Pyrimidine-Fused 1,4-Benzodiazepines. Reaction of 1,4-Benzodiazepines with Formamide-$POCl_3$

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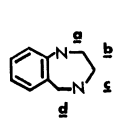
Synthesis of new pyrimidine-fused 1,4-benzodiazepines was achieved practically in a single step by heating 1,4-benzodiazepines with formamide and $POCl_3$ in a sealed tube. A plausible mechanism of the reaction is proposed.

Various 1,4-benzodiazepines (**1**) with an additional ring attached to the parent ring system have been synthesized,[1] their interesting psychopharmacological properties being expected. Thus, 10-chloro-2,3,7,11b-tetrahydro-oxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-ones (**2a**: oxazolam, **2b**: cloxazolam) having an oxazole ring fused to the *d* face of the benzodiazepine system are now being clinically used as antianxiety agents.[2] 8-Chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines (**3a**: estazolam, **3b**: alprazolam) having a triazole ring fused to the *a* face have also been reported to be pharmacologically active and are under extensive clinical evaluation.[3] However, the derivatives having a third ring fused to the *b* face are only scarcely reported.[4] This prompted us to synthesize 1,4-benzodiazepines having a pyrimidine ring fused to the *b* face described in this paper.



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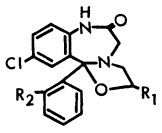
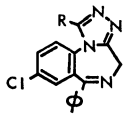


2

a: R_1= CH_3, R_2= H
b: R_1= H , R_2= Cl



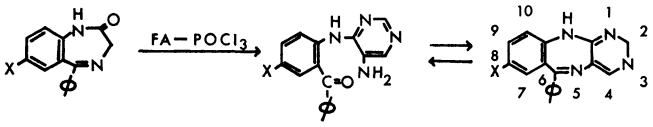
3

a: R= H
b: R = CH_3

Previously, we reported a new synthetic route of pyrimidines from carboxamides containing a methylene group alpha to the carbonyl group. The reaction involves heating of the amides with formamide (FA) and phosphoryl chloride ($POCl_3$) in a sealed tube.[5] Since some pharmacologically important 1,4-benzodiazepin-2-ones (**4** and **7**)[6] possess the carboxamide group adjacent to a methylene group, we envisaged that similar treatment of these 1,4-benzodiazepin-2-ones might lead to the synthesis of new 1,4-benzodiazepines with a pyrimidine ring fused to the *b* face of the benzodiazepine system (Schemes 1 and 3).

Results and Discussion

Attempts to obtain 8-nitro-6-phenyl-11*H*-pyrimido-[4,5-*b*][1,4]benzodiazepine (**6a**) in a single step by heating 1,3-dihydro-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one[7] (**4a**) with FA and $POCl_3$ at 110 °C for 10 hr in a sealed tube were unsuccessful. The main product separated from the reaction mixture was a yellow crystalline compound which was proved to be 5-amino-4-(2-benzoyl-4-nitroanilino)pyrimidine (**5a**, a hydrolysis product of the C=N double bond of **6a**; yield, 25%). Evidences for the structure (**5a**) are mainly based on its mass spectrum, which shows intense peaks at *m/e* 335 (M^+, 100), 317 (62), 270 (38), 258 (43), 230 (83), 184 (41), 105 (33), and 77 (49%). Peaks at *m/e* 258, 230, 184, 105, and 77 are rationalized as shown in Scheme 2. Appearance of peaks at *m/e* 317 and 270 indicates the occurrence of cyclodehydration of **5a** to **6a** upon preheating (200 °C) or under electron impact in a vaporizing vessel of a mass spectrometer, and the concomitant loss of HNO_2 from **6a** (Scheme 2).[8]



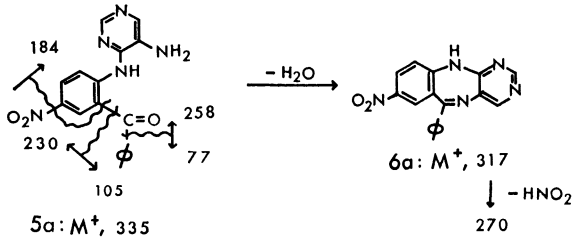
4a: X = NO_2
4b: X = Cl

5a: X = NO_2
5b: X = Cl

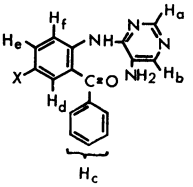
6a: X = NO_2
6b: X = Cl

Scheme 1.

This assignment was corroborated by its NMR spectrum ($CDCl_3$), which displays a broad singlet at δ 3.60 (2H, NH_2), a multiplet at 7.44—7.80 (5H, Hc), a singlet at 8.07 (1H, Hb), a double doublet at 8.40 (1H, J=3 and 9 Hz, He), a singlet at 8.50 (1H, Ha), a doublet at 8.54 (1H, J=3 Hz, Hd), a doublet at 9.18 (1H, J=9 Hz, Hf), and a broad singlet at 11.42 (1H, NH).



Scheme 2.

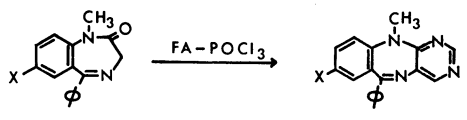


5a: X = NO_2
5b: X = Cl

The NMR spectrum of **5a** measured in DMSO-d_6 at room temperature gives a broad signal not clearly resolved in the aromatic region (δ 7.0—8.5). However, the NMR spectrum determined in DMSO-d_6 at about 100 °C shows a doublet at δ 7.21 (1H, J=9 Hz, C_{10}–H), a multiplet at 7.3—7.7 (6H, C_7–H and phenyl moiety), a double doublet at 8.10 (1H, J=2.5 and 9 Hz, C_9–H), a singlet at 8.29 (1H, C_4–H), a singlet at 8.37 (1H, C_2–H), and a broad singlet at 9.01 (1H, NH). These are rationalized by the structure **6a** (a cyclodehydration product of **5a**). Indeed, the NMR spectrum of **6a** is identical with that of **5a** when determined in DMSO-d_6 at about 100 °C. This result, together with the mass spectral observation, indicates that **5a** would cyclize to **6a** upon heating. In fact, cyclization of **5a** to **6a** easily proceeded when it was heated in DMSO at 100 °C for 10 min.[9] Cyclization of **5a** to **6a** also occurs when a solution of **5a** in a mixture of ethyl acetate and ethyl alcohol (2: 1, v/v) is heated at 70 °C for 1 hr in the presence of *p*-toluenesulfonic acid. The structure of **6a** is further supported by its mass spectrum which displays intense peaks at *m/e* 317 (M^+, 100%) and 270 (M^+-HNO_2, 52%) as indicated in Scheme 2.

The compound **6a** was found to be readily hydrolyzed to the pyrimidine **5a** when an ethyl acetate solution of **6a** was treated with 1 M HCl for a few minutes (Scheme 1).

When 1,3-dihydro-1-methyl-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**7a**)[7] was treated with FA–$POCl_3$, 11-methyl-8-nitro-6-phenyl-11*H*-pyrimido[4,5-*b*][1,4]-benzodiazepine (**8a**) was obtained in a single step in a yield of 20% (Scheme 3); the reaction, though somewhat sluggishly (120 °C, 24 hr in a sealed tube), was not accompanied with hydrolysis. The mass spectrum of **8a** has a strong molecular ion at *m/e* 331 (100%) and the phenyl radical ion at *m/e* 77 (11%). Other important fragmentations are loss of HNO_2[8] (*m/e* 284, 26%), and losses of a phenyl group (*m/e* 254, 16%), and then HCN (*m/e* 227, 11%). The NMR spectrum shows a singlet at δ 3.36 (3H, N–CH_3), a multiplet at 7.35—7.87 (7H, phenyl protons, C_7–H, and C_{10}–H), a double doublet at 8.37 (1H, J=3 and 9 Hz, C_9–H), a broad singlet at 8.56 (1H, C_4–H), and a singlet at 8.72 (1H, C_2–H).



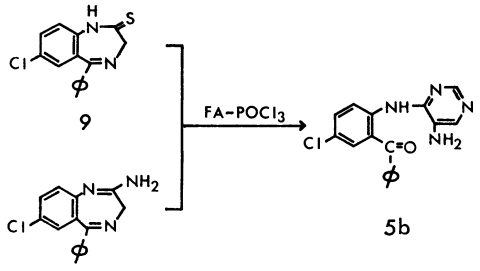
7a: X = NO_2
7b: X = Cl

8a: X = NO_2
8b: X = Cl

Scheme 3.

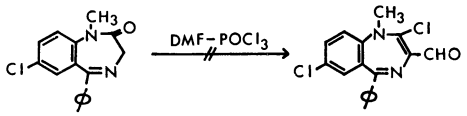
Similar reactions of the chloro derivatives (**4b** and **7b**) proceed along the same pathway. Thus, 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**4b**)[10] reacts with FA–$POCl_3$ to give 5-amino-4-(2-benzoyl-4-chloroanilino)pyrimidine (**5b**; yield, 23%), which cyclized to 8-chloro-6-phenyl-11*H*-pyrimido[4,5-*b*][1,4]benzodiazepine (**6b**) when heated with *p*-toluenesulfonic acid in a mixture of ethyl acetate and ethyl alcohol (1: 1, v/v) at 70 °C for 30 min. Cyclization of **5b** to **6b** was also accomplished when a solution of **5b** in DMSO was heated at 100 °C for 10 min. The NMR spectrum of **5b** ($CDCl_3$) showed a broad singlet at δ 3.49 (2H, NH_2), a multiplet at 7.46—7.68 (7H, Hc, Hd, and He), a singlet at 8.01 (1H, Hb), a singlet at 8.41 (1H, Ha), a doublet at 8.77 (1H, J=10 Hz, Hf), and a broad singlet at 10.80 (1H, NH), supporting the structure **5b**. In contrast, the *N*-methyl derivative[11] (**7b**) produced **8b** in a single step when treated with FA–$POCl_3$ at 110 °C for 40 hr in a sealed tube; yield, 18% (Scheme 3). Compound **6b** was also hydrolyzed easily to **5b** by treatment with 1 M HCl.

Compound **5b** was also obtained when 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione (**9**),[12] and 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (**10**)[13] were treated with FA–$POCl_3$ in yields of 10 and 25%, respectively (Scheme 4).



Scheme 4.

Recently, an introduction method of an α,β-unsaturated β-chloroaldehyde moiety to five,[14] six,[15] and seven-membered lactams[15a] has been reported, and α,β-unsaturated β-chloroaldehydes have been reported to provide pyrimidines when treated with FA at above 150 °C.[16] However, attempts to obtain the corresponding α,β-unsaturated β-chloroaldehyde (**11**) from 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**7b**) by treating with Vilsmeier reagent (DMF–$POCl_3$), have thus far met with failure[17] (Scheme 5).

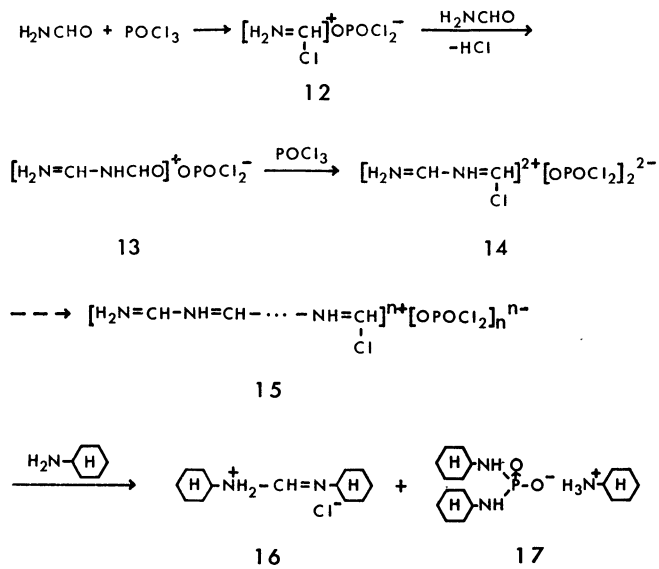


7b 11

Scheme 5.

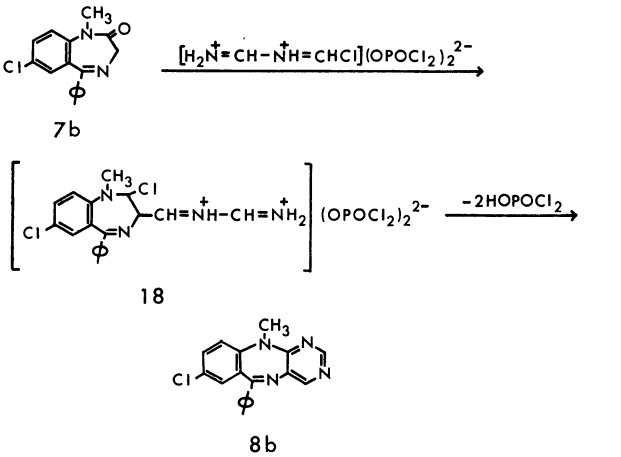
When FA was treated with $POCl_3$ at 120 °C for 1 hr in a sealed tube and the resulting complex was washed with $CHCl_3$, there were obtained hygroscopic pale yellow powders, which were treated with an excess amount of cyclohexylamine to give *N,N'*-dicyclohexylformamidine hydrochloride (**16**) and phosphoric dicyclohexylamidate cyclohexylammonium salt (**17**) (Scheme 6; for details, see Experimental section).

From the above-mentioned experimental results, a possible mechanistic interpretation of the present one-step synthesis can be advanced. The reaction of FA with $POCl_3$ gives a Vilsmeier compound **12**.[18] Its further reaction with FA produces **13**[19] which upon reaction with $POCl_3$ yields **14**. In the absence of **7b**,



Scheme 6.

the polymerization of the Vilsmeier compound would proceed until it reaches a possible intermediate of adenine (**15**, $n=5$) which cyclizes to yield adenine as reported previously.[20] However, when **7b** is present, it would react with **14** to give **18**, which cyclizes to give **8b** as shown in Scheme 7.



Scheme 7.

Another route which involves the reaction of **7b** with **12**, appears less plausible because, as previously mentioned, all attempts to isolate **11** were unsuccessful. Interesting enough, despite the similarity of the present reaction conditions to those of adenine synthesis, formation of adenine was greatly suppressed if **7b** is present in the reaction mixture. For instance, adenine is obtained in 40% yield if **7b** is absent, whereas its yield is quite poor (3%) in the presence of 0.5 mol equivalents of **7b**. These observations could be reasonably accounted for by the assumption that the dimeric Vilsmeier reagent (**14**) is more reactive than the monomer (**12**) for the reaction with carboxamides or formamides. If so, one could ingeniously explain the reason that addition of any alkyl amide or *N*-alkyl formamide to the reaction mixture of FA–$POCl_3$ leads to poor yields of adenine[21] and also that **11** is not produced from the reaction of **7b** with DMF–$POCl_3$ whereas the reaction leads to the formation of **8b** *via* its precursor **18**.

Experimental

Melting points were measured in open capillaries and are uncorrected. NMR spectra were recorded in $CDCl_3$ or in DMSO-d_6 (internal TMS standard) on a Varian T-60, A-60, or HA 100 spectrophotometer. Mass spectra were recorded on a Hitachi RMU-6D double focusing spectrometer with an ionizing voltage of 70 eV at a temperature of 200 °C. IR and UV spectra were recorded on a Hitachi EPI-S_2 recording spectrophotometer and a Hitachi EPS-2 recording spectrophotometer, respectively.

General Procedure. 1,4-Benzodiazepines (0.02 mol) and FA (0.05 mol) were charged in a stainless steel vessel (100 ml). $POCl_3$ (0.07 mol) was added into this mixture with cooling and the vessel was sealed. After being left standing for 10 min at room temperature, the vessel was heated at 110 °C for 10 hr with stirring. The reaction mixture was then cooled and dissolved in EtOAc. The EtOAc extract was carefully washed with 4M NaOH under cooling until the aqueous layer remained basic, and then with water until neutral. The organic layer was dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column (Kieselgel 60, Merck) using $CHCl_3$–acetone (4: 1, v/v) as a solvent. Recrystallization from $CHCl_3$–EtOH gave a pure product.

The following compounds (**5** and **8**) were prepared by the general procedure.

5-Amino-4-(2-benzoyl-4-nitroanilino)pyrimidine (5a). 1,3-Dihydro-7-nitro-5-phenyl-2*H*-benzodiazepin-2-one (**4a**, 5.6 g, 0.02 mol) yielded 1.68 g of **5a**; mp 198—199 °C; MS (*i*): *m/e* 335 (M^+, 100), 317 (62), 270 (38), 258 (43), 230 (83), 184 (41), 105 (33), 77 (49); NMR (δ) $CDCl_3$: 3.60 (2H, bs), 7.44—7.80 (5H, m), 8.07 (1H, s), 8.40 (1H, dd, $J=3$ and 9 Hz), 8.50 (1H, s), 8.54 (1H, d, $J=3$ Hz), 9.18 (1H, d, $J=9$ Hz), 11.42 (1H, bs); IR ν_{max}^{KBr} (cm^{-1}): 1630 (C=O); UV (mμ) λ_{max} (ε) EtOH: 248 (16900), 398 (14000). Found: C, 60.90; H, 3.85; N, 20.83%. Calcd for $C_{17}H_{13}O_3N_5$: C, 60.89; H, 3.91; N, 20.89%.

5-Amino-4-(2-benzoyl-4-chloroanilino)pyrimidine (5b). (i) 7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-bnezodiazepin-2-one (**4b**, 2.70 g, 0.01 mol) yielded 0.75 g of **5b**; mp 201—202 °C; MS (*i*): *m/e* 324 (M^+, 23), 306 (9), 271 (9), 247 (11), 219 (43), 105 (63), 77 (100); NMR (δ) $CDCl_3$: 3.49 (2H, bs), 7.46—7.68 (7H, m), 8.01 (1H, s), 8.41 (1H, s), 8.77 (1H, d, $J=10$ Hz), 10.80 (1H, bs); IR ν_{max}^{KBr} (cm^{-1}): 1630 (C=O); UV (mμ) λ_{max} (ε) EtOH: 253 (20300), 308 (10400). Found: C, 62.58; H, 3.88; N, 17.20%. Calcd for $C_{17}H_{13}ON_4Cl$: C, 62.87; H, 4.03; N, 17.25%.

(ii) 7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione (**9**, 572 mg, 2 mmol) yielded 69 mg of **5b**.

(iii) 2-Amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (**10**, 540 mg, 2 mmol) yielded 165 mg of **5b**

11-Methyl-8-nitro-6-phenyl-11H-pyrimido[4,5-b][1,4]benzodiazepine (8a). 1,3-Dihydro-1-methyl-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**7a**, 738 mg, 2.5 mmol) was heated at 120 °C for 24 hr under the same conditions, yielding 167 mg of **8a**; mp 163—164 °C; MS (*i*): *m/e* 331 (M^+, 100), 284 (26), 254 (16), 227 (11), 77 (11); NMR (δ) DMSO-d_6: 3.36 (3H, s, N–CH_3), 7.35—7.87 (7H, m, phenyl protons, C_7–H, and C_{10}–H), 8.39 (1H, dd, $J=3$ and 9 Hz, C_9–H), 8.56 (1H, bs, C_4–H), 8.72 (1H, s, C_2–H); UV (mμ) λ_{max} (ε) EtOH: 228 (24700), 267 (19600), 303 (21900). Found: C, 64.89; H, 3.84; N, 21.15%. Calcd for $C_{18}H_{13}O_2N_5$: C, 65.25;

H, 3.96; N, 21.14%.

8-Chloro-11-methyl-6-phenyl-11H-pyrimido[4,5-b][1,4]benzodiazepine (8b). 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**7b**, 284 mg, 1 mmol) was heated at 110 °C for 40 hr under the same conditions, yielding 59 mg of **8b**; mp 208—209 °C; MS (*i*): *m/e* 320 (M^+, 100), 285 (24), 243 (36), 216 (44), 77 (56); NMR (δ) $CDCl_3$: 3.31 (3H, s, N-CH_3), 6.93—7.87 (8H, m), 8.53 (1H, bs, C_4-H), 8.66 (1H, s, C_2-H); UV (mμ) λ_{max} (ε) EtOH: 244 (23600), 280 (12800), 303 (12100). Found: C, 67.64; H, 4.11; N, 17.54%. Calcd for $C_{18}H_{13}N_4Cl$: C, 67.40; H, 4.08; N, 17.47%.

8-Nitro-6-phenyl-11H-pyrimido[4,5-b][1,4]benzodiazepine (6a). 5-Amino-4-(2-benzoyl-4-nitroanilino)pyrimidine (**5a**, 1.0 g) and *p*-TsOH·H_2O (50 mg) were dissolved in a mixture of EtOH–EtOAc (100 ml, 2: 1, v/v). The solution was refluxed for 1 hr. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (100 ml). The solution was washed with water and dried over Na_2SO_4, and the solvent was evaporated. Crystallization of the residue from MeOH–$CHCl_3$ gave 0.9 g of **6a**; mp 261—262 °C; MS (*i*): *m/e* 317 (M^+, 100), 270 (52); NMR (δ) DMSO-d_6: 7.21 (1H, d, J=9 Hz, C_{10}-H), 7.3—7.7 (6H, m, C_7-H and phenyl protons), 8.10 (1H, dd, J=2.5 and 9 Hz, C_9-H), 8.29 (1H, s, C_4-H), 8.37 (1H, s, C_2-H), 9.01 (1H, bs, NH); UV (mμ) λ_{max} (ε) EtOH: 227 (25000), 262 (13700), 303 (22000). Found: C, 63.52; H, 3.28; N, 21.97%. Calcd for $C_{17}H_{11}O_2N_5 \cdot 1/4H_2O$: C, 63.45; H, 3.52; N, 21.76%.

8-Chloro-6-phenyl-11H-pyrimido[4,5-b][1,4]benzodiazepine (6b). 5-Amino-4-(2-benzoyl-4-chloroanilino)pyrimidine (**5b**, 250 mg) and *p*-TsOH·H_2O (25 mg) were dissolved in a mixture of EtOH–EtOAc (10 ml, 1: 1, v/v). The solution was heated at 70 °C for 3 hr, then concentrated to about 4 ml and set aside in a refrigerator overnight. The resulting fluffy crystals were collected (226 mg); mp 240—241 °C; MS (*i*): *m/e* 306 (M^+, 100), 271 (76), 77 (6); NMR (δ) DMSO-d_6: 6.80 (1H, d, J=2.5 Hz, C_7-H), 7.21 (1H, d, J=8.5 Hz, C_{10}-H), 7.45 (1H, dd, J=2.5 and 8.5 Hz, C_9-H), 7.55 (5H, s, phenyl protons), 8.36 (1H, s, C_4-H), 8.46 (1H, s, C_2-H), 8.70 (1H, bs, NH); UV (mμ) λ_{max} (ε) EtOH: 244 (27500), 280 (15000), 303 (12800). Found: C, 66.16; H, 3.49; N, 18.33; Cl, 11.60%. Calcd for $C_{17}H_{11}N_4Cl$: C, 66.56; H, 3.62; N, 18.27; Cl, 11.56%.

Hydrolysis of 8-Chloro-6-phenyl-11H-pyrimido[4,5-b][1,4]benzodiazepine (6b). A solution of compound **6b** (122 mg, 0.4 mmol) in EtOAc (40 ml) was shaken with 1 M HCl (10 ml) for 1 min. The organic layer was washed with 5% $NaHCO_3$, then with water, dried over Na_2SO_4, and evaporated. Recrystallization of the residue from EtOH–$CHCl_3$ gave 122 mg of 5-amino-4-(2-benzoyl-4-chloroanilino)pyrimidine (**5b**).

8-Nitro-6-phenyl-11*H*-pyrimido[4,5-*b*][1,4]benzodiazepine (**6a**) was hydrolyzed under the same conditions to give 5-amino-4-(2-benzoyl-4-nitroanilino)pyrimidine (**5a**, 80.3%).

N,N'-Dicyclohexylformamidine Hydrochloride (16) and Phosphoric Dicyclohexylamidate Cyclohexylammonium Salt (17). FA (1.35 g, 30 mmol) was charged in a stainless steel vessel (30 ml), which was cooled with dry ice–acetone. $POCl_3$ (10 g, 66 mmol) was added into a solidified mass of FA and the vessel was sealed tightly. After being left standing for 30 min at room temperature, the vessel was heated at 120 °C for 1 hr in an oil bath. The reaction mixture was cooled and washed with $CHCl_3$ to remove an excess of $POCl_3$. An excess of cyclohexylamine was added into the resulting pale yellow hygroscopic powders. Evaporation of cyclohexylamine under reduced pressure left a residue, which was treated with $CHCl_3$ and then with ethyl ether. The crude **16** (3.0 g) obtained was twice recrystallized from $CHCl_3$–EtOAc(1:1, v/v) to give 1.9 g of pure **16**; mp 230 °C decomp. (lit, mp 229—230 °C decomp.,[22] 228—230 °C decomp.[23]); MS (*i*): *m/e* 208 (M^+, 55), 110 (HC^+=NC_6H_{11}, 100), 98 (C_6H_{11}-NH^+, 50), and 83 (H_2C=$CHCH_2CH_2CH_2CH_2^+$, 52); IR ν_{max}^{Nujol} (cm^{-1}): 3100 (-C=N), 1680 (-C=NH^+-).

The sulfate was prepared by passing the hydrochloride through a column of Amberlite IRA-400 (SO_4^{2-}) and crystallized from EtOAc–EtOH (3: 1, v/v); mp 240 °C decomp. Found: C, 58.53; H, 9.56; N, 10.41; S, 6.00%. Calcd for $C_{13}H_{24}N_2 \cdot 1/2H_2O \cdot 1/2H_2SO_4$: C, 58.64; H, 9.77; N, 10.53; S, 6.02%.

From the recrystallization mother liquor for **16**, 100 mg of fine needles (**17**) was obtained; mp 173—174 °C decomp.; white precipitates were obtained by treatment with $AgNO_3$; positive for $(NH_4)_6Mo_7O_{24}$ reagent;[24] IR ν_{max}^{Nujol} (cm^{-1}): 1120 (monobasic phosphoramidate). Found: C, 60.32; H, 11.04; N, 11.78; P, 8.62%. Calcd for $C_{18}H_{38}O_2N_3P$: C, 60.17; H, 10.59; N, 11.70; P, 8.64%.

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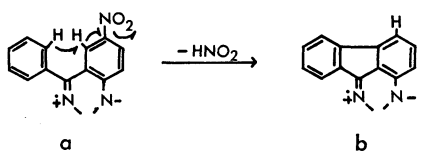

a b

9) When **5a** was heated at 100 °C for 7 hr in various high boiling solvents such as dimethylformamide, nitrobenzene, benzonitrile, and quinoline, no conversion to **6a** was

observed as revealed from tlc [Kieselgel 60 F_{254} pre-coated, Merck: solvent system, chloroform–acetone–ethanol (80:20:1)]. Therefore, DMSO appears to serve as a solvent for promoting dehydration of **5a** and a simple thermal elimination of water must be excluded; *cf.* V. J. Traynelis, W. L. Hergenrother, H. A. Hanson, and J. A. Valicenti, *J. Org. Chem.*, **29**, 123 (1964).

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