given to abolish the corneal reflex. A carotid artery was cannulated for direct and continuous recording of the arterial blood pressure. The trachea was cannulated for continuous recording of amplitude and frequency of respiration. Recordings were made with conventional apparatus. A femoral vein was exposed for the administration of all compounds. Generally, 1 dog was used per compound. After blood pressure and respiration had stabilized, an initial dose of 1 mg./kg. of the experimental compound was given. Thereafter, each succeeding dose was doubled until it was impractical to continue. The time between doses usually varied from 15 to 60 min., depending upon response to the preceding dose.

Antianesthetic effects were determined by testing for the integrity of various reflexes including corneal, blink, and proprioceptive (limb withdrawal to a pinch on the toes). Increased skeletal muscular tone, spontaneous movement of head, trunk, limbs and tail, intact drink reflex, eyeball movement, etc. were additional responses which indicated CNS stimulation or antagonism to the anesthetic.

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6-Amino Derivatives of 5H-Dibenzo[*d*,*f*][1,3]diazepine

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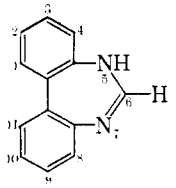
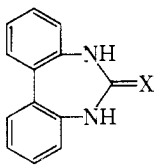
6-Amino and substituted-amino derivatives of 5H-dibenzo[*d*,*f*][1,3]diazepine (I) have been prepared by replacement of the corresponding alkylthio function or by ring closure of 2,2′-diaminobiphenyl with N,N′-dialkylcarbodiimides or S-methylisothiourea.

Compounds containing a 7-membered ring are known to exhibit diverse biological activities. These actions include cardiovascular (*e.g.*, azapetine)[1] and psychopharmacologic (amitriptyline,[2] diazepam,[3] and chlordiazepoxide[4]). We wish to report a series of 6-amino derivatives of 5H-dibenzo[*d*,*f*][1,3]diazepine (I),[5] incorporating a bulky near-planar aromatic moiety as in amitriptyline with a 7-membered cyclic guanidine system. These 6-amino compounds were considered of interest as potential psychotropic agents.

Other derivatives of I, substituted in the 6-position, have been reported to include alkyl,[5-8] aryl,[9-11] alkoxy,[11] hydroxy,[12] and sulfhydryl[13] compounds, the last two existing primarily as the keto and thione forms (IIb,a) respectively.



I



IIa, X=S
IIb, X=O

The simplest member of the series, 6-amino-5H-dibenzo[*d*,*f*][1,3]diazepine (IV), was prepared in one step from 2,2′-diaminobiphenyl (III) by fusion with S-methylisothiourea sulfate (method A).

In that Hungar, *et al.*,[14] have recently employed carbodiimides in the synthesis of 2-(substituted amino)-benzimidazoles, it was of interest to investigate the applicability of similar reagents in the preparation of 7-membered cyclic guanidines such as the 6-monoalkylamino derivatives of I. Two alkylamino derivatives were prepared from III and the appropriate carbodiimide; thus, heating III with N,N′-dicyclohexyl- or N,N′-diisopropylcarbodiimide at 160–200° gave 6-cyclohexylamino- (VIa) and 6-isopropylamino-5H-dibenzo[*d*,*f*][1,3]diazepine (VIb) (method B).

Compounds of type VI were also prepared by another route involving replacement of an alkylthio function by amines (method C). The intermediate methylthio compound(V) was produced in excellent yield by treatment of the 6-thione derivative (IIa) with methyl iodide in tetrahydrofuran. Preparation of VI(c–g, j–t) was accomplished by heating the methylthio compound with the appropriate amine or amine hydrochloride (in some cases, as with high-boiling amines, V was effectively employed as the free base; however, the use of the hydrohalide salt of either the methylthio compound or the amine reagent appeared to be more suitable in the case of low-boiling amines). Reaction temperatures varied from 70–200°, depending upon the reactivity of the amine function and the fusion temperature of the mixture (Table I). The temperature at which the reaction commenced was clearly observable by the evolution of mercaptan. The strong odor lessened considerably as the reaction neared completion, but never disappeared entirely. Yields were generally between 50–90% of analytically pure material; lower yields were usually due to losses in successive recrystallizations.

(1) Ilidar®, 6-allyl-6,7-dihydro-5H-dibenz[*c*,*e*]azepine.
(2) Elavil®, 3-(3-dimethylaminopropylidene)[1:2, 4:5]dibenzocyclohepta-1,4-diene.
(3) Valium®, 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one.
(4) Librium®, 7-chloro-2-methylamino-5-phenyl-3H-1,3-benzodiazepine 4-oxide.
(5) S. Sako, *Mem. Coll. Eng. Kyushu Imp. Univ.*, **6**, 263 (1932); *Chem Abstr.*, **26**, 3246 (1932).
(6) P. T. Charlton, G. Maliphant, P. Oxley, and D. Peak, *J. Chem. Soc.*, 485 (1951).
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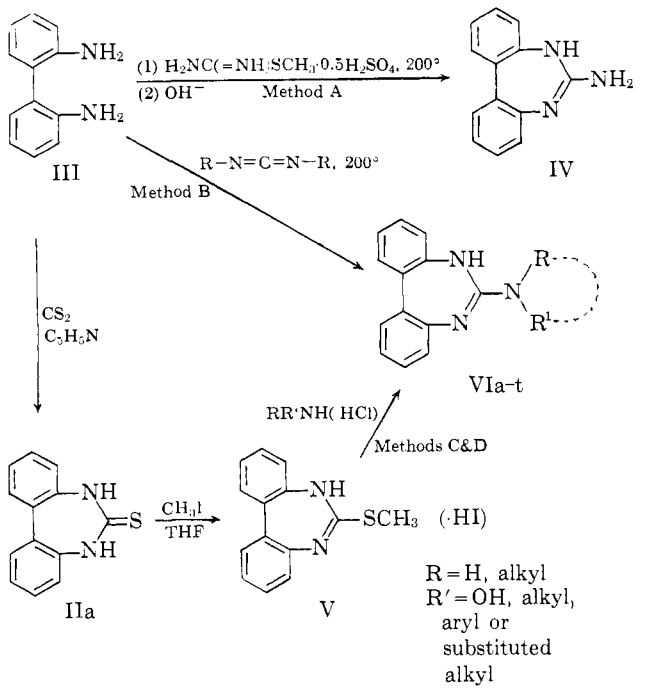
(12) St. von Niementowski, *ibid.*, **34**, 3325 (1901).
(13) R. J. W. Le Fevre, *J. Chem. Soc.*, 733 (1929).
(14) A. Hungar, J. Kebrle, A. Rossi, and K. Hoffman, *Helv. Chim. Acta*, **44**, 1273 (1961).



The reaction of secondary amines with the methylthio compound V was generally analogous to that of primary amines. One exception to this was noted in the case of the diethylamino derivative. Although the 6-dimethylamino derivative (VIk) could be prepared in 54% yield by heating the methylthio compound with dimethylamine hydrochloride at 160–200°, attempts to prepare the 6-diethylamino derivative (VIl) under similar conditions with the appropriate amine hydrochloride led only to cleavage of the methylthio function to give the thione, IIa. After considerable experimentation, a satisfactory preparation of VIl (56% yield) was developed wherein V was heated in an autoclave at 160° with an excess of diethylamine and one equivalent of diethylamine hydrochloride.

Two compounds, VI(h,i) were prepared by a modification of method C, wherein aqueous alkali was used as solvent (method D).[15]

An attempt to prepare compounds of type VI directly from the thione, IIa, by reaction with amines was unsuccessful. After IIa had been heated under reflux with an excess of piperidine for 3 hr. only starting material could be recovered. Equally unsuccessful were attempts to prepare 6-alkoxy derivatives of I by reaction of the methylthio compound (V) with alcohols. Heating V·HI with 1-butanol resulted in the elimination of mercaptan and the isolation of the keto compound (IIb) in almost quantitative yield.

Several of the compounds described in Table I have shown high milligram potency when assayed intraperitoneally in albino male mice for acute neurologic and behavior effects.[16] Excitant, aggressant, and motor stimulant activities were demonstrated by the following compounds[17]: VIb (AED_{50} = 7.5, ALD_{50} = 120), VIl (AED_{50} = 0.5, ALD_{50} = 35), VIo (AED_{50} = 3, ALD_{50} = 80), VIp (AED_{50} = 7.5, ALD_{50} = 34), and VIq (AED_{50} = 1.5, ALD_{50} = 17.5).

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(17) Values are in mg./kg. and AED values are for excitant action.

TABLE I: 6-SUBSTITUTED-AMINO DERIVATIVES OF 5H-DIBENZO[*d*,*f*][1,3]DIAZEPINE

Compound	6-Substituent	Method	Yield, %	Temp., °C.	Crystn. solvent	M.p., °C.	Formula	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N
IV	$-NH_2$	A	36	200	*a*	208–209 dec.	$C_{13}H_{11}N_3$	74.63	5.30	20.09	73.73	5.46	20.09
VIa	$-NHC_6H_{11}$	B	41	200	*b*	231–232	$C_{19}H_{21}N_3$	78.31	7.27	14.42	78.00	7.37	14.64
VIb	$-NHC_3H_7$-*i*	B	52	200	*c*	228–229	$C_{16}H_{17}N_3$	76.46	6.82	16.72	76.38	6.87	16.65
VIc	$-NHCH_3$	C	90	200	*d*	243–245	$C_{14}H_{13}N_3$	75.31	5.87	18.82	75.31	6.19	18.77
VId	$-NHC_2H_5$	C	58	200	*b*	213–215	$C_{15}H_{15}N_3$	75.92	6.37	17.71	75.92	6.66	17.56
VIe	$-NHC_4H_9$-*n*·HCl	C	48	200	*e*	239–241	$C_{17}H_{20}ClN_3$		11.75[f]	13.92		11.96[f]	13.74
VIf	$-NHCH_2CH_2$-NC_4H_8O·2HCl[g]	C	70	75	*a*	277–278 dec.	$C_{19}H_{21}Cl_2N_4O$		17.94[f]	14.17		17.65[f]	13.90
VIg	$-NHC_3H_2NS$[h]	C	89	100	*i*	204–205	$C_{18}H_{12}N_4S$		10.97[j]	19.17		10.80[j]	18.99
VIh	$-NHOH$·HCl	D	90	30	*b*	225–226 dec.	$C_{13}H_{12}ClN_3O$	59.66	4.62	16.06	59.57	4.93	16.00
VIi	$-NHCH_2CO_2C_2H_5$·HCl	D	41	50	*k*	193–194 dec.	$C_{17}H_{18}ClN_3O_2$		10.69[f]	12.66		10.60[f]	12.70
VIj	$-NHC_6H_5$	C	96	185	*l*	255–256	$C_{19}H_{15}N_3$	79.97	5.30	14.73	80.05	5.60	14.93
VIk	$-N(CH_3)_2$·HCl	C	54	200	*b*	>310	$C_{15}H_{16}ClN_3$		12.95[f]	15.35		12.72[f]	15.06
VIl	$-N(C_2H_5)_2$·HCl	C	56	160	*m*	>310	$C_{17}H_{20}ClN_3$		11.75[f]	13.92		11.87[f]	13.70
VIm	$-NC_5H_{10}$[n]	C	67	160	*d*	144–145	$C_{18}H_{19}N_3$	77.94	6.90	15.15	77.76	7.13	15.03
VIn	$-NC_4H_8NCH_3$·2HCl[o]	C	44	100	*m*	>310	$C_{18}H_{22}Cl_2N_4$		19.41[f]	15.34		19.39[f]	15.11
VIo	$-NC_4H_8O$·HCl[p]	C	87	100	*e*	>310	$C_{17}H_{18}ClN_3O$	64.65	5.74	13.31	64.89	5.96	13.37
VIp	$-NC_4H_8$·HCl[p]	C	74	100	*i*	>310	$C_{17}H_{18}ClN_3$		11.83[f]	14.02		11.67[f]	13.79
VIq	$-NC_6H_{12}$·C_2H_5OH[q]	C	53	100	*r*	69–80 dec.	$C_{21}H_{27}N_3O$	74.74	8.07	12.45	74.97	8.11	12.53
VIr	$-N(CH_3)C_2H_4N(CH_3)_2$·2HCl	C	76	200	*e*	250–251	$C_{18}H_{24}Cl_2N_4$		19.31[f]	15.25		19.39[f]	14.92
VIs	$-N(CH_3)C_2H_4N(C_2H_5)_2$·2HCl	C	81	200	*s*	246–247 dec.	$C_{20}H_{28}Cl_2N_4$		17.93[f]	14.17		17.70[f]	13.91
VIt	$-N(C_2H_5)C_2H_4N(C_2H_5)_2$·2HCl	C	68	200	*s*	159–161 dec.	$C_{22}H_{36}Cl_2N_4$		17.32[f]	13.69		17.11[f]	13.51

[a] Ethanol–water. [b] 95% Ethanol. [c] 2-Propanol. [d] Heptane. [e] Methanol–isopropyl ether. [f] Chlorine analysis. [g] NC_4H_8O=morpholino. [h] C_3H_2NS=2-thiazolyl. [i] Dimethylformamide–water. [j] Sulfur analysis. [k] Ethanol–ethyl acetate. [l] Aqueous Cellosolve. [m] Methanol. [n] Piperidino. [o] 4-Methylpiperazino. [p] Pyrrolidino. [q] Hexamethyleneimino. [r] Absolute ethanol. [s] 2-Propanol–ethanol.

Anticonvulsant activity[18] (maximal electroshock seizure, 50 ma.) was demonstrated by several compounds of this series. Compounds VIb, VIm, and VIq had AED_{50} values between 50 and 100 mg./kg. (ALD_{50} values of 150–200 mg./kg.) when administered orally to nonfasted male albino mice. Compounds VIl and VIk had AED_{50} values of 12 and 25 mg./kg. and ALD_{50} values of 35 and 30 mg./kg., respectively.

Experimental[19]

6-Thio-6,7-dihydro-5H-dibenzo[*d,f*][1,3]diazepine (IIa).—Sixty grams (0.32 mole) of 2,2'-diaminobiphenyl (III), prepared according to Ross, *et al.*,[20] was heated under reflux for 15 hr. with a mixture of 300 ml. of pyridine, 250 ml. of carbon disulfide, and 25 ml. of water. The solvents were removed under vacuum at 80–90°. The solid residue was dissolved in acetone and acidified strongly with 20% hydrochloric acid to remove traces of pyridine, which forms a rather stable complex with the product. The mixture was diluted with a liter of water and chilled. The precipitate was collected and recrystallized twice from 95% ethanol to give 52 g. (72%) of colorless prisms melting at 241–243°. Le Fevre[13] reported a melting point of 242–243°, λ_{max}^{KBr} 3.1, 7.1, 8.7, and 13.3 μ.

6-Methylthio-5H-dibenzo[*d,f*][1,3]diazepine Hydroiodide (V·HI).—The thione (IIa) (31.5 g., 0.14 mole) was dissolved in 260 ml. of tetrahydrofuran and stirred for 2 hr. with 21 g. (0.15 mole) of methyl iodide. After the mixture had been allowed to stand overnight, the solid was collected and air-dried to give 41 g. of white powder melting at 233–234° dec. The filtrates afforded a second crop weighing 9 g. and melting at 228–231° dec. The total crude yield was 97%. Recrystallization from butanone–methanol gave colorless prisms melting at 230–232° dec., but resulted in some decomposition (odor of mercaptan).

Anal. Calcd. for $C_{14}H_{13}IN_2S$: N, 7.61; S, 8.71. Found: N, 7.43; S, 8.76.

6-Methylthio-5H-dibenzo[*d,f*][1,3]diazepine (V).—This material was isolated from the hydriodide salt by extraction with a mixture of chloroform and 5% aqueous sodium hydroxide. Evaporation of the organic layer and recrystallization of the residual solid from chloroform–heptane gave the base (m.p. 164–165°) in nearly quantitative yield. The analytical sample was recrystallized once more from the same solvent pair and melted at 165–166°; λ_{max}^{KBr} 3.2, 6.2, 6.7, 7.0, 7.8, 8.8, and 13.2 μ; ϵ_{max} (λ) 42,700 (250), 4600 (285 mμ).

Anal. Calcd. for $C_{14}H_{12}N_2S$: C, 69.96; H, 5.03; N, 11.66. Found: C, 69.96; H, 5.28; N, 11.89.

Preparation of the 6-Amino Derivatives of 5H-Dibenzo[*d,f*][1,3]diazepine. A. 6-Amino-5H-dibenzo[*d,f*][1,3]diazepine (IV).—2,2'-Diaminobiphenyl (III) (6 g., 0.033 mole) was heated with 6 g. (excess) of S-methylisothiourea sulfate to 110° whereupon methyl mercaptan began to be evolved. The temperature of the mixture was raised gradually to 200° and held for 30 min. The brown gum was stirred with an excess of 30% aqueous methanol containing 5% sodium hydroxide (to dissolve precipitated salts) and the mixture was diluted with 200 ml. of water. The tan solid was collected and recrystallized three times from 35% ethanol (slight decomp.) to give 2.5 g. (36%) of pale tan flakes melting at 208–209° dec., λ_{max}^{KBr} 2.9, 3.0, 6.0, and 13.2 μ; ϵ_{max} (λ) 34,900 (240), 3080 (278 mμ).

B. 6-Isopropylamino-5H-dibenzo[*d,f*][1,3]diazepine (VIb).—2,2'-Diaminobiphenyl (III) (9.2 g., 0.05 mole) was heated in an open 100-ml. round-bottomed flask with 6.5 g. (0.05 mole) of N,N'-diisopropylcarbodiimide (Aldrich Chemical Co.). When the temperature of the melt reached 150°, the odor of isopropylamine was evident at the mouth of the flask. The temperature was slowly raised to 200° and held for 30 min. The pale yellow melt was cooled and recrystallized once from ethanol–ethyl acetate and once from 2-propanol to give 6.5 g. (52%) of colorless needles melting at 228–229°; λ_{max}^{KBr} 2.9, 3.0, 3.3, 6.1, 8.1, and 13.1 μ; ϵ_{max} (λ) 43,000 (241), 4540 (275 mμ).

Compound VIb was prepared in a similar manner, as indicated in Table I.

The ultraviolet spectra of the 6-alkylamino and 6-dialkylamino derivatives were very similar. A rather intense absorption was exhibited in the region of 235–243 mμ (ϵ_{max} 38,000–57,000 with the more hyperchromic values occurring in those cases of hydrochloride salts) while a lesser peak appeared at 278–280 mμ (ϵ_{max} 3000–4000).

C. 6-Dimethylamino-5H-dibenzo[*d,f*][1,3]diazepine Hydrochloride (VIk).—Eight grams (0.033 mole) of methylthio derivative (V) was mixed well with 20 g. (excess) of dimethylamine hydrochloride and heated strongly until the mixture melted (about 160°). The temperature was allowed to rise slowly to 200° where it was held for 30 min. The evolution of mercaptan was strong at 160°, but lessened after several min. at 200°. The melt was cooled and stirred with an excess of 30% aqueous 2-propanol containing 5% sodium hydroxide. The gummy precipitate was collected and converted to the hydrochloride. Recrystallization as the hydrochloride (twice from methanol–2-propanol and once from 95% ethanol) gave 5 g. (54%) of colorless needles which did not melt below 310°; λ_{max}^{KBr} 3.3, 3.4, 3.5, 6.0, 6.7, 7.0, and 13.0 μ.

Compounds VIc–g, j, m–t) were prepared in a similar fashion (Table I).

C. 6-Diethylamino-5H-dibenzo[*d,f*][1,3]diazepine Hydrochloride (VIl).—Ten grams (0.04 mole) of V was mixed with 50 ml. (excess) of diethylamine and 4.4 g. (0.04 mole) of diethylamine hydrochloride and heated in an autoclave at 160° for 24 hr. The mixture was transferred to a beaker and evaporated to dryness on the steam bath. The residue was stirred with two 300-ml. portions of dilute base, decanting the aqueous portions. The brown gum was taken up in a small amount of 95% ethanol and acidified strongly with 5 *N* ethanolic HCl. Precipitation of the hydrochloride by addition of ether and recrystallization of the white solid from methanol gave 7 g. (56%) of colorless hexagonal slabs melting above 310°, λ_{max}^{KBr} 3.4, 6.1, 6.8, 7.0, and 13.1 μ.

D. 6-Hydroxylamino-5H-dibenzo[*d,f*][1,3]diazepine Hydrochloride (VIh).—A solution of 3.6 g. (0.09 mole) of sodium hydroxide in 50 ml. of water was combined with a mixture of 11 g. (0.03 mole) of the methylthio hydriodide derivative (V·HI), 4.2 g. (0.06 mole) of hydroxylamine hydrochloride, and 50 ml. of dioxane. The odor of mercaptan was immediately evident. The mixture was stirred at 30° for 18 hr. A white solid appeared after about 2 hr. stirring. The mixture was diluted to 200 ml. with water and filtered. The precipitate was collected, converted to the hydrochloride, and recrystallized from 95% ethanol to give 7.5 g. (90%) of colorless needles (hydrated). The analytical sample was dried over phosphorus pentoxide at 100° for 4 hr. and gave a correct analysis for the anhydrous material, which melted at 225–226° dec., λ_{max}^{KBr} 3.2, 6.0, and 13.2 μ.

D. 6-Carbethoxymethylamino-5H-dibenzo[*d,f*][1,3]diazepine Hydrochloride (VIi).—Compound V·HI (7.4 g., 0.02 mole) was stirred into a solution of 1.5 g. (0.02 mole) of glycine and 0.8 g. (0.02 mole) of sodium hydroxide in 30 ml. of water and 20 ml. of dioxane. The mixture was warmed on a water bath at 40–50° for 24 hrs., diluted to 150 ml., allowed to stand 3 hr., and then filtered. The white precipitate was air-dried to give 5.8 g. of crude base-soluble material melting at 287–288° dec. A 3 g. aliquot was boiled with 30 ml. of 5 *N* ethanolic HCl for 1 hr. The solvents were evaporated and the residue was recrystallized from ethanol–ethyl acetate to give 1.5 g. (41%) of fine colorless needles melting at 193–194° dec., λ_{max}^{KBr} 3.3, 5.7, 6.0, 8.2, and 13.1 μ.

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(19) Melting points were determined on a calibrated thermometer and are corrected for stem exposure. Ultraviolet spectra were determined in 95% ethanol with a Cary Model 14 spectrophotometer. Infrared spectra were obtained with a Beckman IR-4 spectrophotometer. Microanalyses were performed by Mr. Clarence Kennedy, Mead Johnson Research Center.

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