Synthesis of 5-Amino-2,3-dihydro-1*H*-1,4-benzodiazepines (1)

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A number of 5-amino-2,3-dihydro-1*H*-1,4-benzodiazepines (II) have been prepared from the reaction of 5-methylmercapto-2,3-dihydro-1*H*-1,4-benzodiazepine (I) with amines. Another alternate approach based on the cyclodehydration of the ureic compounds (IV) was unsuccessful. The synthesis of I was accomplished by methylation of the 1,2,3,4-tetrahydro-5*H*-5-thioxo-1,4-benzodiazepine (VI) with dimethyl sulfate in methanol-dioxane. Another attempted method for the synthesis of I is also presented.

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The discovery of the interesting properties of chlordiazepoxide (Librium) marks the origin of the intense work carried out on the 1,4-benzodiazepine system (3-5), dealing mainly with the development of new preparative methods, the study of the influence of the substituents on the activity and the search of new ansiolytic agents. A great deal of this work, however, has been devoted to the synthesis of 5-substituted aryl derivatives, the introduction of substituents at positions 1, 3 and 7 as well as the preparation of condensed tricyclic systems by the addition of a third ring at positions 1 and 2 of the benzodiazepine moiety. In marked contrast, the preparation of compounds bearing amino groups at position 5 has been scarcely considered. A literature search for background information of this kind of compound revealed that only three examples are known. Thus, 7-chloro-1-methyl 5-[(2-(diethylamino)ethyl)amino]-2,3-dihydro-1*H*-1,4-benzodiazepine (6,7) and 8-chloro-1-phenyl-5-amino-2,3-dihydro-1,4-benzodiazepine and its *N*-methyl-derivative (8) were prepared by reaction of 5-ethoxy- or 5-chloro-2,3-dihydro-1*H*-1,4-benzodiazepines with ammonia or amines.

Prior to the preparation of tricyclic systems by fusing a new ring at positions 4 and 5 of the 1,4-benzodiazepine nucleus, we report in this work the synthesis of the title compounds (II) carried out by condensation of the 5-methylmercapto-2,3-dihydro-1,4-benzodiazepine (I) with amines (Scheme 1). This nucleophilic displacement of the

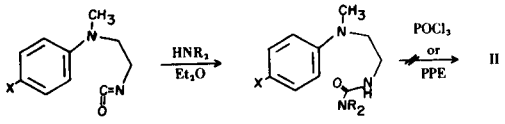
Scheme 1

I II

thioalkoxy group was shown to be particularly effective when a mixture of I and an excess of the starting amine was refluxed for 120-150 hours in the presence of catalytic amounts of glacial acetic acid. The 5-amino compound (IIa) was obtained as its hydroiodide salt by heating I with ammonium iodide in a solution of ammonia in ethanol.

Most of these amidines were isolated and described as hydrochloride, picrate or maleate salts (Table I). The ir spectra of the bases revealed sharp NH stretching bands at 3400 and 3120 cm^{-1} in the 5-amino derivative (IIa) and near 3240 cm^{-1} in III-m, such bands being absent in the rest of the amidines (IIb-k). The C=N absorptions occurred at 1620 cm^{-1}. In the ^1H nmr spectra (deuteriochloroform), all compounds exhibited the signals for the 2 and 3 methylene protons of the 1,4-benzodiazepine moiety as a singlet in the range δ 3.2-3.6. The signals due to the *N*-methyl protons appeared at δ 2.80.

Scheme 2



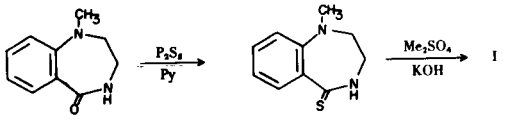
III IV

a, X = H
b, X = Cl

a, X = H, NR_2 = NHC_6H_5
b, X = Cl, NR_2 = NHC_6H_5

A projected alternate approach to II (Scheme 2) involving the cyclodehydration of compounds IV (a,b) *via* a Bischler-Napieralski type reaction was unsuccessful. The intermediate imino thioether (I), not previously reported, was prepared by methylation of the potassium salt of the 1,2,3,4-tetrahydro-5*H*-5-thioxo-1,4-benzodiazepine (VI) (9,10) with dimethyl sulfate in methanol-dioxane (Scheme 3). Minor amounts of the corresponding *N*-methyl isomer

Scheme 3



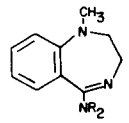
V VI

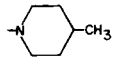
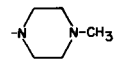
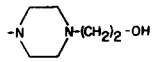
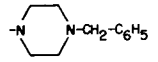
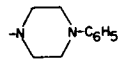
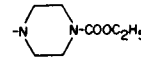
could also be isolated. The ir spectrum showed a strong band at 1610 cm^{-1} due to the C=N link. In the ^1H nmr spectrum, the signal of the methylene protons at C-2 and C-3 occurred as a multiplet centered at δ 3.48.

The synthesis of thioether type compounds (VIIIa,b) was also attempted using a more direct and versatile method (Scheme 4), based on the intramolecular cyclization of the nitrilium salts formed by reaction of the 2-chloroethylaniline (VII) with a thiocyanate-tin (IV) chloride electrophylic complex. This alternative, however, failed in part due to the simultaneous formation of the side compound

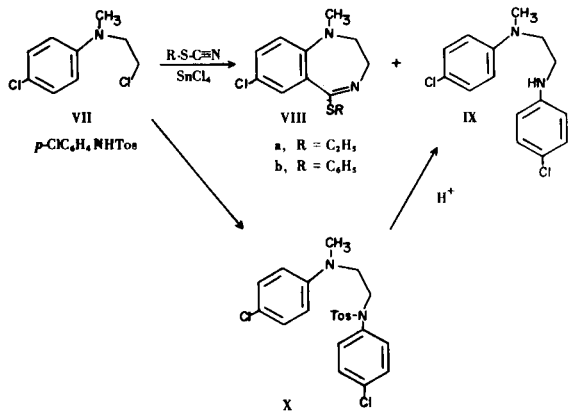
Table I

N,N-Disubstituted-5-amino-1-methyl-2,3-dihydro-1*H*-1,4-benzodiazepines (II)



Compound	NR_2	Yield % (ref. to free base)	M.p., °C or B.p., °C/mm Hg	Recrystallization Solvent	Molecular formula	Analyses % Calcd./Found		
IIa	$-NH_2$	80	Hydroiodide 157	Chloroform-Toluene	$C_{10}H_{14}IN_3$	39.60 39.47	4.62 4.37	13.86 13.67
IIb		70	120-122/0.2	---	$C_{14}H_{19}N_3$	73.32 72.92	8.35 8.63	18.32 17.99
IIc		56	101	Petroleum ether	$C_{15}H_{21}N_3$	74.07 74.04	8.64 8.88	17.28 17.12
IId		78	Picrate 131	Ethanol	$C_{22}H_{26}N_6O_7$	54.32 54.01	5.34 5.39	17.28 16.98
IIe		83	Picrate 197-198	Ethanol	$C_{22}H_{26}N_6O_7$	54.31 54.16	5.38 5.25	17.27 17.09
IIf		85	88	Petroleum ether	$C_{14}H_{19}N_3O$	68.54 68.73	7.80 8.08	17.13 17.40
IIg		46	Dipicrate 238	Acetonitrile	$C_{15}H_{22}N_4$	69.73 69.74	8.58 8.68	21.68 21.97
IIh		73	Dimaleate 166	Methanol-Ether	$C_{24}H_{32}N_4O_9$	55.38 54.95	6.15 5.96	10.76 10.48
IIi		40	Dimaleate 173-174	Methanol	$C_{29}H_{34}N_4O_8$	61.47 61.60	6.04 5.82	9.88 9.71
IIj		45	108-109	Ethyl acetate	$C_{20}H_{24}N_4$	74.96 74.66	7.54 7.35	17.49 17.77
IIk		50	96-97	Heptane	$C_{17}H_{24}N_4O_2$	64.53 64.66	7.64 7.40	17.70 17.55
III	$-NH-(CH_2)_2-N(C_2H_5)_2$	73	Dipicrate 174	Acetonitrile	$C_{28}H_{32}N_{10}O_{14}$	45.90 46.13	4.40 4.50	19.12 19.26
IIm	$-NH-(CH_2)_3-N(C_2H_5)_2$	58	Dipicrate 171	Acetonitrile	$C_{29}H_{34}N_{10}O_4$	46.65 46.49	4.56 4.67	18.77 18.69

Scheme 4



(IX) which decreased the yield of VIII considerably. The structure of IX was established by its analytical and spectral data. Nevertheless, in order to confirm it, we have carried out an unequivocal synthesis by utilizing VII and *p*-chloro-*N*-tosylaniline as starting materials.

EXPERIMENTAL

All melting points (uncorrected) were determined using a Gallenkamp capillary apparatus. The ir spectra were recorded with a Perkin-Elmer Model 257 instrument. ^{1}H nmr spectra were obtained with a Perkin-Elmer R-12 spectrophotometer using TMS as internal reference.

1-Methyl-1,2,3,4-tetrahydro-5*H*-5-thioxo-1,4-benzodiazepine (VI).

This compound was prepared from 1-methyl-1,2,3,4-tetrahydro-5*H*-5-oxo-1,4-benzodiazepine (V)(9), phosphorus pentasulfide and pyridine according to the literature (10).

1-Methyl-5-methylmercapto-2,3-dihydro-1*H*-1,4-benzodiazepine (I).

To a stirred solution of 1-methyl-1,2,3,4-tetrahydro-5*H*-5-thioxo-1,4-benzodiazepine (VI) (49.2 g., 0.25 mole) in anhydrous dioxane (350 ml.), heated at 40°, was added dropwise the fourth part of a solution of potassium hydroxide (70 g.) in methanol (450 ml.) followed of the third part of the whole amount of dimethylsulfate (98.2 g., 0.77 mole). The temperature did not rise above 50°. After stirring 30 minutes, the addition was repeated and stirring continued for 30 minutes more. The rest of the reactants was then added and after one hour the precipitated solid was filtered and washed with methanol. The methanol was evaporated under reduced pressure and the residue was treated with water and extracted with ether. The extracts were dried over anhydrous magnesium sulfate and evaporated. The residue was treated with petroleum ether separating 7.0 g. (13%) of a product characterized as 1,4-dimethyl-1,2,3,4-tetrahydro-5*H*-5-thioxo-1,4-benzodiazepine, m.p. 178° (from 2-propanol); ir (nujol): 1510 cm^{-1} (N-C=S); ^{1}H nmr (deuteriochloroform): δ 2.80 (s, 3, N-CH_3), 3.20-3.80 (m, 4, -CH_2-CH_2-), 3.67 (s, 3, S=C-N-CH_3); 6.80-8.00 (m, 4, aromatic).

Anal. Calcd. for $C_{11}H_{14}N_2S$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.35; H, 6.56; N, 13.85.

Removal of the petroleum ether afforded 36.3 g. (69%) of 1-methyl-5-methylmercapto-2,3-dihydro-1*H*-1,4-benzodiazepine (I), m.p. 66° (from petroluem ether); ir (nujol): 1605 cm^{-1} (C=N); ^{1}H nmr (carbon tetrachloride): δ 2.35 (s, 3, S-CH_3), 2.70 (s, 3, N-CH_3), 3.20-3.70 (m, 4, -CH_2-CH_2-), 6.60-7.40 (m, 4, aromatic).

Anal. Calcd. for $C_{11}H_{14}N_2S$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.26; H, 6.98; N, 13.78.

Preparation of Amidines (IIb-m).

General Method.

A mixture of the 1-methyl-5-methylmercapto-2,3-dihydro-1*H*-1,4-benzodiazepine (I) (0.01 mole), the corresponding amine (0.06 mole) and acetic acid (2 drops) was refluxed for 120-150 hours. The excess of the amine was removed under reduced pressure and the residue was dissolved in 5% acetic acid and extracted with ether. The acidic layer was made basic with 20% sodium hydroxide and extracted with ether several times. The combined ether extracts were washed with water, dried (magnesium sulfate) and concentrated to an oil which slowly crystallized. Purification of these compounds was carried out by recrystallization, vacuum distillation or transformation in the appropriate salts. Yields, physicochemical and analytical data are summarized in the Table I.

1-Methyl-5-amino-2,3-dihydro-1*H*-1,4-benzodiazepine Hydroiodide (IIa).

To a *N* solution of ammonia in ethanol (100 ml.) was added 1-methyl-5-methylmercapto-2,3-dihydro-1*H*-1,4-benzodiazepine (I) (4.12 g., 0.02 mole) and ammonium iodide (2.9 g., 0.02 mole). The resulting solution was heated at reflux temperature for 6 hours. The solution was filtered and the filtrate concentrated to a small volume. Ether was then added and on cooling the salt crystallized. (See Table I).

1-Phenyl-3-(*N*-methylanilino)ethylurea (IVa).

To a solution of aniline (1.9 g., 0.02 mole) in anhydrous ether (15 ml.) was added dropwise a solution of 2-(*N*-methylanilino)-ethylisocyanate (IIIa) (9) in the same solvent (15 ml.). The precipitated urea was filtered and washed with ether, 4.2 g. (87%), m.p. 133-134° (from ethanol).

Anal. Calcd. for $C_{16}H_{19}N_3O$: C, 71.38; H, 7.06; N, 15.16. Found: C, 71.60; H, 6.96; N, 15.43.

1-Phenyl-3-(*N*-methyl-*p*-chloroanilino)ethylurea (IVb).

This compound was prepared in 80% yield from IIIb (9) and aniline under similar conditions which were specified for IVa, m.p. 157° (from ethanol).

Anal. Calcd. for $C_{16}H_{18}ClN_3O$: C, 63.28; H, 5.93; N, 13.84; Cl, 11.66. Found: C, 62.99; H, 5.65; N, 13.65; Cl, 11.66.

Preparation of VIIIa and VIIIb *via* Nitrilium Salts.

7-Chloro-1-methyl-5-ethylmercapto-2,3-dihydro-1*H*-1,4-benzodiazepine (VIIIa).

A mixture of *N*-(2-chloroethyl)-*N*-methyl-*p*-chloroaniline (VII) (20.4 g., 0.1 mole), ethyl thiocyanate (8.7 g., 0.1 mole) and tin (IV) chloride (26.0 g., 0.1 mole), was heated at 130° for 5 hours. After cooling, it was made basic with 20% aqueous sodium hydroxide and extracted with benzene. The organic layer was treated with 20% hydrochloric acid. The acidic phase was alkalinized with 20% aqueous sodium hydroxide and extracted with benzene. The combined extracts were washed with water and dried (magnesium sulfate). The solvent was removed under reduced pressure and the residue taken up in ethyl acetate and chromatographed on a silica gel column with benzene-ethyl acetate (2:1) as eluent. The first fraction was collected. Evaporation of the solvent furnished 12.7

g. (50%) of *N,N'*-di-(*p*-chlorophenyl)-*N'*-methylethylendiamine (IX), m.p. 95-96° (from hexane); ir (nujol): 3450 cm^{-1} (-NH-); ^1H nmr (deuteriochloroform): δ 2.93 (s, 3, N-CH_3), 3.55 (m, 4, -N-CH_2-CH_2-N-), 6.50-7.50 (m, 8, aromatic); mass spectrum: m/e 295 (M^+).

Anal. Calcd. for $C_{15}H_{16}Cl_2N_2$: C, 61.01; H, 5.42; N, 9.49; Cl, 24.06. Found: C, 61.34; H, 5.47; N, 9.77; Cl, 24.21.

The picrate had m.p. 145° (from ethanol).

Anal. Calcd. for $C_{21}H_{19}Cl_2N_5O_7$: C, 48.09; H, 3.62; N, 13.36; Cl, 13.63. Found: C, 48.22; H, 3.65; N, 13.56; Cl, 13.93.

The second fraction gave, after removal of the solvent, 3.8 g. (15%) of 7-chloro-1-methyl-5-ethylmercapto-2,3-dihydro-1*H*-1,4-benzodiazepine (VIIIa) as a yellowish solid, m.p. 81-82° (from 2-propanol); ir (nujol): 1610 cm^{-1} (C=N); ^1H nmr (deuteriochloroform): δ 1.26 (t, 3, CH_3 at S-Et), 2.70 (s, 3, N-CH_3), 3.0 (quartet, 2, -CH_2- at S-Et), 3.50 (m, 4, -N-CH_2-CH_2-N), 6.60-7.50 (m, 3, aromatic).

Anal. Calcd. for $C_{12}H_{15}ClN_2S$: C, 56.58; H, 5.89; N, 11.00; Cl, 13.91; S, 12.57. Found: C, 56.31; H, 6.00; N, 10.74; Cl, 13.88; S, 12.45.

7-Chloro-1-methyl-5-phenylmercapto-2,3-dihydro-1*H*-1,4-benzodiazepine (VIIIb).

This compound was obtained in 7% yield together with IX as the major product (73%), from the reaction of VII and phenyl thiocyanate in the conditions used for VIIIa, m.p. 152-153° (from hexane); ir (nujol): 1610 cm^{-1} (C=N); ^1H nmr: δ 2.75 (s, 3, N-CH_3), 3.50 (m, 4, -N-CH_2-CH_2-N), 6.60-7.70 (m, 8, aromatic).

Anal. Calcd. for $C_{16}H_{15}ClN_2S$: C, 63.49; H, 4.66; N, 9.25; S, 10.60. Found: C, 63.69; H, 4.96; N, 9.26; S, 10.82.

Unequivocal Synthesis of IX.

N,N'-Di(*p*-chlorophenyl)-*N*-tosyl-*N'*-methylethylenediamine (X).

To a stirred solution of sodium (0.55 g., 0.024 mole) in methanol (50 ml.) was added *N*-tosyl-*p*-chloroaniline (5.7 g., 0.020 mole) and stirring was continued until the solution of the aniline was complete. After removal of methanol, *N,N*-dimethylformamide (50 ml.) and VII (4.06 g., 0.020 mole) was added. The mixture was refluxed for 6 hours. Cooling and precipitation with water yielded X as white crystals which were filtered, washed with water and dried, 6 g. (86%), m.p. 115-116° (from ethanol).

Anal. Calcd. for $C_{22}H_{22}Cl_2N_2O_2S$: C, 46.99; H, 6.30; N, 8.02; Cl, 20.34. Found: C, 47.08; H, 6.05; N, 7.85; Cl, 20.22.

N,N'-Di(*p*-Chlorophenyl)-*N'*-methylethylenediamine (IX).

A mixture of X (2 g., 0.0057 mole) and a solution of 81% sulfuric acid (4 ml.) was heated at 145° for 1 hour. After cooling, the mixture was poured on cold water and the resulting solution was made basic with 20% aqueous sodium hydroxide and extracted with ether. The extracts, washed and dried (magnesium sulfate), were concentrated, yielding 1 g. (60%) of a white solid which was identical (m.p., ^1H nmr, ir, *etc.*) with IX.

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