}H_{19}ClN_2O$ (386.9) Calc. C 74.5 H 4.95 N 7.2 Found C 74.3 H 4.97 N 7.3.

2d: Yellow crystals; yield 73%; m.p. 237°.- IR: 1670 (α,β-unsat. CO); 1660 (C=N); 1350 (tert-amino); 820 (*p*-disubst. benzene).- ^{1}H-NMR: δ = 2.30 (s, 3H, NCH_3); 3.11 (s, 6H, $N(CH_3)_2$); 6.21 (s, 1H, C=CH-arom.); 7.73-7.90 (m, 12 H, aromat.).- $C_{25}H_{22}ClN_3O$ (415.9) Calc. C 72.2 H 5.33 N 10.1 Found C 72.1 H 5.36 N 10.3.

2e: White crystals; yield 52%; m.p. 180°.- IR: 1680 (α,β-unsat. CO); 1655 (C=N); 830 (*p*-disubst. benzene).- $C_{23}H_{16}Cl_2N_2O$ (407.3) Calc. C 67.8 H 3.96 N 6.9 Found C 67.9 H 4.10 N 6.8.

2f: Pale yellow powder; yield 40%; m.p. 169°.- IR: 1670 (α,β-unsat. CO); 1650 (C=N); 820 (*p*-disubst. benzene).- $C_{23}H_{16}BrClN_2O$ (451.7) Calc. C 61.1 H 3.57 N 6.20 Found C 61.3 H 3.67 N 6.3.

2g: Yellow crystals; yield 35%; m.p. 216°.- IR: 3400 (OH); 1685 (α,β-unsat. CO); 1640 (C=N); 825 (*p*-disubst. benzene).- ^{1}H-NMR: δ = 2.81 (s, 3H, NCH_3); 6.22 (s, 1H, C=CH-arom.); 7.11-7.92 (br, 12 H, aromat.); 8.63 (s, 1H, Ar-OH).- $C_{23}H_{17}ClN_2O_2$ (388.8) Calc. C 71.0 H 4.41 N 7.2 Found C 70.9 H 4.52 N 7.4.

2h: White crystals; yield 30%; m.p. > 360°.- IR: 1665 (α,β-unsat. CO); 1640 (C=N); 1350 (NO_2); 830 (*p*-disubst. benzene).- $C_{23}H_{16}ClN_3O_3$ (417.8) Calc. C 66.1 H 3.86 N 10.1 Found C 66.3 H 3.81 N 9.9.

2-Substituted-3-aryl-5-phenyl-7-chloro-10-methyl-2,3,3a,10-tetrahydro-pyrazolo[3,4-b]-1,4-benzodiazepines **3a-f**

A mixture of **2a-c** (0.01 mol) and hydrazine hydrate (0.02 mol) in AcOH (20 ml) was heated under reflux for 6 h; after removal of the solvent a little H_2O was added. The mixture was left to cool, and the solid was crystallized from EtOH to give 2-acetyl derivatives **3a-c**.

The above reaction was repeated with phenyl hydrazine hydrochloride using pyridine as a solvent to give the 2-phenyl derivatives **3d-f**.

3a: Brown crystals; yield 55%; m.p. 250°.- IR: 1680 ($N\underline{CO}CH_3$); 1660, 1640 (2 C=N); 1600 (C=C aromatic); 750 (monosubst. benzene).- ^{1}H-NMR: δ = 2.42 (s, 3H, NCH_3); 3.11 (s, 3H, $COCH_3$); 6.32 (d, J = 7.2 Hz, 1H, H-3a); 6.54 (d, J = 8.3 Hz, 1H, H-3); 7.62-7.83 (m, 13 H, aromat.).- $C_{25}H_{21}ClN_4O$ (428.9) Calc. C 70.0 H 4.93 N 13.1 Found C 70.1 H 4.82 N 12.9.

3b: Red-brown crystals; yield 60%; m.p. 230°.- IR: 1690 ($N\underline{CO}CH_3$); 1650, 1640 (2 C=N); 1610 (C=C aromatic); 850 (*p*-disubst. benzene); 1260 (arom.-O-CH_3).- ^{1}H-NMR: δ = 2.43 (s, 3H, NCH_3); 3.11 (s, 3H, $NCOCH_3$); 3.55 (s, 3H, OCH_3); 6.53 (d, J = 7.2 Hz, 1H, H-3a); 6.79 (d, J = 8.1 Hz, 1H, H-3); 7.53-7.88 (m, 12 H, aromat.).- $C_{26}H_{23}ClN_4O_2$ (458.9) Calc. C 68.1 H 5.05 N 12.2 Found C 68.3 H 5.16 N 12.1.

3c: Brown powder; yield 50%; m.p. 220°.- IR: 1685 ($N\underline{CO}CH_3$); 1660, 1630 (2 C=N); 1600 (C=C aromatic); 820 (*p*-disubst. benzene).- $C_{26}H_{23}ClN_4O$ (442.9) Calc. C 70.5 H 5.23 N 12.6 Found C 70.6 H 5.38 N 12.7.

3d: Brown powder; yield 65%; m.p. 210°.- IR: 1630, 1620 (2 C=N); 1600 (C=C aromatic); 750 (monosubst. benzene).- ^{1}H-NMR: δ = 2.32 (s, 3H, NCH_3); 6.16 (d, J = 7.1 Hz, 1H, H-3a); 6.36 (d, J = 8.1 Hz, 1H, H-3); 7.44-7.86 (m, 18 H, aromat.).- $C_{29}H_{23}ClN_4$ (463) Calc. C 75.2 H 5.0 N 12.1 Found C 75.1 H 5.21 N 12.3.

3e: Dark brown crystals; yield 55%; m.p. > 360°.- IR: 1620, 1610 (2 C=N); 1600 (C=C aromatic); 1260 (arom.-O-CH_3); 850 (*p*-disubst. benzene).- $C_{30}H_{25}ClN_4O$ (493) Calc. C 73.1 H 5.11 N 11.4 Found C 73.3 H 5.22 N 11.2.

3f: Brown powder; yield 60%; m.p. 180°.- IR: 1630, 1610 (2 C=N); 1600 (C=C aromatic); 760 (monosubst. benzene).- ^{1}H-NMR: δ = 1.91 (s, 3H, Ar-CH_3); 2.31 (s, 3H, NCH_3); 6.29 (d, J = 7.1 Hz, 1H, H-3a); 6.44 (d, J = 8.1 Hz, 1H, H-3); 7.34-7.55 (m, 17 H, aromat.).- $C_{30}H_{25}ClN_4$ (477.0) Calc. C 75.5 H 5.28 N 11.7 Found C 75.7 H 5.30 N 11.9.

3-Aryl-5-phenyl-7-chloro-10-methyl-3,3a,10-trihydro-isoxazolo[3,4-b]-1,4-benzodiazepines **4a-c**

To the arylidene **2b-d** (0.01 mol) in MeOH (50 ml) an aqueous solution of NH_2OH (0.01 mol) and NaOH (0.03 mol) (10 ml) were added. The reaction mixture was refluxed for 3 h, poured onto H_2O (50 ml), acidified with HCl (5 ml) and cooled. The solid products were recrystallized from dil. EtOH to give **4a-c**.

4a: Dark brown crystals; yield 60%; m.p. 193°.- IR: 1640, 1630 (2 C=N); 1600 (C=C aromatic); 1230 (Ar-O-CH_3); 860 (*p*-disubst. benzene).- ^{1}H-NMR: δ = 2.32 (s, 3H, NCH_3); 3.63 (s, 3H, OCH_3); 5.77 (d, J = 7.6 Hz, 1H, H-3a); 6.19 (d, J = 8.3 Hz, 1H, H-3); 7.51-7.86 (m, 12 H, aromat.).- ^{13}C-NMR: δ = 158.8, 153.9 (2 C=N); 55.3 (C-3); 41.1 (C-3a); 23.3 (OCH_3); 20.9 (NCH_3); 136.1-127.6 (aromatic).- $C_{24}H_{20}ClN_3O_2$ (417.9) Calc. C 69.0 H 4.82 N 10.1 Found C 69.1 H 5.01 N 10.3.

4b: Red-brown crystals; yield 60%; m.p. 284°.- IR: 1650, 1640 (2 C=N); 1600 (C=C aromatic); 850 (*p*-disubst. benzene).- $C_{24}H_{20}ClN_3O$ (401.9) Calc. C 71.7 H 5.02 N 10.4 Found C 71.9 H 5.13 N 10.6.

4c: Brown crystals; yield 50%; m.p. 210°.- IR: 1650, 1630 (2 C=N); 1600 (C=C aromatic); 1340 (tert-amino); 830 (*p*-disubst. benzene).- ^{1}H-NMR: δ = 2.37 (s, 3H, NCH_3); 2.96 [s, 6H, $N(CH_3)_2$]; 5.93 (d, J = 7.1 Hz, 1H, H-3a); 6.24 (d, J = 7.9 Hz, 1H, H-3); 7.61-7.98 (m, 12 H, aromat).- $C_{25}H_{23}ClN_4O$ (430.9) Calc. C 69.7 H 5.38 N 13.0 Found C 69.9 H 5.43 N 13.2.

3-Aryl-5-phenyl-7-chloro-10-methyl-3a,10,10a-trihydro-isoxazolo[5,4-b]-1,4-benzodiazepines **5a-c**

A mixture of the arylidenes **2b-d** (0.01 mol) in EtOH (50 ml), NH_2OH (0.02 mol) and conc. HCl (3 ml) was heated under reflux for 8 h. The resulting solid products were recrystallized from dil. EtOH to give **5a-c**.

5a: Brown powder; yield 20%; m.p. > 360°.- IR: 1630, 1620 (2 C=N); 1600 (C=C aromatic); 1240 (Ar-OCH_3); 860 (*p*-disubst. benzene).- ^{1}H-NMR: δ = 2.13 (s, 3H, NCH_3); 3.52 (s, 3H, OCH_3); 5.91 (d, J = 8.0 Hz, 1H, H-10a); 6.22 (d, J = 7.1 Hz, 1H, H-3a); 7.76-8.33 (m, 12 H, aromat.).-

^{13}C-NMR: δ = 154.7, 154.2 (2 C=N); 56.6 (C-10); 41.5 (C-3a); 23.0 (OCH_3); 21.1 (NCH_3); 135.1-128.3 (aromatic).- $C_{24}H_{20}ClN_3O_2$ (417.9) Calc. C 68.9 H 4.82 N 10.1 Found C 69.2 H 10.11 N 9.9.

5b: Pale brown powder; yield 30%; m.p. > 360°.- IR: 1640, 1620 (2 C=N); 1600 (C=C aromatic); 850 (*p*-disubst. benzene).- $C_{24}H_{20}ClN_3O$ (401.9) Calc. C 71.7 H 5.00 N 10.4 Found C 71.5 H 4.93 N 10.3.

5c: Red-brown powder; yield 40%; m.p. 186°.- IR: 1620, 1610 (2 C=N); 1600 (C=C aromatic); 2330 (tert-amino); 850 (*p*-disubst. benzene).- ^{1}H-NMR: δ = 2.43 (s, 3H, NCH_3); 3.11 [s, 6H, $N(CH_3)_2$]; 5.81 (d, J = 8.3 Hz, 1H, H-10a); 6.12 (d, J = 7.2 Hz, 1H, H-3a); 7.22-7.55 (m, 13 H, aromat.).- $C_{25}H_{23}ClN_4O$ (430.9) Calc. C 69.7 H 5.38 N 13.0 Found C 69.6 H 5.41 N 12.9.

4-Aryl-2(H)-6-phenyl-8-chloro-11-methyl-3,4,4a,11-tetrahydro-pyrimidino-[4,5-b]-1,4-benzodiazepin-2-ones **6a,b** *and 3,6-diphenyl-4-aryl-2(H)-8-chloro-11-methyl-3,4,4a,11-tetrahydro-pyrimidino[4,5-b]-1,4-benzodiazepin-2-ones* **6c,d**

To a solution of urea or *N*-phenylurea in EtOH (20 ml) was added enough HCl to clear the solution, then **2a,b** were added (0.02 mol). The reaction mixture was heated for 10 h, concentrated, cooled and treated with NaOH (10 ml; 2N). The precipitate obtained was recrystallized from MeOH to give **6a-d**.

6a: Brown powder; yield 55%; m.p. > 360°.- IR: 3400 (NH); 1630 (CONH); 1615, 1610 (2 C=N); 1600 (C=C aromatic), 750 (mono-subst. benzene).- ^{1}H-NMR: δ = 2.33 (s, 3H, NCH_3); 4.41 (br, 1H, NH); 6.63 (d, J = 7.9 Hz, 1H, H-4a); 6.86 (d, J = 7.9 Hz, 1H, H-4); 7.81-8.12 (m, 13 H, aromat.).- $C_{24}H_{19}ClN_4O$ (414.9) Calc. C 69.5 H 4.61 N 13.5 Found C 69.6 H 4.73 N 13.6.

6b: Brown powder; yield 62%; m.p. 201°.- IR: 3300 (NH); 1630 (CONH); 1620, 1610 (2 C=N); 1600 (C=C aromatic), 1230 (Ar-O-CH_3), 860 (*p*-disubst. benzene).- $C_{25}H_{21}ClN_4O_2$ (444.9) Calc. C 67.5 H 4.76 N 12.6 Found C 67.5 H 4.68 N 12.7.

6c: Brown crystals; yield 75%; m.p. 182°.- IR: 1620 (CONPh); 1615, 1610 (2 C=N); 1600 (C=C aromatic); 750 (monosubst. benzene).- ^{1}H-NMR: δ = 2.31 (s, 3H, NCH_3); 6.52 (d, J = 7.5 Hz, 1H, H-4a); 6.71 (d, J = 8.1 Hz, 1H, H-4); 7.11-7.63 (br, 18 H, aromat.).- $C_{30}H_{23}ClN_4O$ (491) Calc. C 73.4 H 4.72 N 11.4 Found C 73.6 H 4.61 N 11.3.

6d: Reddish-bown powder; yield 65%; m.p. 203°.- IR: 1630 (CONPh); 1615, 1610 (2 C=N); 1600 (C=C aromatic); 1240 (Ar-O-CH_3); 860 (*p*-disubst. benzene).- ^{1}H-NMR: δ = 2.35 (s, 3H, NCH_3); 3.62 (s, 3H, OCH_3); 6.66 (d, J = 7.3 Hz, 1H, H-4a); 6.87 (d, J = 7.9 Hz, 1H, H-4); 7.33-7.55 (br, 17 H, aromat.).- $C_{31}H_{25}ClN_4O_2$ (521.0) Calc. C 71.5 H 4.84 N 10.7 Found C 71.6 H 4.89 N 10.7.

2-Imino-4-aryl-2(H)-6-phenyl-8-chloro-11-methyl-1,4,11-trihydro-1,3-thiazino[4,5-b]-1,4-benzodiazepines **7a,b**

To the solution of arylidene **2a,b** (0.01 mol) in EtOH (830 ml) was added thiourea (0.01 mol) and aqueous KOH (10 ml; 0.02 mol). The reaction mixture was refluxed for 4 h, diluted with H_2O and acidified with conc. HCl. The solid product was recrystallized from EtOH to give **7a,b**.

7a: Dark brown crystals; yield 40%; m.p. 230°.- IR: 3400, 3300 (2 NH); 1650, 1620 (2 C=N); 1600 (C=C aromatic); 720 (monosubst. benzene).- ^{1}H-NMR: δ = 2.11 (s, 3H, NCH_3); 2.55 (s, 1H, C=NH); 3.42 (s, 1H, NH); 4.91 (s, 1H, H-4); 7.56-7.99 (br, 13 H, aromat).- ^{13}C-NMR: δ = 158.8, 154.0 (2 C=N); 72.5 (C-4); 52.4 (C-11a); 45.3 (C-4a); 23.4 (NCH_3); 135.3-126.8 (aromatic).- $C_{24}H_{19}ClN_4S$ (430.9) Calc. C 66.9 H 4.44 N 13.0 Found C 67.1 H 4.66 N 12.8.

7b: Brown crystals; yield 50%; m.p. > 360°.- IR: 3310, 3220 (2 NH); 1660, 1620 (2 C=N); 1610 (C=C aromatic); 1230 (Ar-O-CH_3); 840 (*p*-disubst. benzene).- ^{1}H-NMR: δ = 2.32 (s, 3H, NCH_3); 2.83 (s, 1H, C=NH); 3.33 (s, 1H, NH); 3.61 (s, 3H, OCH_3); 4.73 (s, 1H, H-4); 7.32-7.89 (br, 12 H, aromat.).- $C_{25}H_{21}ClN_4OS$ (461) Calc. C 65.1 H 4.59 N 12.1 Found C 65.3 H 4.61 N 11.8.

2-Mercapto-4-aryl-6-phenyl-8-chloro-11-methyl-1,4,11-trihydro-pyrimidino-[4,5-b]-1,4-benzodiazepine **(8)**

To the arylidene **2a** (0.01 mol) was added anhydrous NH_4SCN (0.02 mole), xylene (30 ml) and cyclohexanol (5 ml). The mixture was heated under reflux for 20 h. The liberated H_2O was collected and measured by means of a *Dean* and *Stark* trap. After cooling the liquid phase was decanted from the crystalline residue of unreacted NH_4SCN and concentrated under reduced pressure. The viscous syrup was stirred with acetone (50 ml). The solid product was crystallized from EtOH to give **8**.

8: Brown crystals; yield 30%; m.p. > 360°.- IR: 3320 (NH); 2600 (SH); 1620, 1610 (2 C=N); 1590 (C=C aromatic); 730 (monosubst. benzene).- ^{1}H-NMR: δ = 2.23 (s, 3H, NCH_3); 3.45 (s, 1H, NH); 4.61 (s, 1H, H-4); 5.4 (s, 1H, SH); 7.33-7.81 (m, 13 H, aromat.).- ^{13}C-NMR: δ = 167.5, 154.3 (2 C=N); 144.1 (C-4a); 139.9 (C-11a); 69.3 (C-4); 23.1 (NCH_3); 138.1-128.3 (aromatic).- $C_{24}H_{19}ClN_4S$ (430.9) Calc. C 66.9 H 4.44 N 13.0 Found C 66.7 H 4.66 N 13.1.

1-Acetyl-3-cyano-4-aryl-2-(H)-6-phenyl-8-chloro-11-methyl-1,11-dihydro-pyridino[2,3-b]-1,4-benzodiazepin-2-ones **9a,b**

A mixture of ethyl cyanoacetate (0.01 mol), **2a,c** (0.01 mol) and $CH_3CO_2NH_4$ (0.08 mol) was heated at 180-200°C in oil bath for 8 h. After cooling the resultant mass was washed several times with H_2O and recrystallized from dil. MeOH to give **9a,b**.

9a: Pale yellow crystals; yield 50%; m.p. 170°.- IR: 2220 (CN); 1680 (CH_3-CO-N); 1650 (α,β-unsat. CO); 1630 (C=N); 1600 (C=C aromatic); 720 (monosubst. benzene).- ^{1}H-NMR: δ = 2.53 (s, 3H, NCH_3); 3.66 (s, 3H, $NCOCH_3$); 7.12-7.51 (m, 13 H, aromat.).- $C_{28}H_{19}ClN_4O_2$ (478.9) Calc. C 70.2 H 4.00 N 11.7 Found C 69.9 H 4.21 N 11.8.

9b: Yellow crystals; yield 45%; m.p. > 360°.- IR: 2200 (CN); 1690 (CH_3-CO-N); 1650 (α,β-unsat. CO); 1630 (C=N); 1600 (C=C aromatic); 810 (*p*-disubst. benzene).- $C_{29}H_{21}ClN_4O_2$ (492.9) Calc. C 70.7 H 4.29 N 11.4 Found C 70.8 H 4.41 N 11.1.

5-Aryl-3(H)-7-phenyl-9-chloro-12-methyl-2,4,5,5a,12-pentahydro-1,2,4-triazepino[7,6-b]-1,4-benzodiazepin-3-thiones **11a,b**

A mixture of the arylidene **2b,d** (0.01 mol) in EtOH (30 ml) and thiosemicarbazide (0.02 mol) in aqueous KOH (0.02 mol; 10 ml) was refluxed for 4 h. The mixture was cooled, diluted with H_2O and neutralized with conc. HCl. The org. material was extracted with ether and the etheral layer dried by Na_2SO_4. Removal of the solvent under reduced pressure gave an oil that solidified when left in petrol ether bp. 60-80°. The solid product was crystallized from EtOH to give **11a,b**.

11a: Dark brown powder; yield 30%; m.p. > 360°.- IR: 3400, 3300 (2 NH); 1620, 1610 (2 C=N); 1600 (C=C aromatic); 1230 (Ar-O-CH_3); 1200 (C=S); 850 (*p*-disubst. benzene).- ^{1}H-NMR: δ = 2.31 (s, 3H, NCH_3); 3.53 (s, 3H, OCH_3); 4.34 (s, 1H, NH); 4.94 (s, 1H, NH); 6.21 (s, 1H, H-5a); 6.43 (s, 1H, H-5); 7.14-7.71 (m, 12 H, aromat.).- $C_{25}H_{22}ClN_5OS$ (476.0), Calc. C 63.1 H 4.66 N 14.7 Found C 62.9 H 4.54 N 14.5.

11b: Brown powder; yield 35%; m.p. 280°.- IR: 3350, 3200 (2 NH); 1620, 1610 (2 C=N); 1600 (C=C aromatic); 1360 (tert-amino); 1250 (C=S), 820 (*p*-disubst. benzene).- ^{1}H-NMR: δ = 2.41 (s, 3H, NCH_3); 3.14 [s, 6H, $N(CH_3)_2$]; 4.21 (s, 1H, NH); 4.69 (s, 1H, NH); 6.55 (s, 1H, H-5a); 6.78 (s, 1H, H-5); 7.76-7.98 (m, 12 H, aromat.).- $C_{26}H_{25}ClN_6S$ (489) Calc. C 63.9 H 5.15 N 17.2 Found C 63.7 H 5.20 N 17.4.

References

1 D.J. Greenblatt "Benzodiazepines in clinical practice" Raven Press, New York, 1974; L.H. Sternbach, Prog. Drug Res. *22*, 229 (1978).

2 Y. Kayama, T. Hara K. Itoh, and T. Sunami, J. Heterocycl. Chem. *14*, 171 (1977); D.R. Harrison, P.D. Kennewell, and J.B. Taylor, ibid. *14*, 1191 (1977); R.B. Moffet, G.N. Evenson, and P.E. Von-Voigtlander,

ibid. *14*, 1231 (1977); T. Hara, Y. Kayama, T. Mori, K. Itoh, H. Fujimori, T. Sunami, Y. Hashimoto, and S. Ishimoto, J. Med. Chem. *21*, 263 (1978); T. Hara, H. Fujimori, Y. Kayama, T. Mori, K. Itoh, and Y. Hashimoto, Chem. Pharm. Bull. *25*, 2584 (1977); R.B. Moffet, B.V. Kamdar, and P.E. Von-Voigtlander, J. Med. Chem. *19*, 192 (1976); H. Fujimori, Y. Kayama, T. Hara, K. Itoh, and T. Sunami, J. Heterocycl. Chem. *14*, 235 (1977).

3 M. Raban, E.H. Carlson, J. Szmuszkovicz, G. Slamp, C.G. Chidester, and D.J. Duchamp, Tetrahedron Lett. *1975*, 139; K. Kamiya, Y. Wada, and M. Nishikawa, Chem. Pharm. Bull. *21*, 1520 (1973).

4 R.V. Stevens, R.M. Cory, and S. Rosen, J. Chem. Soc. Chem. Commun. *1975*, 742; D.L. Caffen, R.I. Fryer, D.A. Katonak, and F. Wong, J. Org. Chem. *40*, 894 (1975).

5 R. Nakajima, Y. Take, R. Moriya, Y. Saji, T. Yui, and Y. Nagawa, J. Pharmacol. *21*, 497 (1971); J.B. Hester, D.J. Duchamp, and C.G. Chidester, Tetrahedron Lett. *1971*, 1609; J. Schwartz, M. Kramer, and T. Roth, Curr. Ther. Tes. Clin. Exp. *16*, 958 (1974); L.F. Fabre and R.T. Harris, ibid. *16*, 1010 (1974).

6 N.P. Peet and S. Sunder, J. Heterocycl. Chem. *14*, 561 (1977); A. Walser, W.J. Zally, and R.I. Fryer, ibid. *11*, 863 (1974); P.C. Wade, B.R. Vogt, B. Teoplitz, and M.S. Puar, J. Org. Chem. *44*, 88 (1979); T. Miyadera, Y. Kawamo, T. Hata, C. Tamur, and R. Tachlkawa, Chem. Pharm. Bull. *25*, 3247 (1977); K. Kariyone, H. Yazawa, and M. Kohsaka, Chem. Pharm. Bull. *19*, 2289 (1971); V. Stefanovich and M. Ceprini, J. Pharm. Sci. *60*, 781 (1971); A. Walser, G. Silverman, and R.I. Fryer, J. Org. Chem. *38*, 3502 (1973); B.R. Vogt, P.C. Wade, and M.S. Purer, Tetrahedron Lett. *1976*, 1931; E. Aiello, G. Dattalo, G. Cirrincione, S. Plescia, and G. Daidone, J. Heterocycl. Chem. *16*, 209 (1979); K.A. Parker and T.H. Fedynyshyn, Tetrahedron Lett. *1979*, 1667.

7 F. Hoffmann, "The Roch Vademecumm-Roch Products on the Egyptian Market" Balse Switzerland, 129 (1980); S.C. Bell, T.S. Sulkowski, C. Gochman, and S.J. Childress, J. Org. Chem. *27*, 562 (1962).

8 R.P. Barnes and A.S. Spriggs, J. Am. Chem. Soc. *67*, 134 (1945); A.H. Blatt, J. Am. Chem. Soc. *53*, 1133 (1931).

9 R.S. Rasmussen and R.R. Brattain, The Chemistry of Penicillin, p. 400, Princeton University Press, New York 1949.

10 D.H. Williams and I. Fleming, Spectroscopic Methods in Organic Chemistry, p. 65, McGraw-Hill Publishing Co., London 1966; R. Zimmermann, Angew. Chem. *75*, 1025 (1963).

11 H. Mathes, J. Am. Chem. Soc. *75*, 1747 (1953); H. Rupe and E. Hinterlack, Ber. Dtsch. Chem. Ges. *40*, 4764 (1907).

12 A. Sammour, H. Rahim, and A. Khnoukhy, J. Chem. UAR *13*, 421 (1970); C.A. *75*, 5840 (1971). [Ph966]